The Role of TGF-β in the Pathogenesis of Type 1 Diabetes Mellitus

by Nur Rochmah

The Role of TGF-β in the Pathogenesis of Type 1 Diabetes Mellitus

Ike Wahyu Triastuti*, Roedi Irawan, Anang Endaryanto, Nur Rochmah, Muhammad Faizi

Department of Paediatrics, Faculty of Medicine, Universitas Airlangga
Dr. Soetomo General Hospital, Surabaya, 60286, Indonesia

E-mail: ikewahyu.pediatri@gmail.com; roedi.dr.rsds@gmail.com;
anang.endaryanto@fk.unair.ac.id; nur-r@fk.unair.ac.id; Muhammad.faizi@fk.unair.id

*Corresponding author details: Ike Wahyu Triastuti; ikewahyu.pediatri@gmail.com

ABSTRACT

Type 1 diabetes mellitus (T1DM) is a disease caused by dysregulation of the immune system with pancreatic cells as the targeted organ. The incidence of T1DM is increasing every year, with peak incidence at the age of 10-14 years. Genetic susceptibility and environmental exposure play important roles in immune system disorders. The failure of the tolerogenic process is one of the foremost processes causing pancreatic damage through the molecular mimicry process due to repeated infections both prenatally and postnatally. An increase in the expression of MHC class II and co-stimulator will trigger a shift in the balance of the shape of T cells, namely an increase in Th1 and Th7 cell differentiation, but a decrease in the number and function of Treg cells. TGF-β is a cytokine produced by Treg cells that functions to maintain tolerance in the human body. A decrease in TGF-β levels usually appears in the pre-diabetes stage. This review aims to elucidate the role of TGF- in the course of T1DM.

Keywords: T1DM; molecular mimicry; Treg; TGF-β

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an autoimmune disease that mostly affects children [1]. Immune system dysregulation such as failure of T cell-mediated tolerogenic processes, imbalance of pro-inflammatory and anti-inflammatory cytokine production, and formation of autoantibodies are responsible for pancreatic cell damage [2,3]. The prevalence of diabetes mellitus in a decade will increase by about 100 million people [1]. Transforming growth factor-β (TGF-β) is a pleiotropic regulatory protein that is both suppressive and proinflammatory to the immune response [4]. TGF-β contributes to maintaining an effective naive T cell population through regulation of proliferation, homeostasis, and diversity of T cell repertoire [5].

T1DM Pathophysiology

The course of type 1 diabetes mellitus begins with genetic susceptibilities, such as polymorphisms in HLA, especially HLA-DR and HLA-DQ, and exposure to environmental agents. Recurrent viral infections both prenatally and postnatally, such as Coxsackievirus B1 infection and other enteroviruses will directly attack pancreatic cells specifically or through a molecular mimicry process which in turn involves the immune system thus damaging the pancreas [6-8]. The virus infects cells (not the pancreatic cells), then the peptide from the virus will be expressed by HLA class I which is recognized by CD8+ T cells. These viral proteins generally have the same amino acid sequence as pancreatic-cell proteins (e.g., proteins from Coxsackievirus B1 with glutamate decarboxylase) thereby triggering cytotoxic CD8+ T cells against infected cells and pancreatic cells. When virions undergo phagocytosis by macrophages, they are presented to CD4+ T cells via HLA class II, then B lymphocytes are activated and produce anti-viral antibodies and anti-pancreatic-cell autoantibodies [9].

This dysregulation of the immune system results in insulitis, a condition in which the remaining islet cells contain large nucleated cells, some degranulated cells, and chronic inflammatory infiltrate. The chronic inflammatory infiltrate contains predominantly CD8+ cells, the remainder includes CD4+ cells, B lymphocytes, macrophages, and natural killer (NK) cells. Meanwhile, the number of macrophages (CD68+), CD4+ T cells, B lymphocytes (CD20+) and plasma cells (CD138+) decreases. FOXP3+ cells (e.g. regulatory T cells) and NK cells are rarely found in the remaining pancreatic tissue [10]. A decrease in insulin secretion leading to impaired glucose tolerance or plasma glucose surge occurs several months before the onset. Damage to pancreatic cells reaches 90-95%, only a small amount of insulin and serum C-peptide levels remains, therefore exogenous insulin is given to maintain blood glucose levels [10].

TGF-β on the Immune System

The name transforming growth factor-β (TGF-β) comes from its function, which is being able to transform and promote cell growth. The TGF-β family in humans consists of 33 types of proteins according to their coding genes. The most studied clusters of the TGF- family are the three isoforms of TGF-β, namely TGF-β1, -β2, and -β3. The TGF-family has diverse roles in regulating cell proliferation, cell differentiation, wound healing, controlling the immune system, and a key protein in pathological processes in vivo, such as connective tissue disorders, fibrosis, autoimmune diseases including T1DM and cancer. TGF-β polypeptide precursor structure is composed of three segments, namely amino-terminal signal peptide, carboxy-terminal TGF-β family monomer polypeptide, and latency-associated peptides (LAPs) [11].

Transforming growth factor-β (TGF-β) is a pleiotropic regulatory protein that is both suppressive and proinflammatory to the immune response [4]. Several studies have stated that TGF-β determines the type and magnitude of the immune response against microbes, besides that it also plays an important role in maintaining immune tolerance and homeostasis against self-antigens and innocuous antigens in the stable phase. It is TGF-β that contributes to maintaining an effective naive T cell population through the regulation of proliferation, homeostasis, and diversity of T cell repertoire. Sometimes an incomplete negative selection process in the thymus will result in some mature autoreactive T cells reaching the periphery. This autoreactive T cell in the periphery whose number is controlled by TGF-β is called peripheral tolerance [5].

The ability of TGF-β to regulate T cell proliferation depends on the status of T cell differentiation and the cumulative signaling pathway involved in cell activation, for example, TGF-β can inhibit the proliferation of naive CD4+ and CD8+ T cells but cannot inhibit the proliferation of active CD4+ and CD8+ T cells. The process of differentiation of CD4+ T cells into helper T cells 1 (Th1) and 2 (Th2) is inhibited by the TGF-β signal. Inhibition of differentiation of naive CD4+ T cells into Th1 cells is mediated by TGF-β expression through the activation of Smad2 and Smad3 transcription factors [4,12].

As previously mentioned, TGF-β is a pleiotropic cytokine that contributes to maintaining immune homeostasis through the proliferation, differentiation, activation, and function of effector cells of the immune system. Depending on the cytokine environment, TGF-β promotes the differentiation of peripheral CD4+ cells into anti-inflammatory Treg cells as well as Th17 cells and pro-inflammatory Th9 cells [12]. TGF-β also plays a role in promoting the development of Tfh (follicular helper T). TGF-β signaling induces the regulatory activity of naive Foxp3-expressing CD4+ T cells to pTreg. However, in conditions of infection when formations of many pro-inflammatory cytokines and strong costimulatory signals occur, inhibition of Foxp3 induction through TGF-β will occur. This suggests that pTreg cell differentiation is modulated by the microenvironment, with inflammatory conditions that favor effector cells over the production of Treg cells [5]. Another role of TGF-β in the body that has a negative impact is fibrosis which involves the deposition of extracellular matrix (such as collagen and fibronectin) via canonical and non-canonical signaling pathways. The canonical pathway is a TGF-β signaling pathway involving ALK5-Smad2/3, while the non-canonical pathway involves TGF-β/ALK1/SMAD1/5, MAP kinases (ERK, JNK, p38), PI3K/Akt, c-abl, JAK2 /STAT3, and Rho-associated coiled-coil containing protein kinases (ROCKs). Both pathways will work directly or in synergy with Smad protein to regulate protein expression. The active Smad protein will enter the nucleus and interact with DNA through binding to transcription factors (TF), co-activators (CA), and co-repressors (CR) regulating gene expression thereby increasing the production of extracellular matrix (ECM) including collagen, fibronectin, CTGF/ CCN2, and α-SMA) and decreasing MMP protein expression leading to fibrosis [13]. An increase in the amount of TGF-β for a long period will cause fibrosis in important organs such as the kidneys and eyes resulting in complications such as diabetic nephropathy and diabetic retinopathy [14,15].

The Role of TGF-β in the Pathogenesis of T1DM
Treg cells are activated in secondary lymphoid tissue-derived from naive FoxP3-expressing CD4+ T cells with the help of the TGF-β cytokine.

Treg cells, in carrying out their functions in regulating and suppressing both immune and inflammatory responses, produce IL-10 and TGF-β cytokines. Several peripheral tolerance mechanisms played by Treg cells include inhibiting T cell maturation by competing for binding to IL-2 cytokines by IL-2 receptors expressed by Treg cells. Treg cells secrete cytokines such as IL-10 and TGF-β which bind to receptors on active T cells and reduce the activity of these activated T cells. The function of APCs is also inhibited by Treg cells through inhibition of the CD80/86 co-stimulator on APCs which interacts with CTLA4 on Treg cells so that these APCs cannot stimulate T cells to become active. Treg cells are capable of destroying active T cells through perforin and granzyme secretion. Type 1 diabetes mellitus begins with the cells' failure of the tolerance process towards self-antigens. This process is initiated by polymorphisms in MHC class I and II in individuals, resulting in autoreactive CD4+ and CD8+ T cells that recognize pancreatic cell antigens too strongly. When APC introduces antigen to CD4+ T cells, IL-12 is formed which causes polarization, causing CD4+ T cells to become dominant Th1 and increasing the production of IFN-γ cytokine. On the other hand, the number of circulating Treg cells will decrease [16].

The following are some studies examining TGF-β in type 1 diabetes mellitus. A previous study by Azar et al. [17] in children with T1DM, T2DM, and controls who had normal plasma albumin levels succeeded in showing comparisons of TGF-β levels. The study showed something similar to this study, namely serum TGF-β levels would decrease significantly and the levels were lower in the T1DM group, especially those that have been diagnosed for more than 2 years [17]. A study by Ishigame et al., 2013 showed that the absence of a TGF-β signal on T cells in the thymus resulted in polarization, resulting in increased Th1 cell formation, whereas Th17 cells and Fox3+ Treg cells decreased [18].

Deletion of TGF-β signal on effector CD4+ T cells through TGFβRII ablation causes increased production of IFN-γ cytokines and polarization towards Th1, disruption of Treg cell homeostasis which manifests into T1DM (18). A similar result is shown in a study by Roohi et al. [19] claiming that TGF-β levels in the T1DM group were statistically lower than those in the control group. In a meta-analysis study, the result showed that the serum levels of TGF-β in the T1DM group were lower than in the control group [20]. A different result is shown by research by Zorena et al. [21] regarding the relationship between serum levels of TGF-β1 and the duration of illness of T1DM. The results showed that there was a statistically significant relationship between the duration of illness of T1DM and an increase in serum TGF-β1 levels. Patients with a duration of illness of more than 15 years who have elevated serum TGF-β1 1SD levels will have a 25% increased risk of microangiopathic complications.

A study of TGF-β as a diagnostic tool to predict the presence of diabetic retinopathy in T1DM stated that non-proliferative diabetic retinopathy (NPDR) patients had higher serum TGF-β levels than T1DM patients without diabetic retinopathy, while the T1DM group without diabetic retinopathy had higher TGF-β levels than the control group [15]. Factors that affect TGF-β levels include renin-angiotensin inhibitor agents, good glycemic control, normally controlled systolic blood pressure, statin consumption, nonsmoker, and a low protein diet. [22].

TABLE 1: Comparative literature on the role of tgf-β on t1dm pathogenesis

Author, year	Research method	No. of study participants	Main result
Azar *et al.,* 2000	Case-control	26 T1DM patients 25 T2DM patients 27 children in the T1DM control group 15 children in the T2DM control group	• TGF-β will decrease significantly and the level is lower in the T1DM group than in the control group, and the highest in the T2DM group • TGF-β serum levels will decrease significantly in the T1DM group, especially those that have been diagnosed for more than 2 years.
Roohi *et al.,* 2014	Case-control	24 T1DM patients 38 T2DM patients 30 control for T1DM 40 control for T2DM	• TGF-β levels in the T1DM group were statistically lower than controls with a median value (IQR) of 0(0) vs 184.52 (627.22) pg/mL, p=0.001.
Qiao *et al.,* 2016	Meta-analysis	1407 T1DM patients 1373 control	• TGF-β serum levels in the T1DM group were lower than in the control group
Zorena *et al.,* 2013	Case-Control	116 T1DM patients 19 healthy children as the control group	• Patients with a duration of illness of more than 15 years who have elevated serum TGF-β1 1SD levels will have a 25% increased risk of microangiopathic complications. A study of TGF-β as a diagnostic tool to predict the presence of diabetic retinopathy in T1DM stated that non-proliferative diabetic retinopathy (NPDR) patients had higher serum TGF-β levels than T1DM patients without diabetic retinopathy (1530 ± 465 pg/mL versus 758 ± 424 pg/mL, p= 0.003), while the T1DM group without diabetic retinopathy had higher TGF-β levels than the control group (758 ± 424 pg/mL versus 156 ± 49 pg/mL, p = 0.001).

CONCLUSION

Type 1 diabetes mellitus is an autoimmune disease that destroys pancreatic cells. This damage is mediated by the failure of tolerogenic processes that are influenced by TGF-β signals, namely by polarization differentiation of T cells towards Th1 and Th7 cells, while the number of Treg cells decreases. Failure to tolerate pancreatic autoantigens results in insulitis, a condition in which the remaining islet cells contain large nucleated cells, some degranulated cells, and chronic inflammatory infiltrate. The chronic inflammatory infiltrate contains predominantly CD8+ cells, the remainder includes CD4+ cells, B lymphocytes, macrophages, and natural killer (NK) cells. The islet cells remaining in the pancreas are usually less than 20%, therefore unable to keep insulin-dependent metabolism working properly, as occurs in T1DM.

REFERENCES

[1] Saeedi, P., I. Petershon, P. Salpea, B. Malanda, S. Karuranga, N. Unwin, S. Colagiuri, L. Guariguata, A.A. Motala, K. Ogurtsova, J.E. Shaw, D. Bright, and R. William. (2019).Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 157: 10-76.

[2] Lu, J., J. Liu, L. Li, Y. Lan, and Y. Liang. (2020). Cytokines in type 1 diabetes : mechanisms of action and immunotherapeutic targets. Clin Transl Immunology. 9: 1–17.

[3] Mekala, K. C. and Bertoni, A. G. (2020). Epidemiology of diabetes mellitus. Transplantation, Bioengineering, and Regeneration of the Endocrine Pancreas. 1: 49-58.

[4] Takimoto, T., Y. Wakabayashi, T. Sekiya, N. Inoue, R. Morita, K. Ichiyama, R. Takahashi, M. Asakawa, G. Muto, T. Mori, E. Hasegawa, S. Shizuya, T. Hara, M. Nomura and A. Yoshimura. (2010). Smad2 and smad3 are redundantly essential for the tgf- β – mediated regulation of regulatory t plasticity and th1 development. J Immunol. 185: 842-55.

[5] Sanjabi, S., S.A. Oh, and M.O. Li. (2017). Regulation of the immune response by tgf-β: from conception to autoimmunity and infection. Cold Spring Harb Perspect Biol. 9(6): 1–34.

[6] Beyerlein, A., F. Wehweck, A. Ziegler, and M. Pflueger. (2013). Respiratory infections in early life and the development of islet autoimmunity in children at increased type 1 diabetes risk: evidence from the babydiet study. JAMA Pediatr. 167(9): 800-7.

[7] Beyerlein, A., E. Donnachie, S. Jergens, and A. Ziegler. (2016). Infections in early life and development of type 1 diabetes. JAMA. 315(17): 1899-1901.

[8] Laitinen, O. H., H. Honkanen, O. Pakkanen, S. Oikarinen, M. M. Hankaniemi, H. Huhtala, T. Ruokoranta, V. Lecouturier, P. André, R. Harju, and S.M. Virtanen. (2014). Coxsackievirus b1 is associated with induction of β-cell autoimmunity that portends type 1 diabetes. Diabetes. 63(2): 446-55.

[9] Atkinson, M.A and N. K. Maclaren. (1994). The pathogenesis of insulin -dependent diabetes mellitus. N Engl J Med. 331: 1428-36.

[10] Atkinson, M.A., G.S. Eisenbarth, and A.W. Michels. (2014). Type 1 diabetes. Lancet. 383: 69–82.

[11] Morikawa, M., R. Derynck, and K. Miyazono. (2016). Tgf- b and the tgf- b family : context-dependent roles in cell and tissue physiology. Cold Spring Harb Perspect Biol. 8: 1-24.

[12] Kuwahara, M., M. Yamashita, K. Shinoda, S. Tofukuji, A. Onodera, R. Shinnakasu, S. Motohashi, H. Hosokawa, D. Tumes, C. Iwamura, V. Lefebvre, and T. Nakayama. (2012). The transcription factor sox4 is a downstream target of signaling by the cytokine tgf-β and suppresses th 2 differentiation. Nat Immunol. 13(8): 778–86.

[13] Finnson, K. W., Y. Almadani, and A. Philip. (2020). Non-canonical (non-smad2/3) tgf-β signaling in fibrosis: mechanisms and targets. In Seminars in cell & developmental biology. Academic Press. 115-22.

[14] Pertseva, N., I. Borysova, and D. Chub. (2019). Tgf-β1 and vcam-1 serum concentrations as diagnostic biomarkers of diabetic kidney disease progression. Rom J Diabetes Nutr Metab Dis. 26(2): 169-75.

[15] Zorena, K., E. Malinowska, D. Raczyńska, M. Myśliwiec, and K. Raczyńska. (2013). Serum concentrations of transforming growth factor-beta 1 in predicting the occurrence of diabetic retinopathy in juvenile patients with type 1 diabetes mellitus. J. Diabetes Res. 2013: 1-6.

[16] Owen, J.A, J. Punt, S.A. Stranford, and P.P. Jones. (2009). T-cell activation, differentiation, and memory. In: J.A. Owen (Ed). Kuby Immunology. 7th. ed. W.H. Freeman. New York. 357-83.

[17] Azar, S.T., I. Salti, M.S. Zantout, and S.M. Azar. (2000). Alterations in plasma transforming growth factor β in normoalbuminuric type 1 and type 2 diabetic patients. J Clin Endocrinol Metab. 85(12): 4680–2.

[18] Ishigame, H., L.A. Zenewicz, S. Sanjabi, P.L. Limón, M. Nakayama, W.J. Leonard, and R.A. Flavell. (2013). Excessive th1 responses due to the absence of tgf- β signaling cause autoimmune diabetes and dysregulated treg cell homeostasis. Proc. Natl. Acad. Sci. USA. 110(17): 6961-6.

[19] Roohi, A., M. Tabrizi, F. Abbasi, A. A. Jafari, B. Nikbin, B. Larijani, M. Qorbani, A.Meysamie, H. Asgarian-Omran, B. Nikmanesh, and Bajouri. (2014). Serum Il-17, il-23, and tgf-β levels in type 1 and type 2 diabetic patients and age-matched healthy controls. Biomed Res. Int. 2014: 1-4.

[20] Qiao, Y.C., J. Shen, X.Z Hong, L. Liang, C.S. Bo, Y. Sui, and H.l. Zhao. (2016). Changes of regulatory T cells, transforming growth factor-beta and interleukin- 10 in patients with type 1 diabetes mellitus: A systematic review and meta- analysis. Clin Immunol. 170: 61-9.

[21] Zorena, K., D. Raczyńska, P. Wiśniewski, E. Malinowska, M. Myśliwiec, K. Raczyńska, and D. Rachoń. (2013). Relationship between serum transforming growth factor β1 concentrations and the duration of type 1 diabetes mellitus in children and adolescents. J. Inflamm. 2013: 13-8.

[22] McGowan, T. A., Y. Zhu, and K. Sharma. (2004). Transforming growth factor-beta: a clinical target for the treatment of diabetic nephropathy. Curr. Diab. Rep. 4(6): 447-54.

The Role of TGF-β in the Pathogenesis of Type 1 Diabetes Mellitus

10 www.balimedicaljournal.org
Internet Source
1 %

11 H. Ishigame, L. A. Zenewicz, S. Sanjabi, P. Licona-Limon, M. Nakayama, W. J. Leonard, R. A. Flavell. "Excessive Th1 responses due to the absence of TGF- signaling cause autoimmune diabetes and dysregulated Treg cell homeostasis", Proceedings of the National Academy of Sciences, 2013
Publication
1 %

12 Naureen Javeed, Tracy K. Her, Matthew R. Brown, Patrick Vanderboom et al. "Pro-inflammatory β cell small extracellular vesicles induce β cell failure through activation of the CXCL10/CXCR3 axis in diabetes", Cell Reports, 2021
Publication
1 %

13 www.coursehero.com
Internet Source
1 %

14 www.cureus.com
Internet Source
1 %

15 www.krcp-ksn.org
Internet Source
1 %

16 Monika Lodyga, Boris Hinz. "TGF-β1 – A truly transforming growth factor in fibrosis and immunity", Seminars in Cell & Developmental Biology, 2019
<1 %

17   publish.kne-publishing.com
      Internet Source   <1%

18   ashpublications.org
      Internet Source   <1%

19   www.cell.com
      Internet Source   <1%

20   www.wjgnet.com
      Internet Source   <1%

21   Ai-Di Gu, Song Zhang, Yunqi Wang, Hui Xiong,   <1%
      ThomasA. Curtis, YisongY. Wan. "A Critical
      Role for Transcription Factor Smad4 in T Cell
      Function that Is Independent of Transforming
      Growth Factor β Receptor Signaling",
      Immunity, 2015
      Publication

22   Chun-Ching Lin, Liang-Tzung Lin, Ming-Hong   <1%
      Yen, Juei-Tang Cheng, Chung-Hsi Hsing, Ching-
      Hua Yeh. "Renal Protective Effect of Xiao-Chai-
      Hu-Tang on Diabetic Nephropathy of Type 1-
      Diabetic Mice", Evidence-Based
      Complementary and Alternative Medicine,
      2012
      Publication

23   www.researchgate.net
      Internet Source   <1%

24 www.science.gov
Internet Source
<1 %

25 Susan M. Schlenner, Benno Weigmann, Qingguo Ruan, Youhai Chen, Harald von Boehmer. "Smad3 binding to the foxp3 enhancer is dispensable for the development of regulatory T cells with the exception of the gut", The Journal of Experimental Medicine, 2012
Publication
<1 %

26 Vladimír Jakuš, Michal Sapák, Jana Kostolanská. " Circulating TGF- 1, Glycation, and Oxidation in Children with Diabetes Mellitus Type 1 ", Experimental Diabetes Research, 2012
Publication
<1 %

27 dspace.cuni.cz
Internet Source
<1 %

28 www.gather.com
Internet Source
<1 %

29 www.mdpi.com
Internet Source
<1 %

30 He Haiqi, Zhang Yong, Lv Yi. "Transcriptional regulation of Foxp3 in regulatory T cells", Immunobiology, 2011
Publication
<1 %

31 Mark A. Sperling, Joseph I. Wolfsdorf, Ram K. Menon, William V. Tamborlane, David Maahs, Tadej Battelino, Moshe Phillip. "Diabetes Mellitus", Elsevier BV, 2021
Publication

<1 %

32 Shigeru Tanaka, Akira Suto, Taro Iwamoto, Daisuke Kashiwakuma et al. "Sox5 and c-Maf cooperatively induce Th17 cell differentiation via RORγt induction as downstream targets of Stat3", The Journal of Experimental Medicine, 2014
Publication

<1 %

33 Takashi Sekiya, Hiroko Nakatsukasa, Qianjin Lu, Akihiko Yoshimura. "Roles of transcription factors and epigenetic modifications in differentiation and maintenance of regulatory T cells", Microbes and Infection, 2016
Publication

<1 %

34 V. Ganapathy. "Regulation of TCR-induced IFN-gamma release from islet-reactive non-obese diabetic CD8+ T cells by prostaglandin E2 receptor signaling", International Immunology, 06/01/2000
Publication

<1 %

35 researchbank.rmit.edu.au
Internet Source

<1 %

The Role of TGF-β in the Pathogenesis of Type 1 Diabetes Mellitus

FINAL GRADE

/100

GENERAL COMMENTS

Instructor