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Comprehensive Invited Review

The Mechanistic Basis of Infarct Healing

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ABSTRACT

Myocardial infarction triggers an inflammatory cascade that results in healing and replacement of the damaged tissue with scar. Cardiomyocyte necrosis triggers innate immune mechanisms eliciting Toll-like receptor–mediated responses, activating the complement cascade and generating reactive oxygen species. Subsequent activation of NF-κB is a critical element in the regulation of cytokine, chemokine, and adhesion molecule expression in the ischemic myocardium. Chemokine induction mediates leukocyte recruitment in the myocardium. Pleiotropic proinflammatory cytokines, such as TNF-α, IL-1, and IL-6, are also upregulated in the infarct and exert a wide range of effects on a variety of cell types. Timely repression of proinflammatory gene synthesis is crucial for optimal healing; IL-10 and TGF-β-mediated pathways may be important for suppression of chemokine and cytokine expression and for resolution of the leukocytic infiltrate. In addition, TGF-β may be critically involved in inducing myofibroblast differentiation and activation, promoting extracellular matrix protein deposition in the infarcted area. The composition of the extracellular matrix plays an important role in regulating cell behavior. Both structural and matricellular proteins modulate cell signaling through interactions with specific surface receptors. The molecular and cellular changes associated with infarct healing directly influence ventricular remodeling and affect prognosis in patients with myocardial infarction. *Antioxid. Redox Signal.* 8, 1907–1939.

INTRODUCTION

Despite recent declines in the incidence of myocardial infarction, more than 1.5 million Americans have an acute infarct every year; approximately one fourth of all deaths are due to acute myocardial infarction (352). Almost all myocardial infarcts result from coronary atherosclerosis, with superimposition of coronary thrombosis. Sudden induction of ischemia by coronary artery occlusion triggers a series of events that culminates in the death of ischemic cardiomyocytes (165). Cardiomyocyte necrosis sets into motion an inflammatory cascade that serves to clear the infarct of dead cells and matrix debris, but also results in healing and replacement of the damaged tissue with scar. Thus, cardiac repair after myocardial infarction is closely intertwined with the inflammatory response. Infarct healing can be divided into three overlapping phases: the inflammatory phase, the proliferative phase, and the maturation phase (Fig. 1). During the inflammatory phase, activation of chemokine and cytokine cascades results in recruitment of leukocytes into the infarcted area. Neutrophils and macrophages clear the wound of dead cells and matrix debris. Activated macrophages release cytokines and growth factors, leading to the formation of granulation tissue. At this stage, expression of inflammatory mediators is suppressed, whereas fibroblasts and endothelial cells proliferate. During the proliferative phase of healing, activated myofibroblasts produce extracellular matrix proteins, and an extensive microvascular network is formed. Maturation of the scar follows: fibroblasts and vascular cells undergo apoptosis, and a collagen-based scar is formed. Infarct healing results in profound changes in ventricular architecture and geometry, also referred to as "ven-

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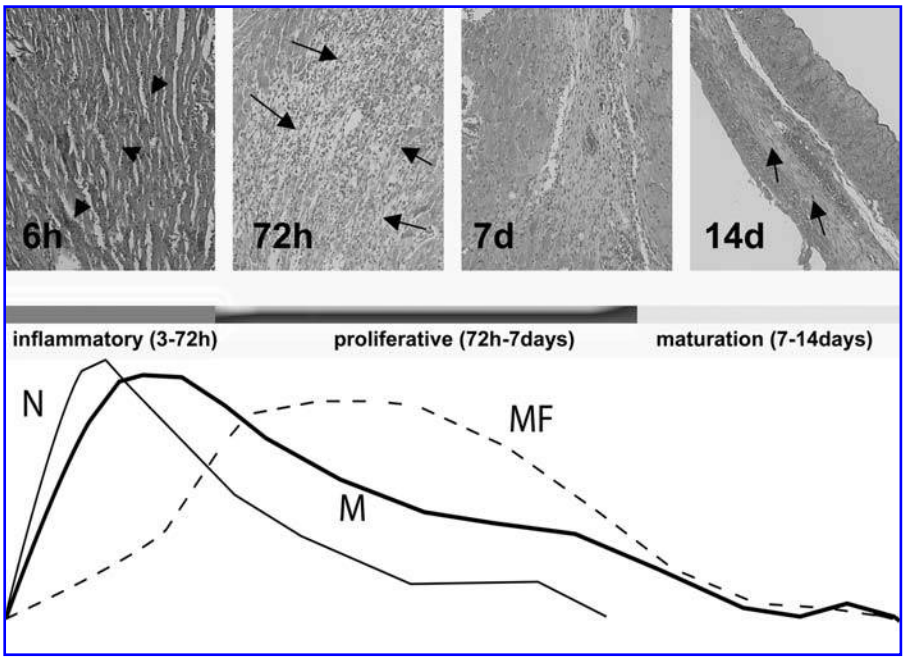

FIG. 1. The phases of healing in reperfused mouse infarcts (1-h coronary occlusion followed by reperfusion). The curves illustrate the time course of neutrophil (thin line, N), monocyte/macrophage (heavy line, M), and myofibroblast (dotted line, MF) in the reperfused mouse infarct. During the inflammatory phase of healing (3–72 h), leukocytes infiltrate the infarcted myocardium (arrowheads) and clear the wound of dead cells and matrix debris. After 72 h of reperfusion, inflammatory mediator synthesis is repressed, and most dead cardiomyocytes are replaced with granulation tissue (arrows), leading to the proliferative phase of healing. At this stage (72 h to 7 days), a wound containing fibroblasts, macrophages, and a rich vascular network is formed. Infarct fibroblasts undergo myofibroblast differentiation and deposit extracellular matrix proteins. The maturation phase follows as fibroblasts undergo apoptosis, most microvessels regress, and a collagen-based scar is formed (arrows). Please note that the time course of events in reperfused mouse infarcts is accelerated in comparison with large-animal models and results in formation of thin scars.

tricular remodeling" (Fig. 2). The molecular and cellular changes associated with ventricular remodeling affect both the cardiomyocytes and interstitial cells and manifest clinically as increased ventricular size, altered shape of the ventricle, and worsened cardiac function. Remodeling is linked to heart-failure progression and is associated with poor prognosis after myocardial infarction. Ventricular dilation after myocardial infarction is an important predictor of mortality (379) and adverse cardiac events (335), including the development of heart failure and ventricular arrhythmias (330, 334). Although the pathways involved in remodeling remain poorly understood, it is clear that the pathologic and structural changes associated with infarct healing directly influence remodeling and affect prognosis in patients with myocardial infarction. After cardiomyocytes die in the infarcted myocardium, granulation tissue cells and the extracellular matrix network provide mechanical stability to the injured tissue. Thus, preservation of the collagenous matrix is important to minimize infarct expansion. In addition, defects in the healing process may be directly involved in the development of lethal complications, such as cardiac rupture and ventricular aneurysm formation (Fig. 3). Cardiac rupture involves tearing of acutely infarcted tissue and results from mechanical weak-

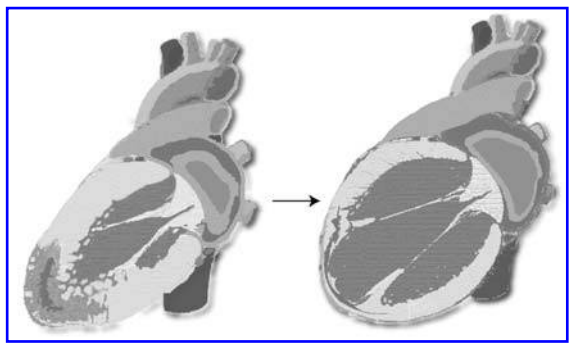

FIG. 2. The process of left ventricular remodeling begins rapidly after myocardial infarction and results in dilatation and geometric distortion of the ventricle, which tends to become spherical. The cellular and molecular changes associated with remodeling are closely intertwined with the healing process.

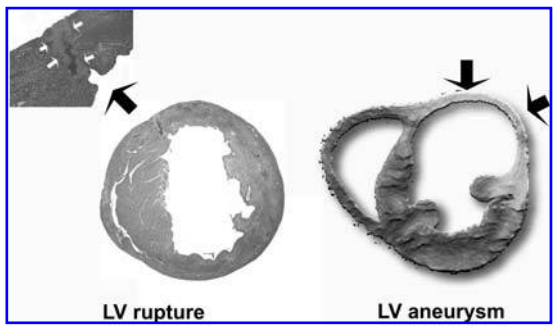

FIG. 3. Cardiac rupture (*left*) is an important cause of death in patients with acute myocardial infarction. Formation of a left ventricular aneurysm often complicates the course of a transmural infarct. Both these complications are associated with defects of the healing response.

ening that occurs in the necrotic and inflamed myocardium. Ventricular aneurysm is a circumscribed noncontractile outpouching of the left ventricle that is usually composed of fibrous tissue and bulges during systole.

Although recent advances in cardiovascular therapeutics have resulted in the development of novel strategies that salvage myocardium and improve early mortality in patients with myocardial infarction, approaches directly targeting the healing process are lacking. Neurohumoral pharmacologic interventions, such as the administration of angiotensin-converting enzyme (ACE) inhibitors, β blockers, and aldosterone antagonists, are the only established therapeutic modalities that reduce adverse remodeling in patients with myocardial infarction. Understanding of the specific events involved in infarct healing is crucial to design novel therapeutic strategies aiming at optimizing cardiac repair and attenuating postinfarction remodeling. The current review examines the cellular and molecular events associated with the inflammatory response after myocardial infarction and explores the mechanistic basis of infarct healing.

THE INFLAMMATORY PHASE OF INFARCT HEALING

Initiation of the inflammatory process in healing infarcts

Because the mammalian heart cannot produce enough energy under anaerobic conditions to maintain essential cellular processes, a constant supply of oxygen is indispensable to sustain cardiac function and viability. Ischemic myocardial injury results in decreased oxygen tension within the cell and subsequent loss of oxidative phosphorylation and decreased generation of ATP. ATP depletion leads to failure of the sodium pump, loss of potassium, influx of sodium and water, and cell swelling. Cessation of aerobic metabolism, ATP depletion, and accumulation of products of anoxic metabolism occur within 10 sec of occlusion. Striking myocardial dysfunction occurs almost simultaneously and is evident within 50 sec. Minutes after the onset of ischemia, reversible ultrastructural cardiomyocyte changes appear, including cellular and mitochondrial swelling and glycogen depletion. Irreversible cardiomyocyte injury, evidenced by sarcolemmal disruption and the presence of small amorphous densities in the mitochondria, develops after 20–40 min of sustained ischemia (165). Cells dying by necrosis release their intracellular contents and initiate an intense inflammatory response by activating innate immune mechanisms. Toll-like receptor (TLR)-mediated pathways, complement activation, and reactive oxygen species generation play a significant role in triggering the postinfarction inflammatory response by activating the nuclear factor (NF)-κB system.

The role of complement activation. The complement system is an important component of the innate immune response and a major effector in a variety of immunopathologic diseases. The complement cascade is activated through three distinct mechanisms designated the classic, alternative, and lectin pathways (104, 259). Numerous studies have indicated that ischemic myocardial injury activates the complement cascade (295). Hill and Ward (146) were the first to demonstrate that leukotactic activity in rat myocardial infarcts was in part due to C3 cleavage products. Subsequently Pinckard and colleagues (281) showed evidence of C1, C3, and C4 consumption in patients with acute myocardial infarction, suggesting that myocardial cell necrosis results in the release of subcellular membrane constituents capable of activating the complement cascade. Further studies (294, 295) have suggested that during myocardial ischemia, mitochondria, extruded through breaks in the sarcolemma, unfold and release membrane fragments rich in cardiolipin and protein. By binding C1 and supplying sites for the assembly of later-acting complement components, these subcellular fragments provide the means to disseminate the complement-mediated inflammatory response to ischemic injury. mRNA and proteins for all the components of the classic complement pathway are upregulated in myocardial infarcts (390).

Complement activation may play an important role in mediating neutrophil and monocyte recruitment in the injured myocardium (75). The contribution of complement activation in mononuclear cell recruitment appears to be particularly important during the first hour of reperfusion (19).

Blocking activation of the complement system can be achieved by consumptive depletion (such as with cobra venom factor injection), by antibody-induced inhibition of individual complement components (*e.g.*, C5), or by infusion of modified native complement components that block complement activation, such as the soluble form of complement receptor type 1(sCR1) (58, 231). Complement depletion using cobra venom factor injection at the time of experimental coronary artery occlusion has been shown to attenuate myocardial necrosis in a variety of animal models (232). However, conclusions derived from studies with a focus on complement depletion overlook the prior systemic activation that may result in deactivation of neutrophils. Administration of C1-esterase inhibitor decreased infarct size in several experimental models of coronary occlusion and reperfusion (33, 34, 148–150); however, high doses were detrimental, possibly due to procoagulant effects mediated through inactivation of the fibrinolytic system (150). In addition, infusion of soluble human complement receptor type 1 (sCR1) significantly decreased infarct size in a rat model of myocardial ischemia and reperfusion (376). These studies raised the possibility that interference with precisely targeted products of the complement system may reduce myocardial injury (177, 220).

Recent clinical trials examined the effects of complement inhibition in patients with acute myocardial infarction. In the COMMA trial, administration of the anti-C5 monoclonal antibody pexelizumab, in patients with ST-elevation myocardial infarction undergoing primary angioplasty, did not affect infarct size but decreased the 90-day mortality rate when administered as a bolus plus infusion (120) (1.8% vs. 5.9% with placebo); the bolus-only group had an intermediate mortality rate (4.2%). In contrast, when used in patients receiving thrombolytics, pexelizumab blocked complement activity but neither reduced infarct size nor improved the clinical outcome (230).

The role of reactive oxygen species generation in the postinfarction inflammatory response. ROS are atoms or molecules with unpaired electrons in their outer orbit. They are highly reactive entities and can participate in a variety of biochemical reactions (118). Molecular oxygen, O_2, is diradical; each oxygen atom contains two unpaired electrons in its outermost shell. Full reduction of oxygen to water requires four electrons; however, the sequential donation of electrons to oxygen during this process can result in generation of ROS as intermediates. Under normal conditions, O_2 is reduced to H_2O in the myocardium via two pathways: mitochondrial electron transport reduces 95% of O_2 without any free radical intermediates (16). The remaining 5%, however, is reduced via the univalent pathway, producing free radicals. Donation of a single electron to molecular oxygen results in formation of the superoxide radical (O_2^-). Donation of a second electron yields peroxide, which then undergoes protonation to yield hydrogen peroxide (H_2O_2). Donation of a third electron results in production of the highly reactive hydroxyl radical.

ROS react directly with cellular lipids, proteins, and DNA, causing cell injury and death, and are critically involved in the oxidative burst reaction, which is essential for phagocyte function. In addition, ROS trigger cytokine and chemokine cascades through NF-κB activation (124, 143, 316). Granger and colleagues (121) have provided evidence for a potential role of reactive oxygen in leukocyte chemotaxis. Potential mechanisms through which reactive oxygen intermediates may generate a leukotactic stimulus include complement activation (319, 320), induction of P-selectin expression (272), chemokine upregulation (197–199), and increase of the ability of endothelial intercellular adhesion molecule (ICAM)-1 to bind to neutrophils (315).

The normal heart possesses substantial ability to counterbalance the generation of ROS through enzymatic pathways (such as catalase, glutathione peroxidase, and the superoxide dismutases) and through intracellular antioxidants. However, in the infarcted myocardium, the antioxidant defenses are overwhelmed, resulting in generation of oxygen-related free radicals. ROS have been shown to exert a direct inhibitory effect on myocardial function *in vivo* and have a critical role in the pathogenesis of myocardial stunning (23, 179, 180). Most of the evidence implicating ROS in the pathophysiology of myocardial infarction is derived from investigations using free radical scavengers. Jolly and co-workers (168) demonstrated that the combination of the antioxidant enzymes superoxide dismutase (SOD) and catalase significantly reduced infarct size in dogs undergoing experimental coronary occlusion and reperfusion, when the infusion started before ischemia or 15 min before reperfusion. In contrast, no effect was noted when antioxidant infusion was started 40 min after reperfusion, suggesting that free radical–mediated injury is an early event (168). Other investigators found similar beneficial effects of antioxidant interventions in experimental models of myocardial infarction. However, a significant number of studies describe a failure of antioxidants to prevent injury or demonstrate an early protective effect that waned with increased duration of reperfusion (286, 362). Recently, transgenic mice that overexpress copper, zinc, and superoxide dismutase (SOD1) exhibited significant protection from postischemic injury (373). In addition, mice overexpressing manganese SOD (MnSOD) demonstrated a significant decrease in infarct size in Langendorff-perfused hearts undergoing left coronary artery ligation (39). However, therapeutic strategies targeting free radical generation have not been successful in clinical practice: two small clinical studies using recombinant human SOD in patients with acute myocardial infarction undergoing thrombolysis (251) or balloon angioplasty (85) demonstrated no significant improvement in left ventricular function. Unfortunately, prolonged coronary occlusion (>2 h) is usually present in the clinical setting of reperfused myocardial infarction and may cause extensive irreversible myocardial damage, leaving fewer myocytes to be affected by free radical–mediated injury (204, 236). In addition, several experimental studies have supported the concept that ROS may also exert protective effects in the ischemic heart, playing an important role in ischemic preconditioning (363).

Activation of TLR-mediated pathways. The TLRs represent a family of pattern-recognition receptors that serve to recognize molecular patterns associated with pathogens and, on binding of their ligands, induce activation of several kinases and NF-κB. Endogenous ligands from damaged tissues, including heat-shock proteins, hyaluronan, and fibronectin, have the capacity to activate TLRs (17). Thus, in the absence of infection, endogenous "danger" signals may activate TLR-mediated pathways initiating the immune response. TLRs activate interleukin (IL)-1 receptor-like intracellular pathways, resulting in nuclear localization of NF-κB. To date, 12 members of the TLR family have been identified in mammals; however, their role in cardiac pathology remains poorly understood. TLR4 is expressed in the heart and is markedly induced in mouse and rat infarcts and in samples obtained from cardiomyopathic hearts (100). A recent study demonstrated that TLR4-deficient mice have decreased infarct size and suppressed inflammation after myocardial infarction, identifying TLR4 as a key component of the innate immune response in the heart (267). In contrast, TLR2-null animals had similar infarct size and comparable inflammatory leukocyte infiltration with their WT littermates, but exhibited decreased fibrosis in the noninfarcted area and attenuated postinfarction ventricular remodeling (324). These findings suggested that TLR-2 signaling may not critically affect the inflammatory response but may (directly or indirectly) modulate fibrous tissue deposition.

The NF-κB system. A critical element in the regulation of cytokine, chemokine, and adhesion molecule expression in the ischemic myocardium involves the complex formed by NF-κB and IκB (208). NF-κB is activated by a large number of agents, including cytokines [such as tumor necrosis factor (TNF)-α and IL-1β] and free radicals. The genes regulated by the NF-κB family of transcription factors are diverse and include those involved in the inflammatory response, cell adhesion, and growth control (336). In resting cells, NF-κB dimers reside in the cytoplasm in an inactive form bound to the inhibitory subunit IκB. On stimulation, IκB is phosphorylated, ubiquitinylated, and ultimately degraded by proteolytic cleavage by the proteasome system. This process results in activation of NF-κB, which translo-

cates to the nucleus and binds to promoter or enhancer regions of target genes, initiating their transcription. NF-κB activation has been demonstrated in various models of experimental myocardial ischemia and reperfusion (37, 188). *In vivo* transfer of NF-κB decoy oligodeoxynucleotides to bind the transcriptional factor, blocking inflammatory gene activation, reduced the extent of myocardial infarction after reperfusion, suggesting a crucial role for NF-κB in the regulation of the postinfarction inflammatory response (246). Furthermore, transgenic mice with cardiac-specific expression of a dominant-negative IκBα, resulting in inhibition of cardiomyocyte NF-κB activation, exhibit significantly decreased infarct size in a model of reperfused infarction (31). Although these studies demonstrated the injurious role of NF-κB in the infarcted myocardium, other investigations have suggested that the NF-κB pathway may also mediate cytoprotective responses (175). Transgenic mice harboring cardiac-restricted expression of a mutated IκBα protein that prevents nuclear translocation of NF-κB in cardiac myocytes had larger infarcts and significantly enhanced myocyte apoptosis in a model of permanent coronary occlusion (242). In addition, retroinfusion of NF-κB oligonucleotides in a porcine model of myocardial ischemia reduced infarct size and improved functional reserve of the area at risk, providing postischemic cardioprotection (189). Furthermore, it has been suggested that NF-κB activation in leukocytes during the resolution phase of the inflammatory process results in upregulation of antiinflammatory genes and induces leukocyte apoptosis (201). However, the significance of this pathway in suppression of the postinfarction inflammatory response remains unknown. Activation of the NF-κB signaling cascade in multiple parallel processes involving various cell types, critical for infarct healing, further complicates understanding of its role in myocardial infarction.

The chemokine response

General properties of the chemokines. The chemokines (11, 12, 226, 263, 291, 305, 372) comprise a superfamily of small highly basic proteins with molecular masses in the range of 8–14 kDa and a strikingly similar tertiary structure (42) (Fig. 4). They have been divided into subfamilies on the basis of the number and sequential relation of their conserved cysteine residues (CXC, CC, XC, and CX_3C subfamilies). Most chemokines contain at least four cysteines that form two disulfide bonds, one between the first and the third, and one between the second and the fourth cysteine. In the CXC chemokine family, one amino acid separates the first two cysteine residues, whereas in the CC chemokines, the first two cysteines are adjacent to each other. Lymphotactin (XCL1) contains only two cysteines, corresponding to the second and fourth cysteines of other classes, and represents the XC subfamily. Fractalkine, conversely, has three amino acids separating the first two cysteines (CX_3C). CC chemokines are the most numerous and diverse family, including at least 25 ligands in humans. CXC chemokines are further classified according to the presence of the tripeptide motif glutamic acid-leucine-arginine (ELR) in the amino-terminal region (222). Chemokines bind to heptahelical G protein–coupled receptors. Most receptors recognize more than one chemokines, and certain chemokines may bind to several receptors.

Chemokines play a critical role in basal and inflammatory leukocyte locomotion and trafficking (114, 247), and their principal targets are bone marrow–derived cells. Most chemokines are secreted, and to induce a chemotactic response *in vivo,* they must be immobilized on cell or extracellular matrix surfaces through interactions with glycosaminoglycans (240). In addition to effects on cell locomotion, certain chemokines are capable of eliciting a variety of other

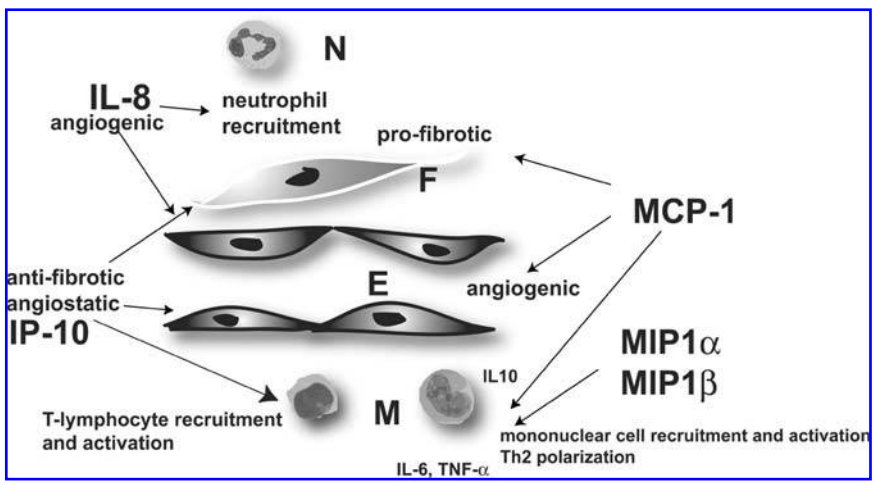

FIG. 4. Chemokines are markedly and consistently induced in healing infarcts, play an important role in leukocyte recruitment, but may also regulate infarct angiogenesis and fibrous tissue deposition. IL-8 and other ELR-containing CXC chemokines are important for neutrophil (N) infiltration and may also promote angiogenesis. In contrast, IP-10 and the non–ELR-containing CXC chemokines do not induce neutrophil chemotaxis but have angiostatic and antifibrotic properties. Early induction of IP-10 in the healing infarct may suppress premature angiogenesis and fibrous tissue deposition, preventing formation of granulation tissue until the wound is cleared of dead cells and debris, and a provisional matrix, necessary to support neovessel ingrowth, is formed. The CC chemokine MCP-1 plays a role in mononuclear cell (M) chemotaxis and activation. In addition, MCP-1 may have actions beyond its monocyte chemoattractant properties, mediated through its angiogenic and profibrotic effects. MIP-1a and MIP-1b are also induced in healing infarcts and may regulate mononuclear cell recruitment. (E), endothelial; (F), fibroblast.

responses affecting leukocyte adhesion (115), activation and degranulation, mitogenesis, and apoptosis. It has been recently recognized that chemokines have a wide range of effects on many different cell types beyond the immune system, including endothelial cells (resulting in angiogenic or angiostatic effects) (340), smooth muscle cells, neurons, and epithelial cells.

Chemokines can be divided broadly into two categories: homeostatic chemokines are constitutively expressed in certain tissues and may be responsible for basal leukocyte trafficking and formation of the fundamental architecture of lymphoid organs, and inducible chemokines, which are dramatically upregulated by inflammatory or immune stimuli, actively participating in the inflammatory reactions by inducing leukocyte recruitment (114, 394, 395). Although this approach is oversimplified, it offers valuable insight into the role of certain chemokines in pathologic states. A wide variety of stimuli can upregulate inducible chemokines, leading to a rapid, marked increase in their local concentration followed by leukocyte infiltration and an inflammatory response. Many cell types are capable of producing chemokines under appropriate conditions. Usually the same cell produces many chemokines concomitantly in response to the same stimulus (polyspeirism). Polyspeirism is particularly striking in endothelial cells and mononuclear phagocytes, which express many CC and CXC chemokines on stimulation with proinflammatory cytokines or lipopolysaccharide.

In addition to effects on cell locomotion, certain chemokines are capable of eliciting a variety of other responses affecting leukocyte adhesion (115), activation and gene expression, mitogenesis, and apoptosis. It has been recently recognized that chemokines have a wide range of effects on many different cell types beyond the immune system, including endothelial cells (resulting in angiogenic or angiostatic effects) (340), smooth muscle cells, fibroblasts, neurons, and epithelial cells.

Expression and role of the CXC chemokines in healing myocardial infarcts. Induction of chemokines appears to be a prominent feature of the postinfarction inflammatory response (Fig. 5) (86, 87, 97). Recent investigations using experimental models of myocardial infarction demonstrated marked induction of various chemokines in the ischemic heart, supporting their role in leukocyte recruitment (19), infarct angiogenesis, and fibrous tissue deposition (89). The prototypic CXC chemokine is IL-8/CXCL8, which was purified by several groups as a monocyte-derived factor that attracts neutrophils, but not monocytes (291, 371). Several other CXC chemokines are also potent neutrophil chemoattractants, and structure/activity analyses show that this property depends on the presence of the ELR (glutamate-leucine-arginine) motif, between the N-terminus and the first cysteine (42, 43). IL-8 is a critical regulator of neutrophil influx and activation in inflammatory processes (249, 393); however, it also exerts potent angiogenic effects (181) and may play a role in wound healing and repair. IL-8 upregulation has been documented in canine (184) and rabbit (160) models of experimental myocardial infarction. The exact role of IL-8 in myocardial infarction remains unclear: a recent study suggested that IL-8 neutralization significantly reduces the degree of necrosis in a rabbit model of myocardial ischemia–reperfusion injury without affecting neutrophil infiltration (25). IL-8 and possibly other neutrophil chemoattractant chemokines synthesized by microvascular endothelial cells may play an important role in granulocyte recruitment in the infarcted myocardium but may also have effects beyond their chemotactic properties (347). IL-8 induces the neutrophil respiratory burst and granule re-

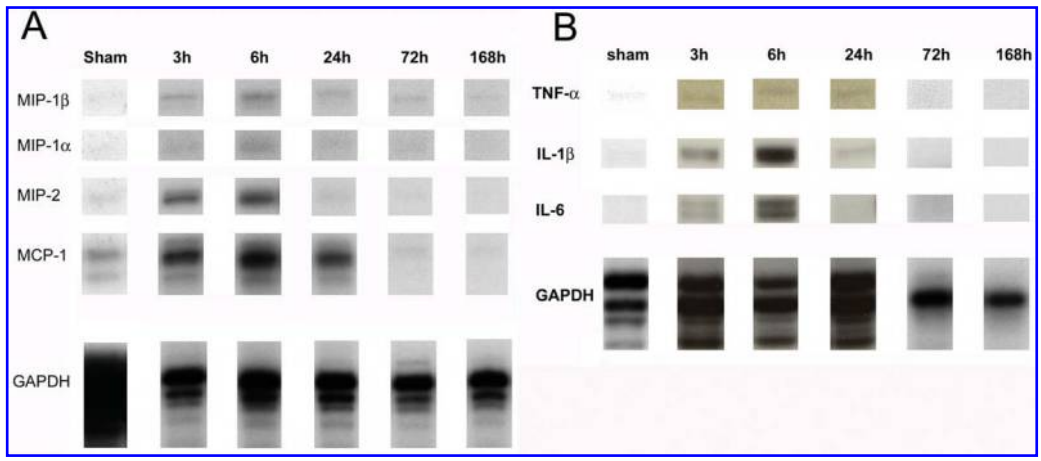

FIG. 5. Induction and repression of cytokine and chemokine mRNA synthesis in mouse myocardial infarcts. (**A**) Representative ribonuclease protection assay (RPA) experiments demonstrate that the chemokines MCP-1, MIP-1α, MIP-1β, and MIP-2 are markedly, but transiently induced in healing infarcts peaking after 3–6 h of reperfusion. MCP-1 mRNA expression shows the highest level of induction. Chemokine mRNA expression decreased after 24 h of reperfusion and is comparable to sham levels after 72 h of reperfusion. (**B**) The proinflammatory cytokines IL-1β and IL-6 also show marked but transient upregulation in the infarcted mouse myocardium. TNF-α is also induced after reperfused murine myocardial infarction, showing relatively modest mRNA upregulation.

lease and enhances cellular adhesion, a β2 integrin-dependent event. Recent experiments suggested that both mitogen-activated protein kinase (MAPK) and protein kinase C (PKC) are activated in response to IL-8 stimulation, and that these may represent independent pathways for β2 integrin activation in neutrophils (347). It appears that neutrophils may need to sample immobilized IL-8 molecules presented by the vessel wall before forming a sufficient number of high-avidity β2 integrin bonds for firm adhesion (72). Neutrophil recruitment in the infarcted myocardium also requires the participation of non–chemokines-associated mechanisms, such as activated complement, leukotrienes, and platelet-activating factor (PAF) (97, 98).

Much less is known about the expression and potential role of other ELR-containing CXC chemokines in myocardial infarcts. Growth-related oncogene (GRO)-α/CXCL1 was so named because of its initial description as the product of a gene differentially expressed in transformed hamster cells that had loss of growth control (3). Independently, its murine homologue was cloned in a differential screening experiment as the platelet-derived growth factor (PDGF)-inducible KC gene (46). GRO-α/KC, a potent neutrophil chemoattractant, is induced in a rat model of experimental myocardial infarction (38); however, its role in regulating the postinfarction inflammatory response remains unclear. GRO-β/CXCL2 and GRO-γ/CXCL3 are closely related proteins that are also potent neutrophil chemoattractants; their expression in myocardial infarcts has not yet been studied. Epithelial neutrophil-activating protein (ENA-78/CXCL5) is another ELR-containing CXC chemokine that exhibits similarities to the GROs. ENA-78 expression is induced in hepatic ischemia and reperfusion (47); however, its function in myocardial infarction remains unknown. Deficiency of CXCR2, the main receptor for the ELR-containing CXC chemokines, resulted in significantly decreased inflammatory leukocyte recruitment in murine infarcts, suggesting a crucial role for these chemokines in inflammatory cell infiltration (351). However, experiments using a Langendorff preparation indicated protective effects of CXCR2 signaling on myocardial viability (351). The molecular basis for the presumed direct effects of CXCR2 signaling on cardiomyocytes remains unclear.

In contrast with ELR-containing chemokines, the CXC chemokines lacking the ELR motif [such as platelet factor 4 (PF4/CXCL4), interferon-γ-inducible protein (IP)-10/CXCL10, and monokine induced by γ-interferon (MIG/CXCL9)] do not induce neutrophil chemotaxis and not only fail to stimulate angiogenesis, but were found to be potent angiostatic factors in the presence of either ELR-CXC chemokines or the unrelated angiogenic factor, basic fibroblast growth factor (bFGF) (340, 341). In addition, IP-10 may have direct inhibitory effects on fibroblast migration (323), serving as an antifibrotic agent. We have recently demonstrated a marked transient upregulation of the angiostatic CXC chemokine IP-10 in reperfused canine myocardial infarcts (89). IP-10 mRNA expression is downregulated after 24 h of reperfusion, whereas IL-8 message levels remain high. IP-10 mRNA and protein was localized in the microvascular endothelium of ischemic myocardial segments (89). *In vitro* experiments demonstrated that TNF-α, which is released early after myocardial ischemia (88), markedly upregulates IP-10 expression in canine venous endothelial cells (89, 92). The exact role of IP-10 upregulation in the infarcted myocardium remains unclear. The early transient induction of IP-10 in the ischemic myocardium may serve to prevent premature wound angiogenesis and fibrous tissue deposition in the infarct, until the injured myocardium has been cleared of dead cells and debris by infiltrating phagocytes and a fibrin-rich provisional matrix is formed to support ingrowth of granulation tissue. Studies using IP-10$^{-/-}$ mice will clarify the exact role of IP-10 in regulating infarct healing.

Stromal derived factor (SDF)-1 is a CXC chemokine with a critical role in cardiovascular development (256) and angiogenesis (302, 303). In addition, SDF-1 induces chemotaxis of CD34^{+} progenitors (1) and primitive hematopoietic cells (167) and controls many aspects of stem cell function (273). SDF-1α induction was recently reported in a rat model of nonreperfused myocardial infarction (280); however, the role of this chemokine in regulating the postinfarction inflammatory response is unknown. Recent experiments identified bone marrow–derived stem cells in the infarcted myocardium (161, 265), suggesting that they may participate in cardiac repair. Although the mechanisms for stem cell homing in the ischemic myocardium remain unclear, SDF-1 may be an important factor regulating their recruitment, maturation, and function in the infarct (9).

Expression and role of the CC chemokines in myocardial infarction. One of the best-studied CC chemokines, monocyte chemoattractant protein (MCP)-1/CCL2, is a potent chemoattractant for monocytes, T cells, and NK cells, and has been implicated in diseases characterized by monocyte-rich infiltrates (126, 292). In addition to its critical role in mononuclear cell recruitment, MCP-1 exerts important actions on nonhematopoietic cells, inducing angiogenic and arteriogenic effects (301) and modulating fibroblast phenotype and activity by increasing collagen expression and by regulating matrix metalloproteinase synthesis (116). MCP-1 upregulation has been demonstrated in a canine (186), a rat (174, 264), and a mouse model (350) of experimental myocardial infarction. To examine the role of MCP-1 in infarct healing, we studied the effects of MCP-1 gene disruption and antibody neutralization in a mouse model of myocardial infarction (68). MCP-1$^{-/-}$ mice had decreased and delayed macrophage infiltration in the healing infarct and demonstrated delayed replacement of injured cardiomyocytes with granulation tissue. MCP-1$^{-/-}$ infarcts had decreased mRNA expression of the cytokines TNF-α, IL-1β, transforming growth factor (TGF)-β, and IL-10, and demonstrated defective macrophage differentiation evidenced by decreased osteopontin (OPN)-1 expression. MCP-1 deficiency diminished myofibroblast accumulation but did not significantly affect infarct angiogenesis. Despite showing delayed phagocytotic removal of dead cardiomyocytes, MCP-1$^{-/-}$ mice had attenuated left ventricular remodeling but similar infarct size when compared with wild-type animals. MCP-1 antibody inhibition resulted in defects comparable to the pathologic findings noted in infarcted MCP-1$^{-/-}$ animals, without an effect on macrophage recruitment (68).

Our findings indicated that MCP-1 has important effects on macrophage recruitment and activation, cytokine synthe-

sis, and myofibroblast accumulation in healing infarcts. The role of MCP-1 extends beyond its monocyte chemoattractant effects: MCP-1 inhibition with a neutralizing antibody results in defects comparable to the pathologic findings noted in infarcted MCP-1$^{-/-}$ animals in the absence of an impairment in monocyte recruitment. Absence of MCP-1 results in attenuated postinfarction left ventricular remodeling, at the expense of a prolonged inflammatory phase and delayed replacement of injured cardiomyocytes with granulation tissue. Suppression of inflammatory cytokine synthesis, decreased macrophage activation, and diminished myofibroblast infiltration may be important mechanisms responsible for attenuated left ventricular remodeling in MCP-1 null mice. In addition, decreased postinfarction remodeling was noted in mice receiving anti–MCP-1 gene therapy (140) and in animals with genetic disruption of the MCP-1 receptor, CCR2 (173).

Little is known about the role of other members of the CC chemokine subfamily in infarct healing. Macrophage inflammatory protein (MIP)-1α/CCL3 and MIP-1β/CCL4 are mononuclear cell chemoattractants, although less efficient than MCP-1 (361). A robust induction of MIP-1α and MIP-1β is noted in murine infarcts (67); however, their importance in myocardial injury and repair has not been investigated. Conversely, increased serum levels of RANTES (regulated on activation, normal T-cell expressed and secreted), a CC chemokine that induces chemotaxis of monocytes, eosinophils, and specific subsets of T cells (307), were found in patients with acute myocardial infarction (270). However, our experiments did not demonstrate induction of RANTES in the infarcted myocardium.

The cytokine cascade

Numerous studies have demonstrated activation of cytokine cascades in the infarcted myocardium. Induction and release of the proinflammatory cytokines TNF-α, IL-1β, and IL-6 is consistently found in experimental models of myocardial infarction (Fig. 5) (67, 88, 99). Complement activation, free radical generation, and NF-κB activation are capable of stimulating cytokine mRNA synthesis in both resident and blood-derived cells, resulting in marked cytokine upregulation in the infarcted area. One of the characteristic features of cytokines is their functional pleiotropy and redundancy: one cytokine exhibits a wide range of biologic effects on various cell types, and similar cytokines exert similar and overlapping actions on the same cell type (178). The multifunctional, overlapping, and often contradictory effects of the cytokines have hampered understanding of their functional role in infarct healing.

Expression and role of TNF-α in healing infarcts. TNF-α release occurs early in the infarcted myocardium and may stimulate expression of other inflammatory mediators by leukocytes and endothelial cells (Fig. 6). Recently, Maekawa and colleagues (229) demonstrated that TNF-α–deficient mice undergoing experimental infarction protocols exhibit decreased chemokine and adhesion molecule expression suggesting an important role for TNF-α in mediating the postinfarction inflammatory response (229). However, the role of TNF-α in myocardial infarction is much more complex than

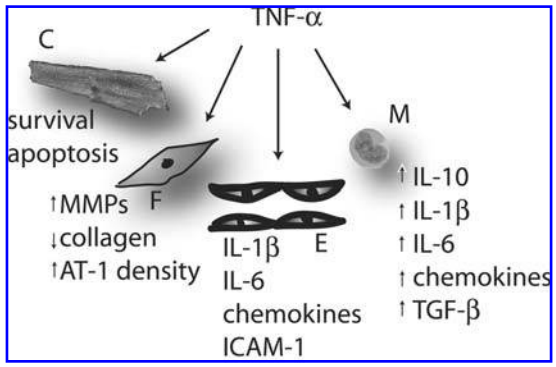

FIG. 6. TNF-α is rapidly released after myocardial infarction and may modulate the phenotypic characteristics and gene expression of several cell types involved in infarct healing. TNF-α may activate mononuclear (M) and endothelial cells (E), inducing expression of cytokines, chemokines, and adhesion molecules. Fibroblasts (F) may respond to TNF-α by increasing AT-1 receptor density, suppressing extracellular matrix protein synthesis, and by increasing MMP expression. Thus TNF-α signaling may enhance the profibrotic effects of angiotensin II but may also directly promote matrix degradation. In addition, experiments using TNFR$^{-/-}$ mice indicated that TNF-α signaling may exert protective effects on cardiomyocytes (C).

simply serving as a trigger of a cytokine cascade (18, 300). Recent experiments investigated the role of TNF-α signaling in the infarcted myocardium using mice lacking TNF receptors (TNFR). TNFR1/TNFR2 double receptor knockout mice undergoing left coronary artery ligation had significantly higher infarct size and increased myocyte apoptosis when compared with wild-type controls (190). These findings suggested that TNF-α may induce a cytoprotective signal capable of preventing or delaying the development of myocyte apoptosis after myocardial infarction. In contrast, Sugano and co-workers (342) reported that treatment with sTNFR1 expression plasmid DNA reduced TNF-α bioactivity in the myocardium, inhibiting cardiomyocyte apoptosis. These studies highlight the pleiotropic actions of the cytokines in biologic processes that may explain the unpredictable effects of cytokine-targeted therapeutic strategies in clinical practice.

Furthermore, TNF-α markedly induces expression of the angiotensin II type 1 receptor, AT-1, on cardiac fibroblasts (129), thus enhancing angiotensin II–mediated effects on cardiac fibroblast proliferation (311) and extracellular matrix protein synthesis (53, 368). Strong temporal and spatial correlations between TNF-α and AT-1 receptor expression in fibroblasts and macrophages infiltrating the periinfarction zone supported the role of TNF-α in regulating fibrous tissue deposition (274) and left ventricular remodeling (128) after myocardial infarction.

The role of IL-1. The IL-1 gene family consists of three members: IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1Ra). IL-1α and IL-1β are agonists, whereas IL-1Ra is a specific receptor antagonist (70). Both IL-1α and IL-1β are capable of inducing the expression of other cytokines,

chemokines, growth factors, and adhesion molecules. Marked IL-1 upregulation has been reported in experimental models of myocardial infarction (67, 144). In addition, a significant increase in IL-1β plasma levels has been documented in patients with acute myocardial infarction (127). However, despite extensive descriptive evidence suggesting involvement of IL-1 in infarct healing, information regarding its biologic role in myocardial infarction is very limited. Cardiac transfection with human IL-1Ra significantly decreased infarct size, reduced apoptosis, and attenuated the inflammatory response in rat hearts undergoing ischemia/reperfusion protocols (345), suggesting an injurious role for IL-1 in the ischemic myocardium. In contrast, another investigation suggested a protective role for IL-1 demonstrating that IL-1β neutralization in the acute phase of myocardial infarction resulted in increased occurrence of cardiac rupture and enhanced adverse remodeling (153). Much like TNF-α, IL-1β also modulates fibroblast phenotype inducing AT-1 receptor expression (128) and upregulating matrix metalloproteinase synthesis (327). As a highly pleiotropic and multifunctional mediator, IL-1 is likely to have a wide range of actions on various cell types involved in the healing response (Fig. 7). Studies using genetically targeted animals are needed to elucidate the mechanistic basis of IL-1–mediated effects in the infarcted heart.

The IL-6 family of cytokines. IL-6 is a member of a larger family of structurally related cytokines with overlapping biologic effects. The family includes IL-11, leukemia inhibitory factor (LIF), oncostatin-M, cardiotrophin-1 (CT-1), ciliary neurotrophic factor (CNTF), and neurotrophin-1/B cell–stimulating factor-3 (NNT-1/BSF-3). All IL-6–related cytokines signal through multisubunit receptors that share the transmembrane glycoprotein (gp)130. Downstream signaling is triggered through gp130 homodimerization, or through heterodimerization of gp130 with the LIF receptor. Extensive experimental evidence demonstrated induction of members of the IL-6 family in healing infarcts (5). IL-6 synthesis is rapidly induced in mononuclear cells and cardiomyocytes of the ischemic myocardium (88, 130, 185). CT-1 is upregulated in fibroblasts and surviving cardiomyocytes and shows a prolonged time course of expression (5, 102), whereas LIF (67) and oncostatin-M (131) are induced during the inflammatory phase of healing. However, the functional role of these cytokines in infarct healing remains unknown. Members of the IL-6 family have profound effects on cardiac myocytes by promoting cardiac hypertrophy, but also by protecting them from apoptosis (385). CT-1 administration resulted in decreased infarct size and reduced cardiomyocyte apoptosis in a rat model of myocardial ischemia and reperfusion (213). In addition, prolonged CT-1 upregulation may also regulate fibroblast proliferation in the infarcted myocardium (101). Although the role of endogenous LIF expression in the infarct remains unknown, gene therapy with LIF cDNA prevented cardiomyocyte death and induced angiogenesis, enhancing recruitment of bone marrow-derived cells into the heart (396). IL-6 is capable of modulating the phenotypic characteristics and gene expression of many cell types involved in infarct healing. IL-6–null mice demonstrated significantly delayed cutaneous wound healing, suggesting a significant role for IL-6 in tissue repair (111). However, Fuchs and co-workers (103) found that the absence of IL-6 did not affect infarct size, left ventricular function, and postinfarction remodeling in nonreperfused infarcts. Although these findings do not preclude biologically significant actions of IL-6 in healing infarcts, it appears that in mice lacking IL-6, other mediators may act in a compensatory manner to activate the JAK/STAT pathway, thereby maintaining STAT3 phosphorylation, which is crucial for the cellular effects of IL-6–related cytokines.

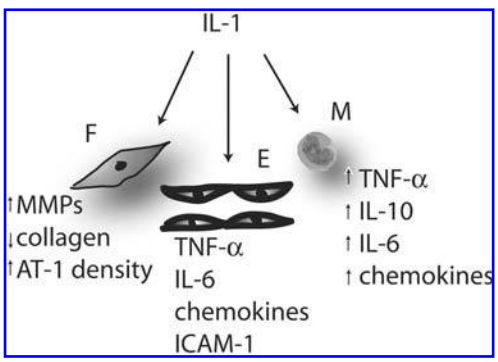

FIG. 7. Although IL-1β is markedly and rapidly induced in healing infarcts, its role in infarct healing remains poorly understood. IL-1β may induce cytokine and chemokine synthesis by endothelial cells (E) and infiltrating mononuclear cells (M). In addition, much like TNF-α, IL-1β enhances AT-1 receptor synthesis and increases MMP expression by cardiac fibroblasts (F).

The leukocyte infiltrate in the infarcted myocardium

The neutrophils. Neutrophil depletion in animals undergoing reperfused myocardial infarction led to a marked decrease in infarct size (216, 293), suggesting that a significant amount of myocardial injury induced by coronary artery occlusion followed by reperfusion may be neutrophil dependent (171). Neutrophils release oxidants and proteases and play an active role in phagocytosis of dead cells and debris; in addition, they may express mediators capable of amplifying cell recruitment. Neutrophil transmigration in the infarcted myocardium requires adhesive interactions with activated vascular endothelial cells.

Neutrophil–endothelial interactions after myocardial ischemia and reperfusion. Extensive evidence indicates that leukocyte–endothelial interactions are regulated by a cascade of molecular steps that correspond to the morphologic changes that accompany adhesion (Fig. 8). This adhesion cascade has been divided into sequential steps based on visual assessment of the postcapillary venules during the early stages of acute inflammation. In the absence of inflammation, leukocytes are rarely seen to interact with the vessel wall. After the inflammatory stimulus is applied, leukocytes roll along the postcapillary venules (but not arterioles or small arteries) at velocities distinctly below that of flowing blood. Some rolling cells can be seen to arrest and, after a few minutes, change shape in apparent response to local chemotactic stimuli. Ex-

FIG. 8. Neutrophil extravasation in healing myocardial infarcts. Neutrophil (N)–endothelial (E) interactions are regulated by a cascade of molecular steps involving specialized adhesion molecules. In the absence of inflammation, leukocytes are rarely seen to interact with the vessel wall. In the ischemic and reperfused myocardium, leukocytes roll along the postcapillary venules at velocities distinctly less than that of flowing blood (1). This process is mediated through the selectins. Some rolling cells can be seen to arrest and, after a few minutes, change shape in apparent response to local chemotactic stimuli (2). Firm neutrophil–endothelial adhesion is dependent on integrin activation. Extravasation into the extravascular tissue follows (3). Recent investigations suggested that JAM-A may play an important role in this process. Extravasated neutrophils may induce myocardial injury by releasing proteases and reactive oxygen intermediates through a Mac-1/ICAM-1–dependent adhesive interaction with injured but viable cardiomyocytes (CMs) (4).

travasation into the extravascular tissue follows. Each of these steps requires either upregulation or activation of distinct sets of adhesion molecules.

The selectins. The selectin family of adhesion molecules mediates the initial capture of leukocytes from the rapidly flowing bloodstream to the blood vessel, before their firm adhesion and diapedesis at sites of tissue injury and inflammation. The selectin family consists of three closely related cell-surface molecules: L-selectin (CD62L), E-selectin (CD62E), and P-selectin (GMP-140, CD62P). Selectins promote leukocyte attachment and rolling at shear stresses characteristic of postcapillary venules. All three selectins are involved in leukocyte entry into tissues. Studies using transgenic mice have improved our understanding of the role of selectins in leukocyte trafficking. L-selectin–deficient mice showed reduced lymphocyte homing to peripheral lymph nodes and decreased leukocyte infiltration to sites of inflammation (353, 354). P-selectin–deficient mice demonstrated virtually total absence of rolling in mesenteric venules and delayed neutrophil recruitment to the peritoneal cavity on experimentally induced inflammation (237). In contrast to P- and L-selectin mutants, E-selectin–deficient mice displayed no significant change in neutrophil trafficking in several models of inflammation (192). However, P-selectin blocking by treatment of the E-selectin–deficient animals with an antimurine P-selectin antibody significantly inhibited neutrophil emigration in two distinct models of inflammation (192), suggesting that E- and P-selectin may share overlapping functions (147). In addition, E-selectin may be required for slow leukocyte rolling, leading to firm leukocyte adhesion *in vivo* (187, 211).

The role of the selectins in myocardial ischemia and reperfusion is not well defined at present and represents an area of active investigation. L-selectin is constitutively expressed in neutrophils in a highly specific distribution, and its shedding on activation may be important in regulating leukocyte rolling velocity and recruitment (132). P-selectin surface expression occurs rapidly on endothelial cells under circumstances likely to be seen during ischemia and reperfusion. It is stored in the Weibel–Palade bodies and is rapidly translocated to the endothelial surface in response to thrombin and/or oxidative stress, both of which would be likely to be found in the ischemic myocardium, and to histamine, which is rapidly released in the ischemic and reperfused myocardium by degranulating mast cells. Experimental studies have suggested that monoclonal antibodies against L-selectin and P-selectin (225, 378) were effective in reducing myocardial necrosis, preserving coronary endothelial function, and attenuating neutrophil accumulation in ischemic myocardial tissue in a feline model of ischemia/reperfusion. In addition, P-selectin–deficient mice showed decreased infarct size after 30 min of coronary occlusion and 2 h of reperfusion (268). In contrast, no difference in infarct size was noted after a 60-min ischemic period (268). In addition, mice with a combined P-selectin and ICAM-1 deficiency demonstrated impaired neutrophil trafficking without a difference in infarct size because of myocardial ischemia and reperfusion (29). Although current concepts suggest a role for the selectins in supporting leukocyte margination under shear stress, the effects of selectin-related interventions in experimental models of myocardial ischemia have been inconsistent (20, 170). Peptide analogues of the soluble selectin ligand P-selectin glycoprotein ligand-1 (PSGL-1) have been constructed and may represent a promising new approach in targeting selectin-dependent interactions. A recombinant analogue of sPSGL-1 significantly reduced myocardial necrosis in a feline model of coronary occlusion and reperfusion (141).

The role of the integrins. Although rolling appears to be a prerequisite for eventual firm adherence to blood vessels under conditions of flow, selectin-dependent adhesion of leukocytes does not lead to firm adhesion and transmigration unless another set of adhesion molecules, the integrins, is engaged. Integrins are a family of heterodimeric membrane glycoproteins that consist of an α and a β subunit; these subunits are associated through noncovalent bonds and transported to the cell surface as a complex (221). For neutrophils, firm adhesion requires activation of the β2 (CD18) integrins, which share the beta chain CD18 paired with CD11a (LFA-1), CD11b (Mac-1), or CD11c (p150,95). This results in binding to one of the intercellular adhesion molecules on the surfaces of endothelial cells. LFA-1, Mac-1, and p150,95 have different and yet overlapping roles in adhesion, in part because of their characteristics of expression on leukocytes. Stationary neutrophils adherent to the luminal endothelial surface frequently change shape and assume the characteristic bipolar configuration of motile cells (328, 329). This event may result from interaction with surface-bound chemokines. Transendothelial migration

follows and leads to neutrophil infiltration in the inflamed tissues. Antibodies that inhibit LFA-1 adhesion are effective in blocking transmigration (106), and LFA-1–deficient mice show dramatically decreased neutrophil extravasation at sites of inflammation (71). In contrast, antibodies that block Mac-1 adhesion are marginally effective (106), and Mac-1–deficient mice demonstrate no deficit in neutrophil emigration (219). These findings suggest that LFA-1 and not Mac-1 is critical for neutrophil extravasation in sites of inflammation.

Integrin-related strategies have been used to mitigate postreperfusion inflammation in various experimental models. Inhibition of CD11/CD18 integrin resulted in significant reduction of infarct size in rat (205), feline (224), canine (6), and primate (10) models of experimental myocardial infarction. However, despite the promising results of the experimental studies, leukocyte integrin inhibition in clinical studies has led to disappointment (74). A recently published multicenter clinical trial (84) demonstrated that patients undergoing primary angioplasty for acute myocardial infarction had no difference in events and no reduction in infarct size on administration of a humanized anti-CD11/CD18 antibody (Hu23F2G). It appears that the effectiveness of different anti-CD18 antibodies in preventing injury is highly dependent on the specific antibody used (276). Recent experiments with genetically targeted animals have contributed to our understanding of the role of integrins in experimental myocardial infarction. CD18–deficient mice demonstrated significant reduction in neutrophil accumulation after myocardial ischemia and reperfusion (269). Furthermore, treatment with an antibody to vascular cell-adhesion molecule (VCAM)-1 significantly attenuated neutrophil emigration in the infarcted myocardium of CD18-null mice but did not diminish myocardial injury (24).

Neutrophil transmigration. Integrin-mediated neutrophil adhesion is followed by infiltration of the leukocytes into the underlying tissue. However, very little is known regarding the mechanisms responsible for neutrophil diapedesis through the vessel wall. A recent investigation suggested an important role for the junctional adhesion molecule (JAM)-A in regulating neutrophil infiltration into the ischemic myocardium (50). JAM-A$^{-/-}$ mice exhibited impaired neutrophil diapedesis after myocardial ischemia/reperfusion. Microscopic examination of the heart microvasculature showed large numbers of neutrophils adherent on the endothelium or entrapped between endothelial cells and the basement membrane. These defects were associated with enhanced cardiomyocyte injury in JAM-A–null infarcts, perhaps due to impaired blood flow caused by prolonged entrapment of neutrophils in the microcirculation (50).

Neutrophil-mediated injury. Infiltrating neutrophils generate free radicals and release enzymes contributing to the clearance of the infarct of dead cells and debris. Over the last 20 years, experimental evidence suggested that neutrophils may directly injure parenchymal cells through release of specific toxic products (162). Obviously, neutrophils accumulating in the ischemic and reperfused areas might release proteolytic enzymes or reactive oxygen species to injure surrounding myocytes. However, under conditions found *in vivo,* these toxic products are almost exclusively secreted by adherent neutrophils. Thus, it appears that a ligand-specific adhesion of the neutrophils to the cardiac myocytes may be critical for the mediation of ischemia-induced myocyte injury. The mechanism of neutrophil–cardiomyocyte adhesion is dependent on CD18 integrin activation on neutrophils and on expression of ICAM-1, one of the primary ligands for the CD18 integrins (2), by injured cardiomyocytes. The *in vivo* significance of neutrophil-induced cardiomyocyte injury remains unknown (369). Although ICAM-1–deficient mice exhibited less myocardial injury at an early stage, they showed no significant difference in infarct size and scar formation after 1–3 weeks of reperfusion (239). In addition, mice with a combined deficiency in both ICAM-1 and P-selectin showed no difference in infarct size due to myocardial ischemia and reperfusion, despite exhibiting impaired neutrophil trafficking (29).

In addition to their controversial injurious effects on cardiomyocytes, neutrophils infiltrating the infarcted myocardium may also induce extracellular matrix damage by releasing large amounts of matrix metalloproteinases, such as MMP-8 and MMP-9 (214).

The potential role of the neutrophils in fibrous tissue deposition. It has been suggested that, in addition to clearing the wound of dead cells and debris, the neutrophils may play a direct role in wound healing by secreting cytokines and growth factors. Although the contribution of the neutrophil to fibrous tissue deposition in the healing infarct cannot be excluded, it is unlikely that this cell type plays a critical role in the events leading to formation of a scar. Neutrophils may contribute to the healing response through their apoptosis and subsequent clearance by macrophages; this process, as is discussed later, releases TGF-β, resulting in resolution of inflammation and transition to fibrosis. In a study performed >30 years ago, Simpson and Ross (326) demonstrated that depletion of circulating neutrophils in guinea pigs treated with antineutrophil serum had no effects on granulation tissue formation in a model of cutaneous healing, suggesting that the neutrophil response may not be essential in the repair process.

The mononuclear cells. As the number of neutrophils declines, the macrophage population increases, and macrophages become the predominant phagocytic cell in the wound. The function of macrophages in tissue repair is not limited to removal of dead cells and debris. Macrophages are capable of producing a wide range of growth factors and cytokines that stimulate fibroblast and endothelial cell proliferation and appear to be key regulators of the healing response (Fig. 9). Early studies demonstrated that depletion of monocytes and macrophages in healing wounds resulted in delayed fibrosis (207) and suggested that these cells release mediators that stimulate fibroblast proliferation (206). Although our knowledge of the properties and functional activities of the monocyte/macrophage system has increased, our understanding of the role of macrophages in the cellular events associated with infarct healing remains incomplete.

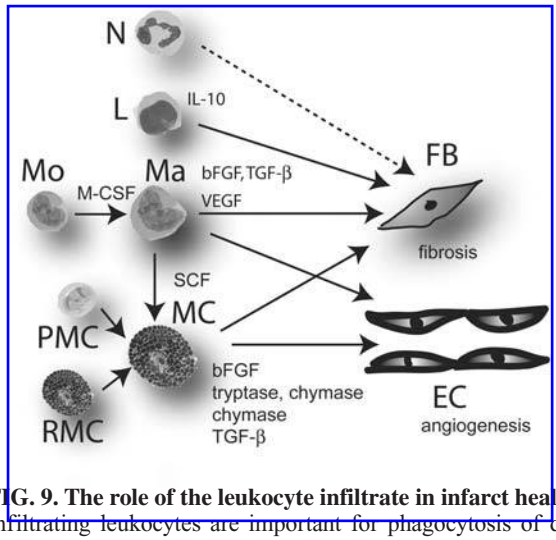

FIG. 9. The role of the leukocyte infiltrate in infarct healing. Infiltrating leukocytes are important for phagocytosis of dead cells and debris; however, they also contribute to the formation of granulation tissue and deposition of extracellular matrix. Monocytes (Mo) differentiate to macrophages (Ma) and synthesize large amounts of growth factors, such as bFGF, TGF-β, and VEGF, promoting fibroblast (F) activation and angiogenesis. Lymphocytes (L) also contribute to the healing response, releasing inhibitory cytokines (such as IL-10) and growth factors. Mast cells (MCs) accumulate in the healing infarct (derived mostly through chemotaxis of circulating precursors, PMCs, and perhaps through proliferation of resident mast cells, RMCs) and induce fibrous tissue deposition and neovessel formation by releasing a wide range of fibrogenic and angiogenic mediators. The potential role of neutrophils (Ns) in the proliferative phase of healing remains controversial. Although they may also play a role in the early stages of infarct healing by producing growth factors, neutrophils are likely to influence fibrous tissue deposition through their apoptotic clearance by macrophages; an event that results in the release of large amounts of macrophage-derived TGF-b. EC, endothelial cell.

The role of monocyte subsets in inflammation. As discussed previously, CCL2/MCP-1 plays an important role in monocyte recruitment in the infarcted myocardium. Other mediators including complement, TGF-β, free radicals, and other chemokines may also play a role in regulating monocyte infiltration. Recently it has been appreciated that peripheral blood monocytes are a heterogeneous population. In mice, two distinct subpopulations have been identified that circulate in approximately equal numbers (113): a CCR2-positive subset with low expression of the fractalkine receptor CX_3CR1 (CX_3CR1 lo), preferentially recruited in inflammatory processes, and a CCR2-negative subpopulation comprising cells with high-level CX_3CR1 expression (CX_3CR1 hi) that home to normal tissues and become resident macrophages. The level of CX_3CR1 expression also defines the two major human monocyte subsets, the CD14(+)CD16(−) and CD14(lo)CD16(+) monocytes, which share phenotype and homing potential with the mouse subsets. These concepts raise the intriguing possibility that various monocyte chemoattractants may recruit distinct subsets of monocytes into the infarct. These subsets may have different phenotypic and functional characteristics, demonstrating distinct cytokine expression profiles and differentiation potentials. The significance of monocyte subsets in inflammation and cardiac repair has not been investigated but raises the potential for novel therapeutic strategies targeting specific macrophage-mediated effects.

Monocyte-to-macrophage differentiation. Recruitment of monocytes in the infarcted myocardium is followed by maturation and differentiation of these blood-derived cells into mature macrophages. This is a complex and poorly understood process that is likely to involve growth factors such as macrophage– colony-stimulating factor (M-CSF) and granulocyte macrophage–colony-stimulating factor (GM-CSF). M-CSF is induced in healing canine infarcts, and its expression is associated with macrophage accumulation and proliferation in the infarct (91). The effects of M-CSF on macrophage phenotype and activity are not fully understood; however, it appears to be crucial for survival of macrophages, permitting them to respond to internal and external cues for their differentiation (195). Differentiated macrophages play multiple roles in the healing infarct. First, they are responsible for phagocytosis of dead cells and debris and for clearance of apoptotic neutrophils and cardiomyocytes. Second, they serve as a source of cytokines and growth factors regulating fibroblast growth and angiogenesis. Third, they contribute to extracellular matrix remodeling by producing matrix metalloproteinases and their inhibitors. The gene-expression profile of infiltrating macrophages may change during the healing process; these dynamic alterations may have a profound effect on infarct repair.

The mast cells: versatile cells with a potential role in infarct healing. Mast cells are multifunctional resident cells, capable of secreting a wide range of inflammatory and profibrotic mediators (Fig. 10). Because of their strategic location, mast cells are likely to play an important role in initiating the inflammatory response through the release of proinflammatory mediators, capable of triggering the cytokine cascade. A possible role for cardiac mast cells in mediating injury was suggested in a porcine model of C5a-mediated myocardial ischemia (159). Our studies (88) indicated a role for mast cell–derived histamine and TNF-α in initiating the cytokine cascade in the reperfused canine myocardium. Significant evidence indicates that mast cells may also participate in the fibrotic process. We have demonstrated a striking accumulation of mast cells during the proliferative phase of healing, predominantly in areas of collagen deposition and cell proliferation (94). The factors responsible for mast cell accumulation in areas of fibrosis remain to be defined. Stem cell factor (SCF) is a potent mast cell chemoattractant that stimulates directional motility of both mucosal- and connective tissue–type mast cells. Subcutaneous administration of recombinant human SCF to baboons produced a marked expansion of the mast cell population, which was reversed when the cytokine was discontinued (110), providing the first direct evidence that a specific factor can regulate mast cell development *in vivo*. Our studies demonstrated significant upregulation of SCF mRNA expression in ischemic segments of canine myocardium after 1 h of ischemia and 72 h of reperfusion (94). SCF immunoreactivity was predominantly localized in a subset of macrophages infiltrating the infarct; surprisingly, fibroblasts and endothelial cells did not stain for SCF (94). At the same

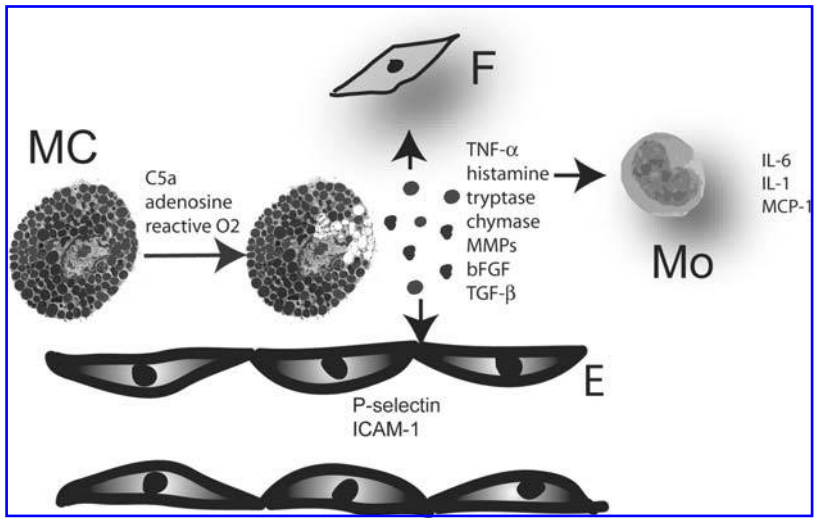

FIG. 10. The role of mast cells in myocardial infarction. Resident cardiac mast cells are perivascular inflammatory cells that contain preformed stores of inflammatory mediators but are also capable of synthesizing large amounts of cytokines and growth factors. Mast cells degranulate after myocardial infarction, releasing histamine and TNF-α, and may initiate the cytokine cascade by inducing monocyte (Mo) and endothelial cell (E) cytokine synthesis. Histamine may play a role in P-selectin mobilization in the endothelial cell surface. During the reparative phase, SCF is induced in the infarct, and mast cell numbers markedly increase. Mast cells produce a variety of fibrogenic and angiogenic mediators such as tryptase, bFGF, and TGF-β, and may activate fibroblasts (F) and induce endothelial cell proliferation. In addition, the mast cell–specific protease chymase may be important in angiotensin-2 generation, promoting fibrosis.

time point, an increase in mast cell numbers is noted in the healing myocardium, and immature mast cell progenitors are found in the infarcted area. Although the contribution of mast cell proliferation cannot be ruled out, chemotaxis of circulating mast cell precursors in the healing myocardium may be the predominant mechanism responsible for mast cell accumulation in the ischemic heart. The role of SCF in infarct healing may not be limited to its effects on the mast cell. Recent investigations indicated that locally delivered bone marrow–derived cells may differentiate to cardiomyocytes and vascular cells, regenerating myocardial infarcts (265). A role for SCF has been suggested in promoting recruitment and homing of these primitive bone marrow–derived cells into the infarct (266).

The exact role of mast cells in postinfarction inflammation and repair remains to be elucidated. Mast cells can produce a wide variety of mediators with pleiotropic actions. The net effect of mast cell degranulation in a biologic process may depend on local environmental cues affecting the gene-expression profile and mediator release by the mast cell. In addition, the response of specific cell types (such as leukocytes, fibroblasts, and endothelial cells) to mast cell–derived mediators may vary at different stages of the healing process. Mast cell–derived histamine may critically affect leukocyte–endothelial interactions by increasing endothelial P-selectin expression and by facilitating recruitment of rolling leukocytes (7). Tryptase, the most abundant protease found in mast cell granules, stimulates granulocyte recruitment (142) and upregulates cytokine and chemokine synthesis (48, 331). Mast cell–derived cytokines, such as TNF-α, may trigger the cytokine cascade in the infarct, regulating adhesion molecule expression and leukocyte recruitment. In addition, many mast cell–derived mediators may influence fibroblast growth and function. Histamine has been shown to stimulate fibroblast growth and collagen synthesis *in vitro* (138). Tryptase induces fibroblast proliferation (299) and chemotaxis and upregulates type I collagen production (125). Furthermore, mast cells are important sources of TGF-β (275), bFGF (282), and VEGF (22), factors that can regulate fibroblast growth, modulate extracellular matrix metabolism, and stimulate angiogenesis (321). Mast cell–derived TGF-β and tryptase may play a significant role in mediating myofibroblast α-smooth muscle actin (α-SMA) expression in the healing scar. Mast cells may also influence healing and tissue remodeling by expressing gelatinases A and B (30, 36, 83), which are implicated in extracellular matrix metabolism. Finally, an important role for the chymase pathway in promoting angiotensin II generation and cardiac fibrosis has been suggested (234). Conversely, experiments using mast cell–deficient rats suggested a protective effect of the mast cells in aging-associated diastolic dysfunction (176); the mechanisms responsible for these effects and their relevance in infarct healing remains unknown. Although evidence suggests important actions of mast cell–derived mediators in postinfarction inflammation and fibrous tissue deposition, direct proof of a critical role for the mast cells in infarct healing and postinfarction remodeling is lacking.

REPRESSION OF INFLAMMATORY GENE EXPRESSION AND RESOLUTION OF THE INFLAMMATORY INFILTRATE

Chemokine induction, cytokine release, and leukocyte infiltration are prominent events in the inflammatory phase of myocardial infarction and play a crucial role in phagocytotic removal of dead cells and debris. However, this acute localized inflammatory response is transient and is followed by resolution of the inflammatory infiltrate and fibrous tissue deposition (67). A crucial commitment is made during the late stages of the inflammatory phase to convert the response from phagocytosis and clearance of dead cells and debris to a mode that promotes tissue repair and scar formation (258). Inhibition of chemokine and cytokine synthesis after a dra-

matic early peak is crucial for the repair process, preventing prolonged expression of inflammatory mediators in the healing infarct and suppressing continuous leukocyte recruitment and injury. Thus, optimal healing requires mechanisms inhibiting chemokine and cytokine synthesis, resulting in resolution of the inflammatory infiltrate and transition to fibrous tissue deposition. These mechanisms involve (a) clearance of the neutrophilic infiltrate, (b) inhibition of cytokine and chemokine synthesis, (c) removal of the fibrin-based provisional matrix, and (d) activation of fibroblasts and collagen deposition. Although very few studies have dealt with the process of resolution of inflammation in the healing infarct, understanding these concepts is crucial for planning strategies targeting the postinfarction inflammatory response.

Clearance of apoptotic neutrophils

Clearance of the granulocytic infiltrate by professional phagocytes is a prerequisite for resolution of the inflammatory process. Apoptosis is the predominant mechanism that determines the functional longevity of neutrophils in inflamed and infarcted tissues (137). Apoptotic neutrophils are recognized and phagocytosed by macrophages in a process that involves macrophage CD44 ligation (40, 135). Ingestion of apoptotic cells by macrophages results in synthesis and release of TGF-β, a mediator crucial for resolution of inflammation (152). In contrast, phagocytosis of necrotic cells leads to release of proinflammatory mediators, resulting in persistent inflammation (80). The relevance of these concepts in myocardial infarct healing remains unknown. However, timely clearance of the leukocytic infiltrate may play a crucial role in suppression of the postinfarction inflammatory response.

IL-10 induction in the infarcted myocardium: Does it play a role in resolution of inflammation?

IL-10, a cytokine predominantly expressed by activated Th2 lymphocytes and stimulated monocytes, possesses potent antiinflammatory properties (245, 248). Among the different cell types affected by IL-10, monocyte–macrophages appear to be particularly modified in regard to their function, morphology, and phenotype. IL-10 inhibits the production of IL-1α, IL-1β, TNF-α, IL-6, and IL-8 by lipopolysaccharide-activated monocytes, suppressing the inflammatory response. Furthermore, IL-10 may play a significant role in extracellular matrix remodeling by promoting tissue inhibitor of metalloproteinases (TIMP)-1 synthesis, leading to stabilization of the matrix (193). The potential role of IL-10 in experimental myocardial infarction has recently been explored (Fig. 11) (90, 388). IL-10 mRNA and protein upregulation was demonstrated in the reperfused infarcted myocardium by using a canine model of myocardial infarction. IL-10 expression was first detected at 5 h and peaked after 96–120 h of reperfusion. In contrast, IL-12, a Th1-related cytokine associated with macrophage activation, was not detected in the ischemic myocardium. IL-10 induction was associated with decreased synthesis of the proinflammatory cytokine IL-6. *In vitro* experiments demonstrated that late postischemic cardiac lymph induced TIMP-1 mRNA expression by isolated canine mononuclear cells. This effect was inhibited when the incubation

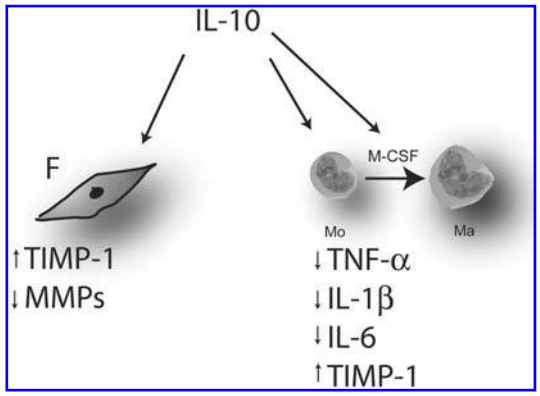

FIG. 11. IL-10 may play an important role in infarct healing by suppressing expression of monocyte-derived inflammatory cytokines and by promoting extracellular matrix accumulation through enhanced TIMP synthesis. In addition, IL-10 enhances M-CSF–mediated monocyte (Mo)-to-macrophage (Ma) differentiation. F, fibroblast.

contained a neutralizing anti–IL-10 antibody (90). IL-10$^{-/-}$ mice show an enhanced inflammatory response after myocardial infarction, demonstrated by increased neutrophil recruitment, elevated plasma levels of TNF-α, and high tissue expression of ICAM-1 (388). These studies underscore the importance of IL-10 in the healing process, suggesting that IL-10 may be involved in inhibition of the postinfarction inflammatory response and in extracellular matrix remodeling.

TGF-β: a key regulator of the healing response

The biology of TGF-β. The TGF-βs are pleiotropic, multifunctional cytokines with a wide range of biologic effects regulating cell proliferation, differentiation, and apoptosis, and modulating the immune response. The complexity and diversity of TGF-β-mediated effects is demonstrated through its multiple roles in immune system suppression, wound healing, and fibrosis. Three structurally similar isoforms of TGF-β (TGF-β1, 2, and 3), encoded by three distinct genes, have been identified in mammalian species (310). These three isoforms signal through the same cell-surface receptors and have similar cellular targets, although each isoform is expressed in a distinct pattern under control of a unique promoter (210). TGF-β1 is the prevalent isoform and is found almost ubiquitously, whereas the other isoforms are expressed in a more limited spectrum of cells and tissues. TGF-β is produced by many cell types as a latent complex, unable to interact with its receptors. Mature TGF-β is secreted as a latent dimeric complex which contains the C-terminal mature TGF-β and its N-terminal prodomain, LAP (TGF-β latency–associated peptide). The extracellular concentration of TGF-β activity is primarily regulated by conversion of latent TGF-β to active TGF-β. Most tissues contain significant amounts of latent TGF-β; activation of only a small fraction of this latent TGF-β generates maximal cellular response (4). A variety of molecules have been described as TGF-β activators. Proteases including plasmin, MMP-2, and MMP-9 are capable of activating TGF-β, coupling matrix degradation with activation of a molecule that has a primary

role in maintaining matrix integrity and stability (4, 155, 287). The matricellular protein thrombospondin (TSP)-1 is a key TGF-β activator, which acts by disrupting the noncovalent interactions between LAP and the TGF-β molecule. Reactive oxygen species generation (14) and a mildly acidic environment (223) are also capable of inducing TGF-β activation.

TGF-β expression and activation in healing myocardial infarcts. TGF-β is markedly upregulated in experimental models of myocardial infarction (356). TGF-β isoforms demonstrate distinct patterns of expression in the infarct: TGF-β1 and β2 are induced early, whereas TGF-β3 shows delayed and prolonged upregulation (65, 67). TGF-β expression in the infarcted heart is attenuated by angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers (344, 391, 392), suggesting that angiotensin II signaling plays an important role in stimulating TGF-β synthesis in the infarct (133). TGF-β expression is predominantly localized in the infarct border zone, associated with expression of Smad2, 3, and 4, the key downstream signaling effectors of the TGF-β family members (61). Although evidence suggests that bioactive TGF-β is released in the cardiac extracellular fluids 3–5 h after reperfused infarction (19), the mechanisms responsible for TGF-β activation in the infarcted heart are poorly understood. Our recent experiments suggested that TSP-1 induction in the infarct border zone may play an important role in activation of TGF-β signaling pathways in mouse and canine infarcts (95).

The role of TGF-β in regulation of infarct healing. Through its pleiotropic effects, TGF-β is ideally suited as a key mediator in the transition from inflammation to fibrosis (Fig. 12). TGF-β suppresses cytokine and chemokine expression by stimulated mononuclear and endothelial cells. TGF-β also inhibits proliferation of most cells and modulates fibroblast behavior by stimulating the synthesis of various extracellular matrix proteins including collagens, fibronectin, tenascin, and proteoglycans (15), and by suppressing matrix degradation through decreased expression of proteinases, such as plasminogen activators and collagenases, and increased synthesis of proteinase inhibitors, such as plasminogen activator inhibitor (PAI)-1 and TIMP-1 (77, 196). In the healing infarct, TGF-β may play a dual role suppressing chemokine synthesis by endothelial cells and leukocytes, while promoting extracellular matrix deposition. Unfortunately, the complex biology of TGF-β activation and its pleiotropic actions have hampered our efforts to understand its role in infarct healing.

TGF-β injection during the inflammatory phase of healing significantly reduced ischemic myocardial injury, presumably by attenuating the deleterious effects of proinflammatory cytokines such as TNF-α (203). Two recent studies showed that inhibition of TGF-β signaling by injection of an adenovirus harboring soluble TGF-β type II receptor in the hindlimb muscles resulted in attenuated left ventricular remodeling by modulating cardiac fibrosis (156, 262). However, early TGF-β inhibition significantly increased mortality and exacerbated left ventricular dilation enhancing cytokine synthesis, suggesting that during the phase of resolution of the inflammatory response, TGF-β signaling plays an important role in suppression of inflammatory mediator synthesis (156).

Our recently published study (95) suggests that TGF-β activation is crucial for chemokine and cytokine downregulation and resolution of the inflammatory process in the healing infarct. TSP-1, a crucial TGF-β activator and potent angiogenesis inhibitor, is markedly and specifically induced in the border zone of healing myocardial infarcts. Our experiments showed that TSP-1–deficient animals had enhanced and prolonged expression of chemokines in the infracted myocardium and exhibited expansion of the inflammatory infiltrate into the noninfarcted area. Phosphorylated Smad2 levels were lower in TSP-1 null infarcts, suggesting impaired activation of the TGF-β signaling pathway. Prolonged and expanded inflammation resulted in increased adverse remodeling of the ventricle (95). These findings suggest an important role for TGF-β signaling in suppressing inflammatory chemokine expression and in regulating the transition to fibrous tissue deposition.

FORMATION OF GRANULATION TISSUE IN THE HEALING INFARCT

The infarct myofibroblasts: critical regulators of extracellular matrix remodeling

Macrophages, mast cells, and lymphocytes create an environment rich in inflammatory cells, capable of regulating

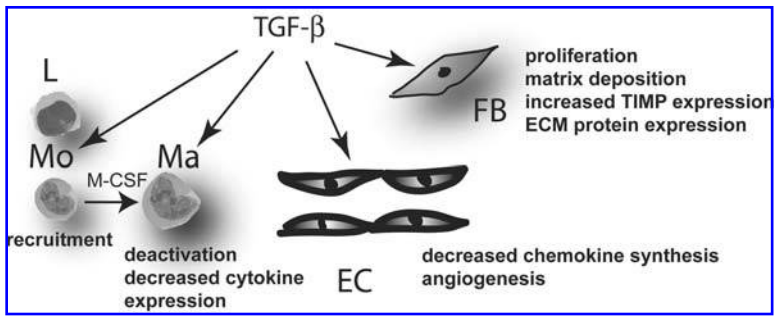

FIG. 12. TGF-β is a pleiotropic and multifunctional mediator with a critical role in infarct healing. TGF-β is a potent monocyte chemoattractant and may be a key factor in the transition from the inflammatory phase to fibrous tissue deposition. TGF-β deactivates macrophages, suppressing expression of proinflammatory cytokines and chemokines, and enhances synthesis of extracellular matrix proteins by fibroblasts. In addition, TGF-β promotes matrix deposition by stimulating TIMP synthesis. Furthermore, TGF-β modulates endothelial cell phenotype by activating both angiostatic and angiogenic pathways in a context-dependent manner and by downregulating endothelial chemokine synthesis.

neovessel formation, fibroblast proliferation, and extracellular matrix metabolism through the production of a variety of cytokines and growth factors. Fibroblasts produce the extracellular matrix constituents needed to support cell ingrowth, and newly formed blood vessels carry oxygen and nutrients necessary to sustain cell metabolism. Willems and colleagues (381) identified and characterized the interstitial nonvascular α-smooth muscle actin (α-SMA)-positive cells, which were present in human myocardial scars 4–6 days after an infarction. These phenotypically modulated fibroblasts, termed myofibroblasts (107–109), develop ultrastructural and phenotypic characteristics of smooth muscle cells and possess a contractile apparatus that contains bundles of actin myofilaments with associated contractile proteins, such as nonmuscle myosin (359) (Fig. 13). Myofibroblasts are the predominant source of collagen mRNA in healing myocardial infarcts (45, 333, 374, 375). They transiently appear during granulation tissue formation and become apoptotic when the scar matures (64).

Origin of the fibroblasts in healing infarcts. The origin of the fibroblasts infiltrating the healing wound is one of the oldest and most controversial concepts in cell biology and has been debated for >100 years (78, 283). Early studies have documented differentiation of leukocytes into fibroblasts and have cultured connective tissue-producing cells from the buffy coat (277, 338). Although it is widely recognized that fibroblasts proliferate in the healing wound, the extent to which connective tissue is the result of an ingrowth of adjacent mesenchymal or fibroblast-like cells versus the hematogenous entry of circulating fibroblast precursors is debated. Early studies of connective tissue repair in implanted polyvinyl sponges and granulating wounds supported the local origin of fibroblasts (78). More recently, Bucala and co-workers (32) described and characterized a circulating population of leukocytes that traffic to fibrotic tissues and sites of injury and differentiate to fibroblasts. The recruitment of blood-borne fibroblast precursors is mediated through chemokine-dependent mechanisms and appears to be important in the development of pulmonary fibrosis (279).

The origin of fibroblasts in healing infarcts remains unclear (Fig. 14). Although numerous studies have documented active proliferation of resident fibroblasts (94, 370, 389), the possibility that at least a subset of infarct fibroblasts may be derived from blood-borne precursors should be considered.

Myofibroblast differentiation and activation in the healing infarct. Fibroblasts infiltrating the infarct undergo myofibroblast differentiation, developing a microfilamentous apparatus expressing α-SMA. They are predominantly localized in the border-zone area and exhibit intense proliferative activity (93, 370). The mechanisms responsible for myofibroblast differentiation in the infarcted heart remain poorly understood; however, the modulation of a fibroblast toward myofibroblast likely results from the combined action of several distinct factors.

1. TGF-β is critically involved in myofibroblast differentiation in healing wounds by regulating α-SMA expression (63) and is likely to play an important role in modulating fibroblast phenotype in infarcts.

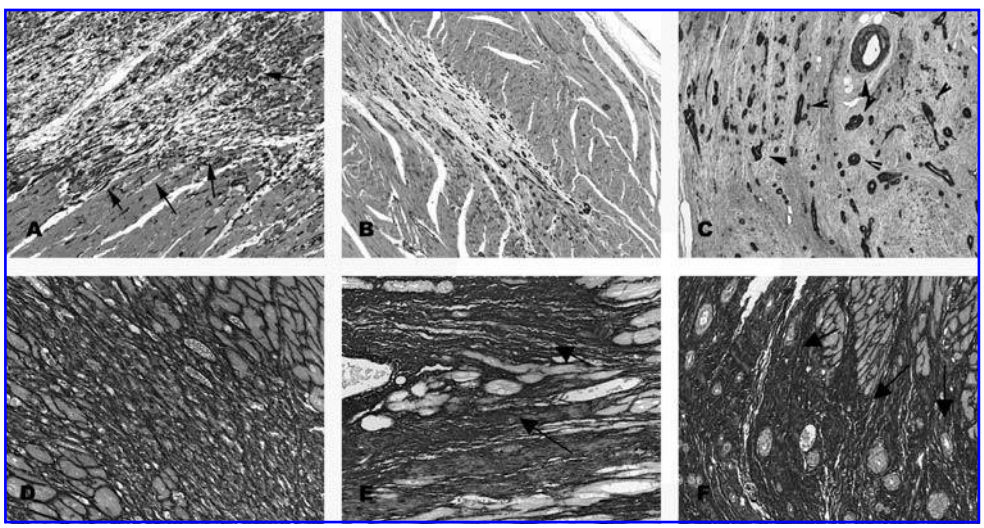

FIG. 13. Fibrous tissue deposition in the healing infarct. (**A–C**) α-SMA immunohistochemistry identifies myofibroblasts and vascular smooth muscle cells in reperfused canine infarcts. After 7 days of reperfusion (**A**), abundant, spindle-shaped α-SMA–positive myofibroblasts (arrows) are found in the infarct border zone. As the wound matures, myofibroblasts undergo apoptotic death, and α-SMA staining is localized predominantly in vascular smooth muscle cells (4 weeks reperfusion; **B**). The number of vessels with a muscular coat (arrowheads) increases after 8 weeks of reperfusion (**C**). (**D–F**) Immunohistochemical staining for type III collagen in reperfused canine infarcts after 7 days (**D**), 4 weeks (**E**), and 8 weeks (**F**) of reperfusion. Extracellular matrix deposition in the infarct increases as the wound matures (arrows). Note that the time course of fibrous tissue deposition in large-animal models of infarction is delayed compared with that in rodents.

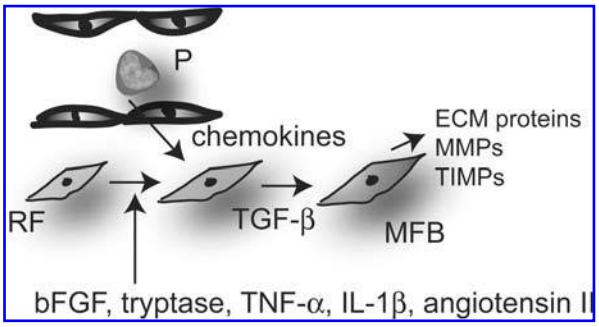

FIG. 14. The origin and role of the fibroblasts in the healing infarct. During the proliferative phase of healing, fibroblasts accumulate in the infarcted myocardium. Extensive evidence has documented proliferation of resident fibroblasts (RFs) in the infarct; however, the role of circulating fibroblast precursors (Ps) should also be considered. Fibrogenic mediators (such as bFGF, angiotensin II, and tryptase) may mediate fibroblast proliferation, whereas chemokines may attract fibroblast precursors. Angiotensin II appears to be a key factor in fibroblast activation; these effects are mediated primarily through interactions with the type 1 receptor, AT-1, and may involve activation of the TGF-β pathway. TNF-α and IL-1β increase AT-1 density on cardiac fibroblasts and may enhance the fibrogenic actions of angiotensin II. TGF-β critically regulates myofibroblast (MFB) differentiation and activates synthesis of extracellular matrix proteins.

2. Alterations in the composition of the extracellular matrix may dictate phenotypic changes in infarct fibroblasts. The splice variant ED-A of cellular fibronectin is crucial for myofibroblastic phenotype induction by TGF-β (317).
3. Mechanical tension induces myofibroblast differentiation but also modulates fibroblast behavior by activating various signal-transduction pathways (227).
4. In reperfused infarcts, the return to normoxic pO_2 after a hypoxic period is perceived as "relative hyperoxia." Perceived hyperoxia induces fibroblast alterations that resemble TGF-β1–induced morphologic changes, including myofibroblast differentiation (297, 298).

Infarct myofibroblasts are aligned in highly organized arrays. Blankesteijn and co-workers (21) found that infarct fibroblasts expressed a homologue of the *Drosophila* tissue polarity gene frizzled (fz2), suggesting a potential mechanism for spatial control of myofibroblast distribution during cardiac repair. Differentiated myofibroblasts can generate contractile force that results in deformation and contraction of the healing infarct (359). In addition, recent studies demonstrated that, apart from their role in structural remodeling, myofibroblasts may directly modulate cardiac impulse conduction (241). These findings suggest that myofibroblast accumulation in the infarct may contribute to arrhythmogenesis.

Fibroblast gene expression is modulated by microenvironmental factors. In normal hearts, resident fibroblasts are responsible for homeostatic maintenance of the extracellular matrix network. Although their contribution in the inflammatory phase of healing is unclear, fibroblasts are capable of producing large amounts of chemokines and cytokines on stimulation with inflammatory mediators (194). The cytokine milieu during the inflammatory phase of healing promotes a matrix-degrading fibroblast phenotype. Stimulation of cardiac fibroblasts with IL-1β and TNF-α mediators, induced and released in the early stages of infarct healing, results in decreased collagen expression and enhanced MMP activity (327). In contrast, during the proliferative phase of healing, signals that promote extracellular matrix synthesis are activated. FGF-2 is released in the infarcted myocardium and may induce fibroblast proliferation (66). TGF-β markedly increases extracellular matrix protein synthesis and enhances TIMP expression, promoting matrix preservation.

Extensive evidence suggests that angiotensin II plays an important role in fibroblast proliferation and matrix synthesis, mediating effects transduced by AT-1 receptors (343, 357). The effects of angiotensin II may be mediated, at least in part, through induction of fibrogenic growth factors, such as TGF-β. Both *in vitro* and *in vivo* studies have shown that angiotensin II directly stimulates proliferation of cardiac fibroblasts and production of extracellular matrix proteins, such as collagen and fibronectin. Administration of ACE inhibitors or AT-1 antagonists significantly decreased cardiac fibrosis after myocardial infarction (309). In addition, AT-$1A^{-/-}$ mice exhibited attenuated geometric and structural remodeling after myocardial infarction (134). Angiotensin type 2 (AT-2)-receptor signaling conversely has been reported to inhibit fibroblast growth and collagen production (261). However, AT-2 gene targeting decreased collagen deposition in healing infarcts, causing cardiac rupture; this effect was presumed due to enhanced PGE_2 expression in the infarcted myocardium (154).

During the maturation phase, infarct myofibroblasts undergo apoptosis, and the highly cellular granulation tissue is replaced by a collagen-based scar (Fig. 13). The mechanisms responsible for apoptotic death and clearance of the fibroblasts have not been investigated.

Infarct angiogenesis

Angiogenesis is an integral part of wound healing. Neovessels are important components of granulation tissue and are required to provide oxygen and nutrients to the highly dynamic and metabolically active cells of the healing wound. Angiogenic growth factors, such as bFGF and vascular endothelial growth factor (VEGF), are induced and released during the first few hours after myocardial ischemia (202, 212), resulting in neovessel growth (89). During the proliferative phase of healing, a rich network of capillaries is formed along with enlarged pericyte-poor "mother vessels" (285). As the vasculature matures, some infarct neovessels are coated with pericytes (Fig. 13), whereas uncoated vessels regress (73). Although the time course of neovessel formation is well described, the mechanisms responsible for infarct angiogenesis remain poorly understood. Hypoxia-inducible factor (HIF)-1α is exquisitely sensitive to hypoxic conditions, making it one of the earliest effectors of the response to ischemia. HIF-1α activation results in VEGF induction and release, playing an important role in mediating endothelial sprouting in the healing infarct (105). VEGF induces endothelial cell migration and proliferation, resulting in the formation of hyperpermeable neovessels. VEGF acts in concert with the angiopoi-

etins. Angiopoietin (Ang)-1 and Ang-2 are ligands for the Tie2-receptor tyrosine kinase, which is present on endothelial cells and endothelial progenitor cells. Ang-1 is widely expressed in the quiescent vasculature. Ang1–Tie2 signaling serves to inhibit endothelial cell activation and thus may impede the efficient initiation of the angiogenic response in the face of hypoxia or tissue injury. Ang-2 is an endogenous antagonist of Tie2 and inhibits Ang1–Tie2 signaling, facilitating endothelial activation in response to inducers of angiogenesis, such as VEGF (49, 82). In healing infarcts, Ang-2 is markedly induced in the early stages of healing, whereas Ang-1 expression is decreased (304). Thus, Ang-2 may act in concert with VEGF as a permissive factor in the earliest stages of infarct angiogenesis by releasing endothelial cells from the inhibitory actions of Ang-1. Several other mediators, such as FGFs, TGF-β, and the chemokines MCP-1, IL-8, and IP-10, are capable of modulating angiogenesis and may participate in the complex process of neovessel formation after myocardial infarction. The composition of the extracellular matrix is also critical for neovascular growth and should be viewed as a dynamic player in the process.

During the maturation phase of infarct healing, granulation tissue is replaced by a collagen-rich scar, which exhibits a relatively low capillary density, but a large number of vessels coated with mural cells (Fig. 13C). Mature coated vessels exhibit decreased angiogenic potential and are protected from regression, whereas uncoated endothelial cells undergo apoptosis. Acquisition of a muscular coat is a dynamic process that may involve PDGF-BB–PDGF-Rβ interactions (Fig. 15). Considering the low metabolic needs of the mature scar and the low number of capillaries, it is likely that coating of infarct neovessels with mural cells does not serve to create effective conduits of blood; it may rather represent a mechanism necessary for inhibition of the angiogenic process.

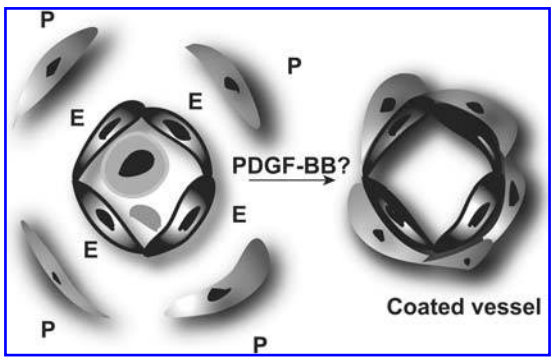

FIG. 15. Vascular maturation in the healing infarct. During the proliferative phase of healing, a rich microvascular network is formed in the infarcted area. As the wound matures, some of these vessels acquire a pericyte coat, whereas uncoated vessels regress. Coated vessels are stable and have decreased angiogenic potential. The mechanism responsible for vascular maturation in the infarct remains unknown but is likely to involve PDGF-BB/PDGFR-β interactions. Vascular maturation contributes to stabilization of the wound. E, endothelial; P, pericyte.

THE EXTRACELLULAR MATRIX NETWORK IN THE HEALING INFARCT

The dynamic changes in composition of the extracellular matrix

During all phases of infarct healing, the composition of the extracellular matrix plays a critical role in regulating cell behavior. Extracellular matrix proteins not only provide structural and mechanical support to the tissue, but also modulate cell signaling through interactions with specific surface receptors. The extracellular matrix in the healing infarct undergoes dynamic changes that dramatically alter the microenvironment and profoundly affect the phenotype of the cells. During the inflammatory phase, a fibrin-based provisional matrix is formed. In addition to its hemostatic role, deposition of the plasma-derived provisional matrix may be crucial in supporting migration and proliferation of infiltrating inflammatory endothelial and stromal cells (44). Release of inflammatory mediators results in increased vascular permeability, causing extravasation of platelets and plasma proteins, such as fibrinogen and fibronectin, in the infarcted area. Thus, a clot is formed, consisting of platelets embedded in a mesh of cross-linked fibrin (derived from thrombin cleavage of fibrinogen), together with smaller amounts of plasma fibronectin and vitronectin. Formation of a fibrin clot not only establishes hemostasis, plugging disrupted vessels, but also creates a provisional matrix network, providing a scaffold for the recruitment and migration of cells into the infarct. In addition, degranulating platelets may serve as a source of cytokines and growth factors. The role of the components of the clot in regulating postinfarction inflammation and infarct healing has not been investigated. A recent study demonstrated that fibrinogen-deficient mice have decreased infarct size compared with wild-type animals (278). However, the exact mechanisms responsible for these effects and the role of the fibrin-based provisional matrix in cardiac repair remain unknown.

Provisional matrix components promote cell proliferation and provide a scaffold for cell migration (51). Subsequently, the initial plasma-derived provisional matrix is lysed by proteolytic enzymes produced by granulation tissue cells and replaced by an organized cell-derived provisional matrix network containing cellular fibronectin and hyaluronan (377). The plasminogen–plasmin system appears to play an important role in clearance of the fibrin network. Proteolytic conversion of plasminogen to the active serine protease plasmin is regulated by a complex system of proteins that includes the urokinase-type plasminogen activator (uPA) and the tissue-type plasminogen activator (tPA). In addition to its fibrin-degrading properties, plasmin may also participate in regulation of MMP activity and in release of growth factors from the matrix. Experiments using genetically targeted animals explored the role of the plasminogen system in infarct healing. Plasminogen-null mice showed delayed infarct healing with impaired migration of inflammatory cells into the infarct (55). In addition, gelatinolytic activity was markedly decreased, suggesting that the effects of plasminogen deficiency may be in part mediated through defective MMP activation. Furthermore, $uPA^{-/-}$ animals showed delayed in-

farct healing but were protected from cardiac rupture; in contrast, tPA deficiency was not protective (145). These findings highlighted the critical role of plasmin-mediated proteolysis in regulation of infarct healing.

Cytokines and growth factors may play a crucial role in regulating extracellular matrix protein synthesis and deposition. Proinflammatory mediators, such as TNF-α and IL-1β, decrease collagen synthesis by cardiac fibroblasts (327), whereas fibrogenic growth factors, such as TGF-β and bFGF, markedly induce extracellular matrix protein expression and deposition in the infarcted area (172). Conversely, extracellular matrix proteins exert a profound influence on cellular behavior and gene expression by detecting, transducing, and coordinating molecular signals originating from the microenvironment and adjacent cells (169).

As the wound matures, collagen is deposited and cross-linked, stabilizing the scar and increasing the tensile strength of the wound (271). Lysyl-oxidase is induced in the infarct and may play an important role in cross-linking collagen fibers (209). Timely maturation of the collagen network in the infarcted heart may be an important factor in preventing adverse remodeling.

The matricellular proteins: critical modulators of cell-matrix interactions in healing infarcts

In addition to structural matrix proteins such as collagen and fibronectin, another class of matrix proteins, termed "matricellular" proteins (including osteopontin, tenascin-C, thrombospondins 1 and 2, and osteonectin), are transiently induced in healing infarcts and may function as adaptors and modulators of cell–matrix interactions (117, 252, 387). Matricellular proteins represent an important component of the extracellular matrix network of the infarct. They are markedly but transiently induced and do not serve a structural role but modulate cell behavior by activating intracellular signaling pathways through binding of specific cell-surface receptors (191, 218). Recent investigations using genetically targeted mice suggested that the dynamic expression of matricellular proteins directly regulates the phenotypic and functional characteristics of many cell types involved in wound healing and critically affects left ventricular remodeling (95, 308).

The tenascins. The tenascins are a highly conserved family of oligomeric glycoproteins built from a common set of structural motifs (41, 151). Four tenascin paralogues have been identified in mammals, each designated with a letter derived from earlier eponyms: C, R, X, and W. Only tenascins C and X are known to modulate cell adhesion, migration, and growth and are considered matricellular proteins. In the normal adult heart, tenascin-C is not found in the myocardium except at the chordae tendinae of papillary muscles (306). However, tenascin-C is markedly upregulated in a variety of pathologic processes associated with inflammation and remodeling of the cardiac tissue (96, 349, 380). In healing myocardial infarcts, tenascin-C is transiently expressed during the proliferative phase of healing, is predominantly produced by fibroblasts (158), and is localized in the border zone between infarcted and viable remodeling myocardium. The mechanisms responsible for tenascin-C induction in the infarct remain unknown. Several cytokines and growth factors, released in healing infarcts (such as TNF-α, TGF-β, and bFGF), are capable of upregulating fibroblast tenascin-C synthesis. In addition, angiotensin II is also known to stimulate tenascin-C expression (228). Tenascin-C expression virtually disappears in the mature infarct (380).

The role of tenascin-C in infarct healing and postinfarction remodeling remains unknown. Its selective expression in the infarct border zone suggests that it may be important in the dynamic events associated with cardiac remodeling after injury. Tenascin-C promotes a deadhesive state and may facilitate migration of fibroblasts and other granulation tissue cells in the infarct. It has been suggested that tenascin-C may modulate adhesion of surviving cardiomyocytes in the infarct border zone, facilitating tissue remodeling (158). In addition, a recent study examined the effects of tenascin-C deficiency in a model of electrical cardiac injury (348), demonstrating that tenascin-C$^{-/-}$ mice exhibit delayed myofibroblast infiltration in the injured site.

The role of the thrombospondins. Considering the complex structure of the TSP-1 molecule, its numerous functional domains, and its many signaling receptors, it is no surprise that it has diverse effects on a variety of cell types, inducing cell deadhesion and modulating cellular proliferation and function. Some of the *in vivo* actions of TSP-1 are particularly important in wound healing and tissue repair. TSP-1 suppresses proliferation and migration of vascular endothelial cells *in vitro* and inhibits neovascularization *in vivo* (339, 358). The angiostatic effects of TSP-1 involve induction of endothelial cell apoptosis and are dependent on CD36 activation (60, 166). In addition, TSP-1 has a crucial role in TGF-β activation (54). Although TSP-1$^{-/-}$ mice have no obvious developmental abnormalities, they develop an acute and organizing pneumonia during the first 4–10 weeks of life (200), presumably due to defective TGF-β activation in the lung epithelium (54). In normal adult hearts, TSP-1 is not expressed; however, it is strikingly upregulated in experimental models of infarction (95, 318). We have recently studied the expression and role of TSP-1 in healing myocardial infarcts. TSP-1 mRNA and protein was markedly and selectively induced in the border zone of healing canine and murine myocardial infarcts. In the absence of injury, TSP-1$^{-/-}$ hearts showed no morphologic abnormalities and exhibited comparable cytokine, chemokine, and growth-factor expression levels with wild-type animals, suggesting that TSP-1 does not play a role in cardiac homeostasis. After reperfused myocardial infarction, TSP-1$^{-/-}$ mice showed enhanced and prolonged expression of chemokines and expansion of the inflammatory infiltrate into the noninfarcted area. Prolonged and expanded inflammation resulted in increased adverse remodeling of the ventricle (95). Decreased Smad2 phosphorylation was noted in TSP-1$^{-/-}$ infarcts, suggesting impaired activation of TGF-β–mediated pathways. These findings suggest an important role for TSP-1 in suppressing inflammatory chemokine expression and in regulating the transition to fibrous tissue deposition. The strikingly localized expression of TSP-1 in the infarct border zone may locally activate TGF-β and inhibit angiogenic activity, suppressing inflammation and preventing expansion of the leukocyte infil-

trate into the noninfarcted area. We postulated that localized induction of TSP-1 in the infarct border zone may result in formation of a "barrier," preventing expansion of the inflammatory infiltrate in the noninfarcted area.

TSP-2 is structurally similar to TSP-1 and has angiostatic properties; however, recombinant mouse TSP-2 does not activate latent TGF-β (313). TSP-2 appears to play a significant role in wound healing. Excisional skin wounds healed at an accelerated rate and with less scarring in TSP-2$^{-/-}$ mice. In the heart, recent investigations suggested that TSP-2 may be a crucial regulator of the integrity of the cardiac matrix that is necessary for the myocardium to cope with increased loading (312, 332). TSP-2 expression was significantly increased in failing rat hearts and in hypertrophied human hearts with systolic dysfunction (312). Angiotensin II induced fatal cardiac rupture in 70% of TSP2 knockout mice and cardiac failure in the surviving animals; this was not seen in wild-type mice. In addition, myocardial infarction in TSP-2$^{-/-}$ mice resulted in a high incidence of cardiac rupture (308), suggesting a crucial role for TSP-2 in formation and structural integrity of the remodeling matrix. The mechanisms responsible for these effects remain to be determined.

SPARC. SPARC ("secreted protein, acidic and rich in cysteine," also known as osteonectin, or BM40), is a 32-kDa glycoprotein found in bone and highly expressed in basement membranes and in capsules of various organs. SPARC binds to structural matrix proteins including the fibrillar collagens (types I, II, III, and V), collagen type IV, and vitronectin (27, 28). Constitutive expression of SPARC appears to be important for organization of the extracellular matrix. SPARC is markedly induced in healing and remodeling tissues. SPARC$^{-/-}$ mice show accelerated dermal wound closure, possibly due to alterations in organization of the collagen network or increased growth factor activity in the healing wound (26). Normal adult hearts contain relatively low amounts of SPARC (288). SPARC synthesis is markedly induced during cardiac remodeling, in models of hypertrophy (79, 233), and myocardial infarction (182, 337). In healing infarcts, SPARC is expressed predominantly by fibroblasts and macrophages and is transiently induced during the proliferative phase of healing. Although SPARC may modulate various aspects of the cellular response in healing infarcts, its effects on repair of the infarcted myocardium and on ventricular remodeling have not been investigated.

Osteopontin (OPN). OPN is a phosphorylated acidic glycoprotein secreted by macrophages and activated lymphocytes, which is abundantly expressed in the extracellular matrix of mineralized tissues and is markedly induced in inflammatory sites (62). OPN interacts with a variety of receptors including the integrins αv (β1, β3, or β5) and (α4, α5, α8, or α9) β1, as well as CD44. The major integrin-binding site in OPN is the arginine-glycine-aspartate (RGD) integrin-binding motif, which is required for the adherence of many cell types to OPN (122). OPN has both pro- and antiinflammatory effects. As a proinflammatory mediator, it promotes T-lymphocyte and monocyte/macrophage chemotaxis (260) and induces Th1-lymphocyte polarization, inhibiting Th2 cytokine synthesis (8). Conversely, OPN may also act as an antiinflammatory agent by inhibiting NO synthesis (62, 314). OPN is markedly induced in the hypertrophied (119, 382) and remodeling myocardium. Murry and co-workers (253) demonstrated OPN upregulation in a model of cryogenic myocardial injury and in tissue from human myocardial infarcts. The transient expression of OPN was localized predominantly in macrophages and was suppressed during maturation of the wound. OPN upregulation is consistently found in experimental models of myocardial infarction (67, 99, 182). In both murine and canine infarcts, OPN induction occurs early after myocardial infarction and is localized predominantly in macrophages. OPN is markedly upregulated during monocyte-to-macrophage differentiation (136, 183); thus, its induction in the infarct may reflect differentiation and activation of infiltrating monocytes.

A recent investigation explored the role of OPN in infarct healing and postinfarction remodeling by using OPN$^{-/-}$ mice (360). Absence of OPN resulted in increased left ventricular dilatation associated with reduced collagen deposition in the infarcted myocardium. These experiments suggested that OPN may play a protective role, attenuating left ventricular remodeling, by promoting collagen deposition in the infarct. The mechanisms responsible for the OPN-mediated effects on matrix remodeling remain poorly understood.

Extracellular matrix remodeling in the healing infarct: the role of the MMPs

Extracellular matrix remodeling in the healing infarct is orchestrated by a family of zinc-containing endoproteinases, termed MMPs (56). The growing list of MMPs includes >20 human members with common functional features (257). MMPs are secreted in a latent proform and require activation for proteolytic activity. They degrade matrix components and are inhibited by specific inhibitors, termed tissue inhibitors of metalloproteinases (TIMPs). The balance between MMPs and TIMPs is critical for remodeling of the extracellular matrix (383). Based on domain organization and substrate specificity, MMPs can be divided into collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs (MT-MMPs), and others. Collagenases (MMP-1, -8, and -13) cleave fibrillar collagens I, II, and III but can also digest other extracellular matrix proteins. Gelatinases (MMP-2 and -9) digest gelatin and various other matrix proteins, such as collagens type IV (an important component of basement membranes), V, and XI, and laminin. Stromelysins (MMP-3, -10, and -11) have a domain arrangement similar to that of collagenases but do not cleave fibrillar collagens. MMP-11 (stromelysin-3) has very weak activity toward matrix proteins but is capable of cleaving serpins. Matrilysins (MMP-7 and -26) lack a hemopexin domain. MMP-7 is induced by hypoxia and plays an important role in the maintenance of innate immunity by proteolytically activating antibacterial peptides such as the prodefensins (35). MT-MMPs (MMP-14, -15, -16, -17, -24, and -25) are activated intracellularly, and active enzymes are likely to be expressed in the cell surface. All MT-MMPs (except MMP-17) activate proMMP-2; in addition, MMP-14 has collagenolytic activity. Finally, seven MMPs (MMP-12, -19, -20, -21, -23, -27, and -28) are not grouped in any of the categories. MMP-12 (metalloelastase), the best-studied mem-

ber of the group, is primarily a macrophage product. It digests elastin and numerous other matrix proteins and appears to be important for macrophage migration (322).

MMP activity is controlled at three distinct levels: (a) transcription, (b) activation of proMMPs, and (c) inhibition by the TIMPs. Most MMPs are expressed in normal adult tissues. In the normal heart, latent MMPs are expressed in fibroblasts and cardiomyocytes and are distributed throughout the cardiac interstitium (244). Early upregulation of MMP expression and activity is found in healing myocardial infarcts (45). Changes in the cytokine milieu are likely to play a key role in regulating MMP synthesis by inflammatory cells and fibroblasts infiltrating the infarcted myocardium. IL-1β and TNF-α increase MMP-2 and MMP-9 activity (327), whereas IL-10 and TGF-β enhance TIMP synthesis, promoting extracellular matrix accumulation (193, 366).

MMP expression may play a role in regulating many cellular processes involved in infarct healing, including leukocyte migration, angiogenesis, degradation of the extracellular matrix, and remodeling. MMP processing also regulates the activity of cytokines and growth factors (112) and may inhibit chemokine-mediated effects by generating CC chemokines-receptor antagonists with antiinflammatory properties (238). Studies using MMP inhibitors and genetically targeted animals have demonstrated the importance of MMP-mediated matrix degradation in infarct healing and in the pathogenesis of left ventricular remodeling. Treatment with a broad-spectrum MMP inhibitor significantly attenuated left ventricular dilation after myocardial infarction (290). Inhibition of the MMP system is currently explored by several laboratories as a strategy with potential therapeutic implications in myocardial infarction (215, 365, 367).

Investigations using mice with targeted gene disruptions of specific members of the MMP family have significantly contributed to our understanding of the role of MMPs in infarct healing. MMP-9$^{-/-}$ mice exhibited delayed healing after myocardial infarction, associated with reduced leukocyte influx into the infarct, and were protected from myocardial rupture (145). In another independent study, mice with targeted deletion of the MMP-9 gene had attenuated postinfarction remodeling and decreased collagen accumulation in the myocardium (76). Two studies demonstrated that MMP-2$^{-/-}$ animals were protected from early rupture and showed decreased adverse remodeling (139, 235). These effects were associated with reduced macrophage infiltration and delayed clearance of dead cardiomyocytes from the infarcted area (235). TIMPs also may play an important role in regulating extracellular matrix remodeling after myocardial infarction. In the absence of injury, TIMP-1$^{-/-}$ mice have increased left ventricular end-diastolic volume in association with a decrease in myocardial collagen content, suggesting a role for TIMP-1 in maintaining normal left ventricular structure and geometry (296). After myocardial infarction, TIMP-1$^{-/-}$ mice exhibited accelerated left ventricular remodeling (57) that was pharmacologically "rescued" by MMP inhibition (157). In contrast, TIMP-1 overexpression in the infarcted heart resulted in complete prevention of cardiac rupture (145). These findings suggest a protective role of TIMP-1 in infarct healing and left ventricular remodeling. TIMP-2 and TIMP-4 (65, 250) are also induced in the infarcted heart; however, their role in healing and postinfarction remodeling has not been studied.

MYOCARDIAL REGENERATION: MYTH OR REALITY?

Although it is widely accepted that the mammalian heart has extremely limited regenerative capacity, evidence suggests that a fraction of cardiomyocytes may be able to reenter the cell cycle and that limited cardiac regeneration may occur through recruitment of resident and circulating stem cells (255, 384). These concepts led to basic and clinical studies exploring the potential administration of progenitor cells in the infarcted myocardium to promote cardiac regeneration through the formation of functional cardiomyocytes. However, the ability of injected bone marrow–derived cells to give rise to cardiac myocytes after myocardial infarction remains controversial. Orlic and co-workers (265) suggested that hematopoietic stem cells can transdifferentiate into cardiomyocytes when injected into the infarcted myocardium, resulting in extensive cardiac regeneration (265). In contrast, other experimental studies found no cardiomyocyte transdifferentiation of hematopoietic stem cells directly injected into the ischemic myocardium (13, 254). Enthusiasm from the early experimental findings fueled numerous small clinical studies examining the effects of cell therapy in patients with acute myocardial infarction (59, 164, 384). Although some of these studies have reported beneficial effects of progenitor cell-transfer in the infarcted heart (163, 386), the mechanisms responsible for these actions remain poorly understood and highly controversial (69). Carefully conducted clinical trials are needed to clarify the role of cell therapy in the treatment of patients with myocardial infarction.

Inflammatory mediators play an important role in mobilizing progenitor cells and may regulate their homing into the infarcted myocardium (364). Stem cell mobilization with SCF and granulocyte–colony-stimulating factor (G-CSF) results in improved function and attenuated left ventricular remodeling after myocardial infarction (266, 384). However, growth factors are pleiotropic and multifunctional and induce a diverse range of effects on a variety of cell types involved in infarct healing. Thus, their potential beneficial actions in the infarcted myocardium may not be mediated through stem cell mobilization.

Under normal biologic circumstances, significant cardiac regeneration in the mammalian heart is impossible. However, recent advances in our understanding of the biology of progenitor cells may eventually result in the development of therapeutic strategies that could fulfill the visionary goal of enhancing cardiac repair through cardiomyocyte regeneration.

CONCLUSIONS

The importance of the healing response in the development of acute complications and adverse remodeling after myocardial infarction has been widely recognized. The extent of left ventricular dilation after myocardial infarction not

only depends on the size of the infarct but also is affected by the qualitative characteristics of the healing wound. Preservation and optimization of the extracellular matrix content of the infarct is likely to be as important as myocyte salvage in improving outcome after myocardial infarction. Studies using genetically targeted animals indicated that disruption of genes critically involved in infarct healing resulted in significant alterations in the time course and extent of left ventricular remodeling. Although experimental studies have suggested potential molecular targets for intervention, a word of caution should be raised regarding the clinical application of specific therapeutic strategies in patients with acute myocardial infarction.

Infarct healing is closely intertwined with an inflammatory cascade triggered by hypoxia and cardiomyocyte death (284). In the past 20 years, a vast body of evidence showed dramatic reduction in infarct size with the use of specific antiinflammatory strategies. However, attempts to mitigate inflammatory injury in clinical practice have been in general unsuccessful. The catastrophic experience of the methylprednisolone trial (289) emphasized the need for a better understanding of the cellular and molecular events associated with the inflammatory response to achieve effective suppression of injurious processes without interfering with healing and cardiac repair. Recently, the disappointing results of the anti-CD18 trials led to criticism regarding the usefulness of strategies targeting the inflammatory cascade in myocardial infarction. It has been suggested that these failures may represent the inherent risk of using animal models, which may have fundamental differences from the human disease process. Although species-specific effects may be significant in some cases, the most important lesson we have learned from studying experimental myocardial infarction is that a sound understanding of the biology is necessary before a specific intervention is pursued on a therapeutic basis.

The inflammatory cascade is based on a complex network of molecular steps mediated by molecules with pleiotropic effects, dictated by critical cellular, spatial, and temporal variables. Typical properties of cytokines in networks are redundancy, pleiotropy, synergistic activity, and antagonistic effects on each other. Thus, cytokines and other inflammatory mediators, which may appear reasonable therapeutic targets considering their injurious role in the early stages of the inflammatory response, may also be necessary as regulators of cardiac repair. For example, TNF-α and IL-6 may play a role in the initial inflammatory injury associated with myocardial ischemia (88, 229); however, they may also represent important regulators of myocyte apoptosis and cardiac repair (111, 190). Interventions that result in impaired healing may enhance adverse remodeling by changing the qualitative characteristics of the scar.

In addition, the timing and localization of the intervention is as important as the choice of the therapeutic target. Effective healing is dependent on a well-orchestrated cellular response and on timely induction and suppression of specific mediators in a locally restricted manner. Thus, interventions targeting inflammatory mediators should take into account both topographic and temporal parameters. An approach that may have favorable effects if locally applied in the center of the infarct may result in deleterious changes in the border zone or the noninfarcted remodeling myocardium. For example, a strategy that decreases the collagen content in the infarcted heart may attenuate interstitial fibrosis in the noninfarcted areas but may also result in enhanced remodeling by suppressing collagen deposition in the center of the infarct, leading to decreased tensile strength and subsequent left ventricular dilation.

Furthermore, certain subgroups of high-risk patients (such as the elderly and diabetics) may exhibit healing defects, resulting from alterations in specific molecular steps. Evidence suggests that in senescent animals, wound neutrophils and macrophages exhibit decreased activity and function (346), and fibroblasts show impaired migratory capacity and blunted responsiveness to growth factors and fibrogenic substances (243, 325). In addition, diabetes is associated with enhanced ischemic injury and delayed repair, in part due to an attenuated and defective inflammatory response (81, 123). Obesity also enhances adverse remodeling after myocardial infarction in experimental animal models, decreasing collagen deposition in the healing scar (355). Impaired healing may be responsible for adverse outcome in these high-risk groups. Identification of specific molecular defects may suggest treatment strategies aimed at optimizing infarct healing in the most vulnerable patients. In addition, some evidence suggests multilevel gender differences in postinfarction remodeling. Women exhibit decreased hypertrophic remodeling after myocardial infarction, presumably related to fundamental differences in cellular responses rather than simply to differences in infarct size or expansion (52). In addition, experimental studies suggested that female rats show a different pattern of ventricular remodeling than do males, with a smaller increase in thickness of the noninfarcted portions of the left ventricle, but comparable cavity enlargement and systolic dysfunction (217). Mechanistic studies are needed to dissect the role played by gender in modulating infarct healing and ventricular remodeling.

Both animal model investigations and *in vitro* studies are continuously enhancing our understanding of the mechanistic basis of infarct healing. Optimal repair requires mechanisms suppressing inflammatory mediator synthesis and limiting the inflammatory infiltrate into the infarcted area, preventing extension of granulation tissue formation in the viable myocardium. Timely resolution of inflammation and containment of the infiltrate in the infarcted area is crucial for formation of an effective scar. Interventions that supplement these inherent protective mechanisms are likely to result in significant attenuation of left ventricular remodeling.

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ABBREVIATIONS

α-SMA, α-smooth muscle actin; ACE, angiotensin-converting enzyme; Ang, angiopoietin; AT-1, angiotensin II

receptor type 1; bFGF, basic fibroblast growth factor; BSF-3, B-cell stimulating factor-3; CNTF, ciliary neurotrophic factor; CT-1, cardiotrophin-1; ENA-78, epithelial neutrophil-activating peptide; G-CSF, granulocyte–colony-stimulating factor; GM-CSF, granulocyte macrophage–colony-stimulating factor; Gp130, glycoprotein 130; GRO, growth-related oncogene; HIF-1α, hypoxia-inducible factor-1α; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; IP-10, interferon-γ–inducible protein-10; JAM-A, junctional adhesion molecule-A; LAP, latency activated peptide; LIF, leukemia inhibitory factor; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; M-CSF, macrophage–colony-stimulating factor; MIG, monokine induced by γ-interferon; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; MnSOD, manganese superoxide dismutase; MT-MMP, membrane-type matrix metalloproteinase; NF-κB, nuclear factor-κB; NNT-1, neurotrophin-1; OPN, osteopontin; PAI-1, plasminogen activator inhibitor-1; PDGF, platelet-derived growth factor; PF4, platelet factor-4; PKC, protein kinase C; PSGL-1, P-selectin glycoprotein ligand-1; RANTES, regulated on activation normal T-cell expressed and secreted; ROS, reactive oxygen species; SCF, stem cell factor; sCR1, soluble complement receptor-1; SDF-1, stromal cell derived factor-1; SOD, superoxide dismutase; SPARC, secreted protein acidic and rich in cysteine; TGF-β, transforming growth factor-β; TIMP, tissue inhibitor of metalloproteinases; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α; TNFR, tumor necrosis factor receptor; tPA, tissue plasminogen activator; TSP-1, thrombospondin-1; uPA, urokinase plasminogen activator; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

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