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THERAPEUTIC TARGETS FOR MYOCARDIAL INFARCTION

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ABSTRACT

Myocardial infarction is characterized by necrosis of the cardiac muscle occurring in a clinical setting consistent with prolonged myocardial ischemia, and usually develops in patients with coronary artery disease. Successful treatment of myocardial infarction requires rapid diagnosis and minimal time to initiation of medical treatment. The immediate therapeutic goal in myocardial infarction is to establish the patency of the infarct-related artery, and this can be accomplished with pharmacotherapy or percutaneous coronary intervention (PCI). To date, thrombolytics, antithrombotics, antiplatelet agents, β-adrenoceptor antagonists, renin–angiotensin system blockers and statins are used in the prevention and treatment of myocardial infarction. However, the search continues for more effective treatment strategies for myocardial infarction and investigators are focusing on identifying novel targets for therapeutic intervention. This article presents those drug targets that are currently under active investigation for the treatment and prevention of myocardial infarction.

INTRODUCTION

Myocardial infarction is defined as necrosis of the cardiac muscle occurring in a clinical setting consistent with prolonged myocardial ischemia. Also known as heart attack, myocardial infarction typically develops in patients with coronary artery disease (CAD), a condition that develops when the blood vessels leading to the heart become narrowed or completely blocked due to atherosclerosis. There are two major categories of CAD: stable and unstable. Unstable CAD encompasses patients with acute coronary syndrome (unstable angina, non-S-T segment elevation myocardial infarction and S-T segment elevation myocardial infarction), whereas stable CAD typically presents as stable angina. Whether caused by plaque rupture or thrombus, myocardial infarction and subsequent reperfusion have profound consequences on the heart. The cascade of events occurring in the wake of reperfusion begins with the generation of reactive oxygen species (ROS) in the ischemic myocardium, which in turn stimulates signal transduction and the production of proinflammatory cytokines. Both ROS and cytokines affect cell survival and cell death and exert cardiodepressant effects. The end result of this cascade of events is left ventricular remodeling, which is a significant source of morbidity and mortality in patients who overcome the acute stage of myocardial infarction (1-3).

The symptoms of a heart attack are varied, but the most frequent sensations are: prolonged (more than 30 min) thoracic pain experienced as pressure or crushing pain in the chest, and sometimes accompanied by sweating, nausea or vomiting; pain extending into the left arm, left shoulder or jaw; tightness in the chest, a sensation comparable to a bad case of heartburn; shortness of breath for more than a few seconds; dizziness; anxiety; or a sensation of imminent death. The American Heart Association estimates that during 2009, 1,255,000 Americans will have suffered a myocardial infarction, of which approximately 785,000 will be first attacks and 470,000 recurrent attacks. In addition, some 195,000 silent attacks (i.e., initially unnoticed but discovered days or months later during a routine examination) are predicted to occur each year (1, 4).

Time from symptom onset to emergency room presentation and time to initiation of medical treatment are both crucial factors for determining treatment success in myocardial infarction. The immediate therapeutic goal is to establish the patency of the infarct-related artery. This can be achieved by pharmacotherapy or percutaneous coronary intervention (PCI). The major classes of drugs discovered and implemented to date for the treatment of myocardial infarction include thrombolytics, antithrombotics, antiplatelet agents, β-adrenoceptor antagonists, renin–angiotensin system blockers and statins (1, 2, 5-7).

In patients presenting with persistent S-T segment elevation myocardial infarction (STEMI), who represent approximately one-third of all acute coronary events, the need for rapid response and initiation of therapy is crucial. Primary PCI with balloon angioplasty and stent is the preferred treatment, if available within 2 h of first medical contact. If PCI is not performed within 2 h, pre- or in-hospital thrombolysis should be executed as soon as possible, and within 30 min at most. Prolonged myocardial ischemia, however, often breaks down the coronary microvasculature, and the flow to the infarcted myocardium may be markedly reduced (i.e., the no-reflow phenomenon). Patients experiencing this phenomenon have poor functional and clinical outcomes and this phenomenon not only cor-

relates with infarct size but also provides additional prognostic information, and thus can predict high-risk patients. As a result, the focus of reperfusion therapy has shifted toward the improvement of myocardial perfusion, which could promote the functional recovery of viable muscle and reduce infarct expansion, which is associated with favorable clinical outcomes. Relief or reduction of pain is also an essential aspect of the treatment. In the absence of contraindications, the analgesic of choice is intravenous morphine, which also reduces patient anxiety and myocardial oxygen consumption via a series of beneficial hemodynamic effects. In addition to analgesics, pain relief may be facilitated by the administration of nitrates or β-blockers, which reduce ischemia. In patients without significant hypotension, nitrates are first administered by the sublingual route and followed by intravenous nitroglycerin. If there are no further signs of ischemia, nitroglycerin is slowly withdrawn after 24 h (1, 5-7).

The search for effective treatment strategies for myocardial infarction continues, with research focusing on the identification of novel targets for drug development. Those targets which are currently under active investigation are discussed below (see Figure 1). Table I provides a selection of products under active development for each target and Table II includes selected patents.

TARGETS

β-Adrenoceptor

β-Adrenoceptors are G protein-coupled receptors (GPCRs) present in effector tissues that bind endogenous catecholamines such as norepinephrine and epinephrine. Three isoforms have been observed. While β_1- and β_2-adrenoceptors are widely distributed, β_3-adrenoceptors are predominantly distributed in adipocytes. All three isoforms are coupled to G_s proteins (the β_2-adrenoceptor is also cou-

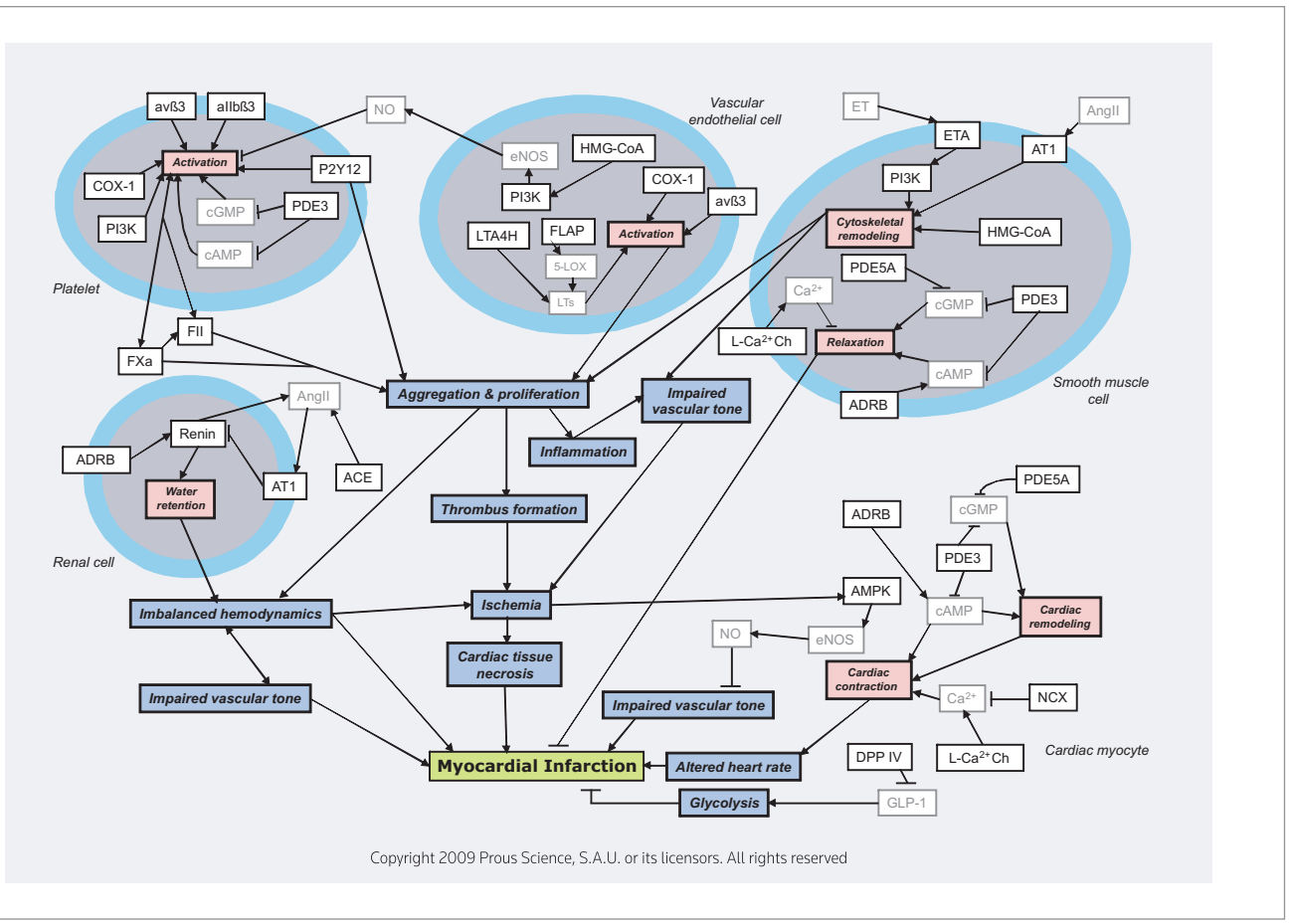

Figure 1. Myocardial infarction targetscape. A diagram showing an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of myocardial infarction and their biological actions. Arrow: positive effect; dash: negative effect. Gray or lighter symbols are targets that are not validated (i.e., targets not associated with a product that is currently under active development for myocardial infarction). Abbreviations: avβ3: integrin $\alpha_v\beta_3$ (vitronectin) receptor; aIIbβ3: integrin $\alpha_{IIb}\beta_3$ (fibrinogen gpIIb/IIIa) receptor; AMPK: AMP-activated protein kinase; AngII: angiotensin II; ACE: angiotensin-converting enzyme; ADRB: β-adrenoceptor; cAMP: adenosine 3',5'-cyclic monophosphate; cGMP: guanosine 3',5'-cyclic monophosphate; COX-1: cyclooxygenase 1; DPP IV: dipeptidyl peptidase 4; eNOS: endothelial nitric oxide synthase; ET: endothelin; ETA: endothelin ET_A receptor; FII: coagulation factor II (thrombin); FXa: coagulation factor Xa; FLAP: 5-lipoxygenase-activating protein; GLP-1: glucagon-like peptide 1; HMG-CoA: hydroxymethylglutaryl-CoA reductase; 5-LOX: 5-lipoxygenase; L-Ca^{2+} Ch: L-type calcium channel; LTA4H: leukotriene A-4 hydrolase; LTs: leukotrienes; NCX: Na^+/Ca^{2+} exchanger; NO: nitric oxide; PDE3: phosphodiesterase 3; PDE5A: phosphodiesterase 5A; PI3K: phosphatidylinositol 3-kinase.

Table I. *Selected targets and products launched or being actively investigated for myocardial infarction (from Prous Science Integrity®).*

Target	Product	Source	Phase
β-Adrenoceptor (nonspecified subtype)	Propranolol hydrochloride Timolol maleate	AstraZeneca Merck Sharp & Dohme	L-1967 L-1976
β_1-Adrenoceptor	Atenolol Metoprolol tartrate Metoprolol succinate	AstraZeneca AstraZeneca/Novartis AstraZeneca	L-1975 L-1978 L-1992
AMP-activated protein kinase (AMPK)	Acadesine	Schering-Plough	III
Angiotensin AT_1 receptor	Valsartan	Novartis	L-2004
Angiotensin-converting enzyme (ACE; isoform A)	Lisinopril Ramipril	Merck & Co. King Pharmaceuticals	L-1987 L-2000
Calcium channel (nonspecified)	Verapamil	Abbot/Eisai	Launched
Coagulation factor II (FII)	Lepirudin	sanofi-aventis	L-2000
Coagulation factor Xa (FXa)	Enoxaparin sodium Rivaroxaban	sanofi-aventis Bayer	L-1993 III
Cyclooxygenase 1 (COX-1)	Acetylsalicylic acid	Bayer	L-1993
Dipeptidyl peptidase 4 (DPP IV)	Sitagliptin phosphate monohydrate	Ludwig-Maximilians-University München	II/III
Endothelin ET_A receptor	BQ-123 Darusentan	Medizinische Universitaet Wien Gilead	II III
HMG-CoA reductase	EN-100	Palmetto Pharmaceuticals	Preclinical
Integrin $\alpha_{IIb}\beta_3$ (fibrinogen gpIIb/IIIa) receptor	MN-447 Eptifibatide	Medicinova GlaxoSmithKline	Preclinical L-1999
Integrin $\alpha_v\beta_3$ (vitronectin) receptor	MN-447	Medicinova	Preclinical
Leukotriene A-4 hydrolase	DG-051	deCODE Genetics	II
5-Lipoxygenase-activating protein (FLAP)	Veliflapon	deCODE Genetics	III
Na^+/Ca^{2+}-exchange protein (NCX)	Caldaret hydrate	Mitsubishi Tanabe Pharma	II
$P2Y_{12}$ receptor	Clopidogrel hydrogensulfate	Bristol Myers Squibb/sanofi-aventis	L-2006
Phosphatidylinositol 3-kinase (PI3K)	TG-100115	TargeGen	I/II
Phosphodiesterase PDE3	Dipyridamole	Boehringer Ingelheim	L-1969
Phosphodiesterase PDE5A	Dipyridamole	Boehringer Ingelheim	L-1969
Renin	Aliskiren fumarate	Novartis	III

pled to G_i). Binding to β-adrenoceptors in cardiac myocytes activates adenylate cyclase, which generates adenosine 3′,5′-cyclic monophosphate (cAMP). cAMP in turn activates protein kinase A (PKA), which phosphorylates the ryanodine receptor (RYR) on the sarcoplasmic reticulum. Phosphorylation of RYR initiates the dissociation of FKBP1B and phospholamban, which modulate the activity of the Ca^{2+}-ATPase SERCA. β-Adrenoceptor kinase (β-ARK; EC 2.7.11.15) is also activated upon binding, which phosphorylates the cytoplasmic tail of the receptor, thus decreasing receptor signaling (negative feedback loop). Stimulation of the β-adrenoceptor has numerous cardiovascular effects, including increasing cardiac output, heart rate, atrial and ventricular myocyte contractility and atrioventricular node conduction; receptor binding also causes renin release from juxtaglomerular cells. While cAMP enhances cardiac myocyte contraction, increases in cAMP in vascular smooth muscle lead to smooth muscle relaxation, where the second messenger inhibits myosin light chain kinase (MLCK), which is responsible for phosphorylating smooth muscle myosin. The first generation of β-blockers were nonselective, antagonizing β_1- and β_2-adrenoceptors. Second-generation β-blockers are more cardioselective and relatively selective for β_1-adrenoceptors, although selectivity can be lost at higher doses. Third-generation β-blockers also exert vasodilating activity via antagonism of vascular β-adrenoceptors. β-Blockers have been shown to reduce the risk of cardiovascular mortality in patients with definite or suspected acute myocardial infarction and who are hemodynamically stable. Targeting the β-adrenoceptor results in cardiodepressant and hypotensive effects, which would be beneficial in the treatment of myocardial infarction. These agents

Table II. *Selected patents for targets being pursued or explored for myocardial infarction (from Prous Science Integrity®).*

Target	Patent	Source	Phase
Angiotensin AT_2 receptor	WO 1991009847	Kaken Pharmaceutical	Biological testing
	WO 2002096883	Vicore Pharma	Biological testing/Preclinical
	WO 2006109048	Vicore Pharma	Preclinical
Integrin $\alpha_{IIb}\beta_3$ (fibrinogen gpIIb/IIIa) receptor	WO 1997001540	GlaxoSmithKline	Biological testing
	WO 1999052872	Meiji Seika Kaisha	Biological testing/Preclinical
	WO 2001054726	Meiji Seika Kaisha	Preclinical
	WO 2003059883	Meiji Seika Kaisha	Biological testing/Preclinical
Integrin $\alpha_v\beta_3$ (vitronectin) receptor	WO 1997001540	GlaxoSmithKline	Biological testing
	WO 1999052872	Meiji Seika Kaisha	Biological testing/Preclinical
	WO 2000061551	Abbott	Biological testing
	WO 2001054726	Meiji Seika Kaisha	Preclinical
	WO 2001096365	Merck Patent	Biological testing
	WO 2002016328	Merck Patent	Biological testing
	WO 2002050039	Merck Patent	Biological testing
	WO 2002051810	Abbott	Biological testing
	WO 2002068410	Abbott	Biological testing
	WO 2003059883	Meiji Seika Kaisha	Biological testing/Preclinical
Renin	EP 1908471	Speedel Experimenta	Biological testing
	EP 1908762	Speedel Experimenta	Biological testing
	EP 1908763	Speedel Experimenta	Biological testing
	EP 1911762	Speedel Experimenta	Biological testing
	WO 2005070870	Speedel Experimenta	Biological testing
	WO 2005070871	Speedel Experimenta	Biological testing
	WO 2007031557	Speedel Experimenta	Biological testing
	WO 2007082907	Speedel Experimenta	Biological testing
	WO 2008107365	Medivir	Biological testing
	WO 2009056617	Speedel Experimenta	Biological testing
	WO 2009071606	Speedel Experimenta	Biological testing

could reduce heart rate, contractility and arterial pressure, thus attenuating work and the oxygen demand of the heart. This improvement in the oxygen supply/demand ratio would decrease the incidence of arrhythmias and inhibit subsequent cardiac remodeling (8-11).

AMP-activated protein kinase (AMPK)

AMPK is a metabolite-sensing heterotrimeric enzyme complex composed of α, β and γ subunits which is activated by AMP. The α subunit contains a typical serine/threonine kinase domain and a carboxy-terminal regulatory domain. The β subunit acts as a scaffold for binding the other two subunits and contains a glycogen-binding domain. The γ subunit contains four cystathionine-β-synthase (CBS) domains that play a role in binding AMP and ATP, the allosteric effectors of the kinase. AMPK is involved in the regulation of intracellular energy and is activated following myocardial ischemia. It is thought that activation of AMPK may be an endogenous cardioprotective signaling mechanism. Increased activation of AMPK increases ATP synthesis and decreases ATP utilization, thus maintaining normal cellular energy stores during ischemia. Activated AMPK stimulates fatty acid oxidation, glucose transport and glycolysis, and increases phosphorylation and the activity of endothelial nitric oxide synthase (eNOS; expressed in cardiac myocytes); activation of AMPK also inhibits triglyceride and protein synthesis. eNOS is activated in both atrial and ventricular myocytes and chronic activation of AMPK also phosphorylates transcription factors, altering gene expression and modulating muscle mitochondrial biogenesis. Chronic activation of AMPK increases phosphorylation of its downstream mediator eNOS and the consequent production of NO has been shown to improve vascular tone and therefore cardiac function and survival. Thus, AMPK improves myocardial glucose and lipid metabolism and prevents ventricular contractile dysfunction in the ischemic heart. Activation of AMPK could therefore play a possible role in vasodilatation of the cardiac cells, making it an important therapeutic target in myocardial infarction (12-15).

Angiotensin AT_1 receptor

The AT_1 receptor is part of the renin–angiotensin–aldosterone system (RAAS), which plays a crucial role in the pathophysiology of cardiovascular disease. AT_1 is a $G_{q/11}$ GPCR activated via binding of the vasoconstricting peptide angiotensin II (AngII). AngII and AT_1 mediate numerous effects, including vasoconstriction, aldosterone synthesis and secretion, cardiac contraction, vascular smooth muscle cell proliferation, decreased renal blood flow, renal renin inhibition, renal tubular sodium reuptake and cardiac contractility, among others. AT_1 is upregulated in congestive heart failure and increased expression of AT_1 receptors has been observed in patients with ischemic heart disease. Moreover, AT_1 signaling may be responsible for the generation of reperfusion arrhythmias following restoration

of blood flow to infarcted myocardium. Blockade of the AT_1 receptor could be a therapeutic strategy for myocardial infarction through attenuation of vasoconstriction. AT_1 blockers have been demonstrated to have benefit in the management of heart failure and exert activity similar to angiotensin-converting enzyme (ACE) inhibitors in patients with left ventricular dysfunction after a myocardial infarction (8, 16-20).

Angiotensin-converting enzyme (ACE)

ACE (EC 3.4.15.1) is an enzyme that cleaves the biologically inactive decapeptide angiotensin I (AngI) to the active AngII. High levels of ACE (normal values = 18-67 U/mL for individuals over age 20) are seen in many disorders (e.g., sarcoidosis, diabetes, Hodgkin's disease, hyperthyroidism, amyloidosis, idiopathic pulmonary fibrosis, pulmonary embolism, scleroderma, tuberculosis, Gaucher's disease, leprosy). Studies have demonstrated that inhibition of ACE attenuates the pathological effects of the RAAS such that acute myocardial infarction can be prevented, morbidity and mortality in congestive heart failure are decreased and renal dysfunction is attenuated. Moreover, ACE inhibitors have been shown to reduce cardiovascular events such as myocardial infarction in patients at high risk (8, 9, 16, 17, 20).

Coagulation factors II and Xa (FII or thrombin; FXa)

Thrombin (EC 3.4.21.5), also known as prothrombin or coagulation factor II (FII), is a member of the peptidase family S1 (trypsin family), which is cleaved to form thrombin in the first step of the coagulation cascade. It in turn cleaves Arg–Gly bonds in fibrinogen and maintains vascular integrity. Factor Xa (FXa; EC 3.4.21.6), also known as prothrombinase, is a vitamin K-dependent coagulation factor that is a member of the peptidase family S1. It is involved in the conversion of prothrombin to thrombin. Thrombin is activated by FXa-mediated enzymatic cleavage of two sites on prothrombin by activated FXa. FXa activity is enhanced by binding to activated FV (FVa), thus creating the prothrombinase complex. Non-S-T segment elevation myocardial infarction (NSTEMI) is usually initiated by disruption of vulnerable atherosclerotic plaque and consequent thrombosis, which causes various degrees of occlusion in coronary arteries. Plaque rupture exposes the lipid core, leading to platelet adhesion and aggregation, activation of the coagulation cascade and formation of FXa. Thrombin formation will cause fibrin deposition and platelet activation, which ultimately leads to formation of stable plaque. Cleavage of prothrombin to thrombin is achieved, promoting the formation of fibrin, which acts as a scaffold in stable thrombus. The thrombus may only incorporate into the plaque or it may cause subtotal or full artery occlusion, which manifests as myocardial infarction. Antithrombotic therapies, including anticoagulants and antiplatelet drugs (e.g., FXa and thrombin inhibitors), are used to avert progressive or recurrent thrombosis and may therefore be effective in the treatment of acute coronary syndrome and its clinical manifestation of myocardial infarction (21-25).

Cyclooxygenase 1 (COX-1)

The COX enzymes (also known as prostaglandin-endoperoxide synthase; EC 1.14.99.1), catalyze the two steps in prostaglandin (PG) synthesis, forming PG_2 and PGH_2 from arachidonic acid. They act both as a dioxygenase and as a peroxidase and are targets for nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., aspirin, indomethacin). The two major forms of the enzyme are COX-1 and COX-2. Recently, COX-3, a distinct COX-1 variant, and two smaller COX-1-derived proteins (partial COX-1, or PCOX-1 proteins) have been cloned and found to be expressed in canine cerebral cortex and in other tissues. Unlike COX-2 which is inducible, COX-1 is constitutive and present in endothelium, stomach and kidney. It is considered a housekeeper enzyme, maintaining homeostasis and participating in cell signaling. COX-1 has been shown to regulate angiogenesis in endothelial cells and is involved in maintenance of platelet and kidney function. PGs can both stimulate and antagonize atherothrombosis, and thus suppression of COX-1 products (particularly thromboxane A_2) may be effective in preventing myocardial infarction. In fact, COX-1 inhibition may be responsible for the cardioprotection observed with low-dose aspirin (26-28).

Dipeptidyl peptidase 4 (DPP IV)

DPP IV (EC 3.4.14.5) is an enzyme that removes *N*-terminal dipeptides from peptide hormones of the growth hormone-releasing factor (GRF) superfamily, including gastric inhibitory polypeptide (GIP), glucagon-like peptide 1 and 2 (GLP-1, GLP-2), glucagon, vasoactive intestinal polypeptide (VIP) and neuropeptide Y (NPY). DPP IV plays a catalytic role in the processes of signal transduction during immune responses, leading to type 2 diabetes. Inhibition of DPP IV is thought to improve glucose tolerance by rescuing intact versions of the incretins GLP-1 and GIP, or by preventing their degradation. In the presence of DPP IV inhibitors, GLP-1 is salvaged and has been shown to have an infarct-sparing effect. GLP-1 has been shown to protect the heart against low-flow ischemia by enhancing glycolysis via activation of AMPK and protein kinase B (PKB)/Akt. Thus, DDP IV inhibitors would rescue active GLP-1 and could therefore be beneficial in the treatment of myocardial infarction (29-31).

Endothelin ET_A receptor

The endothelin ET_A receptor is a GPCR with strong affinity for endothelin-1 (ET-1), a vasoactive peptide (21 amino acids) produced by endothelial and inflammatory cells in pulmonary and systemic circulations via the action of an endothelin-converting enzyme (ECE). Binding of ET-1 to ET_A receptors results in vasoconstriction and antagonism has been shown to reduce ischemic injury via reductions in vascular constriction and improvements in imbalance in the antioxidant status. Thus, ET_A blockade preserves myocardial perfusion response and coronary microvascular integrity during periods of increased myocardial demand. Antagonism of peripheral ET_A receptors also reduces detrusor overactivity. Thus, ET_A is a therapeutic target for the treatment of myocardial infarction (18, 32, 33).

Hydroxymethylglutaryl-CoA reductase (HMG-CoA reductase)

HMG-CoA reductase (EC 1.1.1.88) is a key enzyme that catalyzes the rate-limiting step in the biosynthetic pathway leading from mevalonate to cholesterol. Isoprenoids such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate play a role in protein prenylation, a crucial step in multiple cellular processes. Protein prenylation (i.e., farnesylation and geranylgeranylation) is a posttranslational modification of proteins involving the addition of isoprenoids. Geranylger-

anylation allows the activation of the small GTP-binding proteins Rho and Rac. Activated Rho regulates the activity of nuclear transcription factors such as nuclear factor NF-kappa-B (NF-κB), controls the actin cytoskeleton and induces stress fiber formation. This affects intracellular transport, migration, membrane trafficking, messenger RNA stability and gene transcription. Farnesylation allows the activation of Ras protein. Activated Ras stimulates cytoplasmic signaling pathways such as the mitogen-activated protein kinase (MAPK) pathway that regulates gene transcription and thus growth, proliferation, differentiation and survival of cells. Statins are inhibitors of HMG-CoA reductase and exert pleiotropic effects independent of cholesterol-lowering actions. These include effects on endothelial function, cell proliferation, inflammatory responses, immunological reactions, platelet function and lipid oxidation. Endothelial-derived NO is a major endogenous modulator of platelet function, such that reduced intravascular bioactivity of NO contributes to platelet activation, adhesion and thromboembolic events. Treatment with statins increases NO bioactivity by modulating ROS generation and/or increasing eNOS expression and activity. Thus, statins may be effective in the treatment of myocardial infarction (34-37).

Integrin $\alpha_v\beta_3$ (vitronectin) receptor

Integrin $\alpha_v\beta_3$ is a member of a large family of transmembrane receptors for extracellular matrix (ECM) and plasma proteins and is composed of two noncovalently linked subunits (α_v and β_3) that span the plasma membrane; it also contains the cell-binding sequence Arg–Gly–Asp (RGD). $\alpha_v\beta_3$ is expressed on osteoclasts, vascular smooth muscle cells and endothelial cells and it binds vitronectin, glycosaminoglycans, collagen, plasminogen, plasminogen activator inhibitor 1 (PAI-1), urokinase plasminogen activator surface receptor (uPAR), integrins, complement, heparin and thrombin–antithrombin III (TAT) complexes. Upon ligand binding, these subunits interact with the actin cytoskeleton and FAK complex through their cytoplasmic domains. The result is promotion of cell adhesion. Inhibition of this receptor would inhibit platelet aggregation and may therefore be effective in preventing thrombus formation and consequent myocardial infarction (38-40).

Integrin $\alpha_{IIb}\beta_3$ (fibrinogen gpIIb/IIIa) receptor

The fibrinogen gpIIb/IIIa receptor is an integrin receptor that binds fibrinogen, fibronectin, plasminogen, prothrombin, thrombospondin, von Willebrand factor and vitronectin. It is expressed on platelets, where it plays a crucial role in platelet function. Through formation of the receptor complex (i.e., calcium-dependent association of gpIIb and gpIIIa), stimulated platelets can bind fibrinogen and related adhesive proteins, which are fundamental to platelet aggregation, endothelial adherence and thrombus formation. Inhibition of this receptor constitutes an antiplatelet strategy that could be effective in preventing thrombus development and consequent myocardial infarction (38, 41-44).

Leukotriene A-4 hydrolase

Leukotriene A-4 hydrolase (EC 3.3.2.6) is a bifunctional zinc metalloenzyme that participates in arachidonic acid metabolism, specifically catalyzing the conversion of leukotriene A-4 (LTA-4) to LTB-4. Leukotriene A-4 hydrolase is a neutrophil chemoattractant and spasmogenic and exhibits anion-dependent aminopeptidase and epoxide hydrolase activities. LTB-4 has been shown to play a pathophysiological role in cardiovascular disease, and because leukotriene A-4 hydrolase is involved in the synthesis of this proinflammatory leukotriene, there may be a link between myocardial infarction and inflammation. Studies have shown that variants of the *LTA4H* gene are associated with a risk of myocardial infarction, possibly due to upregulation of the leukotriene pathway. Inhibition of leukotriene A-4 hydrolase could therefore be an effective therapy for preventing myocardial infarction (45-47).

5-Lipoxygenase-activating protein (FLAP)

FLAP is an enzyme required for leukotriene biosynthesis via 5-lipoxygenase (5-LOX). FLAP appears to anchor 5-LOX to the membrane and bind arachidonic acid, possibly playing an important role in the transfer of arachidonic acid to 5-LOX. Genetic variations in the gene for FLAP (*ALOX5AP*) may confer susceptibility to myocardial infarction. Inhibition of FLAP could downregulate leukotriene synthesis and may therefore be an effective therapy for preventing myocardial infarction (45, 48).

L-type calcium channel

The L-type calcium channel is a large transmembrane ion channel with selective permeability for calcium ions. These channels are essential for intracellular signal transduction and are structurally related to T-type calcium channels, exhibit sustained conductance, are slowly inactivating and are regulated by cAMP-dependent protein kinase (e.g., phosphorylation enhances the probability of channel opening). They are found on skeletal, cardiac and smooth muscle cells and within the nervous system, where they are expressed on neurons and neuroendocrine cells. In the cardiovascular system they are responsible for the plateau phase (i.e., slow inward current) of the action potential and they may trigger the release of internal Ca^{2+}. Blockade of the L-type calcium channel inhibits the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle. Studies have shown that calcium channel blockers interfere with the slow inward current in excitable tissues without changing the configuration of the action potential. By decreasing the influx of calcium through the L-type calcium channel, the effective refractory period within the atrial ventricular (AV) node and AV conduction are slowed. Relaxation of vascular smooth muscle (i.e., dilatation of coronary arteries) would decrease peripheral vascular resistance and increase coronary blood flow in ischemic tissue; myocardial energy consumption and oxygen requirements would be reduced. Thus, the L-type calcium channel is an effective target for the treatment of myocardial infarction (10, 49, 50).

Na^+/Ca^{2+}-exchange protein (NCX)

NCX is an antiporter membrane protein that removes Ca^{2+} from cells. It is expressed in the plasma membrane, mitochondria and endoplasmic reticulum of excitable cells. The NCX in the cardiac myocyte is the primary pathway for Ca^{2+} efflux and therefore regulates the excitation–contraction coupling process in the heart. Increased expression of NCX results in a reduction in Ca^{2+} release, and thus impaired contractility and an increased risk of arrhythmias

during the development of cardiac hypertrophy and failure. Studies have demonstrated that NCX is also involved in the arrhythmias and cellular injury associated with ischemia and reperfusion. Hence, NCX blockade represents a potential therapeutic strategy for treating cardiac diseases like ischemia and reperfusion, the outcome of which could be myocardial infarction (51-53).

$P2Y_{12}$ receptor

The $P2Y_{12}$ receptor is a GPCR purinergic chemoreceptor for adenosine diphosphate (ADP) that is expressed on the surface of platelets. It is involved in the regulation of platelet aggregation and clotting. Inhibition of this receptor could be effective in inhibiting platelet activation and/or aggregation, and may therefore be an effective treatment for atherothrombotic diseases and consequent myocardial infarction (54-56).

Phosphatidylinositol 3-kinase (PI3K)

PI3K is a family of related enzymes (including class I, II and III PI3Ks) that are capable of phosphorylating the 3-position hydroxyl group of the inositol ring of phosphatidylinositol, producing phosphatidylinositol 3-phosphate (PIP_3). The enzymes are involved in cell growth, survival and motility. Class I enzymes are heterodimeric molecules composed of regulatory (e.g., p85α, p55α, p50α, p85β and p55γ) and catalytic (p110α, β or σ) subunits. Class II enzymes include three catalytic isoforms (C2α, C2β and C2γ), but no regulatory proteins. Class III enzymes (like those of class I) are heterodimeric and composed of a catalytic (Vps34) and a regulatory (p150) subunit. Class III enzymes appear to be mainly involved in trafficking of proteins and vesicles and may mediate immune responses. Class I enzymes are thought to drive cancer progression following loss of PTEN and with mutations in the p110α catalytic isoform. Moreover, PI3Ks exert cardioprotective effects and have been shown to play a major role in platelet adhesion, which is essential for thrombus formation. Platelets express all type I PI3K isoforms, including p110α, p110β, p110δ and p110γ. Studies indicate that p110γ and p110β are crucial in regulating distinct phases of the platelet activation process. Inhibition of these isoforms results in defects in arterial thrombosis formation. Thus, inhibition of PI3K may be an effective antithrombotic and cardioprotective approach for the treatment of myocardial infarction (35, 57-59).

Phosphodiesterase PDE3

PDE3 (EC 3.1.4.17) is a 3',5'-cyclic phosphodiesterase also known as cGMP-inhibited 3',5'-cyclic phosphodiesterase that catalyzes the hydrolysis of the cyclic nucleotides cAMP and cGMP to their corresponding nucleoside 5'-monophosphates. Both PDE3 isoforms (PDE3A, PDE3B) are expressed in vascular smooth muscle cells and modulate contraction. The isoforms are also involved in regulating cardiac muscle contractility and platelet aggregation. Hypoxia and high cAMP levels alter the expression of both isoforms. High levels of intracellular cAMP in smooth and cardiac muscle cause relaxation and contraction, respectively. Thus, inhibition of PDE3 in order to maintain cAMP levels may be beneficial in the treatment of myocardial infarction. In addition, inhibition of PDE3 blocks platelet aggregation and may therefore also be effective in the treatment and prevention of myocardial infarction (60-63).

Phosphodiesterase PDE5A

PDE5A (EC 3.1.4.35) is a phosphodiesterase isoenzyme also known as cGMP-specific 3',5'-cyclic phosphodiesterase that has a relatively high affinity for cGMP and hydrolyzes cAMP poorly. The enzyme is expressed in many cell types, including vascular smooth muscle cells in the walls of systemic arteries and veins. cGMP relaxes vascular smooth muscle cells and increases vasodilatation. Thus, inhibitors of PDE5 would attenuate the degradation of cGMP and enable increases in smooth muscle relaxation and vasodilatation. Studies using experimental models of myocardial infarction have demonstrated that inhibition of PDE5 results in cardioprotection by substantially reducing ischemic cell death. Other studies have demonstrated that several PDE5-dependent cellular mechanisms in the myocardium may be involved in the pathophysiology of myocardial infarction, heart failure and cardiac dysfunction. Thus, inhibition of PDE5 may be effective in the treatment of myocardial infarction (64-66).

Renin

Renin (EC 3.4.23.15) is an enzyme that is part of the RAAS. It is synthesized as an inactive protein in the kidney and released into the blood in the active form in response to various metabolic stimuli, where it catalyzes the cleavage of the leucine–leucine bond in angiotensinogen, a 60-kDa α-2 globulin produced by the liver. This cleavage occurring in plasma generates the biologically inactive decapeptide hormone AngI, which in turn is cleaved in the plasma by ACE, yielding the biologically active AngII. Active AngII is an octapeptide that can bind to the two angiotensin receptor subtypes (AT_1 and AT_2). The major physiological effects of angiotensin II are mediated via the AT_1 receptor and these include marked vasoconstriction and stimulation of adrenal aldosterone release and renal absorption of sodium, which all lead to increases in blood pressure. Conventional therapies targeting RAAS (e.g., ACE inhibitors, angiotensin receptor blockers [ARBs]) provide incomplete RAAS suppression due to other indirect synthetic pathways or compensatory feedback mechanisms, eventually resulting in increased plasma renin activity. Direct inhibition of renin, which interferes with the first and rate-limiting step in the RAAS cascade (i.e., interaction of renin with its substrate angiotensinogen), would lower activity levels of the enzyme in the bloodstream, thereby reducing plasma renin activity and optimizing suppression of RAAS. Inhibition of renin would render the RAAS quiescent while avoiding the reactive renin rise and subsequent increases in the angiotensin peptides seen with ACE inhibitors and ARBs. Renin inhibitors could therefore be effective in preventing myocardial infarction (9, 17, 19).

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