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# Cytokines and proteoglycans

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*Abstract.* Cytokines play an important regulatory role in the metabolism of proteoglycans. Proteoglycans are found in plasma membranes, but predominantly in the extra-cellular matrix. In the latter they are quantitatively and qualitatively essential components. Especially in a tissue like cartilage without any blood vessels, the cells are dependent on cytokines for the communication among themselves in the extra-cellular matrix and also for communication with the 'outside world'. Various cytokines have been found to be able to penetrate the extra-cellular matrix and inhibit, respectively stimulate the proteoglycan synthesis. Also, the degradation of proteoglycans can be stimulated, respectively inhibited by several cytokines. In addition, some cytokines have been found which regulate the effects of the other cytokines. With respect to proteoglycan metabolism a complex cytokine network is emerging.

Furthermore it is becoming increasingly clear that proteoglycans are connected to the cytokine network by their own bioactive functions. First, they possibly possess cytokine activities themselves. Second, they can function as receptors, protectors, inactivators and storage ligands for cytokines. So the proteoglycans are clearly involved in the feedback signalling from the extra-cellular matrix to the cells that are synthesizing this extra-cellular matrix. Together with agonistic or antagonistic cytokines they are involved in the regulation of proteoglycan turnover during balanced or unbalanced metabolism in normal, respectively pathological situations.

*Key words.* Cytokines; cytokine network; proteoglycans; protoglycan synthesis; proteoglycan degradation.

## *Introduction*

Cytokines are polypeptide mediators which can be produced by a variety of cells. They are produced when the cells are activated in an immunological way (antigen involved) or in a non-immunological way, for instance by a cytokine. Through the production of cytokines the cells send out messages on a local or a systemic level to target cells. Cytokines do not have one kind of cell as target cells and the set of target cells of one cytokine may differ from the set of target cells of another cytokine. Furthermore, cytokines do not have the same effect(s) on each kind of cells in their set of target cells, as will be outlined below. The effects of cytokines can range from the induction, the stimulation or the inhibition of the synthesis of a specific molecule to the proliferation of a target cell. Several cytokines have been described to stimulate or inhibit the synthesis of proteoglycans. Also the increase or decrease of the degradation of proteoglycans as an effect of cytokines has been described.

Proteoglycans consist of a polypeptide core and one or more carbohydrate side chains. Only a few years ago they were solely considered as rather inert building blocks for the extra-cellular matrix in tissues and it was not quite understood how they could form such different tissues as cartilage and vitreous body. In recent years, as more and more different proteoglycans were discovered, more and more became known about differences in the protein parts and in the carbohydrate parts of these molecules. It was also discovered that proteoglycans not only can be found in the extra-cellular matrix around cells, but also in their plasma membrane. Furthermore, it became clear that in the extra-cellular matrix as well as in the plasma membrane the proteoglycans are not mere building blocks. They can have bioactive functions in which either the protein part, or the carbohdyrate part is involved, or both.

In Part I those proteoglycans will be briefly outlined which have been found to be affected by cytokines, or are connected with cytokine activity.

In Part II the cytokines and their activities on the proteoglycan metabolism will be discussed as well as the effects of cytokines on each other within the so called cytokine network.

In Part III the activities of proteoglycans and their connections with the cytokine network will be described.

## *Part I. Proteoglycans*

Proteoglycans contain glycosaminoglycan side chains that are attached to the polypeptide protein chain forms the core of the molecule. (See for reviews: Hardingham et al.[60,61], Heinegard et al.[66]; Oldberg et al.[110]). The number and the type of glycosaminoglycans vary depending on the type of proteoglycan. Different types of side chains can be mentioned: heparan sulphate, chondroitin sulphate, dermatan sulphate and keratan sulphate. Variation in these side chains is possible in the length and the degree of sulphation. Their molecular

Table 1

| Proteoglycans | M | Localization |
|---|---|---|
| Aggrecan | $\approx 3 \times 10^3$ kDa | ECM of cartilage |
| Betaglycan | 200–300 kDa | Plasma membrane and in solution |
| Biglycan | 50–200 kDa | ECM of most tissues |
| Decorin | 50–200 kDa | ECM of most tissues |
| Fibromodulin | 50–200 kDa | ECM of most tissues |
| HSPG | 800 kDa | ECM of endothelial cells |
| HSPG | 150–250 kDa | Endothelial and parathyroid cell membranes |
| M-CSF | 70–90 kDa | In solution |
| Perlecan | 410–475 kDa | Basement membranes |
| Syndecan | 40–100 kDa | Epithelial cell membrane |
| Thrombomodulin | 57 kDa | Endothelial cell membrane |
| Versican | 780–860 kDa | ECM Of most tissues |

ECM, extra-cellular matrix; HSPG, heparan sulphate proteoglycan; M-CSF; macrophage colony stimulating factor.

weights and localizations have been listed in table 1. Presently proteoglycans can be divided into one group (A) that is found in extra-cellular matrices, another group (B) that has been found in the plasma membrane of various cells and (C) a few proteoglycans that have been found in solution. The extra-cellular matrix group can be subdivided in: AI, the large proteoglycans and AII, the small proteoglycans (see table 2).

*AI: Large proteoglycans in the extra-cellular matrix*

*Aggrecan*

Aggrecan, found in the extra-cellular matrix of cartilage, is probably the most investigated proteoglycan. (See for reviews: Hardingham et al.[59,62]). It has 3 globular domains: G1 and G2 next to each other at the amino terminal end and G3 at the carboxy terminal end. The aggregating properties of aggrecan lie in the G1 domain. G1 binds to hyaluronan and this binding is stabilised by a link protein[59]. An aggregate of one hyaluronan chain to which 100 aggrecans are attached can have a relative mass of $2 \times 10^5$ kDa. Such enormous structures are able to attact large amounts of water, contributing to the biomechanical properties of the cartilage, like resilience[91]. In the G3 part a growth factor-like domain can be found that might play a role in the cytokine network. This will be further discussed in Part III of this review. The area between G2 and G3 is the non-globular region to which the glycosaminoglycans (GAG's) keratan sulphate and chondroitin sulphate are attached[61].

*HSPG*

A large heparan sulphate containing proteoglycan has been found in the extra-cellular matrix of endothelial cells[136]. Apart from its structural function, it has cytokine binding properties which will be outlined in Part III.

*Perlecan*

In basement membranes recently another heparan sulphate containing large proteoglycan has been found. It was named perlecan because its structure looks like a number of pearls on a string[107]. Apart from its function as a building block of basement membranes, the multiple domains suggest interactions with a variety of molecules[107]. The possible function of the 2 growth factor domains that have been found will be discussed in Part III.

*Versican*

Versican, found in the extra-cellular matrix of most tissues, is a large proteoglycan that, like aggrecan, can bind to hyaluronan[171]. However, a G2-like domain as in aggrecan is not present in versican[61]. In the carboxy terminal part of the polypeptide chain of versican 2 growth factor domains have been detected that might play a role in the cytokine network. Their possible function will be discussed in Part III. Another difference between versican and aggrecan lies in the lack of keratan sulphate in the GAG attachment region[61].

*AII. Small proteoglycans in the extra-cellular matrix*

*Biglycan*

Biglycan does not bind to collagen and not much is known about its function to date. Although biglycan has structures in the polypeptide and the GAG part that resemble structures in decorin their location is quite different[48,66]. Whereas decorin is present throughout the extra-cellular matrix, biglycan is predominantly found around cells, so they probably have different functions. For biglycan a role in morphogenesis and differentiation has been suggested as a possibility[163].

Table 2. Proteoglycans

| A: Extra-cellular | | B: Plasmembrane | C: In solution |
|---|---|---|---|
| AI: Large | A II: Small | | |
| 1) Aggrecan | 1) Biglycan | 1) Betaglycan | 1) Betaglycan |
| 2) HSPG | 2) Decorin | 2) HSPG | 2) M-CSF |
| 3) Perlecan | 3) Fibromodulin | 3) Syndecan | |
| 4) Versican | | 4) Thrombomodulin | |

*Decorin and fibromodulin*

Of the small proteoglycans in extra-cellular matrices decorin and fibromodulin are thought to play an important role in the processes that determine the structure of the extra-cellular matrix[61]. They both bind the collagen types I and II which affects the speed of collagen fibril formation and the structure of these fibers[162].

*B: Proteoglycans in the plasma membrane*

During recent years several kinds of proteoglycans have been discovered in plasma membranes:

*Betaglycan*

Betaglycan is a proteoglycan that functions as a receptor for the cytokine TGF$\beta$[4,85] and its role with respect to the activity of TGF$\beta$ and other cytokines will be discussed in Part III.

*HSPG*

Heparan sulphate containing proteoglycans are also present in plasma membranes. In different cell types different forms of HSPG have been described[132,136]. Their cytokine binding properties and their function as a cytokine receptor will be discussed in Part III.

*Syndecan*

Actually there is a family of syndecan molecules, since the extra-cellular part of the polypeptide chain can have different forms[90]. There is also a lot of variation in the number and type of GAG side chains. These variations enable syndecan-bearing cells to modulate the binding of ligands. Fibronectin, thrombomodulin and collagen type I, type III and type V can be mentioned in this respect[45]. Furthermore homologies with the Insuline receptor have been found[45], which suggests that syndecan might have a receptor function as well. This idea is supported by the presence of tyrosines in the intracellular part of the syndecan molecule. They might function as a phosphorylation site for a protein kinase and play a role in signal transduction[45]. The possible regulatory role of syndecan with respect to cytokine activity will be discussed in Part III.

*Thrombomodulin*

Thrombomodulin, found on endothelial cells of vascular walls, has multiple anticoagulant activities[46]. These activities are due to the CS side chain as well as the protein part of the molecule[19]. However, thrombomodulin might also be involved in the cytokine network as will be discussed in Part III.

*C: Soluble proteoglycans*

*Betaglycan*

The possible functions of the soluble form of betaglycan are discussed in Part III.

*M-CSF*

M-CSF belongs to the proteoglycans but it is better known as a cytokine. Therefore it will be discussed in Part II.

Even in relatively inert tissues as the connective tissues proteoglycans are constantly turned over. This process requires control and fine tuning in the case of growth, maintenance and repair. Cytokines play an important role in that respect.

*Part II. Cytokines*

The cytokines that have been reported to influence proteoglycan metabolism are listed in table 3 together with their molecular weight and full name. As the table shows, cytokines are mostly rather small protein molecules. This small size allows them to penetrate extra-cellular matrices and reach their target cells, even in tissues without blood vessels like cartilage. At the same time cytokines that are produced by the cells in such tissues can reach other cells in the same tissue, or be released to travel to other tissues. In the case of articular cartilage, the intermittent compressive forces during the use of the respective joint create a forced influx and outflux of tissue fluid[92,109]. This process can carry molecules like cytokines through the extra-cellular matrix of the articular cartilage at a higher speed than diffusion would provide[92,115].

All the cytokines described to date do act on their target cells via a receptor mechanism. After binding of the cytokine to its receptor on the plasma membrane of the target cell the signal of the cytokine can be carried on in different ways. One possibility is the internalization of the cytokine and its transport to the nucleus, where it interacts on the level of transcription. Another possibility is the use of a signal transducing complex in the

Table 3

| Cytokine | M | Full name |
|---|---|---|
| EGF | 6 kDa | Epidermal Growth Factor |
| FGF | 16 kDa | Fibroblast Growth Factor |
| G-CSF | 19 kDa | Granulocyte Colony Stimulating Factor |
| GM-CSF | 22 kDa | Granulocyte Macrophage Colony Stimulating Factor |
| IFN-$\gamma$ | 20–25 kDa | Interferon gamma |
| IGF 1 | 7 kDa | Insulin-like Growth Factor-1 |
| IL-1$\alpha$ | 17 kDa | Interleukin-1 alpha |
| IL-1$\beta$ | 17 kDa | Interleukin-1 beta |
| IL-1RA | 22–25 kDa | Interleukin-1 Receptor Antagonist |
| IL-3 | 15–30 kDa | Interleukin-3 |
| IL-4 | 20 kDa | Interleukin-4 |
| IL-5 | 50 kDa | Interleukin-5 |
| IL-6 | 26 kDa | Interleukin-6 |
| M-CSF | 70–90 kDa | Macrophage Colony Stimulating Factor |
| PDGF | 16 kDa | Platelet-derived Growth Factor |
| TFG$\beta$ | 25 kDa | Transforming Growth Factor beta |
| TNF$\alpha$ | 17 kDa | Tumor Necrosis Factor alpha |

Table 4. Cytokine categories (with respect to progeoglycan metabolism)

| Catabolic | Anabolic | Modulatory |
|---|---|---|
| GM-CSF | EGF | FGF |
| IL-1 | FGF | G-CSF |
| IL-6 | IFN-$\gamma$ | GM-CSF |
| TNF$\alpha$ | IGF-1 | IFN-$\gamma$ |
| | IL-3 | IL-1 |
| | IL-5 | IL-1 RA |
| | IL-6 | IL-4 |
| | PDGF | IL-6 |
| | TGF$\beta$ | M-CSF |
| | | PDGF |
| | | TGF$\beta$ |
| | | TNF$\alpha$ |

plasma membrane that in turn activates a second messenger system like the cyclic AMP system to carry on the signal intracellularly.

A number of cytokines have effects on progeoglycan metabolism and/or on each others' activity. With respect to proteoglycan metabolism these cytokines could be categorized into:

a) catabolic cytokines which inhibit proteoglycan synthesis and/or promote proteoglycan degradation.

b) Anabolic cytokines which stimulate proteoglycan synthesis and/or inhibit proteoglycan degradation.

c) Modulatory cytokines which regulate the effects of the cytokines mentioned under a) and b).

Most cytokines are multifunctional in a sense that they can elicit more than one effect in a target cell. Some of the cytokines have different effects on different target cells. Therefore it is not possible to categorize them all very strictly and several of them will be placed in more than one of the above categories (see table 4). The effects of the cytokines will be described for each cytokine in the alphabetical order of the cytokines.

*EGF*

Epidermal growth factor can be produced by macrophages[53,147] and belongs to the anabolic category of cytokines. EGF stimulates proteoglycan synthesis and inhibits proteoglycan degradation[45,50,155]. Although chondrocytes do not produce EGF themselves, they do have a receptor for EGF[79]. So the proteoglycans in their extra-cellular matrix can be modulated by EGF which is produced in other tissues adjacent to, or at a distance from the cartilage for instance in synovium.

*FGF*

Fibroblast growth factor (also known as endothelial cell growth factor) can be produced by vascular endothelial cells and macrophages[22,149]. FGF exists in 2 forms, an acidic form and a basic form (aFGF and bFGF of which bFGF is more ubiquitous) with a 55% sequence homology[147]. With respect to proteoglycan metabolism FGF belongs to the anabolic category as well as the modulatory category of cytokines. FGF stimulates proteoglycan synthesis on its own[73,102], but also in synergy with IGF-1[102]. Furthermore, FGF enhances the anabolic effects of TGF$\beta$[73]. On the other hand FGF enhances the catabolic effects of IL-1 by up-regulation of the IL-1 receptor[25,31,64]. Combined with IL-1, FGF stimulates the synthesis of enzymes that degrade proteoglycans[152]. Finally, the effects of FGF are subject to a regulatory feedback mechanism, as FGF down-regulates its own receptor[31].

*G-CSF*

Granulocyte colony stimulating factor can be produced by macrophages, fibroblasts, endothelial cells and chondrocytes[23]. G-CSF belongs to the modulatory cytokines as it suppresses the synthesis of TNF$\alpha$[55].

*GM-CSF*

Granulocyte macrophage colony stimulating factor can be produced by T-cells, fibroblasts and chondrocytes[23,82,122]. Although GM-CSF is mainly a modulatory cytokine, it also contributes to proteoglycan degradation by stimulating the synthesis of plasminogen activator[57]. A discussion of the proteases that degrade proteoglycans and the activation of such enzymes is beyond the scope of this review.

The modulatory activities of GM-CSF lie in the induction or stimulation of the synthesis of IL-1[167], IL-IRA the receptor antagonist of IL-1[94,130] and IL-6[159]. If the induced production of IL-1RA is not synchronized with the induced production of IL-1 but takes place selectively it might be possible to make some cells less sensitive for IL-1, while others remain fully sensitive. Since different forms of the IL-1 receptor antagonist have been reported[43,58] a fine tuning of the cell sensitivity for IL-1 might be possible along this line.

*IFN-$\gamma$*

Interferon-$\gamma$ can be produced by T-cells[65,83] and it belongs to the anabolic and to the modulatory category of cytokines. It prevents proteoglycan degradation by blocking the production of degradative enzymes, which were induced by IL-1 or TNF$\alpha$[6,7]. In the synovial fluid of arthritic patients the level of IFN-$\gamma$ is low[6]. This might contribute to high levels of proteases which lead to the cartilage destruction that is seen in arthritic joints.

IFN-$\gamma$ also has modulatory properties since it stimulates the synthesis of TNF$\alpha$[121] and the expression of the receptor for TNF$\alpha$[2,18,156]. So IFN-$\gamma$ stimulates the effects of TNF$\alpha$ on proteoglycan metabolism. Indeed a synergy between IFN-$\gamma$ and TNF$\alpha$ or IL-1 has been reported for in vivo experiments[67].

*IGF-1*

Insulin-like growth factor 1 can be produced by macrophages[147] and belongs to the anabolic cytokines.

In cells like chondrocytes, endothelial cells and granulocytes IGF-1 is able to stimulate proteoglycan synthesis[1, 13, 70, 96, 125, 164, 168]. However, this stimulatory effect of IGF-1 on proteoglycan synthesis is not equal for all proteoglycans and furthermore IGF-1 can have a differential effect on their size[71]. IGF-1 has also been found to diminish proteoglycan degradation[87, 113, 158].

*IL-1*

Interleukin-1 can be produced by various cell-types. (For recent reviews see: Dinarello[37, 38]). It was previously known under names as lymphocyte activating factor or catabolin and is probably the most widely studied cytokine in the field of proteoglycan metabolism. IL-1 belongs to the catabolic and the modulatory cytokine categories and there are two forms of this cytokine: IL-1$\alpha$ and IL-1$\beta$. These species have a sequence homology of only 26% and their isoelectric points are 5, 8 and 7 respectively[36, 72]. In spite of these differences they can both bind to the same receptor[134] and can therefore exert the same effects.

Its inhibitory effect on the synthesis of proteoglycans is well established for cartilage and chondrocytes[10, 16, 26, 69, 105, 157]. During such diminished proteoglycan synthesis the structure of the proteoglycans appeared not to be affected[157]. At a sufficient concentration IL-1 is able to bring about a complete inhibition of proteoglycan synthesis when applied to cultured cartilage explants[106]. In contrast, it has been reported that IL-1 stimulates the synthesis of proteoglycans in fibroblasts[14, 170].

Besides the inhibition of proteoglycan synthesis, it has been reported that IL-1 contributes to the degradation of proteoglycans by inducing the synthesis of proteases and the activation of such proteases[10, 51, 54, 68, 116, 117, 120]. IL-1 has also been reported to reduce the secretion of TIMP, an inhibitor of those proteases[93].

Most of the investigations regarding the inhibitory effects of IL-1 on proteoglycan synthesis have been performed with cartilage. This tissue mainly contains aggrecan as proteoglycan and hardly any data have yet been reported to elucidate whether the above effects of IL-1 can also be found when studying other proteoglycans.

Apart from the catabolic effects of IL-1, several other effects of IL-1 have been described that fit in the modulatory category. They picture the complicated role of IL-1 in the so called cytokine network.

First, IL-1 can stimulate its own production[111, 127] and it can regulate the expression of its own receptor. Depending on the cell type regulation can mean up-regulation or down-regulation. It has been reported that with fibroblasts the IL-1 receptor expression was up-regulated by IL-1[154], whereas with chondrocytes IL-1 down-regulated the IL-1 receptors[95]. So it appears IL-1 is capable of amplifying its own effects in some cells, whereas in others a feedback mechanism might prevent too strong effects.

Second, IL-1 has been found to modulate the activity of other cytokines. IL-1 up-regulates the receptor for PDGF and induces the production of PDGF itself[119]. IL-1 induces in various cell types the production of IL-6[21, 56, 104], TNF$\alpha$[121, 144, 155], G-CSF[23, 98]; and GM-CSF[23, 98, 167]. Furthermore IL-1 up-regulates the receptors for IL-6[148] and EGF[79], but down-regulates the receptor for FGF[31]. In that way IL-1 is able to moderate the effects of FGF and induce and in some cases even amplify the effects of PDGF, IL-6, TNF$\alpha$, G-CSF and GM-CSF. It is clear from these findings that in the cytokine network IL-1 is connected with at least 7 other cytokines, whose own activites are discussed elsewhere in this review. In in vivo experiments a synergy was found for the effects of IL-1 and TNF$\alpha$ on proteoglycan metabolism[67]. However, in in vitro experiments no synergy was observed[166]. This could mean that in vivo another factor is involved in the synergy.

*IL-1RA*

The IL-1 receptor-antagonist can be produced by macrophages, monocytes and epithelial cells[9, 130, 140].

IL-1RA may exist in different forms as different molecular weights have been reported, see table 3[11, 43, 139, 140]. These differences can be due to different forms of glycosylation[58].

IL-1RA can be considered to be a cytokine since it is produced by one cell and interacts with a receptor on another cell. In this case the effect is not an event at a translational level in the target cell, but the prevention of the binding of IL-1 to its receptor. IL-1RA competitively binds to the same binding site as IL-1[37, 139, 140]. Therefore IL-1RA is strictly speaking not an antagonist in the sense that it induces not an effect in target cells opposite to the effect of IL-1.

*IL-3*

Interleukin-3 can be produced by T-cells[146] and belongs to the anabolic category. IL-3 has been found to stimulate the proteoglycan synthesis of eosinophils and to augment the size of those proteoglycans[129]. Whether IL-3 is able to have any effect on the activity of other cytokines that are involved in proteoglycan metabolism is unknown to date.

*IL-4*

Interleukin-4 can be produced by T-cells and mast cells[74, 88] and belongs to the modulatory cytokines with respect to proteoglycan metabolism. IL-4 stimulates the production of the IL-1 receptor-antagonist by monocytes[47, 112]. In consequence, IL-4 is able to moderate the interaction of IL-1$\alpha$ respectively IL-1$\beta$ with its receptor. In fact 2 receptor types have been characterized for

IL-1[32,41]. So IL-4 could be considered as a kind of cytokine opponent for IL-1 in the cytokine network.

*IL-5*

Interleukin-5 can be produced by T cells[63] and belongs to the anabolic category of cytokines.

Like IL-3, IL-5 has been reported to raise the proteoglycan synthesis in eosinophils and its presence also leads to a larger size of the proteoglycans that are synthesized[129].

Furthermore IL-5 induces in B cells the production of the membrane proteoglycan CD 44. With respect to proteoglycan metabolism IL-5 does not seem to modulate other cytokines that influence proteoglycan metabolism, nor has it any effect on those proteoglycans that in their turn affect cytokine activities (described in Part III).

*IL-6*

Interleukin-6 is produced by fibroblasts, chondrocytes and a long list of other cells. (See for a review: Van Snick[159]). It belongs to all three categories of cytokines since it has catabolic, anabolic and modulatory properties. With respect to the catabolic properties: IL-6 has an inhibitory effect on proteoglycan synthesis[106]. However, compared to the inhibitory effects of IL-1 and TNF$\alpha$, the inhibition by IL-6 is rather limited[77,106].

With respect to anabolic properties: IL-6 reduces the breakdown of proteoglycans by stimulating the synthesis of the protease inhibitor TIMP[86]. With respect to modulatory properties: IL-6 is required for IL-1 to be able to inhibit proteoglycan synthesis, possibly by up-regulation of the IL-1 receptor[106].

When the contribution of IL-6 to the inhibition of proteoglycan synthesis and to the inhibition of proteoglycan degradation are in balance this could have an overall effect that proteoglycan turnover is slowed down.

*M-CSF*

Macrophage colony stimulating factor (also known as colony stimulating factor 1) can be produced by macrophages, fibroblasts and endothelial cells[33] and it belongs to the modulatory cytokines. M-CSF induces or stimulates the synthesis of IL-1 and TNF$\alpha$[33,34,146,147].

As can be seen in table 3 M-CSF is a cytokine that is much larger than the other cytokines. In fact M-CSF is at the same time a proteoglycan as it possesses a GAG part[123,153].

As far as is known to date, M-CSF is a proteoglycan that has no properties as a building block of the extracellular matrix or the plasma membrane.

Whether the activity of M-CSF as a cytokine is dependent, or partly dependent on the carbohydrate part of the molecule has not yet been elucidated.

*PDGF*

Platelet derived growth factor can be produced by platelets and macrophages[147] and belongs to the anabolic and modulatory categories of cytokines. In mesangial cells, smooth muscle cells and chondrocytes a stimulation of proteoglycan synthesis by PDGF has been observed[40,70,124,138]. Furthermore PDGF could bring about a structural change in the GAG side chains by raising the ratio of chondroitin-6-sulphate over chondroitin-4-sulphate with a factor 2[138].

The modulatory activities of PDGF lie in the stimulation of the synthesis of IL-6 in fibroblasts and the up-regulation of the receptor for IL-1[80].

Therefore PDGF could be a cytokine with dualistic activities. On the one hand raising proteoglycan synthesis, but on the other hand enabling IL-1-induced inhibition of proteoglycan synthesis and IL-1 induced degradation of proteoglycans. However, that degradation could be counteracted or diminished by TIMP which was evoked by the IL-6 that the PDGF raised. So the overall PDGF effect might contribute to the balancing of proteoglycan metabolism.

*TGF$\beta$*

Transforming growth factor beta can be produced by a number of cell types like chondrocytes, endothelial cells, fibroblasts and macrophages[70,150]. Several types of TGF$\beta$ exist that are either homodimers or heterodimers[27]. TGF$\beta$ has anabolic as well as modulatory activities. Whether the different types of TGF$\beta$ belong to different categories of cytokines is not yet known.

The stimulation of proteoglycan synthesis by TGF$\beta$ is well established for several cell types: chondrocytes[70,73,80,99,125,142], smooth muscle cells[29,30,138], fibroblasts[165], Kupfer cells[97] and hepatic lipocytes[97]. However, for fibroblasts was reported that the synthesis of biglycan and versican was stimulated, whereas the synthesis of decorin was inhibited[75]. In contrast Bassols and Massague reported that the synthesis of decorin was stimulated in fibroblasts and epithelial cells by TGF$\beta$[15].

Furthermore, TGF$\beta$ was found to induce changes in the structure of proteoglycans. In the case of chondrocytes the ratio of chondroitin-6-sulphate over chondroitin-4-sulphate was lowered by TGF$\beta$[125]. Another example of structural changes in proteoglycans under the influence of TGF$\beta$ is that during syndecan synthesis in epithelial cells extra GAG side chains were added[126]. In fact, the amount of chondroitin sulphate was tripled. Without this structural change of syndecan the binding of thrombospondin (involved in the regulation of blood coagulation) to epithelial cells is not possible[126]. Finally, with fibroblasts the presence of TGF$\beta$ leads to changes in proteoglycans that contain dermatan sulphate[165].

Besides the stimulation of proteoglycan synthesis TGF$\beta$ causes the inhibition of proteoglycan degradation. This has been observed in cartilage and cultured chondro-

cytes[6, 8, 24, 100]. TGFβ achieves this inhibition by a reduction of the mRNA level of proteoglycan degrading enzymes[64]. TGFβ can also raise the TIMP production, which will further inhibit proteoglycan degradation[42].
A wide range of modulatory activities is known for TGFβ.
It can stimulate its own production[108] and inhibit PDGF production[119]. It can up-regulate the receptor for EGF[108] and down-regulate the receptor for IL-1[42, 64, 119]. So in more than one way TGFβ is an opponent cytokine for IL-1. Peculiarly, to counteract the effects of IL-1 on chondrocytes it seems to be a prerequisite that TGFβ is added after IL-1 and not before[125].

*TNFα*

Tumor necrosis factor α can be produced by monocytes and macrophages[84, 143] and as far as proteoglycan metabolism is concerned it belongs to the catabolic category of cytokines as well as to the anabolic and the modulatory category. Like IL-1, TNFα has an inhibitory affect on proteoglycan synthesis in cartilage[69, 133, 166, 170], and it stimulates proteoglycan degradation[35, 69, 133]. In contrast the proteoglycan synthesis in fibroblasts is stimulated by TNFα[170]. When an inhibitory potency of TNFα is compared with that of IL-1 it is about 100 times lower[166].
With respect to the effects of TNFα on other cytokines there are more similarities between TNFα and IL-1. TNFα stimulates its own production in monocytes[121] and induces the production of IL-1 in endothelial cells[39, 103] and IL-6 in fibroblasts[80]. Besides that it has been observed that, comparable to IL-1, TNFα up-regulates the receptor for EGF in fibroblasts[114] and the IL-6 receptor in epithelial cells[148]. Furthermore TNFα down-regulates the IL-1 receptor in chondrocytes[95] and induces or stimulates the synthesis of the IL-1 receptor antagonist in neutrophils and the synthesis of G-CSF and GM-CSF in macrophages[39, 118].
So TNFα can amplify its own effects by stimulating its own production and increase its catabolic effect on proteoglycan synthesis by induction of IL-1. However, if EGF is present some counter-balancing effect is evoked in the cytokine network. Since EGF has an anabolic effect on proteoglycan metabolism the up-regulation of the EGF receptor by TNFα will set this effect in motion, or make this effect stronger. Another counter-balancing effect is possible in the stimulation of IL-6 synthesis that in turn will lead to TIMP production and therefore in the end might (partly) prevent the TNFα induced proteoglycan degradation. Also, the induction of IL-1 on one hand and the synthesis of IL-1RA, or the down-regulation of IL-1R on the other hand, could be possible ways of keeping processes balanced in the cytokine network.
The activities of the cytokines that were mentioned above are brought together in a scheme in figure 1. This depicts the cytokine network as far as it is in connection with proteoglycan metabolism. As this figure is a summary of activities observed in many different cell systems, it is possible that certain activities and other counterbalancing activities cannot be found in every tissue. Since many possible interactions have not yet been investigated, many threads in the cytokine network still have to be woven.

*Part III. Connections of proteoglycans with the cytokine network*

In several proteoglycans domains or sequences have been detected which resemble cytokine structures. So proteoglycans might have cytokine activities, either per se, or after these structures have been cleaved. Another function of these structures could be to bind soluble cytokine receptors, thereby regulating cytokine activity indirectly. Besides these kinds of structures proteoglycans have also been described that can bind cytokines and in that way regulate their activity. Finally there are proteoglycans that are a cytokine, or a cytokine receptor themselves. These different properties will be discussed per proteoglycan in the order that proteoglycans have been described in Part I. Only those proteoglycans will be discussed that possess one or more of the above mentioned properties.

*AI: Large proteoglycans in the extra cellular matrix*

*Aggrecan*

In the carboxy-terminal part of the protein core a domain is present that has EGF-like sequences[12, 151] and could have growth factor activities[61, 62], which might play a role in the cytokine network for proteoglycan metabolism.

*HSPG*

The extra-cellular matrix form of heparan sulphate proteoglycan has also been reported to have EGF domains[76, 101]. Apart from that this HSPG is able to bind FGF[136, 160], thereby protecting it against proteolytic attack[135, 161] and inhibiting the activity of this cytokine[29, 52, 161]. However, for bone marrow cells it was found that the cytokine-proteoglycan complex kept cytokine activity[20]. Furthermore the binding of GM-CSF, IFN-τ and IL-3 to HSPG's has been reported[128, 131]. So not only might HSPG or its metabolites play a role in the cytokine network, but it is also involved in the regulation of the activity of several cytokines in the extra-cellular matrix.

*Perlecan and versican*

In perlecan EGF-like domains have been found also[107]
In versican 2 EGF domains have been described[81] for which a signalling function was proposed[151, 171].
The fact that in all large proteoglycans of the extra-cellular matrix EGF domains have been found, could

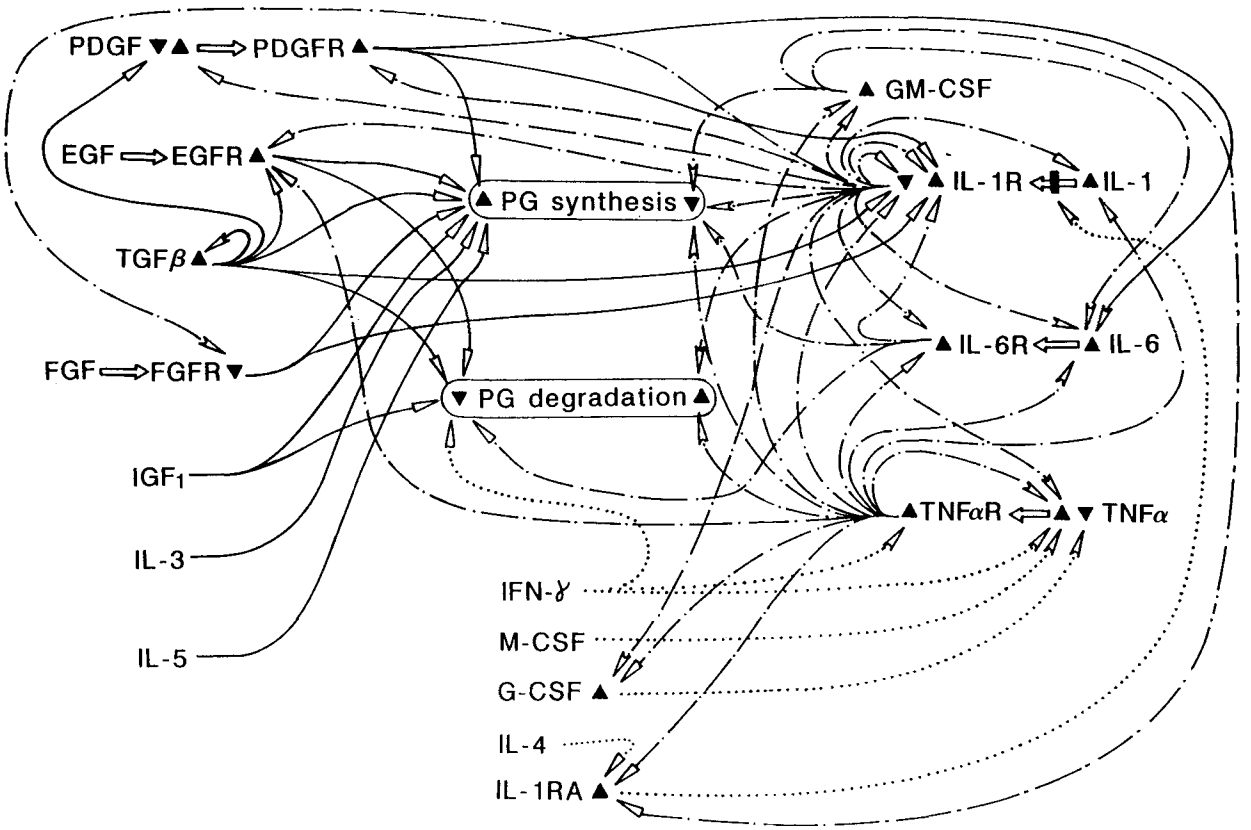


Figure 1. The cytokine network with respect to proteoglycan metabolism. PG, proteoglycan. For explanation of the other abbreviations see table 3. ▲, upregulation; ▼, downregulation; ⇒, cytokine binding to its receptor; ■, blocking of cytokine binding; ——▷, anabolic/modulatory effects; — . —▷, katabolic/modulatory effects; · · · ▷, modulatory/(anabolic) effects.

mean that aggrecan, HSPG, perlecan and versican are possibly actively connected to the cytokine network via the EGF activity they (could) have. This could mean contact of the proteoglycan with the EGF receptor on a cell membrane, or EGF signalling after proteoglycan breakdown.

*AII: Small proteoglycans in the extra-cellular matrix*

*Biglycan*

Biglycan can bind TGFβ[48] in a way that inactivates the cytokine. Since TGFβ stimulates the synthesis of biglycan this system forms a feedback mechanism that is involved in the regulation of extra-cellular matrix formation.

*Decorin*

Decorin also can bind TGFβ[131,169]. The binding to the core protein inactivates the cytokine[169].

So the small extra-cellular matrix proteoglycans are connected to the cytokine network via the regulation of TGFβ activity by binding this cytokine.

*B: Proteoglycans in the plasma membrane*

*Betaglycan*

Betaglycan can bind TGFβ to its core protein and FGF to its heparan sulphate side chain[3]. Betaglycan has been described as a receptor for the TGFβ[5,28,85]. The function of the interaction of FGF and betaglycan is not yet clear.

*HSPG*

The membrane form of heparan sulphate proteoglycan can bind aFGF[78,136] and for parathyroid cells it was proposed that HSPG functions as a receptor for FGF[192]. For adrenocortical cells HSPG was found to contribute to the binding of bFGF to its receptor[137].

*Syndecan*

Syndecan is able to bind bFGF[17,44]. A possible receptor function was proposed[45] on the basis of a discovered sequence homology with the insulin receptor and a possible signal transduction via the tyrosines in the protein core, acting as phosphorylation sites for protein kinases.

*Thrombomodulin*

In thrombomodulin 6 EGF-like sequences have been discovered[19]. Whether these domains actually have cytokine activities has yet to be reported. Since thrombomodulin is a proteoglycan in the plasma membrane the EGF domains most likely have another function than the possible signalling function of the EGF domains in the large proteoglycans in the extra-cellular matrix.

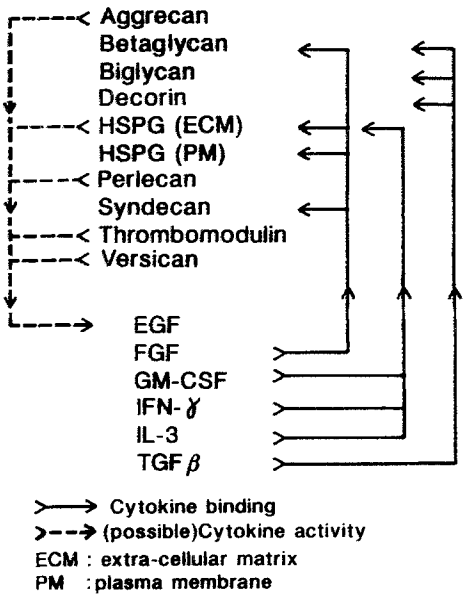


Figure 2. Effects of proteoglycans on the cytokine network.

It is not surprising that for most membrane proteoglycans that were mentioned above a cytokine receptor function has been brought forward. Apart from these proteoglycans functioning as a receptor it could be possible that such cytokine binding structures are expressed without the signal transducing complex connected to it. In that case these proteoglycans would not transmit the message of TGFβ or a/b FGF, but regulate their activity by binding them and lowering their concentration in solution.

*C: Soluble proteoglycans*

*Betaglycan*

Besides the membrane-bound form of betaglycan it has also been observed that betaglycan can act as a soluble form of TGFβ receptor[5, 141]. The question whether betaglycan in this form inactivates the cytokine when bound, or stores it and possibly protects it from proteolytic attack, awaits further investigation.

*M-CSF*

As has been outlined in Part II the macrophage colony stimulating factor is a cytokine that is a proteoglycan or vice versa.

All the connections of these proteoglycans with the cytokine network have been brought together in a scheme that is depicted in figure 2. In order to avoid a very complicated scheme this is kept separate from the cytokine network in figure 1.

*Conclusions*

The emerging picture is that of a very precisely tuned cooperation between cytokines and proteoglycans in the building, turnover and remodelling of tissues. At the same time the difference between cytokines and proteoglycans might fade away when a cytokine turns out to be a proteoglycan and protoglycans turn out to have cytokine properties.

Cytokines influence the synthesis and the degradation of proteoglycans. In figure 1 several examples can be found of possible amplification loops (a) and feedback inhibition loops (b). An example of a): IL-1 upregulates PDGF and PDGFR, PDGF unregulates IL-1R. This leads to an enhanced inhibition of proteoglycan synthesis. An example of b): TNFα upregulates G-CSF, which downregulates TNFα. This leads to moderation of TNFα induced inhibition of proteoglycan synthesis.

The most striking and so far best investigated effects of cytokines on proteoglycans are the effects of synthesis and degradation. However, cytokines also influence the fine structure of the proteoglycans. Differences in the structure of proteoglycans, either part of the extracellular matrix, or of the plasma membrane, can have serious consequences for the bioactivity of these proteoglycans. It could affect their activity as receptors, protectors, carriers and chelators of cytokines, or it could affect their own cytokine activity.

These changes at the cell surface and in the extra-cellular matrix will be sensed in the cytokine network and keep the communication going between cells and their surroundings.

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# Announcements

*Editorial Note:* the information on the following training courses only reached our office at the end of April 1993.

**UNESCO and ICRO (International Cell Research Organization) announce:**

**Theoretical and Practical Course on Molecular Genetics**

*Organization*

The course will be held in November 1993 (1st–13th); Faculty of Biology, University of La Habana, Cuba.

The language of the course will be English.

The theoretical part of the course addresses a limited number of participants (around 50) but of various origins (scientists and advanced students, teachers, engineers). It will cover the recent advances in molecular genetics as well as the specificity of problems of interest to the participants and to their countries.

The practical course is organized along two lines: The first one is the use of methods to analyze nucleic acids' structures and sequences using techniques that do not involve sophisticated laboratory conditions both for research and diagnostic activities (non-radioactive labelling of nucleic acids, probe manipulations). The second topic is the implementation, the characterization and the evaluation of the genetic diversity of populations of interest. It provides the fundamental basis for genetic resources identification and management. The audience to this practical part will be restricted to 20 persons.

*Organizers*

Dr. M. Oliva-Suarez, Facultad de Biologia, Universidad de Habana, Cuba.

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