Platelet-Derived Growth Factor: A Key Factor in the Pathogenesis of Graves' Ophthalmopathy and Potential Target for Treatment

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Key Words

Graves' ophthalmopathy · Platelet-derived growth factor · Orbital fibroblast · Proliferation · Hyaluronan · Cytokines · Thyroid stimulating hormone receptor · Dasatinib · Imatinib mesylate · Nilotinib

Abstract

Activation of orbital fibroblasts resulting in excessive proliferation, cytokine and hyaluronan production and differentiation into adipocytes, is a main determinant of orbital tissue inflammation and tissue expansion in Graves' ophthalmopathy (GO). During the last years we have shown that the platelet-derived growth factor (PDGF) isoforms PDGF-AA, PDGF-AB and PDGF-BB are increased in orbital tissue from GO patients with active and inactive disease. These PDGF isoforms exhibit the capacity to stimulate proliferation, hyaluronan and cytokine/chemokine production by orbital fibroblasts. Moreover, PDGF-AB and PDGF-BB increase thyroid stimulating hormone receptor (TSHR) expression by orbital fibroblasts, which enhances the orbital fibroblast activating capacity of the TSHR stimulatory autoantibodies present in Graves' disease (GD) patients. Of these PDGF isoforms PDGF-BB exhibits the strongest orbital fibroblast activating effects, which is likely related to its ability to bind both the PDGF-receptor (PDGF-R) α and PDGF-R β chains. Thus the PDGF-system fulfills important roles in orbital fibro-

blast activation in both active and inactive GO, which supports a therapeutic rationale for blocking PDGF signaling in GO. Tyrosine kinase inhibitors (TKIs) may be candidates to target PDGF signaling. Of several TKIs tested dasatinib exhibited the highest potency to block PDGF-R signaling in orbital fibroblasts and may represent a promising compound for the treatment of GO as it was effective at low dosage and is associated with less side effects compared to imatinib mesylate and nilotinib. In this review the contribution of PDGF to the pathophysiology of GO as well as therapeutic approaches to target this PDGF-system will be addressed.

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Introduction

Graves' disease (GD) is a common autoimmune disease that affects the thyroid gland. GD associated clinical features such as hyperactivity, heat intolerance, palpitations and weight loss are caused by excessive thyroid hormone secretion induced by thyroid-stimulating autoantibodies [1]. Apart from thyroid-related symptoms, GD patients can also develop extra-thyroidal manifestations such as ophthalmopathy and localized dermatopathy [1, 2]. Dermopathy is relatively rare and is present in approximately 4% of GD patients, while ophthalmopathy is clin-

ically manifest in approximately 25–50% of GD patients and strongly associated with smoking [3, 4].

Symptoms of Graves' ophthalmopathy (GO) are primarily of mechanical origin. An increase in orbital connective and/or muscle tissue within the space-limited bony orbit leads to protrusion of the eye and subsequent ocular symptoms, including upper eye lid retraction, edema, erythema of the periorbital tissues and conjunctivae, proptosis, strabismus, and blindness in severe cases [2]. Based on EUGOGO classification criteria the severity of GO can be categorized based on symptoms mentioned above into mild, moderate-to-severe and sight-threatening GO [5]. Mild GO cases are those having mild symptoms with minor influence on daily life and do not require treatment [5]. Moderate-to-severe cases are those who experience a major influence on daily life with higher degree of exophthalmos and diplopia, and require medical treatment [6]. Sight-threatening GO, including patients with dysthyroid optic neuropathy and/or corneal ulceration, requires immediate treatment [4, 5]. Although other therapeutic approaches apart from corticosteroids, including biologicals targeting TNF- α or B-lymphocytes [7, 8] have been applied in GO, there is at current no convincing evidence for these treatment options and novel strategies are eagerly needed. This requires in depth insight into the complex pathophysiology of GO. In the past few years our group has shown that platelet-derived growth factor (PDGF), a major growth factor in health and disease, is elevated in orbital tissue from GO. In this review we will discuss the pathophysiology of GO and more specifically the role of PDGF herein, as well as potential therapeutic options to target the PDGF-system in GO.

The Pathophysiology of GO

The pathophysiology of GO comprises various cell types, inflammatory mediators and autoantibodies that interact with each other, resulting in orbital inflammation and tissue expansion. Immune cells involved in GO include at least T-lymphocytes, B-lymphocytes, monocytes, macrophages and mast cells, which activate orbital fibroblasts either via secreted factors or direct cell-cell contact [9, 10]. Orbital fibroblast activation with resultant production of cytokines and glycosaminoglycans (especially hyaluronan), proliferation and adipocyte differentiation is considered to fulfill a central role in orbital tissue inflammation and expansion in GO (fig. 1).

Autoantibodies directed against the thyroid stimulating hormone receptor (TSHR) are considered as impor-

tant contributors to GO and TSHR autoantibody titers correlate positively with disease severity and disease activity [2, 11]. Orbital fibroblasts express TSHR, which increases when orbital fibroblasts differentiate into adipocytes [12, 13]. TSHR stimulatory autoantibodies stimulate the production of cytokines, hyaluronan and adipocyte differentiation by orbital fibroblasts [14–18]. So far, however, hardly any information is available on mediators that regulate orbital TSHR expression, but IFN- γ , TGF- β and TNF- α have been shown to downregulate TSHR expression on orbital fibroblasts, while this is enhanced by IL-6 [19, 20]. It has been suggested that insulin-like growth factor-1 receptor (IGF-1R) stimulatory autoantibodies enhance the production of hyaluronan and the T cell chemoattractants IL-16 and CCL5 by orbital fibroblasts and/or recruited fibrocytes [21–24]. These effects appear to depend on physical and functional interactions between the TSHR and IGF-1R, pointing at a functional interplay between TSHR autoantibodies, IGF-1R autoantibodies and their receptors in GO [25]. The contribution of stimulatory autoantibodies directed against IGF-1R in GO is however controversial [26] and therefore more studies are required to fully understand the role of IGF-1R and IGF-1R autoantibodies in the pathophysiology of GO.

The composition of the inflammatory cell infiltrate and inflammatory mediators within the orbital environment likely influences orbital fibroblast behaviour, and several different inflammatory mediators with orbital fibroblast activating capacities have been identified in orbital tissue from GO patients. Orbital inflammation in early GO is dominated by a T-helper 1 (Th1) cytokine environment with abundant production of cytokines such as IL-1 β , IL-2, IFN- γ and TNF- α while in late GO a Th2 dominated cytokine environment with increased production of IL-4, IL-5 and IL-10 might be more prominent [2, 27–29]. Of these it has been shown that IL-1 β stimulates orbital fibroblasts to produce IL-6, IL-8, CCL2, CCL5 and IL-16, which are chemoattractants for B-lymphocytes, neutrophils, monocytes and T-lymphocytes [30, 31]. Moreover, IL-1 β strongly enhances hyaluronan production by orbital fibroblasts and stimulates orbital fibroblasts to differentiate into adipocytes [30, 32]. IFN- γ induces HLA-DR, ICAM-1 and CD40 expression as well as CXCL9, CXCL10 and CXCL11 production by orbital fibroblasts from GO patients, indicating a role in lymphocyte recruitment and immune effector function [33–35]. In addition, IFN- γ stimulates and acts synergistically with IL-1 β on glycosaminoglycan synthesis by orbital fibroblasts [36, 37]. In contrast to IL-1 β , IFN- γ inhibits adipo-

Fig. 1. Pathophysiology of GO. T-lymphocytes, B-lymphocytes, monocytes, macrophages and mast cells are recruited into the orbital tissue where they activate orbital fibroblasts via secreted factors or direct cell-cell contact to produce cytokines/chemokines and hyaluronan, to proliferate, and to differentiate into adipocytes.

Stimulatory autoantibodies directed against TSHR and IGF-1R can activate orbital fibroblasts to produce cytokines/chemokines, hyaluronan and to differentiate into adipocytes. Together these processes contribute to orbital tissue expansion in GO.

genesis by orbital fibroblasts [19]. In the later stage of GO orbital fibroblasts proliferate and produce hyaluronan upon IL-4 stimulation [37, 38] while adipogenesis is not affected by IL-4 [20]. Interaction between CD154 (also called CD40-ligand) expressed by T-lymphocytes and CD40 expressed by orbital fibroblasts stimulates hyaluronan synthesis, ICAM-1 expression and production of various inflammatory mediators by orbital fibroblasts, amongst which IL-6 [39–42]. Next to directing B-lymphocyte effector functions, IL-6 may enhance adipogenesis by orbital fibroblasts in GO [43]. Besides the cyto-

kines discussed above other factors with orbital fibroblast activating activities have been identified in GO and several of them, including their biologic effect on orbital fibroblasts, are given in table 1.

In recent years numerous novel, targeted therapies have been introduced in clinical practice, like the biologicals and tyrosine kinase inhibitors (TKIs). Therapeutic strategies that target specific cytokines, growth factors or autoantibodies that display orbital fibroblast activating activity and are increased in GO may be promising. In the last few years our group has identified platelet-derived growth fac-

Table 1. Factors that influence orbital fibroblast functions

	Effect on orbital fibroblasts				
	proliferation	cytokine production	hyaluronan production	TSHR expression	adipogenesis
IL-1 β		IL-6 [29, 31], IL-8 [39], IL-16 [67] and MCP-1 [68]	+ [30, 32, 68]		+ [30]
IL-4	+ [38, 69]		+ [37]		
IL-6				+ [20]	+ [43]
IFN- γ		CXCL9 [35], CXCL10 [34] and CXCL11 [35]	+ [37]		- [19]
IGF-1	+ [38]		+ [70]		
TGF- β	+ [38]		+ [48, 71]	- [19]	- [19]
CD154	+ [39–42, 69]	IL-6, IL-8 and MCP-1 [39]	+ [40, 42]		
TNF- α			+ [30, 36]		- [19, 30]
Leukoregulin			+ [72]		
TSHR-Ab		IL-6 [15]	+ [14, 16]		+ [17, 18]
IGF-1R-Ab		IL-16 and RANTES [21, 22, 67]	+ [23]		
PDGF-AA	+ [47]	IL-6 [47]	+ [47]	- [54]	
PDGF-AB	+ [47]	IL-6 [47]	+ [47]	+ [54]	
PDGF-BB	+ [47, 48]	IL-6, IL-8, CCL2, CCL-5 and CCL7 [47, 53]	+ [47, 48]	+ [54]	

tor (PDGF) as a major contributor to the pathophysiology of GO and thus an attractive therapeutic target for this disease, which will be discussed in the next sections.

Platelet-Derived Growth Factor

PDGF is a family of growth stimulating polypeptides that exerts broad functions in health and disease [44]. There are four different PDGF genes that encode the peptide chains PDGF-A, PDGF-B, PDGF-C and PDGF-D [44]. Disulfide bridging between PDGF chains results in the formation of the homodimeric molecules PDGF-AA, PDGF-BB, PDGF-CC and PDGF-DD or the heterodimeric PDGF-AB molecule [44]. The pro-peptide chains of PDGF-A and PDGF-B dimerize intracellularly and have to be activated before secretion by removal of their N-terminal ends [44]. PDGF-CC and PDGF-DD are secreted as latent molecules that contain CUB domains at their N-terminal ends [44]. Activation of these PDGF isoforms occurs after proteolytic removal of the CUB domains by proteases such as plasmin and tissue plasminogen activator [44].

PDGF dimers exert their biologic actions via activation of specific receptors consisting of two PDGF receptor (PDGF-R) chains ($\alpha\alpha$, $\alpha\beta$ or $\beta\beta$ chains). The PDGF-A and PDGF-C chains are ligands for PDGF-R α , the PDGF-D chain is a ligand for PDGF-R β , while the PDGF-B chain can bind both to PDGF-R α and PDGF-R β , but with a

higher affinity for PDGF-R β [44]. PDGF-R chains consist of an extracellular and an intracellular part. The extracellular part contains five immunoglobulin-like domains while the intracellular part consists of split kinase domains (fig. 2a). Depending on the PDGF ligand that binds PDGF-R chains dimerize in either one of three dimeric forms; $\alpha\alpha$, $\alpha\beta$ or $\beta\beta$ (fig. 2a). The PDGF-receptor belongs to the tyrosine kinase receptor family and PDGF binding is followed by autophosphorylation of crucial tyrosine residues within the receptor chain (fig. 2b) with subsequent activation of downstream signaling molecules such as RAS-MAPK, PI3K and PLC [44, 45].

In normal physiology, PDGF signaling fulfills important roles in organogenesis, organ/tissue homeostasis and wound healing processes. For instance, PDGF-signaling is involved in alveogenesis, villus morphogenesis, spermatogenesis, nephrogenesis, angiogenesis, glomerulogenesis, tooth morphogenesis and development of dermis and lens [44]. Also in wound healing different PDGF isoforms play an important role as they recruit and activate neutrophils, macrophages and fibroblasts, thereby facilitating the tissue remodeling process [46]. However, sustained or elevated PDGF production and signaling is associated with many different diseases including cancers, vasculopathy and fibrosis [44]. A general characteristic of tissue fibrosis is excessive fibroblast activity with resultant hyperproliferation and extracellular matrix production by these cells, processes highly stimulated by PDGF isoforms and all contributing to GO as well.

Platelet-Derived Growth Factor in GO

PDGF-A and PDGF-B chain expression levels were found to be increased by approximately 2–3 fold in orbital tissue from GO patients, while expression levels of the PDGF-C, PDGF-D, PDGF-R α and PDGF-R β chains were comparable to control orbital tissues [47, 48]. Moreover, PDGF-A and PDGF-B chain expression was equally elevated in orbital tissue from GO patients with active or inactive disease, suggesting a role for the PDGF-AA, PDGF-AB and PDGF-BB isoforms throughout all GO disease stages. Monocytes, macrophages and mast cells, but not T-lymphocytes and B-lymphocytes, were identified as important sources of PDGF-A and PDGF-B chains in orbital tissues from GO patients [47]. Until now it is however unclear whether the orbital PDGF-production in GO is increased on a per-leukocyte basis or results from increased immune cell accumulation, but the more intense PDGF staining in mast cells in GO-orbital tissue compared to mast cells in control orbital tissue, as observed in our immunohistochemical studies, does support that increased production on a per cell basis contributes as well [47]. PDGF production is stimulated by a plethora of cytokines and growth factors, like IL-1 β , IFN- γ , TNF- α and TGF- β [49–52], that are all increased in GO orbital tissue. However, so far factor(s) involved in driving PDGF production by different cell types in GO orbital tissue have not been examined.

PDGF-AA, PDGF-AB and PDGF-BB all stimulate the production of cytokines, amongst which IL-6, IL-8, CCL2, CCL5 and CCL7, by orbital fibroblasts derived from GO orbital tissue as well as control orbital tissue, with PDGF-AA being the least potent and PDGF-BB the most potent inducer [47, 53]. These cytokines have previously been implicated in the pathophysiology of GO and are able to attract and activate B-lymphocytes, T-lymphocytes, neutrophils, mast cells, monocytes and macrophages into the orbital tissue. Therefore PDGF isoforms control immune cell infiltration and activation in orbital tissue in GO through stimulation of cytokine/chemokine production by orbital fibroblasts.

TSHR autoantibody levels and orbital TSHR expression both positively correlate with GO disease activity and TSHR stimulating autoantibodies induce IL-6 and hyaluronan production by orbital fibroblasts, suggesting that TSHR stimulating autoantibodies contribute to development and severity of GO through orbital fibroblast activating properties [2]. Of the three PDGF-isoforms involved in GO it was found that PDGF-AB, but especially PDGF-BB, enhanced TSHR expression on orbital fibro-

blasts, while PDGF-AA did not affect TSHR expression [54]. The PDGF-induced upregulation of TSHR by orbital fibroblasts was associated with increased production of pro-inflammatory cytokines such as IL-6, IL-8, CCL2 and CCL5 by orbital fibroblasts when stimulated with immunoglobulins obtained from Graves' disease (GD-IgG) patients. The GD-IgG effect was abrogated by c-AMP inhibition or a specific TSHR neutralizing antibody, indicating the TSHR-dependence [54]. These data underline the important role for PDGF-AB and PDGF-BB in amplifying the pathologic effects of TSHR stimulating autoantibodies in GO.

PDGF is well recognized for its role in wound healing and tissue fibrosis where it activates fibroblasts to proliferate and produce extracellular matrix components [44]. The orbital tissue expansion in early/active GO includes at least orbital fibroblast proliferation and hyaluronan production [2]. PDGF-AA, PDGF-AB and PDGF-BB all significantly stimulate orbital fibroblast proliferation, with PDGF-BB (inducing approximately 50% proliferation above control) being the most potent and PDGF-AA (inducing approximately 20% proliferation above control) being the least potent [47, 48]. Also hyaluronan production by orbital fibroblasts is stimulated by all three PDGF-isoforms, again with the PDGF-B chain containing isoforms being the most potent [47, 48].

Altogether the data above demonstrate that PDGF-isoforms, especially PDGF-AB and PDGF-BB, can be regarded as master regulators of several major pathophysiological process in GO. PDGF-AA, PDGF-AB and PDGF-BB all stimulate proliferation, hyaluronan and cytokine/chemokine production by orbital fibroblasts, while PDGF-AB and PDGF-BB also increase TSHR expression by orbital fibroblasts (fig. 3). As PDGF-A and PDGF-B chains are elevated in orbital tissue during all GO disease stages, PDGF-AA, AB and BB can be considered to represent true key factors in development and perpetuation of GO.

Inhibition of PDGF Activity: An Attractive Possibility for the Treatment of Graves' Ophthalmopathy?

Currently, the most effective well-tolerated treatment for active moderate-to-severe and sight-threatening GO is (high dose) corticosteroids, while radiotherapy or orbital decompression are considered when patients fail to respond to corticosteroids or for rehabilitating purposes [4, 5]. Effectiveness of corticosteroid treatment relies mainly on the activity of the disease, with a high success

Fig. 2. PDGF and PDGF-receptor. **a** PDGF-A and PDGF-C chains are ligands for PDGF-R α , PDGF-D chain is a ligand for PDGF-R β , while the PDGF-B chain can bind both to PDGF-R α and PDGF-R β . Dotted lines indicate weak interactions or conflicting results [44]. **b** Autophosphorylation of crucial tyrosine residues within the receptor chain results in the activation of downstream signaling molecules.

Fig. 3. Role of PDGF signaling in GO. Monocytes, macrophages and mast cells produce PDGF-A and PDGF-B chains in orbital tissue from GO, resulting in the formation of PDGF-AA, PDGF-AB and PDGF-BB dimeric molecules. These PDGF-isoforms stimulate proliferation, cytokine and hyaluronan production by orbital fibroblasts while PDGF-AB and PDGF-BB also enhance TSHR expression on orbital fibroblasts. In general PDGF-BB is the PDGF-isoform exhibiting the most potent effect on orbital fibroblasts, while PDGF-AA is the weakest.

(For legends 4 and 5 see next page.)

rate when introduced in the initial active inflammatory phase of the disease [4, 5]. However, corticosteroid treatment may negatively influence the tissue remodeling or fibrotic phase when inflammation has subsided [5]. Corticosteroids, such as dexamethasone, stimulate PDGF-B production by macrophages and enhance PDGF-R α expression on fibroblasts, which augments fibroblast effector functions in lung fibrosis [55–57]. In contrast to the ambivalent effects that corticosteroids can have with regard to inflammation, tissue remodeling and fibrosis, the ideal therapy for GO should be effective regardless of the stage of disease. However, so far novel medical treatment options for GO have mainly concentrated on therapeutics directed at immune cells (e.g. B-lymphocytes) or mediators (e.g. TNF- α) that mainly are involved in the active inflammatory phase of GO [7, 8].

PDGF targeting seems an attractive therapeutic option in GO, as PDGF-driven orbital fibroblast activation most likely occurs in all stages of GO (fig. 4). Several approaches to interfere with PDGF-signaling in GO can be thought of: (1) neutralization of PDGF-molecules, for instance with specific neutralizing antibodies or soluble receptor molecules, (2) blockage of the PDGF-receptor chains with neutralizing antibodies or dominant negative ligands and (3) inhibition of PDGF-receptor signaling by using tyrosine-kinase inhibitors that prevent receptor autophosphorylation upon ligand binding (fig. 5) [44].

Although neutralizing antibodies directed towards PDGF isoforms or PDGF-receptors are currently not available for clinical use, such an approach might be of

benefit in the treatment of GO as we found that a neutralizing antibody directed towards PDGF-BB reduced IL-6 and hyaluronan secretion by orbital tissue from GO patients in a newly developed orbital tissue culture approach [47]. Remarkably, in this culture system inhibition of PDGF-AA with a neutralizing antibody was hardly effective, once more underlining the importance of PDGF-B chain containing PDGF isoforms in the pathophysiology of GO.

Several tyrosine kinase inhibitors (TKIs) that exhibit specificity for the PDGF-receptor, amongst which imatinib mesylate and nilotinib, are widely applied to treat BCR-ABL positive chronic myeloid leukemia (CML) as the tyrosine kinase ABL is a target for these TKIs as well [58]. In addition, imatinib mesylate has been used successfully to treat gastrointestinal tumors and mastocytosis by targeting c-Kit kinase activity [59, 60]. We found, that imatinib mesylate and nilotinib both were able to prevent PDGF-induced TSHR expression, proliferation, cytokine and hyaluronan production by orbital fibroblasts from GO patients [47, 48, 53, 54]. Moreover, imatinib mesylate attenuated IL-6 and hyaluronan secretion by cultured GO orbital tissue, while the TNF- α neutralizing agent adalimumab only reduced IL-6 secretion [61]. Although these data point at the attractiveness of TKI usage in the treatment of GO, imatinib mesylate and nilotinib were found to cause serious side effects such as peri-orbital edema, peripheral arterial occlusive disease and cerebrovascular events in CML treatment [62]. Moreover, it was recently shown that imatinib mesylate can stimulate adipogenesis by orbital fibroblasts [63], although this was at high imatinib mesylate concentration. Based on the described adverse effects, imatinib mesylate and nilotinib are not directly regarded as candidate TKIs for a clinical study in GO, at least not when applied in the same dose as used for CML treatment.

Recently, we found that dasatinib, a second generation TKI with FDA approval for CML treatment, effectively inhibits PDGF-BB-induced proliferation, cytokine (CCL2, IL-6, IL-8) and hyaluronan production by orbital fibroblasts as well as cytokine and hyaluronan production by whole orbital tissue from active GO [64]. Although dasatinib is a more promiscuous TKI than imatinib mesylate and nilotinib, it displays the highest inhibitory potency (pIC₅₀) for PDGF-R α and PDGF-R β amongst all TKIs approved for clinical use [65]. In line with this, dasatinib prevented PDGF-induced orbital fibroblast activation at concentrations far lower than that required for imatinib mesylate [64]. Dasatinib has been found to stim-

Fig. 4. A hypothetical scheme of the pathophysiology and treatment of GO. Early GO is characterized by a Th1-dominated inflammatory environment which leads to massive orbital tissue inflammation and edema. In time, this Th1 environment is skewed towards a Th2-dominated environment in which inflammation subsides, but fibrotic tissue remodeling continues. Current mainstream treatment of GO consists of corticosteroids and surgery, of which the corticosteroids have a relatively high success rate when introduced in the active inflammatory phase of the disease, but may negatively influence the tissue remodeling or fibrotic phase when inflammation has subsided. Surgery may be effective in early/active stages of GO, but is predominantly used for rehabilitation of GO patients. Increased PDGF activity contributes to all stages of GO and inhibition of PDGF activity may therefore be effective in all stages of GO.

Fig. 5. Approaches to target PDGF signaling. The PDGF system can be blocked by targeting the PDGF molecule, for instance with a neutralizing antibody, or by targeting the PDGF-Receptor, for instance with a neutralizing antibody or a tyrosine kinase inhibitor with specificity for the PDGF-Receptor.

ulate adipogenesis by human bone marrow-derived mesenchymal stromal cells but not human skin fibroblasts [66]. This implies that an adipogenic effect of dasatinib may be cell type specific, which warrants studies with orbital fibroblasts as well. Although dasatinib is well tolerated some side effects like pleural effusion, skin rash, vomiting, diarrhea, fatigue, headache, anemia, thrombocytopenia and neutropenia have been described [64]. Occurrence of side effects cannot be excluded when dasatinib is used for GO treatment, but the incidences reported in cancer treatment are relatively low, and the occasional occurrence of pleural effusion was reversible upon discontinuation of the therapy. Moreover, the data available so far suggest that dasatinib might be effective in reducing orbital tissue inflammation and expansion at relatively low dose, which may limit the occurrence of side effects as well. Nevertheless, it should be taken into account that GO may show a self-limiting course. Therefore, the use of a compound like dasatinib, with potential side effects, should be introduced in clinics with the greatest precaution.

In summary, PDGF molecules fulfill a central role in the pathophysiology of GO by activation of orbital fibroblasts. Therefore, targeting of the PDGF system should be regarded as therapeutic option for GO.

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