ISSN 0006-2979, Biochemistry (Moscow), 2007, Vol. 72, No. 6, pp. 595-607. © Pleiades Publishing, Ltd., 2007.
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REVIEW

Biochemical Aspects of Inflammation

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Received December 21, 2006
Revision received February 5, 2007

Abstract—This review considers biochemical aspects of inflammation. The international literature until December 2006 has been analyzed, with the principal attention paid to the most dynamic problems: enzymology of inflammation, its regulation by hormones and signal transducers, and negative feedbacks, which underlie intensive current studies on pathogenesis, diagnostics, and therapy of inflammation. Such achievements as discoveries of defensins, toll-like receptors, interconnections of inflammation and iron metabolism, the roles of oxidative stress and antioxidant defense, lipoxins, inflammatory components of "non-inflammatory" diseases, and action mechanisms of effective drugs are discussed.

DOI: 10.1134/S0006297907060028

Key words: inflammation, enzymes, cytokines, hormones, immune response

Inflammation is a defense reaction of the body to penetration of an infectious agent, entrance of antigen, or cell damage. Inflammation is a fundamental biological process and the most frequent sign of disease. The most significant discoveries have led to Nobel Prizes—the roles of cellular and humoral mechanisms (1908), therapeutic use of glucocorticoids (1950), and detection of eicosanoids (1982) and cytokines. The morphology and pathophysiology of inflammation have been investigated for a long time, while studies of biochemical aspects have lagged because of insufficient attention to regulatory and enzymatic mechanisms. But recently biochemistry has revolutionized the science of inflammation, and it continues to make great contributions to its progress. The purpose of this work is to consider the complex of biochemical mechanisms of inflammation based on analysis of the literature of the last five years. This seems to be especially important because involvement of inflammatory reactions has been proved in pathogenesis of various widely distributed diseases (atherosclerosis, myocardial infarction, chronic heart failure, Alzheimer's disease, Parkinson's disease, asthma, diabetes mellitus, osteoporosis, angiotensin II-derived hypertension, etc.) [1-4]. I do not describe the well-known stages of inflammation (alteration, exudation, and proliferation) to concentrate on the biochemical approaches and processes.

BIOCHEMICAL FUNDAMENTALS OF PATHOGENESIS

Inflammation is the major reaction of the natural (congenital) immunity. Already on penetration into the body, microbes meet the first line of defense presented by antimicrobial peptides (mammalian antibiotics) of a family of defensins produced by the epithelial cells of respiratory pathways and the gastrointestinal tract and by neutrophils. Defensins kill gram-positive and gram-negative bacteria, fungi, and some viruses, modulate inflammatory responses, stimulate adaptive immunity, and are involved in tissue repair [5-7].

Inflammation is often induced by products of bacterial degradation (lipopeptides, lipopolysaccharides, peptidoglycans, formylmethionyl peptides, flagellin, microbial DNA), fungi (zymosans), viruses (double-stranded RNA), i.e., of various microorganisms, as well as of the body's own cells upon their damage and death. Degradation products of invasive agents are detected and specifically recognized by a subfamily of 11 specific toll-

Abbreviations: EGF) epidermal growth factor; FGF) fibroblast growth factor; IL) interleukins; NSAIDs) nonsteroidal antiinflammatory drugs; PAF) platelet-activating factor; PDGF) platelet-derived growth factor; PG) prostaglandins; PK) protein kinases; TF) transcriptional factor; TGF) transforming growth factor; Th) T-helpers; TK) tyrosine kinases; TNF) tumor necrosis factor; VEGF) vascular endothelial growth factor.

like receptors (TLRs) located on the plasma membrane and related to interleukin-1 and interleukin-18 (IL-1, IL-18) receptors of the same family. Some TLRs react to tissue damage and chaperons. TLRs are found in insects and plants; obviously, appearance of multicellular organisms was impossible without mechanisms of defense against invasion [8-10]. Thus, instead of unidentified "degradation products" with an unknown mechanism of action, specific processes have been revealed that are mediated by specific molecules. TLRs trigger some nonreceptor protein kinases: IL-1 receptor-associated kinase (IRAK), and then a system of NF-κB and/or protein kinases (PK) from the complex of mitogen-activated PK (MAPK), especially stress-activated PK (SAPK), p38 MAPK, and Jun N-terminal kinase (JNK). They phosphorylate and activate protein transcriptional factors (TF): the inflammatory factor NF-κB and the activation protein (AP-1) consisting of the Fos and Jun proteins. Transcriptional factors transmit signals to inflammation genes. Expression of these genes determines the set of proteins involved in inflammatory reactions [9-14].

Regulatory proteins, peptides, and enzymes expressed as a result of activation of inflammatory genes are especially important. A special role in the initiation and regulation of inflammation is played by regulatory proteins, in particular, tissue protein hormone cytokines, which are growth factors of inflammatory and immune cells and their proliferation and differentiation (more than 60 cytokines are now known). Cytokines involve and control almost all regulatory and effector substances and inflammatory reactions mediated by them. Most often, the action of cytokines is para- and/or autocrine, but they also circulate in blood plasma: normally, they are represented by the transforming growth factor β (TGF-β) and macrophage colony-stimulating factor (M-CSF), and in inflammation they also include tumor necrosis factor α (TNF-α), IL-1, IL-6, and M-CSF [15, 16].

Similarly to glucocorticoids, cytokines are not accumulated in reserve, but are rapidly synthesized when needed. It is often spoken about a net of cytokines, because their functions are overlapping: different cytokines can give the same or opposite effects and every cytokine is pleiotropic (this is not a unique feature of cytokines; many, if not all hormones are pleiotropic [14]). The largest family of cytokines, which includes 50 members (26 interleukins (IL 2-7, 9-17, 19-29), eight interferons, hematopoietins, etc.), is called the hematopoietin family [10, 17], but the term is not good because the majority of the members of this family perform other functions. Pathologists ascribe to cytokines many or all cell growth factors, and some pathologists – even the known circulating hormones (somatotropin, prolactin, leptin, angiotensin II). Similarly to all hormones (and wider regulators), cytokines act through receptors, which in this case are coupled with nonreceptor (intracellular) tyrosine kinases (TK), usually with the Janus family kinases (JAK) and SRC, which phosphorylate and activate signal transducers and activators of transcription (STAT). The latter are directly transferred into the nucleus and activate genes. Note that this process is also triggered by antigens. This family of cytokines transmits proinflammatory signals also through systems of intracellular PK: MAPK including extracellular signal-regulated kinases (ERK), p38 MAPK, and JNK, as well as phosphatidylinositol-3 kinase [10, 11, 13, 14]. Inhibitors of MAPK, and especially of p38 MAPK and JNK, have been shown to display antiinflammatory activities [4, 18-20]. It seems that p38 MAPK plays a central role in inflammation [19]. Second messengers and kinases activate transcriptional factors: the nuclear factor of activated T-lymphocytes (NFAT), NF-κB, AP-1, STAT, the cAMP and Ca^{2+} response element binding protein (CREB) [21, 22].

The other group of cytokines includes highly active inflammatory cytokines subdivided into a subgroup of IL-1 and IL-18 and a subgroup of TNF-α and relative ligands fixed on the plasma membrane (FasL, TRAIL, RANKL, etc.). The two subgroups activate nonreceptor PK (IRAK, SAPK) and then NF-κB, as it has been described for the signal transduction from toll-receptors (see above). NF-κB plays the crucial role: it induces inflammatory cytokines and enzymes, chemokines, cell adhesion molecules, acute phase proteins, and growth factors. It is an immediate early mediator of inflammation, congenital and acquired immune reactions, progress of viral infections, and stress; it can promote the development of a vicious cycle with serious local complications and/or septic shock – and at the same time it is an essential factor of cell survival and inhibition of apoptosis [11, 23-26] and stimulator of proliferation of neuronal stem cells and progenitors through expression of cyclin D1 [27]. Molecular action mechanisms of all these systems are described in works [10-14]. In total, the redundancy of the nonreceptor TK system leads to inflammatory and immune diseases, including severe chronic processes. Not only apoptotic caspases but also inflammatory ones, which provide for maturation of cytokines, have been recently established to play a pathogenic role [28].

Chemokines (chemoattractant cytokines) mainly produced in leukocytes and endothelium form a separate group. They consist of 66-76 amino acid residues and contain at least four cysteines, the positions of which underlie the classification of subfamilies. There are about 50 relatively specific chemokines that provide for chemotaxis of various cells into the focus of inflammation. The following chemokines are differentiated: those acting on neutrophils (IL-8 and the neutrophil-activating protein (NAP)), eosinophils (eotaxin, or ECP), monocyte chemotaxis protein (MCP), macrophage inflammatory protein (MIP), etc. Many chemokines are chemoattractants for some kinds of leukocytes. Moreover, chemokines stimulate cell maturation and activation, differentiation

of immune cells, tissue-specific homing of lymphocytes, support angiogenesis and production of collagens for regeneration, protect cells against HIV infection, because HIV uses receptors of chemokines (together with receptors of T-cells) for penetration into cells [29-31]. Chemokines are called inflammation and pain integrators [32]. As distinguished from other cytokines, chemokines act through the most common receptors, such as G-protein-coupled receptors (GPCR), in many cases through the G_i-protein (and seldom through G_q), and afterwards not only through the secondary messengers cAMP and Ca^{2+}, but also through receptor and nonreceptor TK and NF-κB [10, 33]. This is one of the most demonstrative transactivations of the signal transduction systems [13, 14].

Cytokines also induce and/or stimulate some other proteins (enzymes, cell adhesion molecules, plasma proteins) and peptides. We present a short summary below.

PROTEINS AND PEPTIDES INDUCED BY INFLAMMATION

1. Cytokines.

2. Chemokines.

3. Enzymes: phospholipase A_2 (→polyunsaturated fatty acids), cyclooxygenase-1 and -2 (COX-1 and COX-2) (→prostanoids), 5-lipoxygenase (→leukotrienes), platelet-activating factor synthase (→PAF), inducible NO˙-synthase (→NO˙), matrix metalloproteinases (→proteolysis of intercellular matrix), NADPH oxidases of phagocytes and endothelium (→$O_2^{\cdot}$), xanthine oxidase (→reactive oxygen species), myeloperoxidase (→HOCl), hydrolases (proteolysis, lipolysis), protein kinases, and tyrosine kinases (→phosphorylated proteins) (products or results of enzymatic reactions are presented in parentheses).

4. Molecules of leukocyte and endothelium adhesion (integrins, selectins, addressins).

5. Serum cascade systems of complement, blood coagulation, fibrinolysis, and kinins.

6. Acute phase proteins: C-reactive protein, serum amyloid A-protein, α_1-antipeptidase, α_2-macroglobulin, fibrinogen, haptoglobin, etc.

TNF-α and IL-1 mainly secreted by macrophages activate blood cells (neutrophils, monocytes, eosinophils, basophils, platelets), connective tissue cells (mast cells), and endothelium, whereas IL-6 stimulates synthesis of acute phase proteins in hepatocytes and inhibits apoptosis [34, 35] (Fig. 1). Interferon-γ activates macrophages and natural killers. All these cells are combined in a group of inflammatory cells because they easily and rapidly enter the inflammatory process and release various inflammation effectors, often termed inflammation mediators. Cell adhesion molecules of the immunoglobulin superfamily, selectins, integrins, addressins, etc., initially cause adhesion of blood cells to endothelium cells and then, under the influence of chemokines, promote the penetration of blood cells across vascular walls and emigration into the inflammation focus [26, 36, 37]. Proteolytic cascades trigger blood coagulation, fibrinolysis, complement activation, production of kinins, leukocyte degranulation (with involvement also of histamine and TNF-α), whereas proteases from the degranulated leukocytes induce inflammatory and immune cascades [38].

Hepcidine, an acute phase peptide found in 2000, plays the central role in the metabolism of iron as a negative regulator of its absorption in the intestine via a direct interaction with ferroportin, which is the only iron exporter in mammals. The hepcidine level in serum correlates with the inflammation index, serum ferritin, IL-6, and C-reactive protein, and is considered as a connecting link of iron metabolism with inflammation and congenital immunity and as an adaptive response under conditions of inflammation and disorders in the normal homeostasis of iron [39-41]. It is interesting to compare this concept with data on iron binding by the neutrophil protein lactoferrin and its bactericidal properties [15].

The enzymes perform very important functions. The respiratory chain of mitochondria and numerous oxidases and oxygenases produce reactive oxygen species: free radicals superoxide $O_2^{\cdot}$ and hydroxyl HO˙, molecules H_2O_2, HOCl, the major end product of peroxidation 4-hydroxynonenal, etc. Among oxidases, NADPH oxidase of phagocytes (respiratory burst oxidase) [42], NADPH oxidase of endothelium [43], xanthine oxidase, and myeloperoxidase of neutrophils should be noted; of oxygenases note enzymes of eicosanoid synthesis. Under conditions of hereditary absence of NADPH oxidase, phagocytized bacteria remain alive (incomplete phagocytosis), and this results in chronic granulomatosis with severe recurrent pyogenic infections. In severe cases, granulomas consist of monocyte macrophages literally filled with bacteria [44]. The inducible NO˙-synthase of inflammatory cells, especially macrophages, generates an active nitrogen radical NO˙ which is accumulated in ulcerative colitis and Crohn's disease. Upon interaction of NO˙ with superoxide, the highly active peroxynitrite is produced [45-47]. At physiological concentrations active oxygen and nitrogen species act as regulators; therefore, disorders in their generation reduce immunity; their excess results in oxidative stress, which alters the cells [44, 47, 48].

Important roles in cell death are played by cytolytic proteins (perforins) of T-killers and natural killers, which make pores in the plasma membrane of target cells, and serine proteases (granzymes), which penetrate through these pores and damage the cell from inside; defensins, other lytic enzymes (e.g., lysozyme and lipases), and the complement system (the membrane-attacking complex C5b-C9) are also important [16]. In the intercellular matrix, matrix metalloproteinases decompose connective

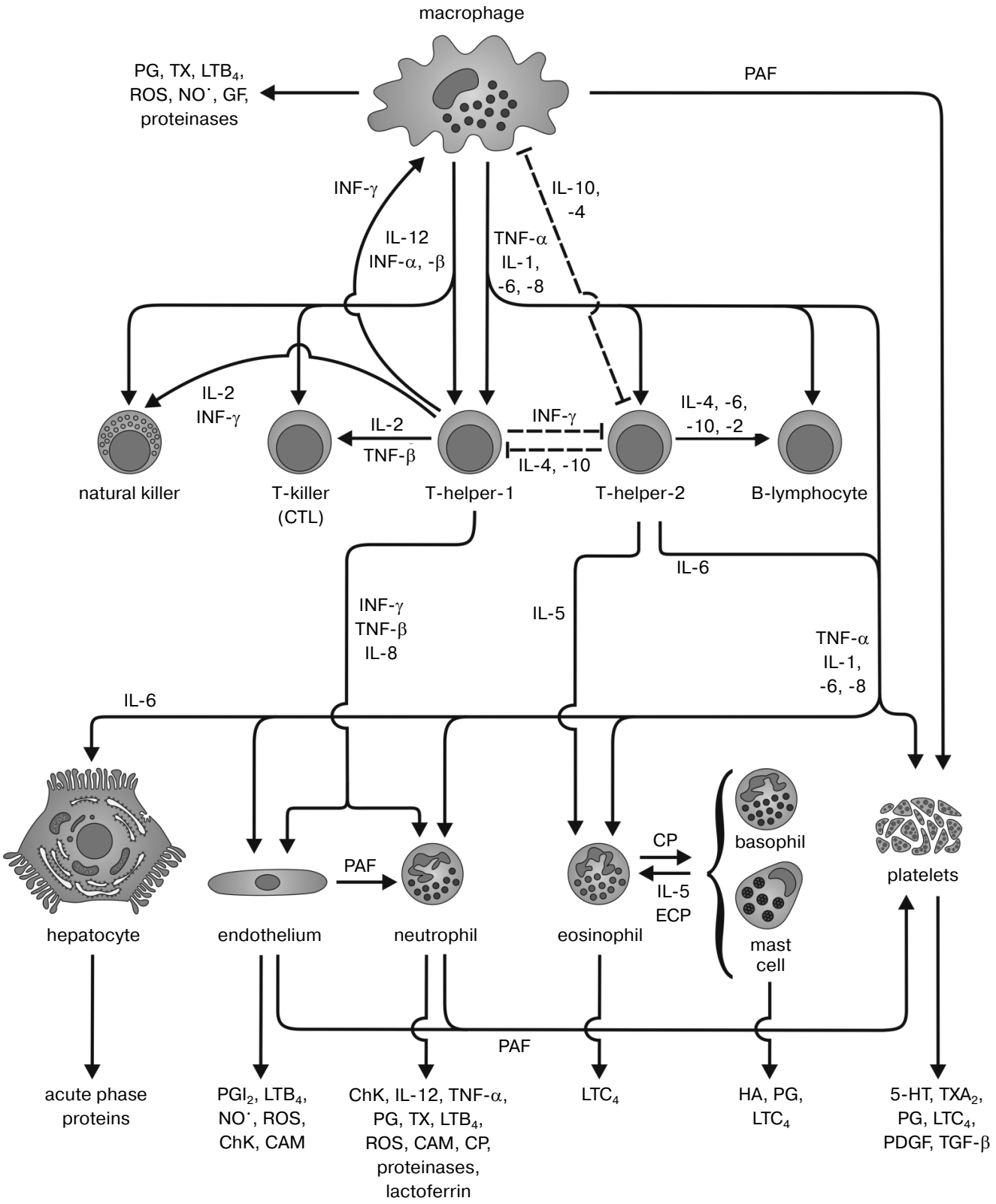

Fig. 1. Interactions of cytokines and tissue hormones in the control of inflammation. Designations: CAM) cellular adhesion molecules; ChK) chemokines; CP) cationic proteins; CTL) cytotoxic lymphocytes; ECP) eotaxin; GF) growth factors; HA) histamine; 5-HT) serotonin; IL) interleukins; INF) interferons; LT) leukotrienes; NO˙) nitric oxide; PAF) platelet-activating factor; PDGF) platelet-derived growth factor; PG) prostaglandins; ROS) reactive oxygen species; TGF) transforming growth factors; TNF) tumor necrosis factor; TX) thromboxane.

tissue proteins and promote cell migration and wound healing and, thus, play an important role in inflammation (and also in other processes) [49]. In pronounced inflammation (demyelinization, amyloidosis), excess TNF-α and/or IL-1 damage tissues (bone, cartilage) [23, 50].

The enzymes produce proinflammatory hormones: lipids (eicosanoids, platelet-activating factor), amines (histamine, serotonin), proteins and peptides (cytokines, chemokines, kinins, angiotensin II, opioids, leptin), $NO^{\bullet}$, and also specific proteins of blood plasma and tissues [15, 51-53]. In addition to cytokines, prostanoids and leukotrienes are the most important inflammatory hormones. They are produced in the inflammatory cells, and their action is paracrine and autocrine. Phospholipase A_2 detaches from phospholipid polyunsaturated fatty acids, which transform into eicosanoids. The constitutive cyclooxygenase-1 and sharply induced by inflammatory cytokines cyclooxygenase-2 form prostanoids, and lipoxygenase (5-LOX) produces leukotrienes.

Prostaglandins (PGE_2 and $PGF_{2\alpha}$) through G_s- and G_q-coupled receptors and then, through cAMP and Ca^{2+}, respectively, induce inflammation, pain, and hyperthermia (PGE_2 also acts as a cytoprotector); leukotrienes, in general, are responsible for inflammation and hypersensitivity (LTB_4 through G_i, LTC_4 through G_q); LTB_4 also induces the emigration and strong chemotaxis of leukocytes; LTC_4 and LTD_4 also cause cell damage [10, 54]. Upon stimulation, mast cells produce PGD_2, which dilates blood vessels but constricts bronchi.

The platelet-activating factor aggregates platelets, releases from their granules histamine and serotonin, activates and degranulates leukocytes, and induces chemotaxis, edema, and bronchospasm [15]. Histamine released upon the degranulation of mast cells not only activates through H_1-receptors acute allergic inflammation associated with increased vascular permeability, edema, secretion of prostacyclin and $NO^{\bullet}$, but also induces chronic inflammatory and immune reactions. Histamine activates various immune cells, affects responses of the antibody isotypes, through its H_2-receptors and then through G_s and cAMP increases the tolerance to antigens [55]. Kinins (bradykinin in plasma and kallidins in tissues) are proinflammatory peptides acting through omnipresent constitutive receptors B2 and G_q-coupled receptors B1 induced by IL-1β and other cytokines and further through Ca^{2+}, or through G_i-coupled B1 and then through a decrease in cAMP and activation of MAPK. Kinins induce strong vascular reactions, exudation of serum proteins, chemotaxis, and pain; they are involved in asthma, rhinitis, edema, and sepsis [56]. When interacting with its major receptor, AT_1 coupled with G_q, angiotensin II manifests a pronounced proinflammatory effect: it increases the concentration of cytokines, chemoattractants, and NF-κB, especially in atherosclerosis: blockers of its receptors and inhibitors of the angiotensin-converting enzyme reduce atherogenesis [51, 53, 57]. Cysteine is a source of a new regulator of inflammation, H_2S, which affects chemotaxis. The release of H_2S is enhanced in pancreatitis, inflammatory edema, and septic shock; on inhibition of H_2S synthesis inflammation decreases [58].

Hormones control all phases of inflammation. Their effects on vascular reactions in inflammation are well known. Hormones, including brain neurotransmitters, also determine the body's general reactions to inflammation: pain, leukocytosis, accumulation of acute phase proteins in blood plasma, fever, and decrease in brain activity and appetite. Penetrating into the brain, IL-1β increases the release of PGE_2 that causes pain and fever [59, 60]. IL-6 also induces PG and displays a pyrogenic effect. In total, hormones control no less than 15 reactions during the development of inflammation and about 10 reactions during its inhibition and resolution.

Many serum proteins possess proinflammatory effects. The complement system mainly consisting of these proteins opsonizes microorganisms (facilitates and stimulates the efficiency of subsequent phagocytosis), and initiates vascular inflammatory reactions and perforation of membranes of bacterial cells. Cationic proteins of neutrophils and eosinophils have bactericidal effects [15, 16, 36]. Dual functions are performed by the C-reactive protein: it activates phagocytosis, release of cytokines, the complement system, matrix metalloproteinases, and has an antiinflammatory effect [61, 62]. Serum amyloid A is a proinflammatory protein activating metalloproteinases and displays regulatory features [63]. The abovementioned transcriptional factors (TF), hormones, serum proteins, and even enzymes are often called inflammation mediators.

However, the congenital defense reaction is frequently insufficient. Then the body turns on immune inflammation (we shall briefly discuss only the most necessary immune mechanisms). Complicated interaction of cytokines and tissue hormones on different inflammatory and immune cells are illustrated in Fig. 1. The macrophage-produced cytokines of inflammation and natural immunity, first of all TNF-α and IL-1 circulating in the blood flow, activate all inflammatory cells. Among them T- and B-lymphocytes are especially important: T-lymphocytes are responsible for the cellular immunity (a direct damage of heterologous and damaged cells), whereas B-lymphocytes ensure the humoral immunity, i.e., synthesis of cytokines and production of immunoglobulins (Ig). Only lymphocytes are capable of molecular recognizing antigens by special T- and B-cellular receptors [64]. T-Cells are first of all represented by regulatory T-helpers Th1 and Th2. The Th1 mainly provide for the immune response to small and the Th2 to high doses of antigen. The main function of Th1 is regulation of cellular immunity (defense against viruses and cancerous cells), whereas Th2 is mainly responsible for humoral immunity (defense against bacteria) [15, 16].

Then lymphocytes switch on the effector link: Th1 through interferon-γ increases the activity of macrophages (positive feedback), stimulates cytotoxic lymphocytes (T-killers) through IL-2 and TNF-β (lymphotoxin), and stimulates natural killers through IL-2 and interferon-γ. Natural killers are also activated by macrophages through IL-12. Both T-killers and natural killers kill microorganisms as a result of their damaging by perforins and granzymes and also via apoptosis. Th2-lymphocytes activate B-lymphocytes and stimulate their division, mainly through IL-10, IL-4, and IL-5; and IL-2 acts similarly. IL-6 induces differentiation of B-lymphocytes into plasma cells with the beginning of IgM production. The subsequent generation of other Ig isotypes (IgG1, IgG2, IgG3, IgA, and IgE) is induced by different cytokines: IL-4, -5, -10, -13, interferon-γ, the transforming growth factor β (TGF-β) [64-66]. All Ig isotypes make various harmless antigens. In total, inflammation is stimulated by IL-1, -2, -3, -5, -6, -8, -12, -18, TNF-α, interferon-α and -γ, chemokines, eicosanoids, platelet-activating factor (PAF), angiotensin II, kinins, histamine, serotonin, ceramide-1-phosphate, and lysolipids [14]. Some cytokines enhance the expression of receptors of other cytokines [67]. This is the most demonstrative example of multiple regulation. In addition to positive feedbacks exemplified by interactivation of macrophages and Th1-lymphocytes, there are also more distributed negative feedbacks: Th1 through interferon-γ inhibits Th2-lymphocytes, and Th2 inhibit Th1 through IL-10 and IL-4. The cell can choose the most reasonable type of immunity.

Both types of feedbacks are equally necessary for the immune and hormonal system: regulation is impossible without them. The functioning of lymphocytes of all kinds and macrophages is mediated by cytokines. The immune system is evolutionarily young and excellently armed with both regulatory and effector lymphocytes and with immunoglobulins: they make antigens harmless and kill heterologous cells. Immune inflammation is the more potent and individually acquired adaptive mechanism. In most cases, it causes the death or elimination of a harmful invasive agent.

Figure 1 presents a general picture of principal cellular and cytokine/hormonal mechanisms. In this picture three levels may be separated: 1) macrophages that give an initial cytokine stimulus for both congenital and immune inflammation; 2) regulatory and effector lymphocytes that specifically determine the totality of immune reactions; 3) effector cells of blood, intercellular matrix, and hepatocytes that transform signals from macrophages and lymphocytes into a diversity of inflammatory hormones and other "inflammation mediators".

It is very important to suppress and then terminate inflammation to prevent damage to healthy cells. This is usually called a resolution of inflammation. It should be emphasized that for a biologist inflammation is first of all a defense reaction, whereas for a physician it is a breach of health. The overexpression of all the abovementioned proteins, especially the accumulation in blood of TNF-α, promotes the change of a local inflammation into a generalized sepsis and severe multiorgan insufficiency [12]. The obvious danger for the body of excess activities of inflammatory cytokines in most cases is balanced by mechanisms of contraregulation. NF-κB stimulates the expression of its inhibitor IκB, and this prevents an excess activity of this transcriptional factor (TF) [68]. Negative feedback is maintained by suppressors of the cytokine system, which lower the generation of cytokines and inhibit their activities. Under deficiency of these suppressors, the inflammation is seriously aggravated and can be lethal when they are absent [69, 70]. The effect of IL-1 is weakened by competition between its functional receptor IL-1R and a physiological antagonist IL-1Ra, as well as by numerous soluble and hence circulating and inactive trap receptors: the second type of the IL-1 receptor, IL-18-binding protein, toll-8, immunoglobulin IL-1-relative receptor, TNF-10C and D, and osteoprotegerin, which binds RANK-ligand in blood plasma, a promiscuity receptor D6 for proinflammatory cytokines, trap receptors for the IL-10 and -13 families, and interferons [71, 72]. All these traps intercept cytokines, decrease their levels, or arrest functioning. IL-4, IL-6, IL-10, IL-13, interferon-α, TGF-β, adenosine, glycine, α-melanocyte-stimulating hormone, cortisol, etc. are shown to have antiinflammatory activities [14]. Catecholamines and glucocorticoids inhibit production of proinflammatory cytokines (IL-12, TNF-α, interferon-γ) and stimulate antiinflammatory cytokines (IL-10, IL-4, and TGF-β) [73]. This can be associated with an especial danger of stress combined with inflammation. Sex hormones decrease the effects of cytokines: estradiol and testosterone affecting those of Th-1- and Th-2-dependent cytokines, respectively [74]. J-2156, a selective agonist of somatostatin, inhibits neuroinflammation and analgesia through a receptor of subtype 4 (GPCR class) [75, 76]. This also confirms the unofficial name of somatostatin as "universal inhibitor".

TGF-β, inhibiting the MAPK-ERK cascade through receptor protein kinases (PK) and then through the TF Smad, strongly slows division of lymphocytes and epithelial cells and their involvement in inflammation, inhibits synthesis of inflammatory cytokines, and stimulates proliferation and activity of fibroblasts (Fig. 2), synthesis of the intercellular matrix, and wound healing [77, 78]. TGF-β is a potent antiinflammatory cytokine, and its switching off leads to development of generalized inflammation [79]. Fibroblast, platelet-derived, and epidermal growth factors (FGF, PDGF, and EGF) also stimulate fibroblasts, and fibroblasts themselves perform an autocrine secretion of TGF-β and PDGF [15]. Angiogenesis is a crucial component and inducer of chronic inflammation triggered by vascular epithelial

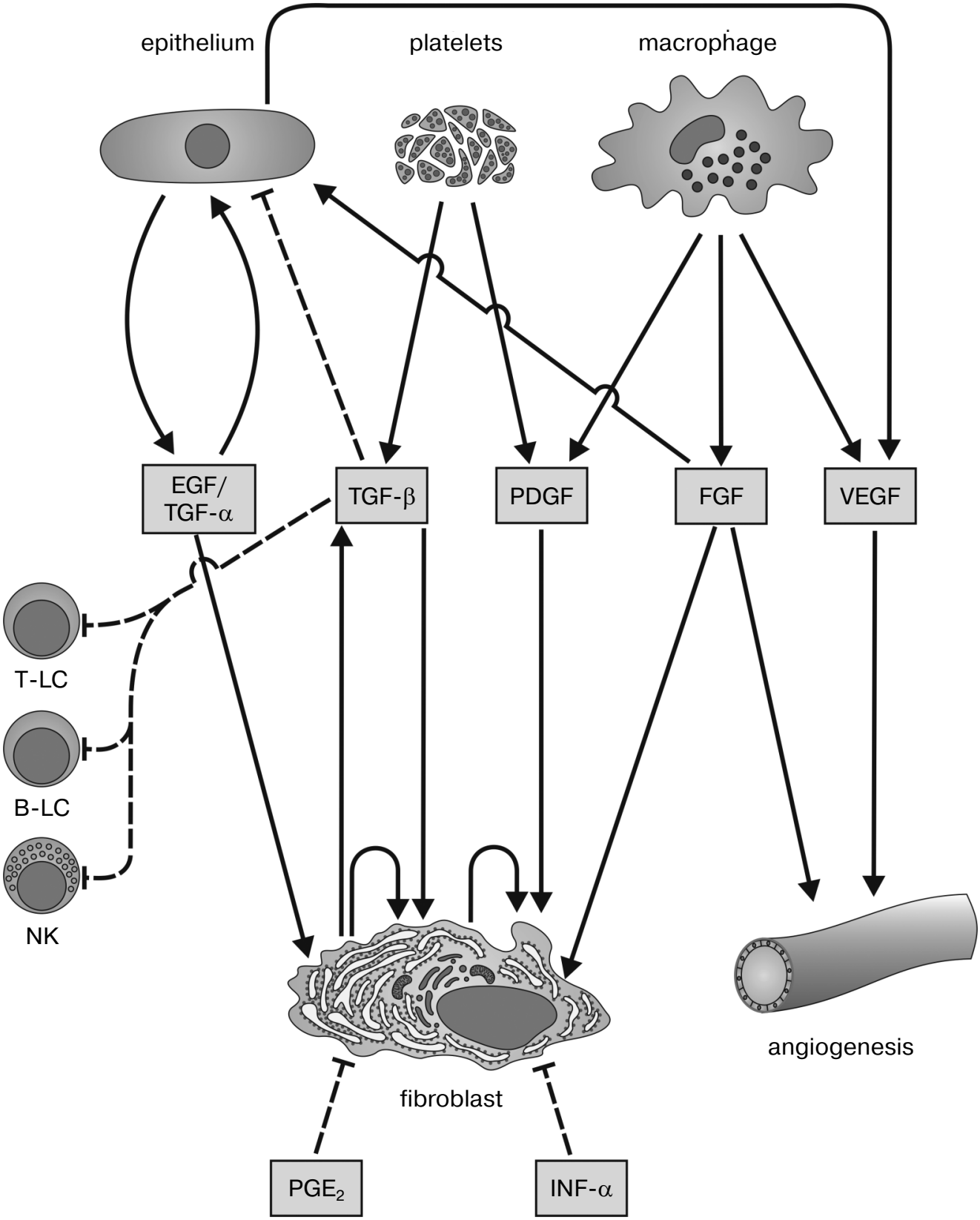

Fig. 2. Inhibition of inflammation and control of fibrosis and angiogenesis. Designations: EGF) epidermal growth factor; FGF) fibroblast growth factor; INF-α) interferon-α; LC) lymphocytes; NK) natural killers; PDGF) platelet-derived growth factor; PGE_2) prostaglandin E_2; TGF) transforming growth factors; VEGF) vascular endothelial growth factor.

growth factor (VEGF). This factor also controls lymphoangiogenesis and vascular permeability. VEGF acts in cooperation with angiopoietins, IL-1, EGF, TGF-β, PDGF, FGF [80-83]. These growth factors act through receptor tyrosine kinases, which transmit signals into the nucleus via the MAPK and phosphoinositol-3-OH kinase (PI3-K) systems [10, 11, 13, 14]. Powerful angiogenesis is specific for diseases accompanied by severe chronic inflammation of the large intestine [81].

Cortisol acting through nuclear receptors strongly inhibits inflammation. Under conditions of insufficiency and especially absence of cortisol, inflammation becomes continuous, severe, and even lethal. An endogenous agonist 15-deoxy-Δ-(12,14)-PGJ_2 of nuclear receptors acts through them upon their activation by peroxisomal proliferators (PPAR-γ) and decreases the NF-κB level and limits its neutrophilic infiltration. This agonist and synthetic agents thiazolidinediones (glitasons) display antiinflammatory effects [84, 85]. There are also other findings that suggest the involvement of an inflammatory component in pathogenesis of type II diabetes mellitus [86]. In the brain, these agonists efficiently prevent inflammation and manifest a direct neuroprotective effect, in particular, in Alzheimer's disease, Parkinsonism, brain stroke, etc. [87].

A significant success of researchers was the discovery of a third type of eicosanoids – lipoxins LXA_4, their 15-epimers (ALX), LXB_4, and resolvins, which display a powerful antiinflammatory effect ("stop-signal"), especially on leukocytes. These substances are produced under conditions of intercellular cooperation with involvement of 15- and 5- or 12- and 5-lipoxygenases and act through GPCR ALX-R. Lipoxins are involved even during the early stage of inflammation, but are the most active by its termination providing for inhibition and resolution of acute inflammation. Lipoxins also have immunomodulatory effects [88-93]. Obviously, in addition to pathogenic effects, lipid hormones also act protectively. Antiinflammatory, immunomodulatory, and cytoprotective effects of glycine are described [94].

The excess accumulation of oxidants is balanced by the antioxidant system, which includes low-molecular-weight reductants (GSH, thioredoxin, tocopherols, polyphenols, a peroxynitrite inhibitor ergothionein, ascorbate, small doses of retinoids, carotenoids), other small molecules (urates, bilirubin, carnosine), and, what is especially important, specific enzymes (superoxide dismutase, glutathione peroxidase, glutathione transferase, glutathione reductase, thioredoxin reductase, catalase) [26, 44, 46, 95, 96]. Resveratrol, which is believed to be associated with the so-called "French paradox" (the usefulness of red wine), also attracts attention [97, 98]. However, $NO^{\cdot}$ is not only an oxidant but also a key protector of the stomach mucosa because it performs dual functions [99, 100]. CO is also shown to have antiinflammatory properties [101]. Antioxidants protect the cells through mediation of a transcriptional factor, the nuclear erythroid-2-bound factor 2 (Nrf2), and further through an antioxidant-responsive element (ARE). The glutathione system plays an important role in this mechanism [102-104]. This system is opposite to the proinflammatory TF NF-κB and AR-1.

The activities of matrix metalloproteinases are decreased by their specific tissue inhibitors [49]. The totality of all these regulators maintains the balance of pro- and antiinflammatory factors and prevents not only progress and aggravation of inflammation, but also the change of an acute process into chronic inflammation. The last defensive line is apoptosis (programmed cell death), which removes clusters of aggressive inflammatory cells or virus-affected cells. An imperfect apoptosis in the mucosa cells considerably aggravates inflammatory disease of the large intestine, but induction of apoptosis is helpful [105].

The inflammation zone is healed by epithelization (first intention) stimulated by EGF-α. Under conditions of suppuration, intense necrosis, large wound, epithelization is insufficient, and TGF-β, as well as other growth factors, activates fibroblasts and fibrosis (second intention), and this, in turn, is inhibited by interferon-α and PGE_2. In the absence of resolution, inflammation turns into a chronic state specific for very serious diseases: asthma, chronic pneumonia, obstructive lung disease, large intestine inflammation, Crohn's disease, glomerulonephritis, arthritis, chronic heart failure, multiple sclerosis. Because of dysregulated and uncontrolled inflammation [106], in these diseases only a temporary improvement can be achieved. Excess fibrosis can develop in various forms and in different organs (pneumosclerosis, cirrhosis, etc.), it is a substantial component of remodeling (structural–functional changes) of heart and vessels caused by excess effects of catecholamines, angiotensin II, endothelin, and aldosterone [107]. Studies are now in progress for obtaining a decrease in fibrosis using blockers of TGF-β receptors and inhibitors of collagen synthesis. Very high doses of vitamin C can promote the development of fibrosis as a result of activated hydroxylation of proline and lysine, which are involved in the transformation of procollagen into mature collagen. Note that a common term "collagenoses" is wrong from the biochemical standpoint: these diseases are pathologies of the connective tissue as a whole and not only of collagen. A continuous chronic inflammation can also be seriously complicated by amyloidosis of internal organs because of incorrect folding, i.e., formation in tissues of pathologic fibrils of amyloid A from serum amyloid A [63].

BIOCHEMICAL DIAGNOSTICS OF INFLAMMATION

Under conditions of acute inflammation, the plasma concentrations of albumins are usually decreased and the

levels of α_1- and α_2-globulins elevated because of increase in the contents of acute phase proteins: protease inhibitors (α_1-antitrypsin, α_2-macroglobulin), α_1-acidic glycoprotein, haptoglobin, and fibrinogen; in chronic inflammation the γ-globulin level is also increased; but specificities of these tests are insufficient [108]. Because of an important role of cytokines in inflammation, their determination (especially of TNF-α, IL-1, and IL-6) in biological fluids has become a useful diagnostic test. However, the determination of individual cytokines is usually insufficient for evaluation of the general picture. The determination of neopterin (an intermediate metabolite in the synthesis of biopterin), which activates NF-κB, production of NO$^{\bullet}$ and TNF-α, is more informative. Neopterin concentrations in blood and urine increase under conditions of immune reactions, chronic inflammations, and every infection (early in viral infections, especially those caused by HIV) and usually correlate with severity and activity of the disease. But a similar increase also occurs in the case of tumors, grafts, and traumas. It is long known that the C-reactive protein level is affected by inflammations – in inflammation its concentration in blood plasma increases dramatically (tens of times). The C-reactive protein has been recently shown to release cytokines, and its level in blood correlates with their concentration. But for determination of the C-reactive protein, a highly sensitive quantitative method (hsCRP) is required [109]. Serum amyloid A increasing two-to-three orders of magnitude under the influence of IL-1 is another protein marker of inflammation. These four tests are already widely used in many countries because they help to evaluate the intensity of inflammation [63]. Increased values obtained in these tests in atherosclerosis, chronic heart failure, and other cardiovascular diseases have proved the presence of an inflammatory–immune component [2, 53, 109-112]. The central role is played by interferon-γ; moreover, it triggers accumulation of reactive oxygen species and oxidative stress [113].

An inflammatory component is also revealed in pathogenesis of Alzheimer's disease and Parkinsonism [114, 115]. Some new integral tests of inflammation have been developed during recent years.

BIOCHEMICAL PRINCIPLES FOR THERAPY OF INFLAMMATION

Considerable progress has been achieved in the treatment of inflammatory diseases. The time when an untreated pneumonia was spoken of to continue for 21 day and for three weeks in the case of a good treatment is long ago. Pneumonia was the cause of death of L. Tolstoy and P. Cezanne. Here we give both the approved drugs and new approaches. From the general biological standpoint, the efficiency of a drug is an argument or a proof in favor of the contemporary theories and concepts.

Synthetic glucocorticoids still remain the best drugs considering their wide use and efficiency. In the 1980s this was explained only by suppression of lipocortin-1 (now annexin-1) associated with inhibition of phospholipase A_2 and the resulting decrease in the synthesis of eicosanoids. But now it is clear that the biochemical action mechanism of glucocorticoids is much more complicated and multiform – it includes inhibition of multiple inflammatory genes: suppression of synthesis of cytokines, eicosanoids, NO$^{\bullet}$, proinflammatory transcriptional factors (and co-activators involved by them), cellular adhesion molecules, and matrix metalloproteinases; a decrease in the migration and activity of blood cells and in the release of histamine and kinins; recruitment of histone deacetylase 2; stimulation of MAPK phosphatase; inhibition of immunity and allergy; apoptosis of lymphocytes and macrophages; inhibition of cell division [22]. Glucocorticoids are thought to be more efficient in the cellular than humoral mechanism of inflammation because they decrease the amount of Th1-cytokines and increase the level of Th2-cytokines [73]. But because of serious side effects (a decrease in immunity, proliferation, etc.) glucocorticoids are more frequently used locally. Bronchial asthma and chronic obstructive lung disease are suitable examples. At present, a combination of inhaled corticosteroids (fluticasone, budesonide) and long acting bronchodilators β_2-agonists (salmeterol, formoterol) is believed to be optimal: their effects are added and mutually strengthened [116, 117]. Using selective agonists of glucocorticoid receptors (SEGRA) and nitrosteroids are new approaches [118].

Because the effects of β_2-adrenoagonists are associated with activation of cAMP production, selective inhibitors of phosphodiesterase-4 (silo-, picla-, and roflumilast), which also increase the level of cAMP, were synthesized. They occurred to be useful in bronchial asthma, chronic obstructive lung disease, and rheumatoid arthritis [119-122]. Selective inhibitors of receptors of leukotrienes C_4 and D_4—montelukast and zafirlukast—are approved as bronchodilators [123].

Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit COX-1 and to a lesser degree COX-2 (table), they reduce inflammation, pain, and hyperthermia, but during the usual long-term treatment damage the stomach mucosa and kidneys, possibly, because of a decreased cytoprotection by prostaglandin E_2. The preferential inhibitor of COX-2 nimesulide and its selective inhibitor celecoxib are similarly active but less harmful for the cells. The first successes induced a rapid synthesis of still more potent inhibitors with a 400-fold increased selectivity [124]. But it has been recently revealed that another inhibitor of COX-2, rofecoxib, increased the risk of heart diseases. Its production was cancelled [125-127]. New drugs NO$^{\bullet}$-NSAIDs are more efficient and less or not damaging the stomach mucosa [100]. As differentiated from aspirin, its nitroxyethyl ester (NOE-Asp) does not

Two cyclooxygenases (COX)

Parameter	COX-1 and COX-2	COX-2
Synthesis	all cells	inflammatory cells
Functions	physiological: platelet disaggregation, cytoprotection	involvement in inflammation, pain, fever
Induction during inflammation	weak (twofold)	very strong (tens of times)
Inhibitors	aspirin (weak), pyroxycam, ibuprofen, naproxen	preferential inhibitor of COX-2 nimesulide, selective inhibitor celecoxib
Effects and complications of the therapy	reduction of inflammation; damage of stomach mucosa, nephropathy	reduction of inflammation; lesser damages; slowing down of progression of some cancers

inhibit wound healing and preserves antiinflammatory activity [128]. Combined inhibitors of COX-2 and 5-lipoxygenase (licofelon, etc.) are under investigation [129, 130]. There is a hopeful report that a combination of both NSAIDs and COX-2 inhibitors with inhibitors of H^+,K^+-ATPase lowers gastrointestinal symptoms and peptic ulceration [131]. Some NSAIDs (flurbiprofen, etc.) and antagonists of NMDA-receptors of glutamate (memantin) manifest a positive effect in Alzheimer's disease [132]. Inhibitors of COX-2 suppress the development of colorectal polyps and decrease the risk of cancer [133]. Prostacyclin antagonists reduce inflammation and pain in acute and chronic arthritis [134]. The antiinflammatory action of NSAIDs and COX-2 inhibitors may be considered as antioxidant effects.

When non-immune inflammation changes into a severe immune inflammation, especially a chronic one, cytokine suppressors are used. In rheumatoid arthritis, ulcerative colitis, inflammatory disease of the large intestine, and psoriasis efficiency has been shown of such drugs as monoclonal antibodies against TNF-α (infliximab, adalimumab) and its soluble and insoluble receptors (etanersept) [105, 106, 135, 136]. These drugs increase apoptosis and improve the patients' condition. For treatment of these diseases antibodies (rituximab, tocilisumab) and abatsept have been suggested, which decrease IL-6 activity [137], an inhibitor of cytokines and MAPK sepamimod [138], a blocker of IL-1 diaserein, IL-1Ra [139], the recombinant IL-10 [140], natalizumab binding integrin α4 [141], and chemokine inhibitors [142]. Modern inhibitors of histamine H_1-receptors (cetirizine, loratidine) effectively reduce the allergic component of inflammation.

Bone damage in a pronounced inflammation can be diminished by bisphosphonates (zoledronate and ibandronate), which inhibit TNF-α and IL-1 and decrease the number and activity of osteoclasts and macrophages and the bone destruction [143]. The first inhibitors of matrix metalloproteinases, doxycycline and especially minocycline, have antiinflammatory effects independent of the antibiotic properties and are already used in arthritis and paradontosis. Minocycline diminishes neuronal inflammation and increases survival [144].

In inflammation of the skin (psoriasis, keratosis, dermatitis) and bones (arthritis, osteoporosis), synthetic analogs of calcitriol (calcipotriol and others) are used [145]. An antiinflammatory activity of α-tocopherol has been described. A high antisclerotic effect of statins is associated not only with inhibition of synthesis of cholesterol and isoprenoids but also with a decrease in expression in the vascular wall of inflammatory cytokines, adhesion molecules, oxidation and proteolysis reactions, and also in the blood level of serum markers of inflammation [111, 146, 147]. Statins improve survival in vascular inflammation and also in sepsis when injected preventively [148].

Obviously, it is necessary to develop drugs capable of strengthening and accelerating the resolution of inflammation. There are searches for such drugs among analogs of TGF-β, lipoxins, antioxidants, substances affecting Nrf2 and ARE; but up to now there are no clinically approved antiinflammatory preparations.

Thus, in accordance with the leading role of proteins in pathogenesis of inflammation, the majority of new drugs act on proteins as ligands of receptors and enzymes. These proteins are responsible for specificity of both pathologic and defense reactions, but the significance of this specificity was underestimated for a long time. The optimal treatment of a pronounced inflammation and other diseases is based on biochemical pharmacology, which studies molecular mechanisms of the drug effects. As it has been ascertained by the outstanding pharmacologist P. Sotherland, "Pharmacology is not yet biochemistry but is more and more changing into it".

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