Thyroid Gland Homeostasis and TGF-β

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Transforming growth factor beta (TGF-β), as a master regulator of immune response, is deeply implicated in the complex pathophysiology and development of autoimmune thyroid diseases.

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1. Introduction

The pathophysiology of autoimmune thyroid diseases (Graves' disease, Hashimoto's thyroiditis, thyroid-associated orbitopathy, thyroid disease in pregnancy, and post-partum thyroiditis) includes complex immune mechanisms and inflammatory phenomena. Transforming growth factor beta (TGF-β) plays a pivotal role in the proper function of the human immune system and is implicated in the pathophysiological spectrum of thyroid autoimmunity [1][2].

Based on the involvement of TGF-β in autoimmune thyroid diseases, it is suggested that novel and reliable prognostic, diagnostic, therapeutic, and follow-up 'tools', regarding thyroid autoimmunity, could be developed based on the 'dual' immunoregulatory (either suppressive or facilitatory) role of this growth factor. The development of these 'tools' entails the fine tuning of the immune effects of TGF-β, in order to avoid adverse effects regarding the 'smooth' function of our immune system [3]. Thus, despite increasing scientific knowledge, it remains unclear whether TGF-β could be effectively and safely exploited to change the way patients with autoimmune thyroid diseases are handled.

2. TGF-β Homeostasis and Its Interplay with the Immune System

2.1. Physiology of TGF-β Biosynthesis, Activation, and Signaling Pathways

TGF-β is a member of a transforming growth factor superfamily, which includes TGF-βs, bone morphogenetic proteins, activins, and growth redifferentiation factors, among other molecules [4]. TGF-β can be found in three isoforms, namely TGF-β1 (the most abundant of the three), TGF-β2 and TGF-β3. TGF-β is synthesized and secreted by almost all human cells, including all white blood cell lineages. It plays an instrumental regulatory role in the generation, maturation, proliferation, and apoptosis of various cell types; vascular, skeletal, and connective tissue homeostasis; physiological immune response and tolerance; inflammation and fibrosis development; tumor

surveillance; and autoimmunity limitation [5][6]. The role of the signaling pathways associated with TGF-β activation and function is fundamental regarding various human cell, tissue, and system properties and homeostasis [7].

All TGF-β isoforms are synthesized and produced as biologically inactive molecules, consisting of the pre-TGF-β homodimers [8]. These interact with latency-associated peptides (LAPs), forming a small latent complex (SLC). The latter cannot be released from the cellular environment until it is bound to the latent TGF-β-binding protein (LTBP). The binding of SLC to LTBP induces the 'construction' of a much larger complex, which is described as a large latent complex (LLC). During the following step, LLC is secreted into the extracellular matrix (ECM) in an inactive form, which is incapable of binding to TGF-β receptors (TβRs). Only after proteolysis of the LAP from LLC can active TGF-β be released, ready to exert its multifunctional role. The complex multilevel procedure that activates TGF-β is mediated by a variety of diverse factors, such as metalloproteases, integrins, thrombospondin-1, pH, and reactive oxygen species including hydroxyl radicals' reactive oxygen species [9].

The majority of human cells express three types of TβRs [10]. TβRI and TβRII are transmembrane serine/threonine kinase receptors, while TβRIII is mainly a type I integral membrane protein co-receptor. Initially, TGF-β binds to TβRII (under the mediation of TβRIII) resulting in the recruitment of TβRI. As a result, heteromeric activation complexes are formed on cell surface, comprising two pairs (dimerization) of TβRI and TβRII, respectively, with each pair binding one of the two chains of active TGF-β. Within this activation complex, TβRII phosphorylates/activates TβRI, thus initiating the cascade associated with TGF-β intracellular signaling [11]. Until now, only some parts of the TGF-β intracellular signaling pathways are decoded, while the full mechanisms remain unclear. A number of these TGF-β activating pathways are unique for distinct cellular/tissue types, while others can be traced to a broad range of different cell/tissue categories [12]. The intracellular signaling pathways of TβRs are mediated by eight structurally resembling proteins, the so-called Smads (homologies to the Caenorhabditis elegans SMA ("small" worm phenotype) and MAD family ("Mothers against Decapentaplegic") of genes in Drosophila). Hence, the Smad-dependent (or canonical) pathway is the primary signaling pathway for TGF-β [13]. In particular, after TβRI is phosphorylated, it can induce downstream Smad 2 and 3 (R-Smads) phosphorylation. Directly after, the binding of phosphorylated R-Smads to the common-partner Smad4 (Co-Smad) takes place, leading to the synthesis of the R-Smads/Co-Smad complex. Following its nuclear translocation, this complex modulates the transcriptional process of TGF-β target genes, which, regarding T-cells, are still not fully specified. Moreover, transcriptional intermediary factor 1γ (TIF1γ) has the ability to bind to the phosphorylated Smad2/3 complex (Smad binding complex or SBE), thus presenting with an antagonizing action to that of Smad4 [14]. Furthermore, inhibitory Smad6 and Smad7 (I-Smads) can also exert a regulatory role regarding TGF-β signaling via negative feedback. The amounts of I-Smads are TβR-dependent and increase in parallel with the intensification of the TGF-β signaling cascade activity [15]. Moreover, it has been shown that a clear association between the TGF-β-mediated suppression of cell proliferation and the Smad-dependent (or canonical) pathway exists [16].

To the contrary, the non-Smad-dependent (or non-canonical) signaling pathway is mediated by the recruitment of Smad7 to the complex comprising either phosphorylated Smad2/3C or activated TβRs [17]. Regarding the Smad-independent signaling pathway, accumulating research data have established the significance of various contributing factors for the uninterrupted and effective signal transmission of the TβR activation complex [18]. More

precisely, factors such as TGF-β-activated kinase 1 (TAK1), p38 mitogen-activated protein kinase (p38 MAPK), extracellular signal regulated kinase (ERK), tumor necrosis factor (TNF), or nuclear factor kappa B (NF-κB) enhance or inhibit the cellular response to non-canonical TGF-β signaling pathways [19]. The dysregulation of both the canonical and non-canonical TGF-β signaling pathways is directly or indirectly implicated in several pathological processes, including autoimmune and inflammatory disorders.

2.2. The Physiological Role of TGF-β Regarding the Immune System

Innate (or natural) and adaptive (or active) immunity are the two main 'arms' of the human immune system [20]. Innate immunity is a born immune antigen non-specific defense mechanism, which is mediated by a variety of immune cells, including macrophages, dendritic cells, neutrophils, monocytes, and mast cells. Interestingly, cell types involved in the innate immune system catalyze the development of adaptive (or acquired) immunity, which is antigen-specific and evolves throughout the human life. The adaptive immune response can be further subdivided in humoral and cell-mediated, which is defined by the involvement of B- and T-cells, respectively [21]. The interplay of TGF-β with both components of the human immune defense mechanisms is complex. Regarding innate immunity, this growth factor modulates the homeostasis and exerts both promoting and suppressing effects on cellular life and function [22].

Equivalently, TGF-β is implicated in the adaptive T-cell immunity either in an immune-enhancing or immune-suppressive manner [23]. Concretely, T-cell physiology and activity is substantially modulated by TGF-β. The role of this molecule is vital regarding every aspect of the synthesis, differentiation, maturation, activation, survival, and destruction of T-cells. Furthermore, TGF-β regulates the immune effects and the regulatory mechanisms, which are catalyzed by T-cells (Table 1). The effects of TGF-β on T-cell homeostasis are regulated by factors associated with and regulated by the extra- and intracellular microenvironment [23][24].

Table 1. Effects of TGF-β in T-cell physiology and development.

TGF-β
• Stimulates naive CD4+ T-cells transformation to effector T-cells • Suppresses the proliferation and differentiation of effector T-cells via inhibition of Th2-produced IL-2 • Alters the type of produced cytokines and mediates phenotypic metamorphosis among effector T-cells • Enhances TNF production by both CD4+ and CD8+ T-cells • Enhances the proliferation of CD8+ cells (in experimental mouse models) • Stimulates transformation of nTregs to iTregs via increased Foxp3 expression

TGF-β
• Promotes Treg-induced inhibition of the exocytosis of granules • Inhibits the generation and activation of CTLs • Suppresses the cytotoxicity of the CTLs via the transcriptional regression of genes encoding proteins, which are vital for CTLs function

immune mechanism [21]. After their development in hematopoietic stem cells, B-cells migrate to the secondary lymphoid organs, where they can be activated, either independently or following interaction with T-cells [25][26]. Antibody secretion is the vital function of B-cells regarding the adaptive humoral immunity. Therefore, it is clear that the role of TGF-β in B-cell physiology is equally important to that in T-cell physiology (Table 2).

Table 2. Effects of TGF-β in B-cell physiology and development.

TGF-β
• Is secreted by B-cells (which express its receptors) • Inhibits B-cell activation and antibodies production • Promotes class switching of IgA in both human and mouse B-cells • Inhibits immunoglobulin synthesis and class switching to the majority of IgG isotypes • Induces apoptosis of immature or resting B-cells by an unknown yet mechanism, which may overlap with its anti-proliferation pathway.

Conclusively, almost the whole spectrum of immune system functions is affected by TGF-β activity. Deeper understanding of the specific factors that stimulate TGF-β secretion and regulate its function is needed to decode the ‘hidden’ immune pathways and ‘neutralize’ or even reverse the destructive consequences of autoimmune disorders.

3. Thyroid Gland Homeostasis and TGF-β

3.1. Interplay between Normal Thyroid Physiology/Function and TGF-β

A delicate modulation of the growth and proliferation of thyroid follicular cells coordinates and controls the thyroid gland homeostasis and function. The former depends, among others, on various growth factors, including those

comprising the superfamily of transforming growth factors and especially TGF-β [27]. Thyroid follicular cells proliferate and differentiate tightly controlled by (a) TSH (thyroid stimulating hormone), which plays a systemically stimulating role and (b) locally produced TGF-β, which exerts an inhibitory paracrine function. More specifically, TGF-β has a major regulatory role in thyroid physiology. More specifically, it inhibits mainly the proliferation and limits the function of thyroid follicular cells. Interestingly, sex steroids modulate intrathyroidal TGF-β synthesis and function [23]. Estrogens activate TGF-β signaling via Smad 2 phosphorylation, while estrogenic effects on thyroid follicular cells are mediated by intrathyroidal produced and secreted TGF-β [28]. It is also known that thyroid follicular cells express both types of estrogen receptors (ERs; ER-α and ER-β) [29]. Interestingly, TGF-β inhibits ERs expression via Smad4. In addition, the activation of ER-β triggers a sequence of TGF-β-regulated actions, resulting in Th17 type responses, while the activation of ER-α prompts Smad2/3 proteins deficiency or depletion, thereby impeding TGF-β signal transduction [30][31]. On the other hand, TGF-β transcriptional responses can be minimized or inhibited via androgen-regulated obstruction of the attachment of Smad3 to the Smad binding complex (or SBE) [32]. Likewise, TGF-β can be impeded by progesterone. This hormone is an antagonist of TGF-β regarding its function on Smad activation and inhibits TGF-β/Smad-induced signaling and transcription pathways [33].

3.2. Association of TGF-β with the Pathophysiology of the Autoimmune Thyroid Diseases

Thyroid autoimmunity development is a result of combined genetic predisposition and immune mechanisms dysregulation. The vital role of TGF-β regarding the pathophysiology of autoimmune thyroid diseases is supported by scientific data, which indicate that this growth factor affects in a disease type-specific manner the intractability, severity, gravity, and/or course of each one of the autoimmune thyroid diseases [1][2]. The exact role of TGF-β (either inhibitory or facilitatory) regarding thyroid autoimmunity depends largely on the synthesis rate of this growth factor, the unique genotypic and phenotypic characteristics of the specific autoimmune thyroid disease, and the activation of distinct signaling pathways.

References

1. Yang, L.; Pang, Y.; Moses, H.L. TGF-β and immune cells: An important regulatory axis in the tumor microenvironment and progression. Trends Immunol. 2010, 31, 220–227.
2. Widder, J.; Dorfinger, K.; Wilfing, A.; Trieb, K.; Pirich, K.; Loebenstein, R.; Niederle, B.; Gessl, A.; Spitzauer, S.; Grubeck-Loebenstein, B. The immunoregulatory influence of transforming growth factor beta in thyroid autoimmunity: TGF β inhibits autoreactivity in Graves' disease. J. Autoimmun. 1991, 4, 689–701.
3. Ouyang, W.; Filvaroff, E.; Hu, Y.; Grogan, J. Novel therapeutic targets along the Th17 pathway. Eur. J. Immunol. 2009, 39, 670–675.
4. Syed, V. TGF-β Signaling in Cancer. J. Cell. Biochem. 2016, 117, 1279–1287.

5. Morikawa, M.; Derynck, R.; Miyazono, K. TGF-β and the TGF-β Family: Context-Dependent Roles in Cell and Tissue Physiology. Cold Spring Harb. Perspect. Biol. 2016, 8, a021873.
6. Santibañez, J.F.; Quintanilla, M.; Bernabeu, C. TGF-β/TGF-β receptor system and its role in physiological and pathological conditions. Clin. Sci. 2011, 121, 233–251.
7. Hinck, A.; Mueller, T.D.; Springer, T.A. Structural Biology and Evolution of the TGF-β Family. Cold Spring Harb. Perspect. Biol. 2016, 8, a022103.
8. Robertson, I.B.; Horiguchi, M.; Zilberberg, L.; Dabovic, B.; Hadjiolova, K.; Rifkin, D.B. Latent TGF-β-binding proteins. Matrix Biol. 2015, 47, 44–53.
9. Wipff, P.-J.; Hinz, B. Integrins and the activation of latent transforming growth factor β1—An intimate relationship. Eur. J. Cell Biol. 2008, 87, 601–615.
10. Massagué, J.; Blain, S.W.; Lo, R.S. TGFβ Signaling in Growth Control, Cancer, and Heritable Disorders. Cell 2000, 103, 295–309.
11. Shi, Y.; Massagué, J. Mechanisms of TGF-β Signaling from Cell Membrane to the Nucleus. Cell 2003, 113, 685–700.
12. Ark, A.V.; Cao, J.; Li, X. TGF-β receptors: In and beyond TGF-β signaling. Cell. Signal. 2018, 52, 112–120.
13. Derynck, R.; Zhang, Y.E. Smad-dependent and Smad-independent pathways in TGF-β family signalling. Nat. Cell Biol. 2003, 425, 577–584.
14. Andrieux, G.; Fattet, L.; Le Borgne, M.; Rimokh, R.; Théret, N. Dynamic Regulation of Tgf-B Signaling by Tif1γ: A Computational Approach. PLoS ONE 2012, 7, e33761.
15. Zandvoort, A.; Postma, D.S.; Jonker, M.R.; Noordhoek, J.A.; Vos, J.T.W.M.; Van Der Geld, Y.M.; Timens, W. Altered expression of the Smad signalling pathway: Implications for COPD pathogenesis. Eur. Respir. J. 2006, 28, 533–541.
16. Colak, S.; Ten Dijke, P. Targeting TGF-β Signaling in Cancer. Trends Cancer 2017, 3, 56–71.
17. Zhang, Y.E. Non-Smad Signaling Pathways of the TGF-β Family. Cold Spring Harb. Perspect. Biol. 2016, 9, a022129.
18. Ábrigo, J.; Campos, F.; Simon, F.; Riedel, C.; Cabrera, D.; Vilos, C.; Cabello-Verrugio, C. TGF-β requires the activation of canonical and non-canonical signalling pathways to induce skeletal muscle atrophy. Biol. Chem. 2018, 399, 253–264.
19. Papageorgis, P. TGFβ Signaling in Tumor Initiation, Epithelial-to-Mesenchymal Transition, and Metastasis. J. Oncol. 2015, 2015, 587193.
20. Egesten, A.; Gordon, S.; Herwald, H. Innate immunity—A clinical perspective. J. Intern. Med. 2019, 285, 477–478.

21. Bonilla, F.A.; Oettgen, H.C. Adaptive immunity. J. Allergy Clin. Immunol. 2010, 125, S33–S40.
22. Kelly, A.; Houston, S.A.; Sherwood, E.; Casulli, J.; Travis, M.A. Regulation of Innate and Adaptive Immunity by TGFβ. Adv. Immunol. 2017, 134, 137–233.
23. Travis, M.A.; Sheppard, D. TGF-β Activation and Function in Immunity. Annu. Rev. Immunol. 2014, 32, 51–82.
24. Oh, S.A.; Li, M.O. TGF-β: Guardian of T Cell Function. The Journal of Immunology 2013, 191, 3973–3979.
25. Rosser, E.C.; Mauri, C. Regulatory B Cells: Origin, Phenotype, and Function. Immunity 2015, 42, 607–612.
26. McCarron, M.J.; Marie, J.C. TGF-β prevents T follicular helper cell accumulation and B cell autoreactivity. J. Clin. Investig. 2014, 124, 4375–4386.
27. Mincione, G.; Di Marcantonio, M.C.; Tarantelli, C.; D'Inzeo, S.; Nicolussi, A.; Nardi, F.; Donini, C.F.; Coppa, A. EGF and TGF-1 Effects on Thyroid Function. J. Thyroid Res. 2011, 2011, 431718.
28. Santin, A.P.; Furlanetto, T.W. Role of estrogen in thyroid function and growth regulation. J. Thyroid Res. 2011, 2011, 875125.
29. Gantus, M.; Alves, L.; Stipursky, J.; Souza, E.; Teodoro, A.; Alves, T.; Carvalho, D.; Martinez, A.; Gomes, F.; Nasciutti, L. Estradiol modulates TGF-β1 expression and its signaling pathway in thyroid stromal cells. Mol. Cell. Endocrinol. 2011, 337, 71–79.
30. Qin, J.; Hanyu, A.; Wayama, M.; Goto, N.; Katsuno, Y.; Kawasaki, S.; Nakajima, Y.; Kajiro, M.; Komatsu, Y.; Fujimura, A.; et al. Estrogen receptor β activation stimulates the development of experimental autoimmune thyroiditis through up-regulation of Th17-type responses. Clin. Immunol. 2018, 190, 41–52.
31. Ito, I.; Hanyu, A.; Wayama, M.; Goto, N.; Katsuno, Y.; Kawasaki, S.; Nakajima, Y.; Kajiro, M.; Komatsu, Y.; Fujimura, A.; et al. Estrogen Inhibits Transforming Growth Factor β Signaling by Promoting Smad2/3 Degradation. J. Biol. Chem. 2010, 285, 14747–14755.
32. Chipuk, J.E.; Cornelius, S.C.; Pultz, N.J.; Jorgensen, J.S.; Bonham, M.J.; Kim, S.-J.; Danielpour, D. The Androgen Receptor Represses Transforming Growth Factor-β Signaling through Interaction with Smad3. J. Biol. Chem. 2002, 277, 1240–1248.
33. Kunzmann, S.; Ottensmeier, B.; Speer, C.P.; Fehrholz, M. Effect of progesterone on Smad signaling and TGF-β/Smad-regulated genes in lung epithelial cells. PLoS ONE 2018, 13, e0200661.