Fibrosis is an important health problem, and its patho-
genetic principles are still largely unknown. It can develop either spontaneously, or, more frequently, as a consequence of various underlying diseases. Irrespec-
tive of the primary cause, however, fibrotic tissue is always infiltrated by mononuclear immune cells. In most instances the reason for the attraction of these cells to fibrotic tissue and their proliferation remains to be determined; however their cytokine profile shows clear-cut proinflammatory and profibrotic characteristics. In this review, we discuss the innate and adaptive immune reactions associated with the development of fibrosis and the molecular basis of the profibrotic mech-
isms taking place in systemic sclerosis (scleroderma), arteriosclerosis and peri-silicone mammary implant fibrosis.

Fibrosis: a disease with an immune-mediated etiology

Fibrosis, i.e. excessive extracellular matrix (ECM) for-
mation, with proliferation and activation of myofibro-
brasts, is a major global health problem, but its etiology, pathogenesis, diagnosis and therapy have yet to be addressed in detail in either basic or clinical research settings. In principle, fibrosis can occur as a consequence of many different pathologic conditions (Figure 1), the most important of which arise either spontaneously, from tissue damage, inflammatory disease, and in response to foreign implants, or from tumors (see Table 1).

Although the pathologic conditions initiating and per-
petuating these processes are rather diverse, from a bio-
chemical and pathohistological view the end stage of the development of fibrosis seems to be very stereotypic. Thus, in all cases studied, the early stages of fibrotic conditions are characterized by immunologic-inflammatory hall-
marks, viz. a perivascular infiltration by mononuclear cells and the subsequent imbalance of anti- and profibrotic cytokine profiles. In most of these instances, the original antigenic stimuli triggering the lymphoid infiltration have not been identified.

The emphasis of this review is placed on the general role of innate and adaptive immunity, and the respective cytokines involved in the development of fibrosis.

Modulation and amplification of fibrosis by innate immunity

In recent years, an important role of the innate immune system in the development of various fibrotic diseases has become apparent. Early events of fibrosis comprise inflam-
matory changes, including proliferation of ECM-producing cells and the occurrence of mononuclear inflammatory infiltrates. In this context, macrophages and mast cells have been implicated as important participants in inflam-
matory processes involving fibrosis. However, the initial events in the activation of host defence mechanisms are still largely unknown. Several mutually non-exclusive hy-
potheses have been proposed, including infection, reaction to altered self, overproduction of reactive oxygen species (ROS) and nitric oxide (NO), or mechanical stress, e.g. at sites of arterial bifurcation subjected to turbulent flow conditions [1–4] (Box 1, Figure 2). The link between these could be the Nalp3 (also called cryopyrin) inflammasome [5]. Recent studies have shown that various danger signals leading to fibrosis, e.g. the antibiotic bleomycin, silica dust, asbestos, and uric acid (the latter of which is produced upon cellular stress), depend on the activation of the Nalp3 inflammasome [6,7]. Activated macrophages regulate inflammatory ECM turnover through the release of chem-
okines, cytokines, ROS and growth factors, as well as ECM-degrading enzymes. One of the most prominent activ-
ators of mononuclear cells and fibroblasts are hyaluronan fragments that not only induce the expression of various cytokines (IL-1, IL-12, and TNF-α), chemokines (MPI-1A, MCP-1, IL-8) and inducible nitric oxide synthase (iNOS), but also trigger the expression and secretion of macro-
phage-derived matrix metalloproteinases (MMP) [8], i.e. enzymes essential for ECM cleavage. Macrophages are of essential importance in liver fibrosis, where they use MMP-13 to remodel fibrotic tissue. The CD11b-diphtheria toxin receptor (DTR)-transgenic mouse model that enables selective depletion of scar-associated macrophages, shows a 5-fold reduction in MMP-13 levels in response to chemi-
scally induced liver damage [9]. The chemokine MCP-1 and its major receptor, CCR2, are likely to play crucial roles in both renal and pulmonary fibrotic responses. CCR2<sup>−/−</sup> mice display an impaired profibrotic signalling cascade in response to various stimuli, and seem, at least in part, to be protected from inflammation-induced fibrosis [10].

Another important component of cellular innate immu-
nity are mast cells. These can play a role in fibrosis by their
Figure 1. Pathogenesis of fibrosis. Tissue injuries, caused by infection, chemicals, mechanical stress or autoimmune reactions, activate the immune system and repair mechanisms. Effective healing is usually characterized by a dominant Th1 response, whereas a shift of the balance towards Th2 cells, alternatively-activated (M2) macrophages, and myofibroblasts leads to chronic inflammation that can ultimately result in fibrosis.

Table 1. Examples of principal conditions associated with fibromatous lesions.

<table>
<thead>
<tr>
<th>Tissue damage</th>
<th>Inflammatory diseases</th>
<th>Foreign implants</th>
<th>Spontaneous</th>
<th>Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative adhesions</td>
<td>Infections</td>
<td>Silicone mammary implants</td>
<td>Keloids</td>
<td>Stroma of parenchymatous</td>
</tr>
<tr>
<td>Burns</td>
<td>Arteriosclerosis</td>
<td>Cardiac pacemakers</td>
<td>Dupuytren's contracture</td>
<td>tumors Fibromas</td>
</tr>
<tr>
<td>Alcoholic and post-infectious liver fibrosis and cirrhosis</td>
<td>Connective tissue diseases e.g. scleroderma</td>
<td></td>
<td>Peyronie disease</td>
<td>Neurofibromatosis</td>
</tr>
</tbody>
</table>

Box 1. Arteriosclerosis

Arteriosclerosis, the leading cause of human mortality in developed countries, is characterized by thickening and hardening of the arterial wall that, together with other events, finally result in vascular clogging with catastrophic outcomes, such as stroke and myocardial infarction. Arteriosclerosis starts as an inflammatory-immunologic process in the innermost arterial layer, the intima, characterized by an accumulation of mononuclear cells and smooth muscle cells (SMCs) at arterial branching sites where endothelial cells are subjected to turbulent rather than laminar shear stress conditions [77,78]. We have shown that the antigenic trigger for the immune reaction in the intima is the expression of a stress protein (heat shock protein 60 – HSP60) by arterial endothelial cells when they are confronted with classical arteriosclerosis risk factors [4].

Pathophysiologic hallmarks of arteriosclerosis:

- Immigration of T cells into the intima precedes that of monocytes and SMCs [4].
- Classical arteriosclerosis risk factors lead to simultaneous expression of adhesion molecules and HSP60 by endothelial cells [79].
- Mononuclear cells and an elaborate network of dendritic cells are present at arterial branching sites already in healthy children (vascular associated lymphoid tissue – VALT) [80].
- Imbalance of pro-fibrotic vs anti-fibrotic cytokines produced by mononuclear cells lead to fibroblast proliferation and hyperproduction of ECM proteins [81,82].
- Monocytes promote transgression through the endothelium and the basement membrane by increased production of MMPs [83].
- Dysequilibrium between the production and enzymatic cleavage of collagenous ECM components by MMPs, and increased production of tissue inhibitors of metalloproteinases (e.g. TIMP-1) further contribute to arterial thickening and hardening [78].
- SMCs proliferate in the intima and produce ECM proteins upon being subjected to TGF-β1 and PDGF [84].
- Intralesional T cells produce IFNγ that inhibits collagen production by SMCs but also promotes further T cell and NK-cell activation. Activated T cells secrete CD40L and IL-1, thus triggering macrophages to produce MMP-1, -8 and -13 [85].
- The imbalance between ECM – mainly collagen – production, deposition and cleavage by MMPs results in rupture of arteriosclerotic plaques with deleterious consequences [86,87].
- The distribution pattern of various ECM proteins in different areas of normal and arteriosclerotic arteries can be demonstrated clearly by immunohistology.
secretion of tryptases, thereby contributing to connective tissue breakdown. As a consequence of activation of pro-collagenase and induction of a cascade of MMPs, the connective tissue becomes more penetrable for infiltrating leucocytes during inflammation. Moreover, mast cell-derived tryptase indirectly induces fibroblast proliferation by stimulating the synthesis of cyclooxygenase and prostaglandins. These effects are especially prominent in models of cardiovascular diseases [11,12].

Natural killer (NK) cells display predominantly anti-fibrotic properties in several fibrosis model systems. SCID-Beige mice, which lack T and B cells and have defective NK cell function, are more prone to chemically-induced liver and lung fibrosis even when T cell function is reconstituted.
Similarly, natural killer T (NKT) cell-deficient mice challenged with bleomycin show larger fibrotic lesions in the lungs, and have worse clinical outcomes, than wild-type controls [13–15]. Inhibition of liver fibrosis is mediated by NKT-derived interferon (IFN)-γ, which induces cell cycle arrest and apoptosis in hepatic stellate cells in a STAT1 transcription factor-dependant manner [13]. Hepatic stellate cells participate in upregulation of various ECM components, MMPs and tissue inhibitors of metalloproteinases (TIMPs), and their deletion therefore mitigates fibrosis. Furthermore, IFN-γ inhibits the production of the pro-fibrotic cytokine transforming growth factor beta (TGF-β1) both in vivo and in vitro [16]. Low numbers of NK cells have been reported in lymphocyte subsets from post-burn hypertrophic scar tissues, lymphocytes isolated from bronchoalveolar lavage fluid from patients with lung fibrosis, and in peripheral lymphocytes of workers occupationally exposed to mineral fibres [17–19]. Patients with chronic and acute liver disease also show impaired NK cell function in the target organ [20].

**Initiation and regulation of fibrosis by adaptive immunity**

Cells and cytokines of the adaptive immune system play a prominent role in the initiation and progression of fibrosis. Traditionally, Th1 cells are thought to mediate tissue damage, whereas Th2 cells and their corresponding cytokines are linked with fibrogenesis. Th1 and Th2 cytokines play opposing roles in fibrosis: the Th2 cytokines IL-4 and IL-13 are strongly pro-fibrotic, whereas the Th1 cytokines IFN-γ and IL-12 suppress the development of tissue fibrosis [21]. In parasitic infections, a shift from Th1 cytokine (IFN-γ) to Th2 cytokine (IL-4, IL-10, IL-13) production can be observed, with a strong correlation between IL-13 levels and fibrosis in chronic helminth infection such as schistosomiasis [22]. Parasitic antigens exert an immunoregulatory effect by up-regulating IL-10 and down-regulating IL-12 [23]. In addition, the early parasite-induced inflammatory phase is characterized by increased expression of IL-1β, TNF-α, TGF-β, collagens type I and III, and MMPs (MMP-2, -9), while in later stages, increased expression of TIMP-1, -2 and -3 contributes to fibrosis [24]. Several studies have shown high levels of Th2 cytokines in a variety of fibrotic diseases, including systemic sclerosis (SSc), idiopathic pulmonary fibrosis, and foreign body encapsulation, supporting the notion that fibrosis is mainly a consequence of a Th2 cytokine-dominated inflammatory response. Surprisingly, effector CD8+ T cells in patients with SSc produce abnormally high levels of IL-13 associated with increased dermal fibrosis [25,26]. Furthermore, adoptive transfer of Th2-polarized cells induces fibrosis in a murine model of granulomatous lung disease [27].

Since the more recent discovery of the IL-17 producing T cell subset (Th17 cells), IL-17 expression has not only been implicated in the pathogenesis of various autoimmune diseases, but also in some fibrotic disorders. T cells from SSc skin and lung have been shown to express increased IL-17 mRNA levels [28]. Analyzing the influence of IL-17 on fibroblast proliferation and collagen synthesis in monolayer cultures, Kurasawa et al. [28] demonstrated the proliferation of normal and SSc fibroblasts, but no stimulation of collagen synthesis. From these results, it was concluded that IL-17 overproduction could play an important role in the pathogenesis of SSc. However, the demonstration of increased IL-17 expression in affected tissues and of elevated IL-17 serum levels is circumstantial, and does not prove unequivocally a pathogenic role for Th17 cells [28]. IL-17 is not a pure Th17 cell-derived cytokine, but is also made by a variety of other cells, including NK cells, macrophages, neutrophils, and γδ T cells, the latter often being the major source [29–31]. Interestingly, IL-17-producing γδ T cells even seem to have a protective function in bleomycin-induced lung injury. γδ T cell receptor (TCR) knockout mice show increased interstitial pulmonary inflammation and collagen deposition, and delayed epithelial repair after bleomycin administration, whereas wild type (WT) animals display a controlled immune response, characterized by increased IL-17 production by infiltrating γδ T cells [32]. Therefore, IL-17 seems to have both pathogenic and protective functions during inflammation, and although IL-17 is likely to be an important cytokine in the pathogenesis of inflammatory fibrotic conditions, the exact roles of Th17 cells and IL-17 in the development of fibrosis needs further clarification. Moreover, most of the evidence suggesting that Th17 cells are key mediators of autoimmune disorders have resulted from studies on experimental diseases in mice, while preliminary human studies have revealed significant differences between murine and human Th17 pathways, making it difficult to judge the role of this T cell population in the pathogenesis of human diseases at present [33,34].

An outstanding feature of the Th17 lineage is the low susceptibility to regulation by autologous regulatory T (Treg) cells (CD4+CD25highFoxp3+) [35]. This sustains the hypothesis that Th17 cells might play an important role in maintaining inflammatory processes, i.e. "auto-immune-like phenomena", as Treg cells are known to be crucial for the maintenance of peripheral immunologic self-tolerance, as well as for the homeostasis and regulation and immune responses to foreign antigens via suppression of effector cells. Depletion or decreased numbers of Treg cells correlates with allergy and other immunopathological processes, e.g. autoimmune diseases, such as type 1 diabetes and multiple sclerosis [36]. Treg cells also seem to play a role in ameliorating fibrosis, because effective anti-fibrotic therapies are associated with increased numbers of Treg cells [37]. In this context it is important to note that TGF-β1, also produced by Treg cells, has both anti-inflammatory and pro-fibrotic effects. Which effect predominates seems to depend on the local microenvironment.

**Myofibroblasts: the main culprits of fibrosis**

Fibroblasts are key effector cells in fibrosis development, and it has recently been recognized that they form a very heterogeneous cell population. Not only do fibroblasts from diseased tissues differ in their cytokine patterns, and chemokine and ECM synthesis from their healthy counterparts [38], but they also seem to have a very different origin as well. They can be derived from local quiescent connective tissue fibroblasts by proliferation, but there is also ample evidence that at least some of them originate from
myeloid precursors in the blood or bone marrow that then migrate to sites of injury [39,40]. Furthermore, reports of fibroblast trans-differentiation from hepatic stellate cells, skeletal muscle cells, cells of the neural crest and other cell types, have shed additional light on their heterogeneity [41,42].

Fibroblasts vary in lineage, origin, expression of cell surface markers (e.g. CD34, CD14, CD11b, CD80, CD86, MHC class II), as well as in their mechanisms of activation (once in an active state, they are designated as myofibroblasts). Fibroblasts also show a surprising diversity of properties. Myofibroblasts express α-smooth muscle cell actin (α-SMA), produce increased amounts of ECM proteins, such as collagen type I and fibronectin, proliferate and show contractile properties. Their usual activators are IL-6, and TGF-β1, although they can also be activated by a variety of other cytokines, chemokines, growth factors, components of microbial cell walls, and members of the oxidative burst cascade [21].

Fibroblasts also receive stimuli from direct cross-talk with lymphocytes via the CD40-CD40 ligand (CD40L or CD154) pathway. CD40 ligation results in nuclear translocation of the transcription factor NF-κB, and, subsequently, the synthesis of IL-6 and IL-8, hyaluronan, as well as the adhesion molecules ICAM-1 and VCAM-1. Interestingly, some human lung fibroblasts have been shown to express not only CD40, but also CD40L, and these are found at increased levels in fibroblasts from fibrotic tissue [43]. Thus, fibroblast-derived CD40L might play a role in perpetuating fibroblast activation once inflammatory cells have left the nascent area of fibrosis.

Pro- and anti-fibrotic growth factors and cytokines
As mentioned earlier, the pathophysiology of fibrosis is similar in many fibrotic disorders regardless of the underlying primary disease or affected tissue(s). Various stimuli released in the course of the underlying diseases cause the secretion of certain cytokines, chemokines, and growth factors by inflammatory cells and activated resident cells. These cytokines, chemokines, and growth factors perpetuate inflammation, cause further cell injury and induce fibrotic events, e.g. activation, differentiation and proliferation of fibroblasts, as well as increased production of collagen and other ECM proteins (Figure 3).

Among the various pro- and anti-fibrotic cytokines, TGF-β isoforms seem to play a key role in the development of fibrosis (Figure 3). TGF-β represents a large family of closely related proteins that share structure, use similar receptors and signaling pathways, and exert overlapping, but non-identical, biological functions. In mammals, three TGF-β isoforms have been identified, TGF-β1, -β2 and -β3, with cellular actions ranging from anti-inflammatory to fibroblast chemo-attraction and regulation of ECM formation [44]. The effects of the various TGF-β isoforms are target cell-specific and context-dependent. A fibrogenic role of TGF-β1 has been shown in many experimental models and fibrotic disorders, while TGF-β3 has anti-fibrotic properties. Studies on the role of TGF-β2 in the pathogenesis of fibrotic diseases are rare, and the results are contradictory. Findings from our own studies using the University of California at Davis-200 (UCD-200) chicken – the only spontaneous animal model showing all the hallmarks of human SSc, i.e. primary vascular alterations, inflammation, autoimmunity, and fibrosis of skin and internal organs [45] – revealed that TGF-β2, in contrast to general belief, can act as a potent anti-fibrotic cytokine [46] (Box 2). It was shown in vitro by observing that chicken embryonic fibroblasts (CEF) from UCD-200 chickens, which express more of a profibrotic proc2(I)mRNA variant compared to the CEF from normal White Leghorn (NWL)
induced by TGF-β, connecting the cell surface to the ECM. CTGF is a member of the CCN family of matricellular proteins (CCN2) that all function as adaptor molecules, leading to proliferation of the cells and collagen synthesis, whereas activation in the presence of insulin-like growth factor (EGF) or other mitogenic factors results in myofibroblast differentiation and increased collagen production. Furthermore, it has been demonstrated that the induction of α-SMA by TGF-β1 is adhesion- and integrin-dependent, supporting the notion that integrins are functional receptors for CTGF.

CTGF is a member of the CCN family of matricellular proteins (CCN2) that all function as adaptor molecules connecting the cell surface to the ECM. CTGF is induced by TGF-β1 and some other pro-fibrotic mediators, and can be expressed by fibroblasts, endothelial cells, smooth muscle cells, chondrocytes, and various cancer cell lines. In fibroblasts, CTGF expression is induced selectively by TGF-β1, via a unique TGF-β response element in the CTGF promoter. It is abundantly present in the lesions of various fibrotic disorders, e.g. systemic sclerosis, Dupuytren’s contracture, liver fibrosis, glomerulosclerosis, idiopathic pulmonary fibrosis, and cardiac fibrosis.

Fibrosis is a common consequence of silicone-containing active and passive implants. Excessive peri-SMI connective tissue capsule formation is a paradigmatic example of this.

Pathophysiologic hallmarks of peri-SMI capsule formation

- Ample presence of T cells, macrophages, dendritic cells and scarce B cells in SMI capsules [100-102].
- Serum proteins from many protein families adhere to silicone surfaces and mediate adhesion of fibroblasts, macrophages and ECM proteins [2].
- Macrophages are activated by cryptic or altered protein domains exposed on silicone surfaces or by silicone degradation products that are also ingested [103].
- Activated intracapsular lymphoid cells stimulate transdifferentiation of fibroblasts to myofibroblasts by CTGF, IL-1, and TNFx. Macrophages contribute to this process by the production of TGFβ1 and IL-6 [104].
- Soluble ICAM-1, procollagen III, circulating immune complexes and anti-polymer antibodies are elevated in sera of women with strong fibrotic reactions to silicone [105].
- A special ELISA-based test system (SILISA®) demonstrating the “signature” of serum protein adhesion to different silicone types can be used to determine the potential risk of fibrosis development in SMI carriers [106].
- Tight immunoregulatory mechanisms counteract early stages of fibrosis, intracapsular CD4+, CD25high, Foxp3+ Tregs being the most important candidates (E. Rabensteiner, MD thesis, Innsbruck Medical University, 2009).

Another cytokine required for TGF-β1-induced myofibroblast differentiation is osteopontin (OPN). This requirement was demonstrated in the response of cardiac fibroblasts from OPN-null mice to TGF-β1 and confirmed by selectively downregulating OPN-mRNA in WT fibroblasts using siRNA. In contrast to WT fibroblasts, TGF-β1-stimulated
OPN\(^{-/-}\) fibroblasts showed no increase in the expression of α-SMA and CTGF, suggesting an early effect of OPN in the fibrotic response [57]. Further studies will be needed to elucidate the role of OPN in CTGF gene expression. OPN has been implicated in the pathogenesis of several fibrotic conditions, e.g. liver fibrosis, cardiac fibrosis, and idiopathic pulmonary fibrosis [58,59]. Studies in OPN-deficient mice also demonstrated the pro-fibrotic effects of OPN, i.e. OPN\(^{-/-}\) mice developed altered bleomycin-induced lung fibrosis characterized by a reduced collagen type I expression [60]. A recent study has shown that macrophage- and mast cell-derived platelet-derived growth factor (PDGF) induces the expression of OPN by fibroblasts, and that knockdown of OPN leads to reduced scarring in mouse skin wounds [61]. This suggests that inflammation-triggered OPN expression might contribute to the development of fibrosis. As mentioned above, the Th2 cytokine IL-13, which is considered to be anti-inflammatory, is also strongly pro-fibrotic. Its pro-fibrotic activities involve direct and indirect mechanisms. Thus, IL-13 can, directly and independently of TGF-β, stimulate collagen expression in fibroblasts [62], or induce TGF-β production by signaling through IL-13Rα2 [63].

In addition to the above-mentioned cytokines, IL-4, IL-6, IL-10, IL-21, basic fibroblast growth factor (bFGF), EGF, insulin like growth factor-1 (IGF-1), PDGF, oncostatin M, and endothelin 1 (ET-1) [64] all promote fibrosis, whereas IFN-γ, and IL-12 are anti-fibrotic. IL-5 [21] and TNFα [65] seem to be Janus-like, exerting either pro- or anti-fibrotic activities depending on the disease, animal model, and experimental settings, respectively.

**Therapeutic implications**

The best approach to treat fibrotic diseases would be the early identification and subsequent elimination or control of the initial triggering factor of a particular fibrotic disorder. However, the ultimate etiology of many fibrotic diseases is still unknown, and the triggers are diverse. A more feasible approach might be a cytokine-directed therapy. For example, TGF-β1 has been considered as a promising therapeutic target, but a placebo-controlled phase I/II trial with anti-TGF-β1 antibody therapy in SSc patients not only showed a lack of efficacy, but also increased morbidity and mortality [66]. This is not surprising, since TGF-β1 is a pleiotropic cytokine that, in addition to its role in fibrogenesis, has essential functions in normal tissue repair, angiogenesis, and immune regulation [67]. As mentioned above, TGF-β2, in contrast to TGF-β1, can act as a potent anti-fibrotic cytokine, at least in an animal model of SSc [46]. While our group has demonstrated a direct anti-fibrotic effect of TGF-β2 in vitro, another group has shown an indirect anti-fibrotic effect via the induction of tolerogenic antigen presenting cell-dependent CD8\(^+\) Treg cells in a murine model of autoimmune pulmonary interstitial fibrosis [68]. Considering the fact that some studies have shown reduced TGF-β2 expression in the skin of SSc patients [47], we deem it worthwhile to study the potential therapeutic effect of TGF-β2 in the UCD-200 model, which shows striking similarities to human SSc. Another approach to avoid clinical problems associated with broadly targeting the TGF-β1 axis could be to selectively target pro-fibrotic mediators downstream of TGF-β1. Recently, it has been shown that targeting CTGF expression with siRNA prevents carbon tetrachloride-induced liver fibrosis in rats [69], and anti-CTGF neutralizing antibodies have been shown to ameliorate TGF-β-induced fibrosis in mice [70]. Blocking CTGF can inhibit both TGF-β1 and CTGF-mediated ECM synthesis. An alternative approach to inhibiting TGF-β1 signaling is via tyrosine kinase inhibitors. Reduction of ECM protein production in vitro reduced the number of myofibroblasts and reduced skin thickness in an experimental dermal fibrosis model [71], but blocking TGF-β1 activity might lead to overt activation of the immune system and impaired wound healing [72]. A very recent publication described the promising anti-fibrotic effect of Imatinib in experimental animal models of fibrosis. Imatinib is a small molecule tyrosine kinase inhibitor

### Table 2. List of proteins found to be deposited on the surface of silicone mammary implants (SMI) after in vitro incubation with human serum\(^{-}\).

<table>
<thead>
<tr>
<th>Mediators of host defence:</th>
<th>Extracellular matrix and associated proteins:</th>
<th>Intracellular proteins:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulin G, A, E</td>
<td>Fibronectin</td>
<td>Actin</td>
</tr>
<tr>
<td>Complement C2 precursor</td>
<td>Vitronecin</td>
<td>Heat Shock Protein 60</td>
</tr>
<tr>
<td>Complement C1s</td>
<td>Fibrinogen</td>
<td>PR02619</td>
</tr>
<tr>
<td>Complement C3 precursor</td>
<td>Collagen I, IV, VII</td>
<td>γ-glutamyltransferase</td>
</tr>
<tr>
<td>C reactive protein</td>
<td>Procollagen III</td>
<td>NADH dehydrogenase</td>
</tr>
<tr>
<td>Myeloid related protein 8, 14</td>
<td>Laminin</td>
<td>α-spectrin</td>
</tr>
<tr>
<td>Alpha1-microglobulin/bikunin precursor</td>
<td>Matrix metalloproteinase 2</td>
<td>Vimentin</td>
</tr>
<tr>
<td>RT1B1</td>
<td>Fibroblast growth factor 11</td>
<td>Myosin binding protein H</td>
</tr>
<tr>
<td>AMBP protein precursor</td>
<td>Transport proteins:</td>
<td>Glyceraldehyde-3 phosphate dehydrogenase TGF-β1</td>
</tr>
<tr>
<td>Integrin beta-4</td>
<td>Apolipoprotein A1</td>
<td>Flavin reductase</td>
</tr>
<tr>
<td>Integrin beta-2</td>
<td>Apolipoprotein A1</td>
<td>Creatin Kinase M-type</td>
</tr>
<tr>
<td>T cell receptor fragment</td>
<td>Apolipoprotein A3</td>
<td>Gamma-glutamyl transferase</td>
</tr>
<tr>
<td>Monocyte chemotactic protein-2</td>
<td>Alpha2-macroglobulin precursor</td>
<td></td>
</tr>
<tr>
<td>Eosinophil peroxidase</td>
<td>Haptoglobin 1</td>
<td></td>
</tr>
<tr>
<td>Interleukin 10, 19</td>
<td>Hemoglobin</td>
<td></td>
</tr>
<tr>
<td>Kininogen</td>
<td>Plasma-retinol binding protein</td>
<td></td>
</tr>
<tr>
<td>Coagulation factor V</td>
<td>Vitamin D binding protein fragment</td>
<td></td>
</tr>
<tr>
<td>Von Willebrand Factor</td>
<td>Apolipoprotein A3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apolipoprotein E3</td>
<td></td>
</tr>
</tbody>
</table>

\(^{-}\)Modified from reference [2].
targeting both the TGF-β and the platelet-derived growth factor (PDGF)-signal transduction pathways. Importantly, this drug not only inhibits the development of fibrosis, but also stops its progression, and even leads to regression, of preexisting fibrosis [73].

Concluding remarks and open questions

The fibrotic consequences of various primary diseases, ranging from tissue damage resulting from inflammatory conditions, reactions against foreign material, to “spontaneous” fibrosis, remains a major unsolved diagnostic and therapeutic medical problem. In our experience, all fibrotic tissues derived from patients and experimental animals with diseases falling into one of these groups display signs of a chronic immune-mediated inflammation during the earliest periods of their development. This fact obviously raises questions about the specificity of lymphocytes occurring in fibrotic tissue, as well as about a possible imbalance of pro- and anti-fibrotic cytokines produced by components of the mononuclear cell infiltrate. One question that remains to be answered is how the Nalp3 inflammasome and the inflammasome-dependent cytokines IL-1β and IL-33 are involved in the development of fibrotic disorders. Interestingly, IL-1 has been shown to be crucial in regulating the Th2 response in gastrointestinal nematode infection [74], and IL-33 to induce the expression of the Th2-associated cytokines IL-4 and IL-13 [75] – cytokines that, in turn, lead to the development of alternatively activated macrophages [76]. Since optimal biomarkers for the diagnosis and staging of fibrosis are not yet available, more detailed knowledge on the cellular and molecular basis of fibrogenic processes is urgently needed. This is also essential for the development of new evidence-based therapeutic concepts.

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