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Review article

Roles of four targets in the pathogenesis of graves' orbitopathy

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ABSTRACT

Graves' orbitopathy (GO) is an autoimmune disease that involves complex immune systems. The mainstays of clinical management for this disease are surgery, targeted drugs therapy, and no-targeted drugs drug therapy. targeted drugs can improve therapeutic efficacy and enhance the quality of life for GO patients. However, as a second-line treatment for GO, targeted drugs such as tocilizumab and rituximab have very limited therapeutic effects and may be accompanied by side effects. The introduction of Teprotumumab, which targets IGF-IR, has made significant progress in the clinical management of GO. The pathophysiology of GO still remains uncertain as it involves a variety of immune cells and fibroblast interactions as well as immune responses to relevant disease targets of action. Therfore, learning more about immune response feedback pathways and potential targets of action will assist in the treatment of GO. In this discussion, we explore the pathogenesis of GO and relevant work, and highlight four potential targets for GO: Interleukin-23 receptor (IL-23 R), Leptin receptor (LepR), Orbital fibroblast activating factors, and Plasminogen activator inhibitor-1 (PAI-1). A deeper understanding of the pathogenesis of GO and the role of potential target signaling pathways is crucial for effective treatment of this disease.

1. Introduction

Graves' orbitopathy (GO), also known as Thyroid-associated ophthalmopathy and Thyroid eye disease, is caused by an autoimmune disorder involving B cells, T cells, and $CD34^{+}$ fibroblasts infiltrating the orbit. This results in inflammation, ocular muscles enlargement, adipogenesis, and edema (caused by glycosaminoglycans accumulation), ultimately leading to tissue remodeling [1]. EUGOGO classifies the disease as mild, moderate-to-severe, or sight-threatening according to the impact of the disease on the patient's quality of life and the risk of vision loss [2]. Treatment interventions vary depending on disease severity, and additional factors such as pregnancy, hepatitis, age, smoking, thyroid function, dosing, and mode of administration must also be considered. Available treatment for GO include corticosteroids, orbital radiation therapy, orbital decompressive surgery, combination therapy, and specialized immunosuppressive therapy. Orbital decompressive surgery is indicated in inactive moderate-to-severe and sight threatening GO. Intravenous methylprednisolone plus mycophenolate is the first-line treatment options for moderate-to-severe or active GO in Europe. However, this medication is associated with adverse side effects, like liver dysfunction [3,4]. Orbital decompression surgery is the main therapy for inactive GO [5]. For symptoms like dysthyroid optic neuropathy that impair eye movements and threaten vision, glucocorticoids combined with orbital decompression surgery may be advantageous [5,6]. Targeted drugs are preferable to corticosteroids, radiotherapy, and surgical treatment techniques in terms of patient and clinical demands. In recent years, Targeted

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immunotherapies such as Tocilizumab (targeting the IL-6R), Rituximab (targeting the CD20), Etanercept, Adalimumab, Infliximab (all *Anti*-TNF) have shown limited improvements in the clinical treatment. while teprotumumab was recently approved by the FDA for its effectiveness in treating GO through targeting IGF-IR. So far, teprotumumab has become the second first-line drug for the treatment of GO after intravenous methylprednisolone plus mycophenolate. Identifying prospective therapy targets and understanding the disease's signaling pathways is crucial in developing more effective treatment options for GO.

2. Pathogenesis

Lymphocytes, fibroblasts, cytokines, chemokines, and inflammatory agents all play a role in the pathogenesis of GO (Fig. 1). Early symptoms of GO are thought to be linked with Th1/Th2 imbalance and $CD4^+$ T cells [7]. Studies have shown that early-stage GO patients had significantly higher ratios of CD8-/IFN-γ+ T cells and CD8-/IFN-γ+ T (Th1) cells to CD8-/IL-4+ T (Th2) cells [8,9]. Helper T (Th) cells constitute the majority of $CD4^+$ T cells, while cytotoxic T (Tc) and suppressor T (Ts) cells form the majority of $CD8^+$ T cells. Th cells boost humoral or cellular-mediated immunity, whereas Ts cells have a suppressive role in controlling Th cell activity and/or

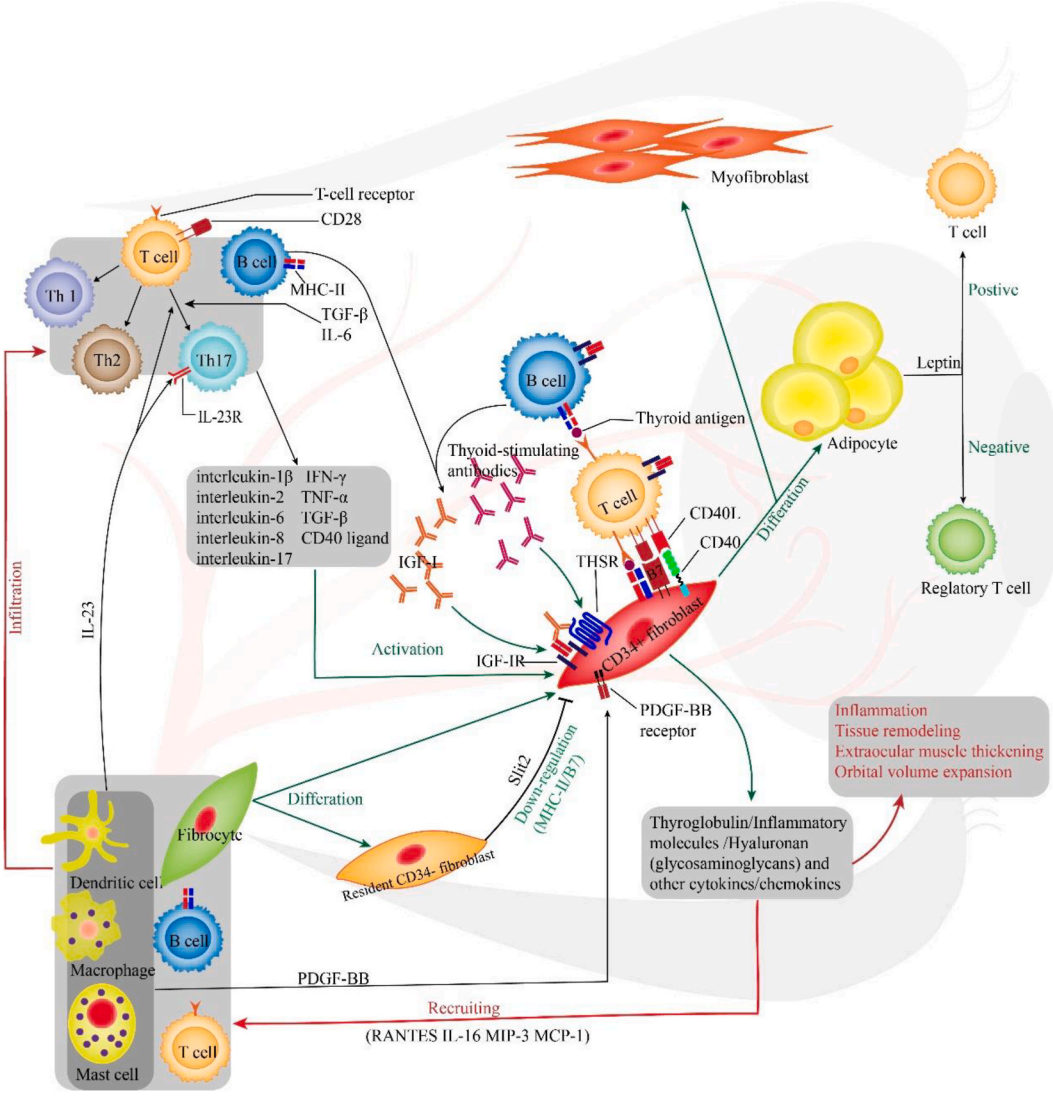

Fig. 1. Schematic representation of the GO pathogenesis: The orbit is infiltrated by B cells, T cells and $CD34^+$ fibroblasts. $CD34^+$ fibroblasts are activated and further differentiated into adipocytes and myofibroblasts. $CD34^+$ fibroblasts are activated as autoantigen target cells by stimulation of cytokines produced by resident CD34-fibroblasts, infiltrating lymphocytes. Thyrotropin and insulin-like growth factor stimulate thyrotropin receptor and insulin-like growth factor receptor complexes on the cell membrane surface of $CD34^+$ cells leading to cytokine and hyaluronic acid production, resulting in enlarged orbital tissue and protruding eyeballs. PDGF-BB also stimulates $CD34^+$ fibroblasts to produce hyaluronic acid and other glycosaminoglycans. adipocyte production of leptin may also play a role in promoting local inflammation. In addition, adipogenesis and proliferation of myofibroblasts further lead to orbital tissue expansion, orbital protrusion and optic nerve compression.

transformation. The activated $CD4^+$ T cells produce cytokines and inflammatory substances, forming the Th1, Th2, Th17, and Treg subpopulations that contribute substantially to the emergence of GO [10]. For example, orbital fibroblasts from GO patients produce a substantial amount of B cell activating factor after being stimulated by inflammatory cytokines TNF-α and IFN-γ, which promotes $CD20^+$ B cell survival in retrobulbar tissues and ultimately leads to antibody production [11,12]. These antibodies activate $CD34^+$ fibroblasts that further promote GO development. Dysfunctional deficiencies of regulatory B cells that produce IL-10 in suppressing IFN-γ and Th17 cell activation could also contribute to the pathophysiology of GO [13]. Moreover, high levels of regulatory T cells and CTLA-4 dysfunction were discovered in GO patients, revealing their potential association with the disease [14]. Recent research also suggests that the $CD4^+$ Cytotoxic T cell subtype expressing cytotoxic, chemotactic, and inflammatory responses mediates orbital inflammation and remodeling [15]. Lastly, $CD34^+$ fibroblasts are also significant in the moderate to severe phases of GO.

The homogenous population of GO orbital fibroblasts contains both $CD34^+$ and $CD34^-$subtypes, indicating a lack of uniformity. These fibroblasts, along with CD34 + OFs, are present in both the orbit and circulation and play active roles as target and effector cells in the expansion of orbital tissue [16]. while healthy ocular tissues' fibroblasts are CD34-fibroblasts, it is unclear whether infiltrated cells or other source produces $CD34^+$ fibroblasts [16]. During GO, an imbalance between lymphocytes and fibroblasts is suggested by increased expression of IL-17 R, CD80, and CD86 on orbital fibroblast surfaces. This interaction between fibroblasts and Th17 cells stimulates the inflammatory response in orbit tissues, while macrophage inflammatory protein 3 recruits and maintains Th17 cells' phenotype [14]. Moreover, fibroblasts, B cells, and T cells in GO exhibit overexpression of IGF-IR (Insulin-like Growth Factor-I Receptor), which, when bound to thyroid-stimulatory immunoglobulin Gs (IgGs), can activate a cellular response in fibroblasts [17–20]. Fibroblast proliferation drives the expansion of orbital tissue within the bony orbit [21]. Notably, IGF-IR structurally correlates with THSR, forming a structural complex on the membrane surface of orbital fibroblasts [19,22,23]. The TSHR and IGF-IR receptor complexes can be activated by pathogenic IgGs and IGF-I. This activation leads to the production of inflammatory molecules and glycosaminoglycans, which contain hyaluronic acid [24]. Additionally, the TSHR/IGF-IR receptor complex is responsible for inducing MHC II and B7 proteins (CD80, CD86, and programmed death-ligand 1) in fibroblasts. Fibroblasts are responsible for delivering antigens to T cells via B7 protein, CD40, and MHC II to T cells. The differentiation of these two cell types are interdependent in terms of differentiation [25,26]. Inhibition of IGF-IR can reduce the expression of MHC-II and B7 proteins in fibroblasts, limiting the tandem activation of T cells and B cells. CD34-fibroblasts produced and secreted Slit2, which inhibited MHC-II and B7 protein expression in CD34+fibroblasts. Adipocytes also play a role in the development of GO [27]. In response to TNF-α, adipocytes produce Monocyte chemoattractant protein 1 (MCP-1), which recruits macrophages. Once activated, these macrophages emit inflammatory chemicals including TNF-α, triggering an inflammatory response around adipose tissue [28,29]. MCP-1 may be one of the factors encouraging $CD34^+$ fibroblast migration [30].

Research on GO's at a molecular level has revealed significant differences, including varying degrees of gene changes and expression in GO patients [31,32]. Proteomic investigations of ocular tissues from GO patients have identified 13 proteins (listed in Table 1) that are significantly overexpressed and that have connections to tissue inflammation, adipose tissue differentiation, lipid metabolism, and tissue remodeling. Furthermore, analysis of differentially expressed genes (DEGs) in orbital adipose tissue samples led to the identification of 12 hub genes (listed in Table 2) [33,34].

Table 1
Protein expression profile in orbital tissue.

Gene symbol	Gene description	Up-regulation	Function	Reference
PTRF	polymerase I and transcript release factor	3.4 fold	May be involved in the interaction between Fasn and Cav 1, induced intracellular fat accumulation	[35,36]
SPTN4	beta IV spectrin	6.2 fold	regulating VEGF signaling	[35,37]
REXO1	cell-cycle elongin A binding protein 1	6.2 fold	regulation of transcription elongation	[35,38]
AOC3	semicarbazide-sensitive metalloproteinase amine oxidase 3	3.4 fold	Increasing leukostasis	[35,39]
GTPB2	GTP-Binding Protein 2	5.6 fold	Involvement in adipogenesis and lipid metabolism	[35,40]
XYLB	xylulokinase homolog	4.1 fold	Regulatory factors of glucose metabolism and lipogenesis	[35,41]
H4	protein pointing to cell proliferation histone H4	2.8 fold	Maintaining cell genome integrity and cell proliferation	[35,42,43]
ATS14	ADAM metallopeptidase with thrombospondin type 1 motif 14	2.7 fold	Perhaps a new extracellular matrix (ECM) remodeling molecule	[35,44]
POTEF	POTE ankyrin domain family member F	5.4 fold	Involved in protein, nucleotide, and ATP binding, and other biological functions; affecting enzyme regulation, catalytic activity, transporter, and transferase activity	[35,45]
LCN1	lipocalin 1	3.6 fold	Roles in cell growth regulation, signal transduction pathways, and cell-cell adhesion through membrane/cytoskeletal organization	[35,46,47]
KIF1A	KIF1A kinesin family member 1 A	3.6 fold	Motor proteins for directional movement along the plus ends of neuronal axon microtubules	[35,48]
ANXA2	protein annexin A2	3 fold	Maintain vascular integrity and prevent inflammatory leukocytes from being recruited to the injured site	[35,49]
CAV1	cavin	3 fold	Proteins necessary for the formation of caveolae with endocytosis, signal transduction, lipid transport and cholesterol transport functions	[35,36]

Table 2
Differentially expressed genes of orbital adipose tissue samples.

Gene Symbol	Gene Description	Expression changes	Function	Reference
IRX1	Iroquois homeobox protein 1	Log2 fold change: +4.24	Regulating cell cycle	[34,50]
HOXB2	Homeobox B2	Log2 fold change: +3.32	Regulating cell proliferation and cell migration	[34,51]
S100B	S100 Ca-binding protein B	Log2 fold change: +2.8	Control of intercellular communication and cell growth	[34,52]
KCNA4	Potassium voltage-gated channel A member 4	Log2 fold change: +2.57	mediating the voltage-dependent potassium ion permeability of excitable membranes	[34]
FABP4	fatty acid binding protein 4	up-regulation	Nuclear transcription factors improving inflammation and fibrosis	[34,53]
PPARγ	peroxisome proliferator-activated receptor-γ	up-regulation	Nuclear transcription factors improving inflammation and fibrosis	[34,54]
POMC	Proopiomelanocortin	up-regulation	Involvement in immune and neuroendocrine responses	[33,55]
GNG3	G protein subunit gamma 3	up-regulation	regulating the function of intracellular Golgi membranes through this translocation; Cell signal transduction function	[33,56]
CXCR4	CXC motif chemokine receptor 4	up-regulation	Stimulating the activation of JAK2/STAT3 and JAK3/STAT6 signals; promoting cell growth and metastasis	[33,57,58]
TLR4	Toll-like receptor 4	down-regulation	controlling inflammatory and immunological responses	[33,59]
CSF1R	colony stimulating factor 1 receptor	down-regulation	Signaling cascades that bind to CSF1 cause the proliferation and differentiation of monocyte, macrophages	[33,60]
LPAR3	lysophosphatidic acid receptor 3	up-regulation	Cell migration, proliferation and lipid metabolism	[33,61–63]

3. Interleukin-23 receptor

Interleukin-23 (IL-23) is a crucial member of the IL-12 family that is released by Toll-like receptor response signals on the surface of dendritic cells (DCs), macrophages and monocytes. While the differentiation of Th17 cells heavily relies on transforming growth factor-β (TGF-β) and IL-6, IL-23 plays a pivotal role in the differentiation, stability, survival, and IL-17 secretion of these cells [64–67]. Upon binding to its receptor, IL-23 activates Janus Kinases (Jak2 and Tyk2), which phosphorylate IL-23 R at distinct sites forming docking sites for the STATs. Subsequently, Jaks phosphorylate the STATs allowing them to dimerize and translocate to the nucleus where they activate the transcription of IL-17 and INF-γ(Fig. 2) [68]. This leads to an increased release of IL-17 upon the conversion of $CD4^+$ T cells of the Th1 subtype to the Th17 subtype. Th17 and IL-17 enhance fibroblast antigen presentation and stimulation, upregulatiing of MHC-II and CD40 on CD34+fibroblasts [14]. These cells, along with the cytokines they secrete, stimulate T cells to release cytokines and chemokines like IL-6, IL-8, intercellular adhesion molecule-1, granulocyte-macrophage colony-stimulating factor or granulocyte colony-stimulating factor, activating and attracting neutrophils into the GO orbital tissue.

An IL-23/IL-23 R/PGE2/EP2+EP4/IL-23 R feedback loop has been identified that contributes to the activation of pathogenic Th17 and exacerbates the development of Graves' orbitopathy (GO). In addition to the IL-23/IL-23 R/IL-17 pathway, the interaction between IL-23 and EP2+EP4 receptors on peripheral blood mononuclear cells upregulates IL-23 R, which promotes IL-17 production, leading to a worsening of inflammation in GO [69–71]. Apart from circulating peripheral blood mononuclear cells, PGE2 is also synthesized by GO orbital fibroblasts (GO-OFs) induced by IL-β and the expression of PGHS-2 [72]. Co-culturing mast cells and GO-OFs has been shown to activate the latter and increase the production of PGE2 and hyaluronic acid, albeit temporarily [73]. Targeting IL-23 R has been proposed as a potential therapeutic strategy for GO. Another study found that IL-38 can inhibit the expression of IL-23 R in PBMCs, reduce inflammatory and chemokine mRNA expression, inhibit glycosaminoglycan formation, and exhibit antifibrotic properties, affecting both transcription and protein levels [69,70].

4. Leptin receptor (full-length isoform, Ob-Rb)

Adipose tissue predominantly produces leptin, which is a 4-helix bundle cytokine that regulates the immune system's various cells, including T cells, B cells, NK cells, macrophages, and dendritic cells (DCs) (Fig. 3A). Leptin expression is increased in preadipocytes, adipocytes, thyroid cells, and orbital tissues of GO patients [74,75]. Leptin receptor (LepR) expression is likewise elevated (Fig. 3B) [74,75]. The LepR isoforms can be categorized into three groups: long isoforms, short isoforms, and secreted isoforms, where all immune cells contain the Full-length isoform (Ob-Rb). According to an associated immunogenetic study, LepR expression enhances antigen presentation in thyroid cells and regulates protein secretion, adipogenic pathway activity, immune cells adhesion, and T-cell phenotypic differentiation in orbital tissue [76,77].

In vitro T-cell polarization assays, demonstrate that leptin enhances immune responses and promotes Th1 cells' survival while inhibiting the polarization of Th2 cells and regulatory T (Treg) cells [78]. DCs functions are activators of antigen-presenting cells and primitive T cells in the initial stages of an immunological response. Thus, for a complete understanding of GO pathophysiology, investigating the effects of leptin on DCs and T cells. DCs differentiated in a leptin-deficient environment had normal antigen and processing capacity, expressing lower levels of MHC-II and costimulatory molecules. but surprisingly, differentiated DCs show a stronger ability to activate T-cell phenotypic differentiation in vitro experiments. In particular, they increase the ability of DCs to

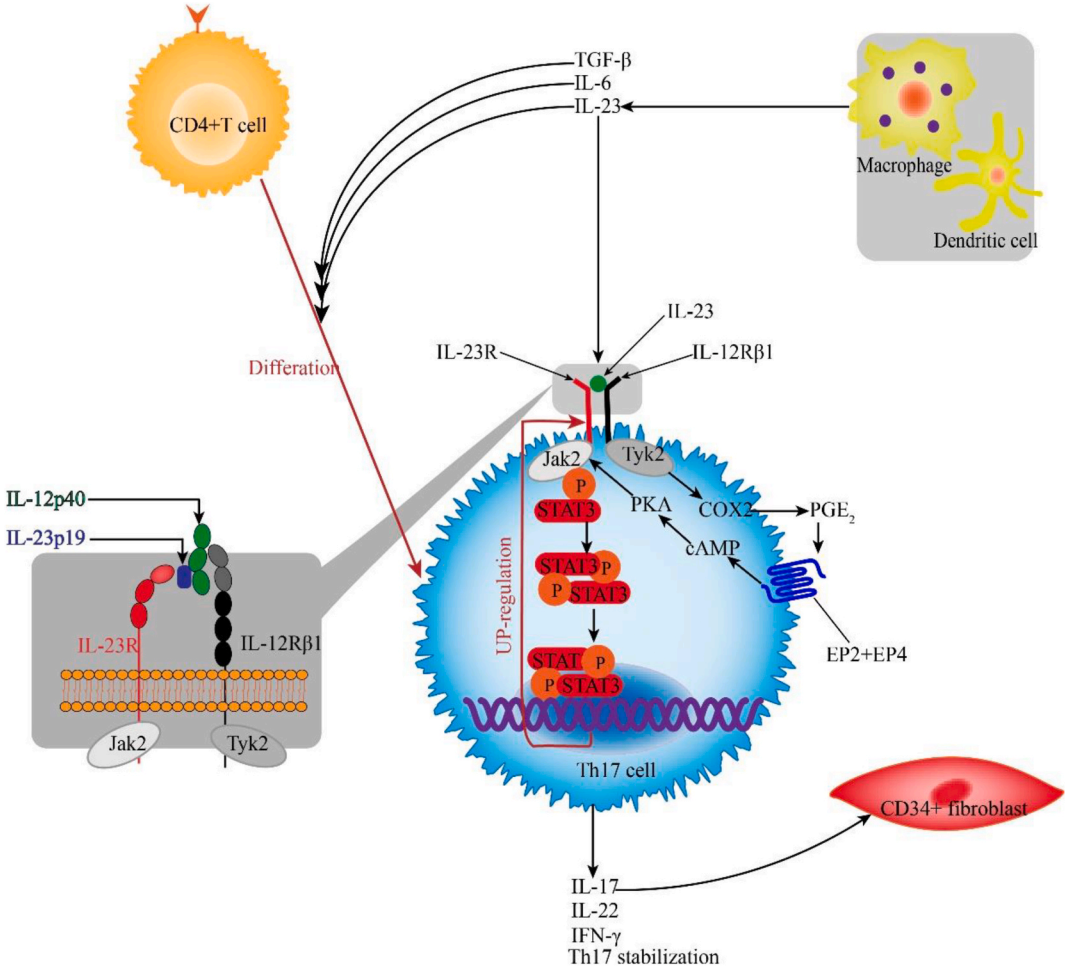

Fig. 2. Mechanism of the IL-23/IL-23 R signaling circuit: The IL-23 R protein comprises two subunits: IL-12 Rβ1 and IL-23 R. IL-23 itself is a heterodimer that consists of two helical-bundle subunits, namely IL-23p19 and IL-12p40. IL-23p19 subunit binds to IL-23 R, which then recruits IL-12 Rβ1 to IL-12p40 for triggering a response. 12 Rβ1 to bind to IL-12p40 to initiate a response. COX2, Cyclooxygenase-2; EP2+EP4, prostaglandin E receptor 2+ prostaglandin E receptor 4.

induce Th17 cells [79,80]. Further research has ruled out the possibility that leptin levels in bovine serum in culture medium affect Lep^{ob}-sDC levels and T cell activation phenotype [79,80]. This suggests that leptin regulates T-cell activity by interacting with DCs. However, this research used high levels of leptin stimulation on DC cells, and the function of DC cells was determined by the mice strains used [80,81]. Studies where leptin directly influences T-cells have reported thatLepR deficiency in $CD4^+$ T cells impair their capacity to develop towards the Th17 phenotype through stimulation of the JAK/STAT-3 signaling pathway and its downstream targets [82]. This work revealed that Lep-deficient $CD4^+$ T cells were unable to produce appropriate pSTAT3 to achieve full Th7 development, which prevented them from differentiating into Treg and Th1 cells. The process of Th17 differentiation involves IL-6, TGF-β, and IL-23, and STAT3's expression and phosphorylation are mediated by IL-6 and IL-23. Therefore, the research mentioned above could indicate feedback between LepR effects and IL-23/IL-23-related signaling circuits. Combining leptin and lepR may cause local tissue inflammation in GO.

5. Platelet-derived growth factor

The activation of orbital fibroblasts can result in excessive proliferation and production of cytokines, hyaluronic acid, as well as differentiation into myofibroblasts and adipocytes. These factors play a major role in the inflammation and reorganization of GO orbital tissues. Orbital fibroblast activators include PDGF-B and Basic fibroblast growth factor (bFGF). PDGF-BB, which is composed of two PDGF-B chains, is a potent mitogen for fibroblasts and contributes to neurofibrosis in several organ systems. Cytokines such as IL-1, IFN-γ, TNF-α, and TGF-β increase the synthesis of PDGF in GO. PDGF-AB and PDGF-BB secreted by activated mast cells, monocytes, and macrophages can also promote the proliferation of orbital fibroblasts [83,84]. Moreover, PDGF-BB has been shown to cause ocular inflammation and tissue remodeling in GO, to increase adipogenesis in orbital fibroblasts, and to have an additive effect on

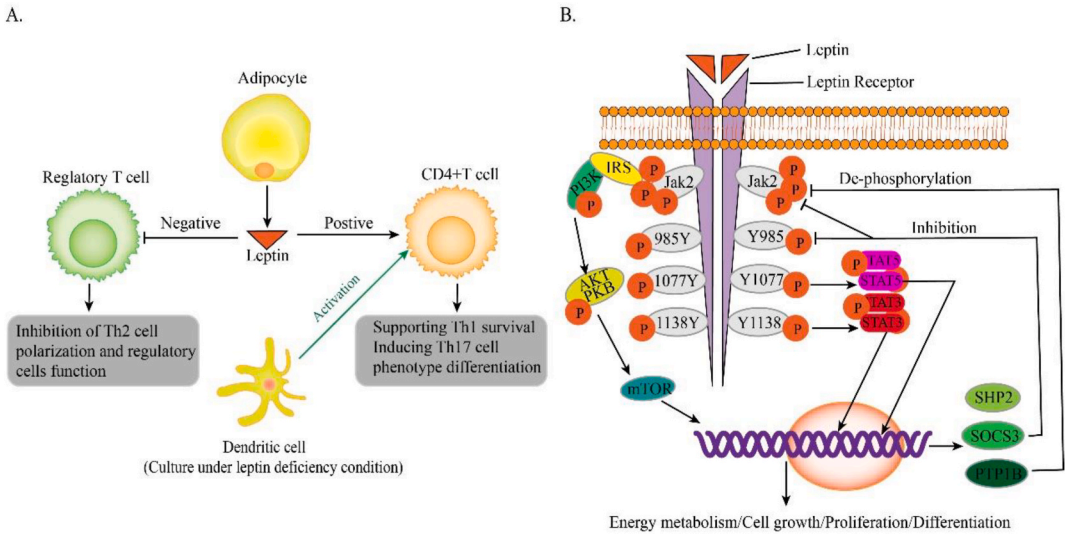

Fig. 3. Effect of leptin on T cell function and its intracellular signaling pathways: A) Leptin has various effects on T cell function. Specifically, it inhibits Th2 cell polarization and regulates $CD4^{+}$ cell differentiation to different phenotypes; B) Leptin's effects are mediated by binding to LepR, leading to activation of JAK2 and subsequent phosphorylation of three tyrosine residues: Y985, Y1077, and Y1138. Each phosphorylation site evokes a specific signaling pathway with distinct physiological functions of leptin. Y985 activates SHP-2, which mediates negative feedback signaling in the leptin pathway. Y1077 leads to STAT5 signaling, which affects reproductive outcomes. Finally, Y1138 activates STAT3 signaling, which regulates energy homeostasis and neuroendocrine function. cytosine signaling-3 (SOCS-3) and phosphotyrosine phosphodiesterase-1B (PTP1B) act as negative regulators of leptin signaling, with SOCS-3 blocking leptin signaling by binding to Y985 and JAK2, and PTP1B completing signal blockage by mediating Jak2 dephosphorylation.

adipogenesis when combined with bFGF) [85,86]. Although there is no change in the expression of PDGF-B mRNA between active and inactive GO patients, PDGF-BB levels are significantly higher in GO patients [87]. It has been suggested that PDGF-BB might play a role in the development of GO. In comparison to the other two PDGF isoforms, PDGF-BB significantly increased TSHR expression, orbital fibroblast proliferation, and the production of several cytokines including hyaluronic acid, IL-6, IL-8, CCL2, CCL5, and CCL7 [87–90]. PDGF-BB uniquely increased THSR expression in orbital fibroblasts, resulting in self-stimulatory antibody activation and the production of cytokines linked to edema and inflammatory cell infiltration. also facilitated orbital fibroblast differentiation into adipocytes and IL-6 production in the initial phases of differentiation, although these effects were not related to IL-6 autocrine signaling [91]. Studies have demonstrated that miRNA-21-mediated downregulation of Programmed cell death 4 occurs due to PDGF-BB stimulation of orbital fibroblast growth, resulting in the progression of GO [92]. Additionally, PDGF-BB is thought to promote the altered expression of HDAC4 and decreased acetylation of H3K9, resulting in raised orbital fibroblast proliferation and extracellular matrix synthesis [93]. While bFGF was found to have no impact on orbital fibroblast production of IL-6, PDGF-BB effectively synergized with this process [94]. The observed improvement in hyaluronic acid synthesis suggests that PDGF-BB may be involved throughout the pathogenetic phase of GO.

6. Plasminogen activator inhibitor-1 (PAI-1, SERPINE1)

Tears obtained from GO (Graves' ophthalmopathy) patients were observed to have elevated levels of various cytokines including TNF-, IL-1, IL-6, IL-18, IL-17 A, IL-13, RANTES, and PAI-1 [95]. While PAI-1 is known for maintaining the integrity of the ocular surface in healthy eyes, its expression was found to contribute to the fibrosis of GO tissue in response to INF, TGF, and TNF [96]. PAI-1 is produced by several types of cells such as vascular endothelial cells, adipocytes, macrophages, cardiomyocytes, and fibroblasts. In cases where excessive deposition of ECM proteins occurs due to fibrosis resulting from excessive fibroblast proliferation, the expression of PAI-1 genes becomes crucial. PAI-1 helps with wound healing by blocking the activation of urokinase-type or tissue-type plasminogen activator, plasmin formation, and plamin-dependent MMP activation. However, prolonged activity of PAI-1 can lead to the accumulation of collagen and fibronectin in different tissues ultimately leading to tissue and organ fibrosis. Conversely, expression levels of PAI-1 promoting cardiac-selective fibrosis are thought to be minimal. In vitro studies have demonstrated that PAI-1 plays a crucial role in promoting adhesion and migration of smooth muscle cells and human corneal epithelial cells, acting as an inducible chemokine [97,98]. Investigations involving corneal myofibroblasts have shown that PAI-1 also participates in Vitronectin-modulated cell migration in the extracellular matrix (ECM) [99]. Binding of PAI-1 to Vitronectin spatially hinders integrins from binding to Vitronectin, thereby reducing cell adhesion. Several studies have investigated PAI-1 silencing in various fibrotic diseases. For instance, injection of the exogenous mutant PAI-1R leads to reduced integrin-mediated binding through competing with PAI-1 to bind Vitronectin [100]. This leads to an increase in tissue plasminogen activator (uPA) activity, thereby reducing ECM accumulation in fibrotic disorders. Furthermore, in elevated intraocular pressure of glaucoma, the secreted protein acidic and rich in cysteine (SPARC), found

in ECM proteins, regulates TGF-2-mediated activity, which is extensively contributed by tissue remodeling by PAI-1 [101,102].

Research on pulmonary fibrosis has found that PAI-1-deficient mice's lungs secrete prostaglandin E2 (PGE2), an antifibrotic lipid mediator [103]. PGE2 plays a crucial role in the feedback loop between IL-23/IL-23 R/PGE2/EP2+EP4/IL-23 R, contributing to late GO fibrosis actively. Although it is not conclusively proven, additional research may establish the involvement of PAI-1 and PGE2 in GO.

7. Concluding remarks

The article discusses the challenges in treating GO, which is a complex immune disease that can significantly reduce patients' quality of life. The current preferred method of treatment for GO is intravenous glucocorticoids and Teprotumumab, but the disease requires a multidisciplinary approach of ophthalmology, orbital decompressive surgery, radiation oncology, and immunology. This can lead to long and cumbersome treatment periods, affecting patients' quality of life. However, improving the understanding of GO's signaling pathways may lead to more effective immune-targeted therapies. The article identifies four possible targets that may be involved in different stages of GO pathogenesis. Different targets may play a key role depending on the stage of the disease, indicating the complexity of the condition. To analyze each target's function and evaluate it for research purposes, researchers must locate the target receptor protein in studies. Overall, this article highlights the need for a comprehensive approach to treating GO due to its complex pathogenesis. Improving our understanding of the disease's mechanisms may provide long-term benefits to GO patients by enabling the development of more effective therapies.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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