PATHOLOGICAL PHYSIOLOGY

UDC 616-097

Transforming growth factor beta 1. Biological role and clinical significance

O. O. Mosunova¹, E. A. Dementyeva²

¹ First St. Petersburg State Medical University named after Academician I. P. Pavlov,
6–8, ul. Lva Tolstogo, St. Petersburg, 197022, Russian Federation
² St. Petersburg State Pediatric Medical University,
2, Litovskaya ul., St. Petersburg, 194100, Russian Federation

For citation: Mosunova O. O., Dementyeva E. A. Transforming growth factor beta 1. Biological role and clinical significance. Vestnik of Saint Petersburg University. Medicine, 2020, vol. 15, issue 1, pp. 49–55. https://doi.org/10.21638/spbu11.2020.106

One of the most important representatives of the cytokine family is the transforming growth factor beta 1 (TGF beta 1). The purpose of the review is to study the biological role and clinical significance of TGF beta 1. Using PubMed databases, eLIBRARY, Google Scholar, keywords “cytokines”, “TGF beta 1” found 25,518 sources, 50 selected for analysis. TGF beta 1 is a polypeptide cytokine first isolated from platelets in the 1990s. TGF beta 1 belongs to the family of dimeric polypeptides with a molecular weight of 25 kDa. The gene encoding TGF beta 1 is found in humans on chromosome 19. TGF beta 1 has a pleiotropic effect on the proliferation and differentiation of a wide range of cells, and therefore regulates many physiologic and pathophysiologic processes: immune response, apoptosis, fibrogenesis, and carcinogenesis. TGF beta 1 has an effect on almost all organs and tissues. TGF beta 1 is a key marker that can be used in the diagnosis of a number of diseases. It is necessary to further study the role of TGF beta 1 in the pathophysiologic mechanisms of various diseases, as well as in the development of approaches to targeted therapy.

Keywords: transforming growth factor beta 1, TGF beta 1, cytokines, cell proliferation, immune response, carcinogenesis, fibrogenesis.

Introduction

Cytokines are a group of polypeptide mediators that are involved in the regulation of normal physiological functions and the formation of protective reactions of the body. Their study began in the 1940s of the 20th century and by 2020, more than 200 cytokines...
are already known [1]. New cytokines are discovered every year. By acting on the synthesis or action of cytokines, it is possible to prevent the development and treatment of various diseases.

One of the most important representatives of the cytokine family is the transforming growth factor beta 1 (TGF beta 1). It has a pleiotropic effect on the proliferation and differentiation of a wide range of cells, and therefore regulates many physiological and pathophysiological processes: immune response, apoptosis, fibrogenesis, and carcinogenesis in various organs [2–4].

The purpose of the REVIEW is to study the biological role and clinical significance of TGF beta 1.

Materials and methods

Using PubMed databases, eLIBRARY.ru, Google Scholar, keywords “cytokines”, “TGF beta 1” found 25,518 sources, 50 selected for analysis.

Results

In 1978, representatives of the TGF beta 1 family were first described. This group of cytokines got its name due to its ability to induce the transformation of the phenotype of normal cells in culture [5–7].

TGF beta 1 is a polyvalent cytokine first isolated from platelets in the 1990s. TGF beta 1 belongs to the family of dimeric polypeptides with a molecular weight of 25 kDa, and is widely represented in tissues. The gene encoding TGF beta 1 is located in humans on chromosome 19 [8–10]. The sources of TGF beta 1 are mainly monocytes and macrophages, which contain it constantly, but secrete it only when activated. TGF beta 1 can also produce fibroblasts, endotheliocytes, neutrophils, eosinophils, mast cells, smooth muscle cells, as well as cells of many types of malignant tumors [11; 12].

TGF beta 1 has inhibitory activity in relation to T-and B-cell proliferation, as well as to maturation and activation of macrophages, i.e. it is an element of reverse regulation of the immune response, primarily the inflammatory response. TGF beta 1 inhibits the activity of NK cells, suppresses the cytotoxic activity of CD8+ lymphocytes, lymphokine-activated killers, and blocks the production of cytokines and the secretion of certain immunoglobulins [13; 14]. It is a growth inhibitor in lymphoid, epithelial, and endothelial cells [15]. TGF beta 1 participates in repair processes in wounds, modulating inflammatory processes [7]. Thus, TGF beta 1 has an impact on all organs and tissues.

A number of studies have studied the effects of TGF beta 1 on the kidneys. The role of TGF beta 1 in the formation of nephron structures, in particular, the wonderful network of the glomerulus of nephrons [11; 16].

Histone acetylation has been found to be an important modulator of gene expression in fibrosis. Fibrogenic cytokine TGF beta 1 affects the acetylation of histone 3 (H3) and its regulatory kinetics in renal myofibroblasts. Kidney fibroblasts of rats suffering from ureteral obstruction were treated with recombinant TGF beta 1 for 48 hours. TGF beta 1-induced activation of myofibroblasts was accompanied by a decrease in total H3 acetylation. Thus, TGF beta 1 produces metabolic reprogramming in renal fibroblasts [17].
The dynamics of the amount of TGF beta 1 in the blood serum of rats with experimental chronic kidney disease was studied. It is shown that as this disease develops, there is an increase in serum concentration of TGF beta 1 until the 4th month, while at the 6th month there is a slight decrease in its level [18].

It is also noted that TGF beta 1 is a key mediator of diabetic nephropathy [19; 20].

TGF beta 1 participates in the formation of renal fibrosis by increasing the content of miR-21 via a Smad3-dependent mechanism [21].

Other organs are also affected by TGF beta 1.

TGF beta 1 affects changes in the structure of the liver, so the use of immunohistochemical diagnostics of the degree of TGF beta 1 expression is proposed to assess the degree of liver fibrosis [22].

Elevated levels of TGF beta 1 have been reported in endometriosis. It has been experimentally proven that TGF beta 1 potentiates the adhesion of ectopic endometrial cells by enhancing the signal transmission axis of integrin and FAK, as well as migration through cadherin-mediated signal cascades of EMT and RHOGTPase [23].

It has been confirmed that TGF beta 1 contributes to the invasion of human gastric carcinoma cells SGC7901, causing autophagy [24].

The effect of TGF beta 1 on gum inflammation was studied. TGF beta 1 is an immunosuppressive cytokine that stimulates wound healing. An increased concentration of cytokine in an inflamed gum can counterbalance destructive inflammatory reactions [25].

The high sensitivity, specificity, and accuracy of TGF beta 1 determination, along with the serum protein survivin, make them promising markers for early detection and follow-up of patients with retinoblastoma [26].

In relation to tumor cells, TGF beta 1 serves as a tumor suppressor (inhibition of cell proliferation, induction of apoptosis, reduction of telomerase activity) and a tumor promoter (transdifferentiation, induction of angiogenesis, immunosuppression) [27].

Determination of TGF beta 1 in peripheral blood is recommended in the diagnosis of various diseases associated with chronic inflammatory process, such as Alzheimer’s disease, acquired immunodeficiency syndrome, Parkinson’s disease, glomerulonephritis, nephropathy, diabetes, glomerulosclerosis, systemic lupus, autoimmune hepatitis, chronic fatigue syndrome, sepsis, stroke, various tissue tumors, etc. Elevated levels of TGF beta 1 are detected in patients with chronic fatigue and Guillain–Barre–Strohl syndromes [28–30].

The inverse correlation of TGF beta 1 level with disease activity is described in Kawasaki disease in patients with IgA deficiency [31].

It is proved that TGF beta 1 contributes to fibrotic processes, so its definition can be used for myelofibrosis and myeloid metaplasia.

Increasing the serum level of TGF beta 1 in patients suffering from thrombocytopenic purpura implies its participation in hematopoiesis.

It has been shown that determining the level of TGF beta 1 in serum and cerebrospinal fluid in multiple sclerosis is of great importance for monitoring remission and the active phase of the disease [29; 32].

TGF beta 1 plays an important role in bone marrow metabolism and can be considered a marker for osteoporosis [33].

TGF beta 1 may play a modulating role in tumor formation. In the early stages, TGF beta 1 proteins act, in some cases, as tumor suppressors. The definition of circu-
lating TGF beta 1 may reflect different stages in solid tumors, such as cervical cancer. An increase in its level was detected in prostate cancer, bladder cancer, and liver cancer [28; 34; 35].

It was found that in patients with ischemic heart disease, serum levels of TGF beta 1 were significantly higher than in healthy individuals. TGF beta 1 deficiency is one of the factors of atherosclerotic plaque destabilization [36; 37]. It has been shown that TGF beta 1 together with other cytokines, such as tumor necrosis factor and interleukin-1, is involved in the process of vascular remodeling [5; 38]. Development of acute coronary syndrome is accompanied by a significant increase in TGF beta 1 [36; 39]. In the early stages of myocardial infarction, TGF beta 1 can play an important role in the inflammatory response by deactivating macrophages, suppressing endothelial chemokine receptors, and synthesizing cytokines. At a later stage, it includes fibrogenetic pathways, inducing deposition of the extracellular matrix, and can also contribute to the pathogenesis of left ventricular remodeling by activating fibroblasts and hypertrophy of the non-infarcted myocardium [36; 40; 41].

It is assumed that TGF beta 1 can cause thymus involution [42].

In recent years, it has been shown that an excess of TGF beta is of great importance in the formation of manifestations of hereditary connective tissue disorders. An increase in the concentration of this cytokine can be caused either by a mutation in the TGF beta receptors, or by a violation of the activation control of the TGF beta molecule [43–45]. Structural abnormalities of the connective tissue framework of the heart were associated with activation of the TGF beta signaling pathway in patients with connective tissue dysplasia (mitral valve prolapse, aortic half-moon asymmetry) [46]. It has been shown that antibodies to TGF beta inhibit the development of Marfan syndrome in transgenic mice with a genetic model of this disease [47; 48]. Thus, a modern therapeutic strategy is being developed in the treatment of connective tissue dysplasia, aimed at suppressing TGF beta 1.

It is assumed that dysregulation of glucose metabolism, leading to the development of hypertension, may be due to excessive activity of TGF beta 1 [49]. Anti-TGF beta therapy is a promising direction in the treatment of acquired vascular diseases, such as angiopathies associated with diabetes [50].

**Conclusion**

TGF beta 1 has an effect on almost all organs and tissues. TGF beta 1 is a key marker that can be used in the diagnosis of a number of diseases. It is necessary to further study the role of TGF beta 1 in the pathophysiological mechanisms of various diseases, as well as in the development of approaches to targeted therapy.

**References**

1. Verlan N. V. Interferon use: immunological and clinical aspects. *Tsitokiny i vospalenie*, 2016, vol. 15, no. 1, pp. 12–21. (In Russian)
2. Blobe G. C., Schiemann W. P., Lodish H. F. Role of transforming growth factor beta in human disease. *N. Engl. J. Med.*, 2000, vol. 342, no. 18, pp. 1350–1358.
3. Lee S. J., Kim K. H, Park K. K. Mechanisms of fibrogenesis in liver cirrhosis: the molecular aspects of epithelialmesenchymal transition. *World J. Hepatol.*, 2014, vol. 6, no. 4, pp. 207–216.
4. Wynn T. A. Cellular and molecular mechanisms of fibrosis. *J. Pathol.*, 2008, vol. 214, no. 2, pp. 199–210.
5. Zubova S. G. Influence of ionizing radiation on the expression of transforming growth factor beta. *II Bulleten’ eksperimental’noi biologii i meditsiny*, 1998, vol. 126, no. 11, pp. 529–533. (In Russian)

6. Zubova S. G. Synthesis and expression of transforming growth factor beta by activated macrophages. *Voprosy onkologii*, 1996, vol. 42, no. 5, pp. 80–85. (In Russian)

7. Bakin A. V., Rinehart C., Tomlinson A. K., Arteaga C. L. p38 mitogen-activated protein kinase is required for TGF-beta-mediated fibroblastic transdifferentiation and cell migration. *J. Cell. Sci.*, 2002, vol. 115, Pt 15, pp. 3193–3206.

8. Barton D., Foellmer B. E., Du J., Tamm J., Derynck R., Francke U. Chromosomal mapping of genes for transforming growth factors beta-2 and beta-3 in man and mouse: dispersion of TGF-beta gene family. *Oncogene Res.*, 1988, vol. 3, no. 4, pp. 223–331.

9. Lee C. G., Cho S. J., Kang M. J., Chapoval S. P., Lee P. J., Noble P. W., Yehualaeleshet T., Lu B., Flavell R. A., Milbrandt J., Homer R. J., Elias J. A. Early growth response gene 1-mediated apoptosis is essential for transforming growth factor β1–induced pulmonary fibrosis. *J. Exp. Med.*, 2004, vol. 200, no. 3, pp. 377–389.

10. Xaubet A., Marin-Arguedas A., Lario S., Ancochea J., Morell F., Ruiz-Manzano J., Rodriguez-Becerra E., Rodriguez-Arias J. M., Inigo P., Sanz S., Campistol J. M., Mullol J., Picado C. Transforming growth factor-beta 1 gene polymorphisms are associated with disease progression in idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine*, 2003, vol. 168, no. 4, pp. 431–435.

11. Blobe G. C., Schiemann W. P., Lodish H. F. Role of transforming growth factor beta in human disease. *N. Engl. J. Med.*, 2000, vol. 342, no. 18, pp. 1350–1358.

12. Engel M. E., Datta P. K., Moses H. L. Signal transduction by transforming growth factor beta: a cooperative paradigm with extensive negative regulation. *J. Cell. Biochem. Suppl.*, 1998, no. 30-31, pp. 111–122.

13. Pelipenko L. V., Sergienko A. V., Ivashev M. N. Effects of transforming growth factor beta-1. *Mezhdunarodnyi zhurnal eksperimental’noi obrazovaniia*, 2015, vol. 3, no. 4, pp. 558–559. (In Russian)

14. Clement A., ERS Task Force. Task force on chronic interstitial lung disease in immunocompetent children. *Eur. Respir. J.*, 2004, vol. 24, no. 4, pp. 686–697.

15. Ivchik T. V., Kokosov A. N., Yanchina E. D. Risk factors for chronic obstructive pulmonary disease. *Pul’monologiia*, 2003, no. 3, pp. 6–15. (In Russian)

16. Stern D. A., Morgan W. J., Wright A. L., Guerra S., Martinez F. D. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet*, 2007, vol. 370, no. 9589, pp. 758–764.

17. Smith E. R., Wigg B., Holt S. G., Hewitson T. D. TGF-β1 modifies histone acetylation and acetyl-coenzyme A metabolism in renal myofibroblasts. *Am. J. Physiol. Renal. Physiol.*, 2019, no. 316, pp. F517–F529.

18. Ses’ P. S., Gavrisheva N. A., Fedulov A. V., MacMillan J. C. Dynamics of the content of transforming growth factor beta 1 and tumor necrosis factor alpha in serum in experimental chronic renal failure. *Meditsinskaia immunologiia*, 2003, vol. 5, no. 1–2, pp. 133–136. (In Russian)

19. Kanwar Y. S., Wada J., Sun L., Xie P., Wainier E. I., Chen S., Chugh S., Danesh F. R. Diabetic nephropathy: mechanisms of renal disease progression. *Exp. Biol. Med.*, 2008, vol. 233, no. 1, pp. 4–11.

20. Soldatos G., Cooper M. E. Diabetic nephropathy: important pathophysiologic mechanisms. *Diabetes Res. Clin. Pract.*, 2008, vol. 82, no. 1, pp. S75–S79.

21. Zhong X., Chung A. C., Chen H. Y., Meng X. M., Lan H. Y. Smad3-mediated upregulation of miR-21 promotes renal fibrosis. *Clin. J. Am. Soc. Nephrol.*, 2011, vol. 22, no. 9, pp. 1668–1681.

22. Kempinski R., Neubauer K., Poniewierka E., Kaczorowski M., Halon A. The immunoreactivity of TGF-B1 in non-alcoholic fatty liver disease. *Folia Histochem. Cytobiol.*, 2019, vol. 57, no. 2, pp. 74–83.

23. Soni U. K., Chadchan S. B., Kumar V., Ubba V., Khan M. T. A., Vinod B. S. V., Konwar R., Bora H. K., Rath S. K., Sharma S., Jha R. K. A high level of TGF-B1 promotes endometriosis development via cell migration, adhesiveness, colonization, and invasiveness. *Biol. Reprod.*, 2019, vol. 100, no. 4, pp. 917–938.

24. Shen J., Zhao D. S., Li M. S. TGF-β1 promotes human gastric carcinoma SGC7901 cells invasion by inducing autophagy. *Eur. Rev. Med. Pharmacol. Sci.*, 2017, vol. 21, no. 5, pp. 1013–1019.

25. Steinsvoll S., Halstensen T. S., Schenck K. Extensive expression of TGF-B1 in chronically-inflamed periodontal tissue. *Journal of clinical periodontology*, 1999, vol. 26, no. 6, pp. 366–373.

26. Shehata H. H., Abou Ghalia A. H., Elsayed E. K., Ahmed Said A. M., Mahmoud S. S. Clinical significance of high levels of survivin and transforming growth factor beta-1 proteins in aqueous humor and serum of retinoblastoma patients. *J. AAPOS*, 2016, vol. 20, no. 5, pp. 444.e1–444.e9.
27. Babyshkina N. N., Malinovskaya E. A., Staheeva M. N., Volkomorov V. V., Ufandeev A. A., Slonimskaya E. M. The role of transforming growth factor TGF-β 1 in the pathogenesis of breast cancer. Siberian onkologicheskiy zhurnal, 2010, vol. 6, no. 42, pp. 63–70. (In Russian)
28. Bierie B., Moses H. L. TGF-beta and cancer. Cytokine growth factor. Rev., 2006, no. 17, pp. 29–40.
29. Kuwano K., Kawasaki M., Maeyama T. Soluble form of fas and fas ligand in BAL fluid from patients with pulmonary fibrosis and bronchiolitis obliterans organizing pneumonia. Chest, 2000, vol. 118, no. 2, pp. 451–458.
30. Matyas G., Naef P., Tollens M., Oexle K. De novo mutation of the latency-associated peptide domain of TGF-β3 in a patient with overgrowth and Loeys-Dietz syndrome features. Am. J. Med. Genet., 2014, vol. 164A, no. 8, pp. 2141–2143.
31. Graycar J. L., Miller D. A., Arrick B. A., Lyons R. M., Moses H. L., Derynck R. Human transforming growth factor-beta-3: recombinant expression, purification and biological activities in comparison with transforming growth factors-beta-1 and beta2. Molec. Endocr., 1989, vol. 3, no. 12, pp. 1977–1986.
32. Hagimoto N., Kuwano K., Miyazaki H. Induction of apoptosis and pulmonary fibrosis in mice in response to ligation of fas antigen. Am. J. Respir. Cell Mol. Biol., 1997, vol. 17, no. 3, pp. 272–278.
33. Horikoshi T., Maeda K., Kawaguchi Y., Chiba K., Mori K., Koshizuka Y., Hirabayashi S., Sugimori K., Matsumoto M., Kawaguchi H., Takahashi M., Inoue H., Kimura T., Matsuue Y., Inoue I., Baba H., Nakamura K., Ikegawa S. A large-scale genetic association study of ossification of the posterior longitudinal ligament of the spine. Hum. Genet., 2006, vol. 119, no. 6, pp. 611–616.
34. Lee B. S., Nowak R. A. Human leiomyoma smooth muscle cells show increased expression of transforming growth factor-beta (TGF-beta) and altered responses to the antiproliferative effects of TGFbeta. J. Clin. Endocr. Metab., 2001, vol. 86, no. 2, pp. 913–920.
35. Siegel P., Massague J. Cytostatic and apoptotic actions of TGF-beta in homeostasis and cancer. Nat. Rev. Cancer., 2003, vol. 3, no. 11, pp. 807–821.
36. Beffagna G., Occhi G., Nava A., Vitiello L., Ditadi A., Basso C., Bauce B., Carraro G., Thiene G., Towbin J. A., Danieli G. A., Rampazzo A. Regulatory mutations in transforming growth factor-beta-3 gene cause arrhythmogenic right ventricular cardiomyopathy type 1. Cardiovasc. Res., 2005, vol. 65, no. 2, pp. 366–373.
37. Bertoli-Avella A. M., Gillis E., Morisaki H., Verhagen J. M. A., de Graaf B. M., van de Beek G., Gallo E. et al. Mutations in a TGF-beta ligand, TGFβ3, cause syndromic aortic aneurysms and dissections. J. Am. Coll. Cardiol., 2015, vol. 65, no. 13, pp. 1324–1336.
38. Moustakas A., Pardali K., Gaal A., Heldin C. H. Mechanisms of TGF-beta signaling in regulation of cell growth and differentiation. Immunol. Lett., 2002, vol. 82, no. 1–2, pp. 85–91.
39. Moren A., Ichijo H., Miyazono K. Molecular cloning and characterization of the human and porcine transforming growth factor-beta type III receptors. Biochem. Biophys. Res. Commun., 1992, vol. 189, no. 1, pp. 356–362.
40. Dickinson M. E., Kobrin M. S., Silan C. M., Kingsley M. J., Miller D. A., Ceci J. D. et al. Chromosomal localization of seven members of the murine TGF-beta superfamily suggests close linkage to several morphogenetic mutant loci. Genomics, 1990, vol. 6, no. 3, pp. 505–520.
41. Feng X. H., Filvaroff E. H., Derynck R. Transforming growth factor-beta (TGF-beta)-induced down-regulation of cyclin A expression requires a functional TGF-beta receptor complex. Characterization of chimeric and truncated type I and type II receptors. J. Biol. Chem., 1995, vol. 270, no. 41, pp. 24237–24245.
42. Dementyeva E. A., Gurina O. P. Immunological changes accompanying the development of experimental neoplastic process. Pediatrician (St. Petersburg), 2015, vol. 6, no. 2, pp. 96–108. (In Russian)
43. Rudoy A. S. TGF-beta-dependent mechanisms of pathogenesis of Marfan syndrome and related disorders. Arterial’naia gipertenziia, 2009, vol. 15, no. 2, pp. 223–226. (In Russian)
44. Judge D., Dietz H. Marfan’s syndrome. Lancet, 2005, vol. 366, pp. 1965–1976.
45. Kalashnikova A. V., Mudzhikova O. M., Noda M., Ses’ T. P., Stroev Yu. I., Churilov L. P. Role of autoantigens in pathogenesis of endocrine disorders in non-syndromal marfanoid phenotype. Vestnik of Saint Petersburg University. Medicine, 2009, vol. 11, no. 4, pp. 5–16. (In Russian)
46. Timofeev E. V., Malev E. G., Luneva E. B., Zemtsovsky E. V. The activity of transforming growth factor-β in young age with marfanoid habitus. Pediatrician (St. Petersburg), 2019, vol. 10, no. 1, pp. 49–56. (In Russian)
47. Mizuguchi T., Matsumoto N. Recent progress in genetics of Marfan syndrome and Marfan-associated disorders. J. Hum. Genet., 2007, vol. 52, no. 1, pp. 1–12.
48. Neptune E. R., Frischmeyer P. A., Arking D. E., Myers L., Bunton T. E., Gayraud B., Ramirez F., Sakai L. Y., Dietz H. C. Dysregulation of TGF-beta activation contributes to pathogenesis in Marfan syndrome. *Nat. Genet.*, 2003, vol. 33, no. 3, pp. 407–411.

49. Coucke P., Willaert A., Wessels M. et al. Mutations in the facilitative glucose transporter GLUT10 alter angiogenesis and cause arterial tortuosity syndrome. *Nat. Genet.*, 2006, vol. 38, pp. 452–457.

50. Li B., Khanna A., Sharma V. et al. TGF–β1 DNA polymorphisms, protein levels, and blood pressure. *Hypertension*, 1999, vol. 33, pp. 271–275.

Authors' information:

*Olga O. Mosunova* — Student; ole4kamosunova97@gmail.com

*Elena A. Dementyeva* — Junior Researcher; zorra2@yandex.ru

Received: March 18, 2020
Accepted: August 18, 2020