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## PATHOLOGICAL PHYSIOLOGY

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### Transforming growth factor beta 1. Biological role and clinical significance

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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 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. 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 20<sup>th</sup> 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 4<sup>th</sup> month, while at the 6<sup>th</sup> 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 RHO GTPase [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.

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