Cytokine-mediated proteolysis in tissue remodelling

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Summary. Proteolytic enzymes play a key role in a variety of physiological processes in which the degradation of macromolecules is essential: angiogenesis, embryogenesis, bone and tissue remodelling, blood hemostasis and cell migration. The action of these enzymes is also crucial in the development of many pathological conditions such as wound healing, neoplasia, inflammation and arthritic disorders.
The activity of proteases is negatively affected by specific protease-inhibitors. Various growth factors and other cytokines modulate the synthesis and secretion of both proteases and protease-inhibitors. The study of this regulation results in a better insight into (patho)physiology at the molecular level and promises to result in alternative treatment strategies.
Key words. Proteases; cytokines; growth factors; protease-inhibitors; tissue remodelling.

Introduction

Proteases have the capacity to hydrolyze peptide bonds in other proteins, and play an important role in a variety of (patho)physiological processes. They can change the composition of structural components of the body or modify the activity of functional enzymes. Physiological processes in which the breakdown of proteins is essential include the migration of cells in embryogenesis, the invasion of endothelial cells into tissues during angiogenesis[29, 37, 61], bone resorption and remodelling[4, 13, 33], migration of macrophages and other white blood cells into and within tissues[83, 84]. Proteases are also important as effector molecules in pathological processes such as wound healing, blood coagulation and fibrinolysis, inflammation and cancer[5, 73, 81]. The excess secretion of certain proteolytic enzymes can lead to protein breakdown in muscle during inflammation[2, 31], to cartilage degradation or bone resorption in rheumatoid arthritis or osteoarthritis[12, 19, 22, 35, 62] and to gingival or periodontal recess in gingivitis or periodontitis, respectively[54]. Proteases secreted by tumor cells affect tumor cell invasion and metastasis in tissues[55, 81].
Early studies of proteases were almost exclusively directed towards understanding the structure and function of digestive enzymes (pepsin, trypsin, chymotrypsin,...). These studies provided a wealth of information on the basic mechanisms of hydrolysis of peptide bonds. In the last decades, interest has focused on the proteases that play regulatory roles in physiological processes. Regulatory proteases are more specific than the digestive enzymes and often exert their regulatory effect by activation through limited proteolysis of precursor molecules (pro- or prepro-enzymes or zymogens).
The interest of scientists has long concentrated on the protease molecules themselves; on the characterization and classification of the proteases according to their substrate specificity or mode of action, and more recently on the determination of the amino acid sequences of the protease molecules and the DNA-sequences of their genes. Only in the last few years has knowledge begun to accumulate on the regulation of protease secretion and activity[65].
The activity of regulatory proteases themselves can be modified by limited proteolysis or by inhibition by specific protease-inhibitors[65]. Protease-inhibitors are proteins that can bind to specific protease molecules forming an enzyme-inhibitor complex. They thus prevent the proteases from exerting their proteolytic activity. The table describes several proteases and their inhibitors. All these have been extensively studied from both structural and functional points of view.
A central role in the control of protease and protease-inhibitor production and activation seems to be played by cytokines. These are (glyco)peptide signal mediators secreted by mononuclear phagocytes, polymorphonuclear cells and a variety of other cells. They act at the site of production. Cytokines are capable of influencing the activities of various target cells. They are responsible for communication between cells of the same type or between different cell types. Many of the cytokines are known as inflammatory mediators (interleukins, tumor necrosis factor, interferons,...). They are released by infiltrating leukocytes during inflammation, and exert an effect on other cells of the immune system (T-cells, B-cells,...). Cytokines interact with specific cellular receptors and can thus regulate intracellularly the gene expression of their target cells. In general, cytokines act more locally (paracrine or autocrine) as compared to the glandulotrophic (endocrine) hormones.
The activity of the proteases and their inhibitors is, furthermore, regulated at the genomic level. Agonists and antagonists are being described that up- or downregulate the expression of their genes. Among these, the importance of cytokines is becoming increasingly appreciated. The classical hormones can also regulate the secretion of proteases, and cytokine-regulated secretion of microbicidal (e.g. complement factors[41]) or cytocidal (e.g. perforin) proteases has been documented. These two subjects were covered in recent reviews[79, 81] and will not be

Endopeptidases involved in cytokine/hormone-regulated proteolysis. The proteases were classified on the basis of the mechanism of catalysis[50, 81]. For each active protease representative examples are given. Some information on the main sources, substrates and inhibitors is included.

Class	Active protease	Source and occurrence	Effect	Inhibitors	Ref.
Neutral (metallo) proteases	Collagenase	Connective tissue cells, fibroblasts, synovial cells, chondrocytes, macrophages	Degradation of collagen type I, II, III	α_2-macroglobulin TIMP	62, 81, 83
	Proteoglycanase (stromelysin)	Connective tissue cells, fibroblasts, synovial cells, chondrocytes	Degradation of proteoglycan, collagen type, IV, matrix glycoproteins	TIMP	14, 81, 83
	Gelatinase	Connective tissue cells, fibroblasts, synovial cells, chondrocytes	Degradation of denaturated interstitial collagens, collagen type IV, V	TIMP	81, 83
Serine proteases	Plasminogen activators (uPA–tPA)	Connective tissue cells, endothelial cells, fibroblasts, plasma, urine	Plasminogen ↓ plasmin	Serpins e.g. PAI-1, PAI-2, α_2-macroglobulin	16, 81
	Plasmin	Hepatocytes, plasma	Fibrinolysis, degradation of matrix components	α_2-antiplasmin protease nexin	16, 81
	Thrombin	Hepatocytes, plasma	Coagulation (fibrinogen → fibrin)	Antithrombin III protease nexin	16
	Elastase	Leukocytes, elastic tissues	Degradation of elastin, collagen type III and IV, degraded collagens	α_1-antitrypsin	81, 84
Cysteine (thiol) proteases	Cathepsins B and H	Intracellularly (lysosomal) in liver kidney, spleen, lung	Proteolysis	Thiol proteinase inhibitors	81
Aspartic (acid) proteases	Pepsin	Gastric juice	Proteolysis	e.g. pepstatin	81

Abbreviations used: TIMP, tissue inhibitor of metalloproteinases; uPA, urokinase-type plasminogen activator; tPA, tissue-type plasminogen activator; PAI-1; PAI-2, plasminogen activator inhibitor type 1 or 2.

further discussed here. This review will focus on the connection between cytokines and proteolytic activity and on the role of cytokines in the regulation of proteolytic degradation of extracellular matrix molecules in defined physio(patho)logical processes.

Model systems

For many of the aforementioned processes in which proteases seem to play a role, model systems have been developed. These mainly use the in vitro culture of cells or cell lines, and also the development of pure (recombinant) cytokines and growth factors and highly specific probes, to detect the proteases or their mRNAs (monoclonal antibodies, cDNA- and cRNA-probes). Repair of vascular lesions and angiogenesis, in which new blood vessels are formed by infiltrating endothelial cells (e.g. during development or during vascularization of tumors), have been studied in cultures of human or bovine capillary endothelial cells or of human umbilical vein endothelial cells[27, 37, 61, 64]. Resorption or remodelling of bone tissue, occurring to a limited extent in healthy individuals, but also in patients with osteoarthritis, is mainly studied in tissue cultures of human or rabbit articular chondrocytes or in explants of bone tissue (e.g. mouse calvariae, rat fetal bone)[4, 30, 33].

The effect of inflammatory cytokines on proteases degrading the extracellular matrix and their inhibitors has been studied in cultures of synovial cells[18, 19, 38, 48, 56, 59] and of articular chondrocytes[10, 22, 28, 30, 78] as model systems for rheumatoid disorders such as rheumatoid arthritis or osteoarthritis. These processes are also studied in vitro in explants of bovine nasal septum cartilage or human articular cartilage[35, 39, 40, 44, 72].

Cultures of dermal fibroblasts have been used to investigate the effects of cytokines in the process of wound healing during injury[17, 32, 70, 71], while periodontal disease has been studied in cultures of gingival fibro-

blasts[54,57]. Various tumor cell lines can be used to study the effects of cytokines on the production of proteases originating from tumor cells[42,55,73].

Cytokines and proteases in rheumatoid disorders

Inflammatory processes such as rheumatoid arthritis and osteoarthritis involve the degradation of extracellular matrix proteins (e.g. collagens, proteoglycans) by proteases secreted by chondrocytes or synovial fibroblast-like cells in the inflammatory region[62]. Cytokines, in particular interleukin-1 (IL-1), seem to play an important role in the activation of these protease-secreting tissue cells. Interleukin-1 (IL-1α and IL-1β) is the name given to two different polypeptides interacting with the same receptor. They mediate a diverse range of biological activities. Mononuclear cell factor (MCF), synovial factor (SF), lymphocyte activating factor (LAF), endogenous pyrogen and catabolin are all functional names for IL-1 and show in a 'plastic' way the multiplicity of IL-1 activities[24].

Many studies focus on the in vitro effect of interleukin-1 on cultures of rabbit articular chondrocytes and of human or rabbit synovial fibroblast-like cells. Interleukin-1 from different sources (human, murine) and in different forms (α- or β-form, purified, recombinant, from macrophage conditioned media) has been shown to stimulate the de novo production and secretion of latent neutral metalloproteinases, particularly collagenase, gelatinase and proteoglycanase (stromelysin) in chondrocytes[1,12,22,24,28,30,35,51,67,77] and in synovial fibroblasts[12,14,17–20,32,51,56]. This stimulation depends on the IL-1 concentration and can lead to increased degradation of extracellular matrix proteins such as collagens, degraded collagens and proteoglycans. While stimulating the production and secretion of proteases, IL-1 decreases the production of the tissue inhibitor of metalloproteinases (TIMP), promoting tissue breakdown[51]. Tumor necrosis factor α (TNFα/cachectin), in a much smaller dose, is also capable of stimulating synovial fibroblasts to produce collagenase[17,25].

The metalloproteinases which are secreted under the influence of cytokines appear in a latent form, that can be activated by other proteases, particularly plasmin, kallikrein and cathepsin B[81,82,85].

Interleukin-1 also affects the production and the activity of plasminogen activators (proteases which convert plasminogen into plasmin)[16] in chondrocytes and synovial cells. Most authors detect a stimulation of plasminogen-activator (PA) production by IL-1 in chondrocytes[10,11,52] and in synovial cells[38,48,59], although some authors find a decrease in PA production on IL-1 or TNFα/cachectin-treated chondrocyte cultures which is not due to the presence of plasminogen-activator inhibitors[28,77]. This IL-1 induced production of plasminogen activator seems to be mediated through prostaglandin E_2 synthesis[8,12,48,58].

Besides its effects in cell cultures, IL-1 has also been shown to be capable of causing a dose-dependent loss of extracellular matrix in organ cultures. IL-1 (and also TNFα/cachectin) stimulates proteoglycan and collagen release from bovine nasal cartilage and human articular cartilage in vitro[35,39,40,44,72,74]. IL-1, TNFα/cachectin and TNFβ/lymphotoxin also stimulate bone resorption in vitro[4,13,34].

Growth factors (which can also be classified as cytokines) such as transforming growth factor β (TGFβ) and basic fibroblast growth factor (bFGF) also have important regulatory functions in bone and cartilage resorption and formation[13]. Fibroblast growth factor, for example, synergizes with interleukin-1 to increase protease synthesis by rabbit articular chondrocytes[69].

In vivo, IL-1 causes a dose-dependent loss of proteoglycan from cartilage in rabbit knee joints[68].

Some other cytokines have been tested for their effects on extracellular matrix degradation and have been found to have no measurable influence in vitro: interleukin-2 (IL-2)[1,30,77,78], TNFα/cachectin in some cases[30,78] and interferon α and γ (IFN-α and -γ)[17,78] had no effect on metalloproteinase production in cell culture, and IL-2 caused no proteoglycan loss from cartilage in vivo[68].

Figure 1 summarizes the possible mechanisms involved in joint destruction during inflammatory disease processes such as rheumatoid arthritis and osteoarthritis. Cy-

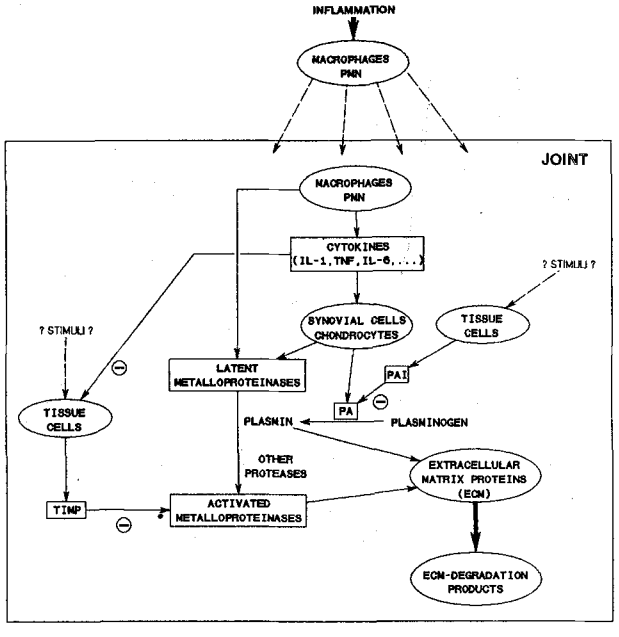

Figure 1. Model of joint destruction in arthritic disorders. Various inflammatory stimuli (including viruses, other infectious agents, lipopolysaccharide[23], denatured immunoglobulins[10], agalactosyl immunoglobulins[66] stimulate macrophages and other polymorphonuclear cells to invade the joint tissues. There they release cytokines and activate other cells to secrete proteases, which degrade extracellular matrix molecules. At several levels proteolysis is controlled by specific inhibitory mechanisms.

Abbreviations used: PMN, polymorphonuclear cells; IL-1, IL-6, interleukin-1, -6; TNFα, tumor necrosis factor α; PA, plasminogen activator; PAI, plasminogen activator inhibitor; TIMP, tissue inhibitor of metalloproteinases; –, inhibitory effect.

tokine mediators (IL-1, TNFα/cachectin) released by inflammatory cells (monocytes/macrophages; polymorphonuclear cells) directly stimulate cells in the synovial joint to produce latent neutral metalloproteinases, such as collagenase, proteoglycanase and gelatinase. Moreover, the infiltrating cells themselves can secrete proteases. The cytokines also stimulate the synovial cells to produce increased levels of plasminogen activators. These plasminogen activators convert plasminogen into plasmin, which can 1) activate the latent metalloproteinases and 2) directly degrade extracellular matrix proteins. The latent metalloproteinases can also be activated by a variety of other extracellular proteases.

Inhibitors of proteinases (tissue inhibitor of metalloproteinase (TIMP), plasminogen activator inhibitor type 1 and 2 (PAI-1 and -2)) play a role in the control of matrix degradation: the balance between protease molecules and protease-inhibitor molecules can determine the extent of matrix degradation as it does for other biological processes such as blood clotting and fibrinolysis.

IL-1 has also been reported to affect the synthesis of extracellular matrix components. Both stimulatory and inhibitory effects of IL-1 on matrix component synthesis have been published [12, 45]. As a result of these complex processes, the extracellular matrix in the joint is degraded and remodelled.

Cytokines and proteases in invasive processes

In angiogenesis

The process of angiogenesis plays an important role in vascularization during normal development as well as in neovascularization of tumors and wounded tissues. Capillary endothelial cells are stimulated to produce certain degradative enzymes, which cause proteolysis of basement membranes and tissue components, enabling the secreting endothelial cells to migrate and proliferate, forming new blood vessels [37, 55].

Various substances have been shown to stimulate the processes of invasion, migration and proliferation of endothelial cells through the extracellular matrix [29]. Basic fibroblast growth factor, for example, has potent angiogenic activity in vivo and can induce capillary endothelial cells to invade a three-dimensional collagen matrix in vitro and to organize themselves in blood capillary-like structures. bFGF also stimulates the endothelial cells to produce plasminogen activator [60].

Penetration of the surrounding tissues requires the elaboration of proteases by the penetrating capillary endothelial cells in order to degrade the proteins of the capillary basal lamina and the surrounding stroma [37]. An increase in PA and latent collagenase levels might provide the proteolytic activities necessary for the penetration of endothelial cells into surrounding tissues. Angiogenic factors are cytokines present in tissue extracts of various origin (e.g. retinal extract [37], mouse adipocyte conditioned medium [37], human placenta [61]). They have been found to increase plasminogen activator and latent collagenase release by cultured bovine capillary endothelial cells in a dose-dependent manner [37, 61]. Fibroblast growth factor, epidermal growth factor or endothelial cell growth supplement were shown not to be responsible for this effect [37].

In other invasive processes

Cells capable of invading tissues, such as macrophages or tumor cells, have been shown to secrete proteases (e.g. collagenase and elastase, PA) after triggering with chemical substances (thioglycollate, phorbol ester ,...) or other stimuli [9, 36, 49, 55, 76, 81, 83, 84]. The invasion of tumor cells through basement membranes into the surrounding tissues depends on the relative amounts of proteases and their inhibitors that are present; these are mainly secreted by the tumor cells themselves, but also by the surrounding normal tissue cells. In the case of excessive matrix destruction in neoplasia the balance leans towards increased proteolysis due to an increased ratio of proteinase to inhibitor. Tumor cells produce collagenase, cathepsin B, proteoglycanases, elastase, gelatinase and plasminogen activators [16, 42, 73, 81].

The mechanism of tissue destruction is analogous to the one described for arthritic disorders in the joints (fig. 1); secreted latent metalloproteinases are activated by other proteases (e.g. by plasmin, cathepsin B) and cause protein degradation. Various proteinase-inhibitors are capable of modifying these destructive processes [55, 81].

Recently it was shown that tumor cells can express a molecule that anchors proteolytic activity to the cells: the urokinase receptor [6, 7, 80]. This discovery introduces the concept of restricted pericellular proteolysis in the degradation of extracellular matrix molecules. It might also explain seemingly contradictory results correlating plasminogen activation with invasive or metastasizing activity of tumor cells.

Very little is known about the natural substances responsible for the stimulation of proteolytic activity in tumor cell and macrophage invasion, but cytokines and growth factors certainly contribute to it [81].

Cytokines and proteases in blood hemostasis and wound healing

Various authors have shown that the inflammatory cytokines interleukin-1 and tumor necrosis factor play a crucial role in the maintenance of blood hemostasis. The balance between tissue-type plasminogen activators (tPA) and their inhibitors in plasma determines to a great extent the fibrinolytic potential of the plasma. IL-1 (purified or recombinant α- and β-types) and TNF (recombinant human α-form) stimulate the synthesis and release of cell-associated and secreted plasminogen activator inhibitor type 1 (PAI-1) by cultured human umbilical vein endothelial cells and fibrosarcoma cells [5, 21, 27, 53, 64, 75]. They decrease the rate of synthesis of tissue-type plasmi-

nogen activator itself[5, 53, 75]. Their effects are not additive but seem to be mediated at least in part by a common pathway[75]. The decrease in tPA (up to 50%) is much less spectacular than the increase in PAI-1 concentration (up to 300–400%). The net effect of IL-1 and TNFα/cachectin on endothelial cells in vitro thus seems to be a suppression of the fibrinolytic activity of the cells leading to a shift of the endothelial hemostatic balance toward the generation and maintenance of fibrin[5]. Human recombinant interferon-γ and natural human IL-2 have also been tested on umbilical vein endothelial cells and have been found to have no effect on PA or PAI-1 production[75].

Few data are available concerning the in vivo effect of cytokines on plasma concentrations of plasminogen activators or their inhibitors. Infusion of IL-1 (human purified or recombinant) into rats resulted in a small but significant increase in PAI-1 activity in rat plasma[27].

Cytokines and proteases in fibroblast function

The effects of cytokine mediators on synovial fibroblast cells have been studied in detail because of their importance in arthritic disorders (see above). Nevertheless, other fibroblast-like cells can also play a role in various inflammatory conditions via an analogous mechanism. IL1-α and -β[32, 70, 71] and TNFα/cachectin[17] cause human dermal fibroblasts to produce and secrete increased levels of latent collagenase, proteoglycanase and gelatinase but also of the collagen matrix itself[71]. In parallel with an increase in these protease levels, IL-1 also increases production of tissue inhibitor of metalloproteinases (TIMP) by dermal fibroblasts[63, 71]. Growth factors, in particular epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and bFGF, induce the synthesis of collagenase, stromelysin and TIMP in human fibroblasts[3, 15, 26]. Transforming growth factor β (TGFβ) modulates the effect of the other growth factors by inhibiting collagenase induction while causing a synergistic increase in TIMP production. The net result of TGFβ in the presence of other growth factors is thus an inhibition of extracellular matrix breakdown[26]. TGFβ also stimulates the synthesis of plasminogen activator as well as that of some inhibitors (protease nexin, PAI-1) in skin fibroblasts and lung fibroblasts, resulting in an enhancement or a decrease of plasminogen activator activity depending on the protease/inhibitor ratio[43, 46, 47].

Dermal fibroblasts are crucial in the repair response that follows tissue injury and in inflammatory processes in the skin. The precise outcome of the regenerative or degenerative process depends on a complex array of interactive pathways that generate interleukins and other modulators of chemotaxis, cell growth, matrix component synthesis and degradation[71].

Inflammation of the supporting tissues of teeth due to bacterial infection is a major cause of dental disease. Destruction of these tissues can be restricted to the gingival tissue (gingivitis) or can involve the periodontal ligament and bone (periodontitis). The role of inflammatory cytokines in periodontal disease has been investigated in tissue cultures of human gingival fibroblasts. The possible mechanisms whereby bacteria-induced inflammation of gingival tissues can result in periodontal disease are similar to those described for arthritic disorders (fig. 1). Activated monocytes/macrophages at the inflammatory site produce interleukin-1 which activates gingival fibroblasts to produce various molecules: latent neutral metalloproteinases such as collagenase and stromelysin, plasminogen activator, and a tissue inhibitor of metalloproteinases, which is able to inactivate the activated metalloproteinases by forming a stable enzyme-inhibitor complex. Furthermore, gingival fibroblasts can themselves produce IL-1, which possibly stimulates collagenase production by osteoblasts in periodontal bone. The activated metalloproteinases can eventually cause degradation of periodontal tissues, depending on the balance between the proteases and their inhibitors[54, 57]. How osteoclasts are activated to cause resorption of periodontal bone in periodontitis is still an unanswered question.

Conclusion

Regulation of the different processes of tissue degradation and remodelling involves a complex network in which proteases, cytokines, growth factors, protease-in-

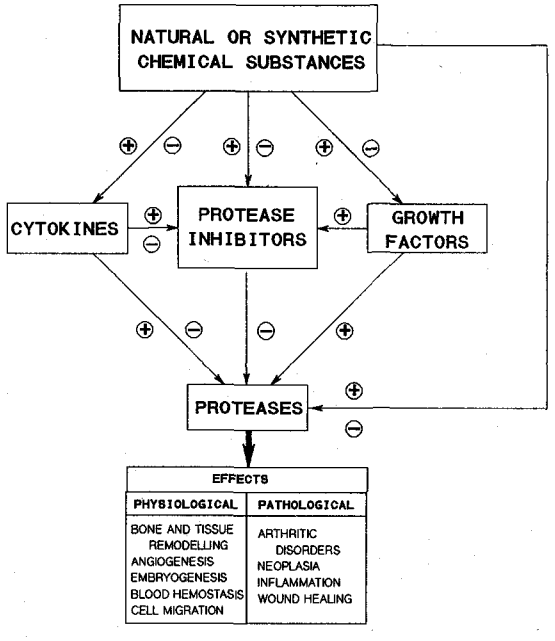

Figure 2. Schematic model of protease regulation. Protease production and activity is directly stimulated or sometimes inhibited by growth factors and other cytokines. Proteases are negatively controlled by (specific) inhibitors, which are in turn regulated by growth factors/cytokines. Various chemical substances can interfere in these processes at different levels through their effects on proteases, cytokines/growth factors and/or protease inhibitors.

hibitors and various other chemical substances play a role. Figure 2 shows a schematic model including some of the important regulatory steps in protease production and secretion.

Protease production and secretion by a variety of tissue cells is positively or negatively regulated by cytokines. IL-1 and TNFα/cachectin in particular stimulate chondrocytes, synovial or skin fibroblasts, endothelial cells and other cell types to produce and secrete proteolytic enzymes (metalloproteinases, plasminogen activators, ...). These enzymes play a role in normal physiological processes (angiogenesis, embryogenesis, cell migration, bone resorption and remodelling, regulation of blood hemostasis) and in disease processes (arthritic disorders, tumor invasion and metastasis, periodontal disease, inflammation, wound healing).

Proteases are negatively controlled by specific protease-inhibitors (PAI-1, TIMP, protease nexins, ...), which can in turn be positively or negatively influenced by cytokines. Growth factors such as bFGF, TGFβ, EGF, PDGF often work in concert with other cytokines and can positively affect protease production directly, or can have a negative indirect effect via their stimulation of protease-inhibitor production. Various naturally occurring or synthetic chemical substances can have a positive or negative effect on protease production directly. They can also indirectly influence protease production by influencing growth factor or cytokine production or by regulation of protease-inhibitor activity.

A detailed insight into these regulatory processes could provide valuable information regarding the treatment of disease conditions where excessive tissue-remodelling plays a damaging role, as in inflammation, tumor invasion, rheumatic diseases and psoriasis. The understanding of these regulatory processes includes the study of the mechanism of action of the cytokines, proteases and their antagonists. The study of regulatory elements of these substances at the genomic level as well as their transacting factors will also provide further insight into the pathogenesis of, for example, inflammation, invasion and metastasis.

Antagonization of proteases or interference with the cytokine-induced production of proteases seems to be a promising alternative for the treatment of inflammatory and neoplastic diseases, and certainly warrants further basic and clinical research.

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Abbreviations used: IL-1, IL-2, interleukin 1, 2; TNFα, TNFβ, tumor necrosis factor α, β; IFNα, IFNγ, interferon α, γ; PA, plasminogen activator; tPA, tissue-type plasminogen activator; uPA, urokinase-type plasminogen activator; PAI-1, PAI-2, plasminogen activator inhibitor type 1, 2; TIMP, tissue inhibitor of metalloproteinases; TGFβ, transforming growth factor β; bFGF, basic fibroblast growth factor; EGF, epidermal growth factor; PDGF, platelet-derived growth factor.

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Host defense against infections and inflammations: Role of the multifunctional IL-6/IFN-β2 cytokine

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Summary. IL-6/IFN-β2 appears to be one of the important mediators of the response to viral and bacterial infections and to shock. The biological effects now associated with IL-6/IFN-β2 include: stimulation of immunoglobulin secretion by mature B lymphocytes (BSF-2 activity), growth stimulation of plasmacytomas and hybridomas (HGF activity), activation of T cells, stimulation of hepatic acute phase protein synthesis (HSF activity), stimulation of hematopoiesis, cell differentiation (DIF activity), inhibition of tumor cell growth (AP activity) and other IFN-like effects. As a typical cytokine, IL-6/IFN-β2 is secreted by many cell types and acts in various combinations with other interleukins and interferons.
Key words. Interferon-β2; interleukin-6; B-lymphocytes; T-lymphocytes; acute phase response; hematopoeisis; differentiation; growth inhibition.

The IL-6/IFN-β2 cytokine: an important mediator of host defense

Since their discovery in virus-infected egg allantoic membranes by Isaac and Lindenman, a major motivation for the study of interferons (IFNs) has been their involvement in the defense of the organism against the infectious process. IFNs are typical cytokines, i.e. cell-secreted proteins carrying messages between cells, such as a warning message against the spread of infection. The type I IFN α and β genes do indeed appear to be principally activated by exposure of cells to viruses and virus-derived inducers such as double-stranded (ds) RNA [1, 2]. The multiple α IFN genes are mainly active in lymphoid and myeloid leukocytes, whereas fibroblastic, epithelial and other cells in solid tissues express essentially the IFN-β gene. It was of considerable interest when another cytokine was discovered, which is similarly induced in fibroblasts by viruses and dsRNA. This cytokine, originally named IFN-β2 [3, 4], but now classified as interleukin-6 (IL-6), appears to be one of the major mediators of the reaction to viral and bacterial infections, inflammation and shock [5, 6]. Although the full extent of its activities on various cells is still not completely settled, the major