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Transforming growth factor β1 (TGFβ1) in physiology and pathology

Transformujący czynnik wzrostu β1 (TGFβ1) w fizjologii i patologii

Dariusz Kajdaniuk[1], Bogdan Marek[1], Halina Borgiel-Marek[2], Beata Kos-Kudła[1]

[1]Department of Pathophysiology and Endocrinology, Medical University of Silesia, Zabrze, Katowice, Poland
[2]Department and Clinic of Maxillofacial Surgery, Medical University of Silesia, Katowice, Poland

Abstract

This review describes precisely the consequence of TGFβ1 prevalence in the organism, and its significant influence on physiological and pathophysiological processes. Organ and tissue distinctiveness hinder unambiguous characterisation of the cytokine. However, there are constant functions of TGFβ1 inducing no controversy: it participates in foetal development, control of cell growth and differentiation, induces fibrosis and scar formation (the process of 'wound healing'), causes the suppression of immune response, is involved in angiogenesis, the development of tumours, and inflammatory processes. Thus, TGFβ1 is a multifunctional cytokine. There are three fundamental directions of its activities: I. TGFβ1 regulates cell proliferation, growth, differentiation and cells movement. II. TGFβ1 has immunomodulatory effects. III. TGFβ1 has profibrogenic effects. TGFβ1 action can be local and systemic. This review describes TGFβ1 in pathology: colitis ulcerosa, Crohn's disease, coeliac disease, diabetic nephropathy, diabetic retinopathy and diabetic foot, pulmonary hypertension, and Alzheimer's disease. TGFβ1 and its receptors are also of interest to endocrinologists. Lack of TGFβ1-dependent growth control may result in oncogenesis: papillary, follicular and anaplastic thyroid cancers, prostate, breast and uterine cervical cancer, oesophagus, gastric, colorectal and liver cancers, NSCLC, and malignant melanoma. Excessive TGFβ1 activity is an integral part of the fibrotic processes occurring in the response to injury. An increased TGFβ1 expression has been observed in patients with pulmonary, kidney, and liver fibrosis. In chronic hepatitis, the prolonged stimulation of hepatic stellate cells being the result of chronic damage to hepatocytes results in the release of profibrogenic abundant factors such as TGFβ1 and leads to the development of liver cirrhosis. The results of experimental procedures and treatment known as anti-TGFβ1 strategy acting against the fibrosis in various tissues leads to hope regarding the use of anti-TGFβ1 strategy in clinical practice. **(Endokrynol Pol 2013; 64 (5): 384–396)**

Key words: *TGFβ1, TGF beta 1, TGFβ1, transforming growth factor beta 1, endocrine gland, liver, cancer, neoplasm, fibrosis, angiogenesis, physiology, pathophysiology, pathology*

Streszczenie

W artykule poglądowym szczegółowo opisano konsekwencje rozpowszechnienia TGFβ1 w organizmie oraz jego wpływ na szereg procesów fizjologicznych i patofizjologicznych. Istotne odrębności narządowe i tkankowe utrudniają jednoznaczną charakterystykę tej cytokiny. Istnieją jednak stałe funkcje TGFβ1 nie wzbudzające kontrowersji: uczestniczy w rozwoju płodu, regulacji wzrostu i różnicowania komórek, indukuje proces włóknienia i bliznowacenia (proces „gojenia rany"), powoduje hamowanie odpowiedzi immunologicznej, uczestniczy w angiogenezie, w rozwoju nowotworów, w procesach zapalnych - jest więc cytokiną wieloczynnościową. Można wyróżnić trzy fundamentalne kierunki jego działania: I — TGFβ1 reguluje proliferację, wzrost, różnicowanie i przemieszczanie komórek; II — TGFβ1 wykazuje działanie immunomodulujące; III — TGFβ1 wykazuje działanie profibrogenne. Działanie TGFβ1 może mieć charakter miejscowy i systemowy. Opisano udział TGFβ1 w stanach patologicznych: wrzodziejące zapalenie jelita grubego, choroba Crohna, celiakia, cukrzyca (nefropatia, retinopatia, stopa cukrzycowa), nadciśnienie płucne, choroba Alzheimera. TGFβ1 i jego receptory są również przedmiotem zainteresowania endokrynologów. Brak zależnej od TGFβ1 kontroli wzrostu może skutkować onkogenezą: rak brodawkowaty, pęcherzykowy i anaplastyczny tarczycy, prostaty, sutka, szyjki macicy, przełyku, żołądka, jelita grubego, wątroby, NSCLC, czerniak złośliwy. Nadmierna aktywność TGFβ1 jest integralną częścią procesów włóknienia zachodzących w odpowiedzi na uszkodzenie. Zwiększoną ekspresję TGFβ1 stwierdzono m.in. u chorych ze zwłóknieniem płuc, nerek i wątroby. U chorych z przewlekłym zapaleniem wątroby długotrwała stymulacja komórek gwiaździstych będąca wynikiem przewlekłego stanu uszkadzania hepatocytów skutkuje obfitym uwalnianiem profibrogennych czynników, w tym TGFβ1 prowadząc do rozwoju marskości wątroby. Wyniki eksperymentalnego postępowania i leczenia, określanego jako strategia anty-TGFβ1, przeciwdziałającemu procesowi włóknienia w różnych tkankach stwarzają nadzieję na jego zastosowanie w praktyce klinicznej. **(Endokrynol Pol 2013; 64 (5): 384–396)**

Słowa kluczowe: *TGFβ1, TGF beta 1, TGFβ1, transformujący czynnik wzrostu beta 1, gruczoł endokrynny, wątroba, rak, nowotwór, włóknienie, angiogeneza, fizjologia, patofizjologia, patologia*

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Dariusz Kajdaniuk M.D., Ph.D., Department of Pathophysiology and Endocrinology, Medical University of Silesia, Zabrze, Pl. Traugutta 2, 41–800 Zabrze, Poland, fax: +48 32 271 26 41, e-mail: patofizjozab@sum.edu.pl

TGFβ1 and its receptors

The name transforming growth factor (TGF) was introduced by Moses et al. [1], who found so called transformation fibroblast stimulating factor to the cancer cell phenotype. Later it turned out that there are factors TGF α and β, and the latter also has isoforms. TGFβ's previously used names were a reflection of the first descriptions of its actions. It was called factor inhibiting differentiation, stimulating cartilage growth, and sarcoma growth factor. Now it is known that TGFβ1 activity is much wider (as described below). In turn, TGFβ2 and TGFβ3 regulate cell proliferation, growth, differentiation and migration. They participate in adipogenesis, chondrogenesis, embryogenesis, tissue remodelling, wound healing, and tumour formation. Transforming growth factor β, and 40 other proteins, including inhibin A and B, and activin A, AB, B, C, E, BMP2-15 (bone morphogenetic proteins) are included in the family of modulators of cell proliferation, differentiation and apoptosis, extracellular matrix (ECM) synthesis. These proteins play an important role in prenatal development, postnatal growth, reconstruction and maintenance of normal organs structure. TGFβ was isolated in 1978 [2–4].

TGFβ is a polypeptide constructed from 112 amino acids, encoded by a gene located on the long arm of chromosome 19. TGFβ exists in five isomeric forms marked with symbols from β1 to β5, homologous in 60–80%. TGFβ1-3 are present in humans, mammals and birds. TGFβ4-5 occur in birds and amphibians. In humans, the predominant isoform is TGFβ1, which is synthesised by almost all cells. Other isoforms are expressed in a limited spectrum of cells and tissues. TGFβ2 is synthesised in large amounts in glioma cells and keratinocytes. TGFβ3 is observed mainly in embryonic heart and lung tissue, and to a negligible extent in the liver, spleen and kidneys [5–7]. TGFβ1 is synthesised primarily by platelets, macrophages/ /monocytes, lymphocytes, fibroblasts, epithelial cells [8] and dendritic cells [3]. *In vitro,* TGFβ isoforms have a similar biological effect on the tissues, but *in vivo* the effect is varied [9]. *In vivo,* these isoforms show differences in the biological effects mainly conditioned by their different tissue distribution, the degree of target cells differentiation and TGFβ concentration [3]. In the liver, both healthy and with fibrosis, TGFβ1 is the most common isoform [10].

TGFβ1 is a homodimer with a mass 25 kDa. The sequence of amino acids in TGFβ1 proteins from different species are very stable, which leads to the conclusion that in the process of evolution, TGFβ has been only slightly altered, and that both in humans and in animals, its function is similar. This hypothesis is confirmed by the properties of TGFβ demonstrated in *in vitro* studies on human and animal cells [3, 5]. TGFβ1 is released from cells as an inactive precursor containing TGFβ1 and propeptide LAP (Latency-Associated Protein) that are connected by non-covalent linkage [11]. In this embodiment, TGFβ1 can be stored in the granules of platelets or on the cell surface. TGFβ1 is connected (through the LAP) by a disulphide bond with LTBP (Latent TGFβ Binding Protein). LTBP1-4 is a component of the ECM, and is necessary both for the synthesis of TGFβ1 and its storage [7]. Changing the conformation of LTBP by the ECM glycoprotein — thrombospondin-1 leads to the release from the complex of an active form of TGFβ [11]. In the blood, TGFβ1 occurs in an inactive form with a half life of 90 minutes. The half-life of the active form reaches only a few minutes. Thus, the LAP and LTBP 'mask' the epitopes of TGFβ1, and the active form is almost undetectable in the blood and tissues (regardless of the method). In the initial phase of TGFβ1 activation, a tissue transglutaminase is involved. TGFβ1 release from the inactive complex occurs during its proteolysis under the influence of plasmin and thrombin [7]. It is believed that certain factors regulate TGFβ1 activity by increasing its synthesis, and others by increasing its bioavailability. TGFβ1 synthesis is stimulated by physical, mechanical, and biochemical factors [12]. Increased TGFβ1 activity has been observed in response to angiotensin II [13–16], LDL, glucose, thromboxane A2. Natural inhibitors of TGFβ1 are follistatin, decorin, and α2-macroglobulin [12]. In the organism, a series of interactions between the ligands TGFβ and their natural inhibitors occur.

TGFβ signalling activity in the cells is possible only when they have specific membrane receptors which occur as dimeric proteins [6]. So far, nine different types of molecules (receptors and proteins) having the ability to bind TGFβ have been identified. The best known receptors are types I, II, and III [11]. The operation of all TGFβ isoforms is done by these three types of receptors for TGFβ — TGFβRI, TGFβRII, and TGFβRIII [17]. TGFβRI is a dimer of molecular weight 53 kDa, dimer TGFβRII weight 75 kDa, and TGFβRIII has a mass 280 kDa [17, 18]. TGFβRI and TGFβRII are the family of transmembrane receptors, their intracellular fragments have domains with serine-threonine kinase activity [19]. The extracellular part of TGFβRII by binding the ligand (TGFβ) activates the intracellular domain of the receptor. The created complex joins TGFβRI that determines specificity of TGFβ recognition [20]. This heteromeric complex is formed by two molecules (dimers) TGFβRI, TGFβRII and TGFβ [18, 21–24]. Activated TGFβRII kinase phosphorylates serine fragments of sequence TTSGSGSG in GS domain (domain rich in glycine and serine) of TGFβRI, thus leading to activation of serine-

threonine kinase in the receptor, and thereby starts the signal transduction cascade inside the cell [2, 11, 18, 21–27]. TGFβRII can indeed bind TGFβ independently of the presence the TGFβRI, but without TGFβRI is unable to transduce a biological signal [28]. On the other hand, in the absence of TGFβRII, the cells are insensitive to the action of TGFβ [29]. TGFβRII is activated in the process of autophosphorylation, while activation of TGFβRI requires a connection to complex of TGFβ1-TGFβRII, -TGFβRIII [19]. TGFβ1 and TGFβ3 have a high ability to bind with TGFβRII. TGFβ2 exerts its effect only after a previous presentation by TGFβRIII to the other receptors I and II [30, 31]. TGFβRIII is called a betaglycan, which is anchored in the membrane proteoglycan having no enzymatic activity [19], without exerting any intracellular activity. Its role is to present TGFβ to the other two receptors. TGFβRIII is the most abundant receptor subtype in most cells [32, 33]. TGFβRIII is located on the cell surface binding the ligand [34] — it has a high affinity for all three isoforms of TGFβ. In its absence, the cells do not respond to TGFβ2, whereas the response of cells to the other two isoforms of the cytokine is maintained [27]. The action of TGFβ in hepatic stellate cells (HSC) can be modulated by TGFβRIII [34]. In these cells, it is additionally important because the expression of TGFβ2 here is low [35]. TGFβRIII may also be an inhibitor of the signal transduction by prevention of TGFβ connections to TGFβRII and TGFβRI in the mechanism independent from ligand binding. In such a situation, it fulfills the function of regulating the ligand binding with the remaining two receptors [36]. TGFβRIII's soluble form, by binding the ligand, neutralises it [34]. The final effect of TGFβ1 depends on its bioavailability, the distribution of receptors in tissues, and the target cell type [12, 37].

After binding TGFβ with receptors, signal transduction occurs to the nucleus with the participation of proteins Smad present in the cytoplasm, which ultimately results in the influencing of the processes of transcription and translation of TGFβ-dependent genes i.e. showing typical for TGFβ activity [18]. System of intracellular transmitters Smad proteins is thus a specific link between receptors and the cellular nucleus [2, 38–40]. After activating serine-threonine kinase in TGFβRI, it comes to further signal transduction by phosphorylation of cytoplasmic proteins Smad2 [23] and Smad3 [23, 41] binding to receptors. Similar in the structure Smad2 and Smad3 are classified as a group called R-Smad (receptor regulated Smads). Phosphorylated R-Smad can be separated from the connection to the receptor and from protein SARA [23]. Auxiliary protein SARA (Smad Anchor for Receptor Activation) is a cytoplasmic protein anchored in the cell membrane that binds both the R-Smad and TGFβ/ /TGFβRII/TGFβRI. SARA participates in the early stages of signal transduction — recognising the non phosphorylated R-Smad joins it to the the newly formed receptor complex, and is dissociated itself [42]. Phosphorylated R-Smad forms a complex with the co-Smad (common partner Smad) namely Smad4, and so the newly formed complex is transported to the nucleus [26, 42], where it regulates the transcription of TGFβ-dependent genes [43]. Thus, phosphorylated Smad act as transcription factors, which by binding to specific DNA sequences are responsible for the transcription of specific genes [2, 11, 19, 41]. Smad4 co-operates with other transcription factors in the regulation of TGFβ-dependent gene expression — therefore it is a grasping point for these factors. Signal transduction from the receptor to the nucleus can be inhibited by a protein Smad6 and Smad7 called I-Smads (Smads inhibitors), which despite the absence of motif in its structure which can be phosphorylated by receptor kinases, are able to interact with membrane receptors, thus impairing their interaction with the R-Smad [26]. Smad7 expression is induced by TGFβ, leading to inhibition of the cellular response to this cytokine. It is therefore an autoregulation in the negative feedback mechanism [26, 42]. Smad7 forms a stable complex with activated TGFβRI and thus impairs the phosphorylation of Smad and inhibits signalling cascade [38, 43, 44]. There are known also proteins Smad 1, 5, 8, which transmit impulses from other ligands related to TGFβ, including BMPs [23]. Overall in the Smad system, ten different proteins carrying a signal have been identified which were activated by the TGFβ-receptor complex RI-III [2]. Under disease conditions, Smads also interact with other signalling pathways, such as the mitogen-activated protein kinase and nuclear factor-κB pathways [45].

TGFβ1 in physiology and pathophysiology

The consequence of TGFβ1prevalence in the organism is its significant influence on a number of physiological and pathophysiological processes. As a result of this, interrelations with other cytokines and biologically active substances as well as organ and tissue distinctiveness hinder unambiguous characterisation of TGFβ1. However, there are constant functions of the cytokine inducing no controversy: it participates in foetal development, control of cell growth and differentiation, induces fibrosis and scar formation (the process of 'wound healing'), causes the suppression of immune response, is involved in angiogenesis, the development of tumours, and inflammatory processes [6, 11, 42, 46–48]. Thus, TGFβ1 is a multifunctional cytokine.

There are three fundamental directions of its activities:

I. TGFβ1 regulates cell proliferation, growth, differentiation and cells movement. Growth factors/ /cytokines may affect stimulating or inhibiting on the cell proliferation and differentiation by linking to specific receptors, which triggers a cascade of signals leading to the activation or repression of various genes. Growth factors acting on cells in the resting state or in the G_0 phase introduce them into the cell cycle. Growth factors called 'competence factors' bring the cells into the G_1 phase and conduct them through this phase, while under the influence of growth factors termed 'progressive factors' DNA synthesis occurs. Passing through the G_1 phase requires stimulation by growth factors throughout its duration (a few hours). If this stimulating signal is broken, the cell returns to the G_0 phase. In G_1 phase, there is a critical point at which the simultaneous operation of 'competence' and 'progressive' factors is necessary. Then, only the presence of the latter is required [47–49]. It has been shown that TGFβ1 inhibits the cell cycle in the G_1 phase, which explains the fact that this cytokine is a potent inhibitor of cell proliferation [11]. In addition to TGFβ1, interferon and tumour necrosis factor (TNF) can antagonise the pro-proliferative effect of growth factors. In the case of TGFβ1, such an effect is noticeable even in the late G_1 phase [49]. The regulatory impact of TGFβ1 on quantitative cellular changes is the result of, on the one hand, the possibilities of inhibition of cells proliferation, and on the other hand, the induction of apoptosis. The action of TGFβ1 results in decline of Fas expression and in increased expression of Bcl-2 [12]. Thus, TGFβ1 is an endogenous factor controlling apoptosis in normal and pathological tissues, and thereby is a factor controlling the balance between replication and cell death [50]. In certain cell types, the absence of growth factors alone induces their apoptosis [49]. TGFβ1 plays a role in regeneration (repair — 'wound healing') of damaged tissues and organs, bone remodelling, malignant processes (tumour formation, metastasis), and the generation of histopathological lesions like fibrosis [4, 7, 11]. It is involved in organogenesis during intrauterine life (embryogenesis), hematopoiesis, and adipogenesis. It promotes chondrogenesis and angiogenesis [11]. It is involved in skin formation. TGFβ1 operates differently on the target cells, and this effect depends on the target cell type [51, 52]: TGFβ1 usually stimulates the proliferation of certain cell types of mesenchymal origin such as hepatic stellate cells, fibroblasts and osteoblasts both *in vitro* and *in vivo* [4, 51, 53]. TGFβ1 (and TGFβ2) intensifies the Schwann cells proliferation [53]. During bone resorption, osteoclasts release and activate TGFβ1 from the bone matrix; thus, elevated bone resorption increases the level of active TGFβ in the local environment during ageing [4]. TGFβ1 inhibits the growth of epithelial cells (including the intestine), endothelial, hematopoietic (including megakaryocytes and erythrocytes precursors), keratinocytes [7, 11, 51, 54, 55]. TGFβ1 is a potent inhibitor of the hepatocytes proliferation *in vitro* and *in vivo* - in humans and animals [6, 42, 55, 56]. The degree of inhibition of cell proliferation by TGFβ1 depends among others on the cells types, this cytokine concentration, and its interactions with biologically active substances. For example, the most sensitive to the inhibitory effect of TGFβ1 are lung epithelial cells and keratinocytes. TGFβ1 in a concentration of 1–2 fg/cell inhibits the growth of smooth muscle cells, fibroblasts, and chondrocytes; in higher concentrations, it has the opposite effect - it stimulates the growth of these cell types [53]. TGFβ1 plays a role in tissue regeneration, on the one hand by promoting cell differentiation [57], and on the other by inhibiting excessive cell proliferation [58, 59]. TGFβ1 is an important factor inducing apoptosis of liver cells *in vitro* and *in vivo* [42, 60]. TGFβ1 inhibits liver regeneration in rats, in contrast to hepatocyte growth factor (HGF) [61] and transforming growth factor α (TGFα) [61, 62]. TGFβ1 inhibits hepatocyte growth even in the healthy liver and thus may contribute to the maintenance of a constant mass of the organ. That has been demonstrated by introducing TGFβRII into the liver cells of healthy rats (adenoviruses were the vectors) which led to the inhibition of DNA synthesis in the liver [63]. In certain tissues and organs, TGFβ1 promotes repair processes caused by trauma or pathological lesions. In the repair processes TGFβ1 stimulates fibroblast migration to sites of injury and stimulates the synthesis of ECM proteins [57] as fibronectin, collagen, and proteoglycans. These proteins are the ligands for integrins i.e. surface receptors of the cells involved in the response to tissue injury which means that they can move to the place of their action [7, 54]. Under physiological conditions, TGFβ1 protects the intestinal mucosa from damage [7]. The intestinal mucosa revealed the presence of TGFβ1-3 and their receptors I–III [64]. *In vitro* TGFβ1 inhibits the proliferation of intestinal epithelial cells and promotes their differentiation [57, 59]. TGFβ1 synthesised by enterocytes and cells of the lamina propria colonic mucosa [64] plays here a role in regulation of proliferation, differentiation and apoptosis [2]. Despite the properties of inhibiting the proliferation of epithelial cells, in the case of damage of the intestinal mucosa TGFβ1 promotes the healing process. It is also possible due to the ability to induce and encourage migration of mature, functionally efficient epithelial cells from the environment which leads to cover the wound within a few hours [7, 54]. TGFβ1 also acts as an inhibitor of atherosclerosis — inhibits the prolifera-

tion of smooth muscle and endothelial cells. Reduction of TGFβRII expression and its mutations have been shown in populations of cells from atherosclerotic lesions [3]. TGFβ1 and TGFβ2 promotes repair of experimentally caused skin injuries in rats which occurs with excessive exposure of fibrous tissue [65]. Under physiological conditions TGFβ1 and other growth factors contained in the tear film are responsible for the normal state of the cornea [66].

II. TGFβ1 has immunomodulatory effects. It is involved in the suppression of the immune response [6, 42, 67]. It inhibits the proliferation, differentiation and activity of cells involved in humoral and cellular responses, reduces the expression of MHC molecules, the cellular toxicity, the production of antibodies, and inhibits the secretion of cytokines [68]. On the surface of B cells are located receptors for TGFβ1 — their stimulation leads to inhibition of B cell proliferation and production of immunoglobulin G and M (IgM, IgG) and to increased IgA secretion [53, 69, 70]. TGFβ1 inhibits T cell proliferation [53] in response to polyclonal mitogens [71]. On the other hand, in the inflamed tissues an increase of activation of T helper cells CD4 + which produce TGFβ1 is seen [70, 72]. This cytokine exerts an inhibitory effect on some of the NK cells functions [69] e.g. on their cytotoxic activity [53]. In addition, it inhibits macrophages' maturation and activity [53, 67, 71]. Environmental conditions can determine the reactivity of the cells to TGFβ1 e.g. activated T cells do not react with TGFβ1 in the absence of interleukin (IL) –10 [73]. TGFβ1 is required for the maintenance of immune homeostasis. TGFβ1 by reducing apoptosis of B cells leads to prolongation of their life and elongation of long-term immunological memory [74]. The immunosuppressive and anti-inflammatory effects of TGFβ1 [42] have been confirmed *in vitro* [11, 67, 75] and *in vivo* [11, 75]. In mice, lack of TGFβ1 gene causes multiple organ inflammatory response, and lethal cachexia develops within two weeks [76]. In transgenic mice lacking the TGFβ1 gene (knock out), inflammation of the small intestine and colon develops [59]. In transgenic mice with Smad7 overexpression glomerulonephritis develops caused by antibodies against the basement membrane [77] and inflammation of the respiratory tract [38]. In transgenic mice lacking Smad3 gene, a massive inflammation of the gastrointestinal tract was detected [44]. An excessive suppressive effect of TGFβ1 on the the immune system increases susceptibility to infection [53]. Mouse model studies have demonstrated that TGFβ1 is involved in the pathogenesis of autoimmune diseases — systemic administration of TGFβ1 suppress autoimmune disease while the anti-TGFβ1 antibodies caused its progression. It has been demonstrated that mutations in the TGFβ1 gene result in the development of phenotype with characteristics typical of autoimmune diseases [3].

III. TGFβ1 has profibrogenic effects. This activity is carried out through the ability for stimulating the ECM synthesis which has fundamental importance for the processes of scarring and tissue reconstruction [6]. TGFβ through increasing the production of ECM proteins and their receptors [6, 26] becomes the strongest inducer of the synthesis of collagen type I, II, III, V, VI, X and fibronectin, osteopontin, osteonectin, thrombospondin, proteoglycans and alkaline phosphatase [26]. Some of them, such as fibronectin and tenascin, are absent at physiological conditions. TGFβ1 has profibrogenic action via stimulation of mesenchymal cells and fibroblasts to synthesise ECM proteins [68]. TGFβ1 stimulates the proliferation and/or synthesis of ECM components in cultures of fibroblasts obtained from skin [8], lung [78] and stimulates collagen synthesis in pancreatic [8] and liver [79] fibroblasts. It simultaneously blocks the destruction of newly synthesised ECM by inhibiting the synthesis of matrix-metalloproteinases (MMPs) — enzymes involved in the degradation of ECM proteins - and by increasing the expression of genes responsible for the production of tissue inhibitor of metalloproteinases (TIMPs) — TIMP-1 [80] and plasminogen activator inhibitor-1 (PAI-1). TGFβ1 exacerbating the expression of PAI-1 reduces the conversion of plasminogen to plasmin — protease that directly degrades ECM proteins and activates MMPs [26, 41]. TGFβ1 mitogenic effect on fibroblasts is mediated by connective tissue growth factor (CTGF) — a cytokine that promotes fibrosis in the skin, lungs, kidneys, and liver [81, 82, 83]. Furthermore, TGFβ1 stimulates the production and release of vasoactive factors such as endothelin I, nitric oxide (NO), C natriuretic peptide, PGE2 which may also affect the ECM production and the proliferation of ECM-producing cells. Finally, TGFβ1 potentiates its own production and thus biological activity [68]. TGFβ1 stimulates the secretion of cytokines such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and IL-6. After repairing the damaged tissue, the release and biological activity of TGFβ1 are ruptured - this occurs in the acute process. In chronic processes, the excessive and persistent production of TGFβ1 occurs which leads to progressive fibrosis [7, 47, 48, 68]. Synthesis and profibrogenic action of TGFβ1 are intensified by angiotensin II which is therefore another mediator of ECM production in the liver [13, 14–16]. TGFβ1 is one of the key mediators of fibrogenesis.

TGFβ1's action can be local and systemic. TGFβ1, released locally as a result of injury or the immune response, has pro-inflammatory properties (e.g. it stimulates granulocyte macrophage chemotaxis and the release of pro-inflammatory cytokines (TNF, IL-1, IL-6) [7, 47, 48] and profibrogenic properties

[7, 54]. Among the systemic properties of TGFβ1, an immunosuppressive effect seems to be the most important [7, 47, 48].

TGFβ1 in pathology

Elevated TGFβ1 plasma levels and a positive correlation of levels with the degree of damage to the intestinal mucosa have been shown in patients with colitis ulcerosa [84]. These values were increased slightly during treatment; after successful treatment confirmed by clinical and endoscopic activity, index returned to the normal range [59]. Although the quoted results suggest TGFβ1 participation in the processes of repair intestinal tissues that were previously destroyed in autoimmune mechanism, it cannot be excluded that TGFβ1 is involved in the initiation of the disease process [84]. Crohn's disease, in which the inflammatory process covers the entire wall of the intestine, and repair processes can lead to the formation of solid wall stenosis, higher levels of TGFβ1 expression in intestine miofibroblasts were found significantly in patients with a form of the disease with strictures extending [85]. There was a positive correlation between the TGFβ1 mRNA expression in the intestinal mucosa and the severity of the inflammatory response [5]. In children with coeliac disease, low TGFβ1 expression in intestinal epithelium was found [86]. Antibodies against endomysium (EmA) are routinely determined in patients with coeliac disease; in fact, there are anti-transglutaminase antibodies which change the complex of TGFβ1 inactive to an active one. It is known that circulating antibodies against transglutaminase may lead to a deficiency of TGFβ1 and hence to the development of autoimmunity. This may be the explanation for the tendency of patients with coeliac disease to develop autoimmune diseases [7]. In 79% of children with allergic enteropathy, a decreased TGFβ1 mRNA expression in intestine epithelium was shown [87]. Reduced TGFβ1 levels in the inflamed duodenum [88] and accelerated healing of gastric ulcers after injection of TGFβ1 in the ulcer area [89] have been shown in the immunohistochemical assessment. TGFβ1 is involved in the development of kidney diseases such as fibrosis, diabetic nephropathy, and glomerulosclerosis [68]. Serum concentrations of TGFβ1 may be an additional parameter in predicting the occurrence of diabetic retinopathy in juvenile patients with type 1 diabetes mellitus [90]. In 95% of children with atopic dermatitis, specific TGFβ1 gene polymorphism coexisted with decreased TGFβ1 production [91]. In patients with diabetic foot and leg ulcers due to chronic venous insufficiency, locally reduced levels of TGFβ1 and its receptors have been shown [92]. In patients with resistant-to-treatment leg ulcers, a reduced TGFβRII expression in fibroblasts has been demonstrated [93]. In asthma, reduced TGFβRII expression has been demonstrated which may be one of the mechanisms leading to thickening of the bronchial basal lamina [94, 95]. Severe pulmonary inflammation induced by elevated levels of cytokines (therein TGFβ1), combined with increased viral replication due to decreased interferon-γ levels, may contribute to worsening respiratory symptoms in patients with bronchial asthma and A (H1N1) 2009 infection [96]. Mutations in the genes for TGFβ receptors are the causative agent of Rendu-Osler-Weber disease, vascular dysplasia with autosomal dominant inheritance [3]. Discontinuation of TGFβ1 activity is also in hereditary chondrodysplasia, and pulmonary hypertension [23]. Decreased serum levels of the angiogenic factors VEGF and TGFβ1 in Alzheimer's disease and amnestic mild cognitive impairment. These observations suggest that angiogenesis might be involved in the onset process of Alzheimer's disease and the decrease of angiogenic factors might be related to the severity of cognitive impairment [97].

TGFβ1 in endocrinology and oncology

TGFβ1 (and other growth factors) and its receptors are also of interest to endocrinologists [47, 48, 72, 98–102]

TGFβ isoforms are present in the front lobe of the pituitary, where they modulate growth and secretory function of cells. In the pituitary cell lines, TGFβ1 stimulates VEGF production in a dose-dependent manner and dependent on the type of target cells [103]. Among the pituitary cells, lactotroph cells produce the most TGFβ1 and contain too the most TGFβRII. TGFβ1 inhibits lactotroph cells proliferation and PRL secretion. Synthesis of TGFβ1 in lactotroph cells is reduced during the oestrogen administration in ovariectomised rats. During the oestrogen administration, decreased mRNA TGFβRII expression in oestrogen-sensitive tissues is found which additionally influences the lactotroph cells growth and prolactin secretion. The development of pituitary tumours in mice has been associated with resistance to TGFβ [104]. TGFβ1 could be a potential serum marker for invasiveness of prolactinomas — the simultaneous determination of TGFβ1 and PRL levels could improve the noninvasive assessment of prolactinoma behaviour [105]. TGFβ1 is thought to have important roles in several stages of folliculogenesis [106]. Maurya et al.'s [107] study demonstrates the importance of the liberation of biologically active TGFβ1 from its latent complex during embryo implantation period and its regulation by oestradiol [107]. TGFβ1 and its receptor soluble endoglin are altered in polycystic ovary syndrome during controlled ovarian stimulation [108].

Lack of TGFβ1-dependent growth control may result in oncogenesis [6, 11, 109]

The changed expression of growth factors and their receptors is an element of neoplastic transformation and tumour progression [110]. In normal conditions, TGFβ1 is a potent inhibitor of the growth of many cell types, including neoplastic [11]. In the early stages of cancer development, its cells respond to antimitotic effect of TGFβ1 [18]. However, at the entry of tumour cells into the phase of uncontrollable growth, most of them lose sensitivity to the inhibitory effect of TGFβ1. It is surprising that this occurs despite the presence on the tumour cell surface of the receptors for TGFβ1. What's more, these cancer cells begin to secrete TGFβ1 themselves [11]. The TGFβ1-dependent immunosuppressive activity, stimulating angiogenesis [11, 18, 47, 48], increasing the affinity of cancer cells to cell adhesion molecules [11] creates a microenvironment favourable to tumour growth and its metastasis — increases cancer cells invasiveness [18]. Additionally, TGFβ1 induces the death of the surrounding healthy cells and thus eliminates their effect designed to inhibit tumour growth [50]. It appears that cancer cells to receive anti-mitotic stimulus carried by TGFβ1 need higher TGFβ1 concentrations than normal cells. On the other hand, higher TGFβ1 concentrations have more potent anti-mitotic and pro-apoptotic effects on tumour stromal cells and have a more immunosuppressive effect on the environment and strongly stimulate angiogenesis in the environment. The results of clinical and experimental studies indicate that the molecular reasons for the lack of cell response to TGFβ1 during malignant transformation are caused by mutation in the TGFβRII receptor [111] and/or within the intracellular proteins Smad2, Smad3, Smad4 [39] responsible for providing information to the nucleus or Smad7, which is an inhibitor of TGFβ1 activation [38, 44].

In the tissues of papillary thyroid carcinoma (PTC) follicular and anaplastic thyroid cancers, zero or reduced TGFβRII expression has been found compared to benign tumours and normal tissues (in immunohistochemical studies with anti-TGFβRII) [112]. In the differentiated and undifferentiated tissues of the thyroid cancers, resistance to TGFβ1 coexisted with a reduction in mRNA and protein TGFβRII expression [113]. TGFβ1 mRNA expression in papillary thyroid cancer cells was higher compared to the surrounding tissues, while the TGFβRII was lower. An inverse correlation between TGFβRII and tumour size was found, and there was no such correlation with respect to TGFβ1, which suggests that primarily TGFβRII plays a role in the pathogenesis of papillary thyroid cancer [114]. Metastatic thyroid cancer can also be characterised by a decreased sensitivity to the action of TGFβ1 [115]. In human PTC, higher expression levels of TGFβ1 were closely related with lymph node metastasis, whereas for α-smooth muscle actin (α-SMA) and Smad3 expression increased significantly with advanced tumour stages. Moreover, a significant correlation was found between higher TGFβ1 expression in PTC cells and increased α-SMA levels in the fibroblasts surrounding the cancer cells. These findings suggest that the activation of TGFβ/Smad3 pathways in cancer cells influence tumour growth [116].

Prostate cancer is characterised by a loss of expression of receptors for TGFβ and is resistant to antiproliferative and pro-apoptotic activity of TGFβ1. In humans, high expression of TGFβ1 and the lack of expression of its receptors in prostate cancer tissues are associated with a particularly poor prognosis [117], and TGFβRII overexpression restores sensitivity to TGFβ1 and transmission of signals in the cancer cells. TGFβ1 *in vitro* is, however, an inhibitor of breast cancer cells proliferation. Progression of tumour *in vivo* can be taken from the fact that TGFβ1 secreted by the tumour may lead to suppression of immune response and to an enhancement of angiogenesis in the tumour environment [55]. The polymorphisms in the genes related to angiogenesis - PAI-1 (675 4G/5G) and TGFβ1 (G-800A), segregated solely or combined, might contribute to the increased susceptibility to uterine cervical cancer [118].

TGFβRII loss of gene expression occurs in primary oesophagus cancer. Mutations being the microsatellite instability within the TGFβRII in gastric cancer tissues have been found [119] and they coexisted with mutations of the p53 gene [120]. In colorectal cancer tissue, the presence of mutations in the TGFβRII (> 10–20% cases) [2], microsatellite instability within the receptor (60–90% cases) [111] and mutations in the Smad (10% cases) have been revealed [40]. *In vitro* colon cancer cells exhibit increased synthesis of TGFβ1 concomitant with uncontrolled proliferation and constant growth of the tumour mass [11]. In colon cancer, abnormal TGFβRI expression has been also described [3]. There is evidence that TGFβ1-induced disruption of apoptosis as well as growth inhibition is an integral part of a multi-step process of developing HCC (primary liver cancer, hepatocellular carcinoma) [121]. TGFβ1 induces apoptosis of normal liver cells [42, 122] including hepatocytes through the autocrine way. However, HCC cells are resistant to TGFβ1 which generates through the paracrine way TGFβ1-mediated apoptosis of cells neighbouring the tumour, which facilitates its expansion *in situ* [122]. TGFβRII mutation is the cause of the lack of HCC cells response to TGFβ1 [123]. Immunohistochemical analysis revealed increased expression of TGFβ1 [124, 125] and lower TGFβRII expression in HCC tumour tissues compared to their surrounding tissues,

including normal [125]. Recently, in an experimental study, HCC cells were divided into those in which the expression of TGFβ1 comes late, which was associated with their increased invasiveness and shorter survival of mice, and those in which the expression of TGFβ1 appeared early, and where the prognosis was better [126]. In relation to infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), the TGFβ1 participation in malignant transformation and HCC progression were highlighted [124, 127]. TGFβ1 expression in HCC tissues was correlated with the degree of HBV replication and did not correlate with sizes and number of the tumours. Patients with HCC in the course of HBV infection demonstrated higher TGFβ1 blood levels compared to controls (non-cancerous liver diseases) [124]. Higher TGFβ1 serum concentrations in HCC patients were found compared to patients with chronic hepatitis C. In HCC patients, there was no difference in the TGFβ1 levels between one and other genotypes of HCV [128]. The TGFβ1 concentration in blood [129, 130] and expression of its mRNA in the liver [130] were significantly higher in patients with HCC compared to patients with chronic hepatitis, liver cirrhosis and healthy subjects. The plasma TGFβ1 levels after treatment resulting in clinical improvement, although decreased, however did not correlate with α-fetoprotein [129]. It has even been suggested that in patients with HCC and low production of α-fetoprotein, a finding of increased TGFβ1 concentration in urine may be useful in the diagnosis [131]. In addition, the way of Smad3 phosphorylation, resulting in the creation of two possible isoforms, alters the final effect of TGFβ1. It has been demonstrated that in patients with chronic hepatitis C comes to the formation such Smad3 isoform which is able to change the way of TGFβ1 signal transduction from one that inhibits the tumour development to one that amplifies the fibrogenesis and increases the risk of developing HCC [41].

The expression of TGFβ1 and TGFβRI-III were twice higher in well-differentiated non-Hodgkin's lymphoma compared to low-differentiated [71]. In some forms of leukemias, the malignant cells have no receptors for TGFβRII and TGFβRI that causes, that they are not sensitive to the inhibitory effects of TGFβ1 and resulting from this the excess of TGFβ1 leads to inhibition of proliferation of normal cells. In addition, the overproduction of TGFβ1 by leukemia cells, monocytes and megakaryocytes is the cause of bone marrow fibrosis. TGFβRII gene mutations or lack of the gene expression in some T-cell leukemias and disorders in TGFβRI gene expression in chronic lymphocytic B-cell leukemia and in cutaneous form of T-cell lymphoma have been described. TGFβRII gene mutations or lack of the gene expression have also been described in lung cancer tissues [3], and reduced TGFβRII expression (but not TGFβRI) may participate in urethane-induced carcinogenesis in the lungs of mice [132]. TGFβ1 genotypes polymorphisms (rs1800469, rs1982073) could be useful for predicting distant metastasis-free survival in patients with inoperable non-small cell lung cancer (NSCLC) treated with definitive radiation therapy [133]. TGFβ-induced expression of IGFBP-3 regulates IGF-I receptors signalling in human osteosarcoma cells [134]. Bronchioloalveolar invasion in NSCLC is associated with tumours expression of TGFβ1 assessed with immunohistochemical staining using anti-TGFβ1 antibody [135]. It was also found a higher concentration of TGFβ1 (4.2 x) and TGFβ2 (1.5 x) (but not TGFβ3) in the blood of patients with metastatic malignant melanoma in contrast to the initial development chase which indicates a systemic immunosuppressive TGFβ1 activity in the terminal stage of the disease [136].

TGFβ1 and fibrosis

The relationship between TGFβ1 and fibrosis of various tissues and organs is increasingly being described. Although TGFβ1 plays a critical role in tissue repair, overproduction of the cytokine can lead to an excessive, uncontrolled depositing fibrous tissue [65]. Each of the processes participating in the 'wound healing' (hemostasis platelet, influx of inflammatory cells and fibroblasts, formation of ECM and blood vessel) is associated with TGFβ1 that not only stimulates the formation of scar tissue but also reduces the production of ECM-degrading enzymes. Moreover, the cells involved in 'wound healing' are stimulated to produce TGFβ1 which multiplexing effect of its actions. Overexpression of TGFβ1 caused by chronic and repetitive injuries of tissues or dysfunction of regulation the expression of this cytokine is a major factor in the pathogenesis of organ fibrosis [3, 47, 48]. An increased TGFβ1 expression was observed among others in patients with pulmonary, kidney, and liver fibrosis [11] and with scleroderma [3]. In patients with pulmonary fibrosis, the coexistence of the TGFβ1 gene polymorphism with an increased synthesis of this cytokine and intensification of ECM formation has been shown [137]. Induction of renal fibrotic genes by TGFβ1 requires epidermal growth factor receptor (EGFR) activation, p53 and reactive oxygen species [138]. In patients with scleroderma, the enhanced response to TGFβ1 caused by Smad7 mutations also results in intensified synthesis of fibrous tissue [38]. In patients with chronic hepatitis, the prolonged stimulation of hepatic stellate cells being the result of chronic damage to hepatocytes results in the release of profibrogenic abundant factors as TGFβ1 and leads to the development of liver cirrhosis. TGFβ1 leads to the ECM accumulation in the

mechanism: 1) directly increasing the synthesis of ECM components as procollagen 1α (I), 2) inhibition of tissue collagenases expression, 3) increasing synthesis of ECM-degrading enzyme inhibitors (as PAI-1, TIMPs) [41, 139, 140]. In chronic hepatitis, hepatocyte proliferation inhibitory effect of TGFβ1 is attached to the abovementioned mechanisms [141]. TGFβ1 is a link between hepatic inflammatory and fibrosis processes [41, 47, 48]. Benzoubir et al. [142] presented a paradigm where HCV may be related to liver pathogenesis through its ability to induce a local, intrahepatic TGFβ activation. They argue for a dual impact of HCV core on liver fibrosis and liver carcinogenesis: HCV core could act both as autocrine and paracrine factors modulating TGFβ responses within hepatocytes and in stromal environment through TGFβ activation [142].

Progress in understanding the phenomena being arranged in a network of regulatory processes associated with organ fibrosis facilitates the use of currently known drugs as the search for new drugs targeting various stages of fibrogenesis. These drugs, used regardless of the aetiology of disease, could lead to arrest or even regression of fibrosis. Excessive TGFβ1 activity is an integral part of the fibrotic processes occurring in the response to injury. The results of experimental procedures and treatment known as anti-TGFβ1 strategy acting against the fibrosis in various tissues including liver, lung and kidney create hope regarding the use of anti-TGFβ1 strategy in clinical practice [38, 143]. Since in patients with chronic hepatitis B and C the activation of TGFβ1-receptors system is observed, the goal of therapy of anti-TGFβ1 could be any of the system components. For this, antibodies against TGFβ1, TGFβ1 soluble receptors, substances blocking TGFβ1 receptors and binding TGFβ1 have been used experimentally. These substances used *in vivo* often do not achieve a sufficient concentration in the target cells or produce extrahepatic side effects. The specific drug carrier which would give it to hepatic stellate cells is still being sought [144]. The introduction of TGFβRII (using adenovirus) that does not transmit signals to the liver in rats has significantly reduced the extent of experimentally induced fibrosis [145, 146]. Similarly, liver fibrosis caused by biliary damage was significantly inhibited as a result of inducing the formation of complexes Fc domain of immunoglobulin G and extracellular part of TGFβRII which gives the effect of binding the receptor [147]. Promising results have been obtained on the same path in experimentally induced glomerulonephritis concomitant with renal fibrosis [148]. The Ling et al. [149] in rat model demonstrates that murine neutralising TGFβ monoclonal antibody 1D11 can reverse pre-existing hepatic fibrosis induced by extended dosing of thioacetamide. The regression of fibrosis (evaluated using hepatic TGFβ1 mRNA, tissue hydroxyproline, plasminogen activator inhibitor 1: PAI-1) was accompanied by a marked reduction in concomitantly developed cholangiocarcinomas. This suggests that therapeutic dosing of a TGFβ antagonist can diminish and potentially reverse hepatic fibrosis and also reduce the number and size of attendant cholangiocarcinomas. Growing knowledge about the routes of intracellular signalling TGFβ1 [23, 24] leads to the development of further ways of interrupting the signals cascade in hepatic stellate cells, and the results cited above by Dooley et al. [43] indicate that Smad7 analogues could be transposed into anti-fibrosis treatment. In contrast to the pathogenic role of active TGFβ1, latent TGFβ1 plays a protective role in renal fibrosis and inflammation. TGFβ/Smad signalling plays a regulating role in microRNA-mediated renal injury. Thus, targeting TGFβ signalling by gene transfer of either Smad7 or microRNAs into diseased kidneys has been shown to retard progressive renal injury in a number of experimental models [45]. *In vivo* Smad7 has the same effect as the soluble receptors TGFβRII used in experimental models of liver fibrosis [147, 150]. The application of TGFβRII acting as false transmitters in rats [145, 150] and soluble TGFβRII in mice [151] with liver fibrosis were associated with improvements in outcome aspartate aminotransferase, alanine aminotransferase and bilirubin (which was not observed in relation to the applied Smad7 [43]). However, we do not know what the long-term consequences of Smad7 overexpression in hepatocytes are. The Smad7 overexpression can lead to neoplasmatic transformation. There are hopes that such risk might be overcome by using suitably modified adenoviruses. On the other hand, antagonists of TGFβ signals might find application only in chronic liver injury because in acute failure TGFβ1 triggers a cascade of signals Smad2-4 simultaneously with the activation of Smad7 which in negative feedback mechanism inhibits the transmission of signals. This results in a transient production of ECM involved in tissue reparation. In chronic liver injury, cascade of signals Smad is not expired because Smad7 activity is very low that is manifested by liver fibrosis [139]. *In vitro* it has been demonstrated that cyclosporin analogue NIM811 which was deprived of immunosuppressive activity is able to reduce collagen production by hepatic stellate cells and increase activity of MMP-1 (matrix-metalloproteinase -1) through inhibition of TGFβ signalling (inhibits phosphorylation of Smad2 and Smad3, enhances phosphorylation of Smad7) [152]. Resistin-induced TGFβ1 from Kupffer cells enhanced HSC collagen I expression. Resistin directly and indirectly modulates HSC behaviour towards a more pro-fibrogenic phenotype [153]. It has been shown that blockade of thrombospondin 1 (TGFβ1 activator) protects rats from liver damage and fibrosis induced by dimethylnitrosamine [154] and the inhibition of

TGFβ1 by providing anti-TGFβ1, decorin (binds TGFβ1), antisense oligonucleotides reduces the accumulation of ECM in glomerulonephritis [68]. There are also interesting observations concerning the activity of mineralocorticoids and approved in the treatment of autoimmune liver diseases glucocorticosteroids. In hepatic stellate cells and in miofiobroblasts, the presence of receptors for these above hormones has been detected. Up to eight hours after glucocorticosteroids administration, the TGFβRIII expression was increasing in a dose dependent manner and time of their administration, while TGFβRI and TGFβRII expression did not change. Glucocorticosteroids through modulation of mRNA TGFβRIII expression can influence the final effect of TGFβ1. Since TGFβ1 and glucocorticosteroids have immunosuppressive activity and after glucocorticosteroids administration tissue sensitivity to the TGFβ1 is increased, it can be assumed that they act synergistically. Thus, the beneficial effects of glucocorticosteroids in autoimmune hepatitis may be a result of such synergistic mechanism of intensifying immunosuppression. Due to the profibrogenic TGFβ1 action, in this situation an immunosuppressive effect seems to be clinically more important and the above explanation is not justified in the case of chronic hepatitis other than an autoimmune aetiology. It has been found that the degree of induction of TGFβRIII expression is dependent on the nature of stimulating hormone — dexamethasone, hydrocortisone, aldosterone and their doses. Glucocorticosteroids through modulation of expression of mRNA TGFβRIII affect the final effect of TGFβ1. On the other hand, the increase of mRNA TGFβRIII expression in hepatic stellate cells by aldosterone is appeared through mineralocorticosteroids receptors present in the cells [37], and mineralocorticosteroids antagonist are candidates for drugs acting against liver fibrosis [155]. Glucocorticosteroids and mineralococorticosteroids and their receptors interact with signal transduction of TGFβ1 at the transcription and translation level [37]. We still do not know how to select the candidates for the anti-TGFβ1 strategy or anti-TGFβ1 treatment. At this stage, it is difficult to predict the side effects of preparations whose primary purpose is interfering with the activity of TGFβ1 and its receptors. There are, however, commonly applied drugs, and one of the additional (or recently discovered) measures is the antifibrogenic effect.

In various clinical conditions, attempts are being made to apply TGFβ1. There have been thus obtained acceleration of healing of skin ulcers, scar formation in post-operative wounds, scarring skin lesions in psoriasis, and healing in the process of merging the bone [6]. In turn, the demonstrated ability to inhibit tumour growth via TGFβRII, and the discovery of factors inducing the expression of this receptor in tumour cells, may be relevant to the treatment of malignant disease.

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