Review

Biology

Transforming Growth Factor-β1 and Tumor Development

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Transforming growth factor-β (transforming growth factor-β, TGF-β) is a cytokine with multifunctional biological activities. It is highly expressed in a variety of tumors and is closely related to the occurrence, development, and prognosis of tumors. In most cells, TGF-β1 can conduct signal transduction through the classical pathway (depending on Smad) and the non-canonical pathway (independent of Smad), exerting its biological effects. Studies have shown that TGF-β1 mainly affects the development of tumors through epithelial-mesenchymal transition, immune cells in the tumor microenvironment, and carcinoembryonic antigen receptors. Elucidating the molecular mechanism of TGF-β1 carcinogenesis will provide new therapeutic methods to prevent tumor recurrence and delay its metastasis.

Keywords: Transforming Growth Factor-β1; Neoplasm; Epithelial-Mesenchymal Transition; Prognosis; Mechanism

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THE leading cause of death in cancer patients is metastasis, especially distant metastasis (1). There are many factors that affect tumor progression, including genetics, biology, environmental factors, and lifestyle. Cytokines, which are biological factors, play a key role in the development of cancer (2). Transforming growth factor-β (TGF-β) is a newly discovered superfamily that can regulate cell growth and differentiation (3). In recent years, it has been found that TGF-β has important regulatory effects on cell growth, differentiation, and immune function, such as inhibiting the growth of epithelial cells and endothelial cells, inhibiting lymphocyte differentiation and the proliferation of immune active cells (4). Obviously, these biological functions inhibit the occurrence and development of tumor cells. However, studies have shown that TGF-β1 can promote the invasion and metastasis of tumor cells when regulating the cellular immune system and tumor microenvironment (5, 6). This paper briefly reviews the role and molecular mechanism of TGF-β1 in tumorigenesis and development.

Molecular Biological Characteristics of TGF-β1

Physiological Properties of TGF-β1

The TGF-β cytokine superfamily consists of more than 40 proteins, including TGF-β, activins (A, AB, B, C, E), inhibins (A, B), bone morphogenetic proteins (BMPs) and growth differentiation factors (GDFs) (7). Human TGF-β cDNA sequence research showed that monomeric TGF-β is a polypeptide containing 112 amino acid residues, and its gene is located on chromosome 19q13. Human TGF-β has three subtypes of TGF-β1, TGF-β2, and TGF-β3, and there are two subtypes of TGF-β4

and TGF-β5 in birds and amphibians. The role of TGF-β1 is pleiotropic, and almost all cells in the human body can synthesize and secrete it (8). It plays an essential regulatory role in the growth and differentiation of cells, the formation of extracellular matrix, immune regulation, angiogenesis, apoptosis and the occurrence and development of tumors (9).

Signal Transduction of TGF-β1

TGF-β1 needs to bind to its receptor and be activated before it can exert its biological effects. Common receptors are TβRI (53 kDa), TβRII (75 kDa) and TβRIII (280 kDa) (10). TβRI and TβRII are transmembrane proteins that have serine protein kinase activity in cells. TβRII first binds to the ligand to be activated, then recruits TβRI and binds to it, and together they determine the recognition characteristics of TGF-β. Activated TβRII can phosphorylate the TβRI serine fragment sequence TTSGSGSG, further activate the serine protein kinase activity of the receptor, thereby stimulating the cascade reaction of cell signal transduction (11). Activated TβRI can promote the phosphorylation of Smad2 and Smad3 proteins (RSmads, receptor-regulated Smad proteins), connect with the "pocket" structure of the MH2 region of Smad4 protein, form R-Smad-Smad4 oligomers, enter the nucleus, and further regulate the transcription of target genes (12). Smads protein is the central link of TGF-β1 signal from cytoplasm to nucleus, and Smad pathway is the classic pathway of TGF-β signal transduction. In addition, TGF-β signal transduction activity is also regulated by I-Smads (inhibitory Smads: Smad6, Smad7) through a negative feedback loop (13). It is well known that TGF-β can also conduct signal transduction through non-canonical pathways (Smad-independent). So far, Smad-independent pathways mainly include RhoA-Rock1, RAS, ShcA, ERK1/2 and p38 MAPK pathways (14). TGF-β1 also regulates cell migration and invasion through the MAPK pathway (15).

The Role of TGF-β1 in Tumorigenesis and Development

TGF-β1 in the Early Stage of Tumor

Under physiological conditions, TGF-β1 can effectively inhibit the growth of various cells, including tumor cells (16). The mechanism of action of TGF-β1 to inhibit normal cell growth is to regulate genes so that the cell proliferation phase is in a dormant phase. In the early stage of tumors, it inhibits the proliferation of cancer cells through anti-mitosis. TGF-β1 controls cell proliferation mainly by preventing cell cycle progression and inducing or activating cyclin dependent kinase (CDK) inhibitors such as p27Kip1 (17). However, when the tumor develops to an uncontrollable stage, TGF-β1 loses this inhibitory effect on most tumor cells. At this time, tumor cells begin to secrete TGF-β1, which promotes angiogenesis by up-regulating the expression of microRNAs, increase the ability of cancer cells to bind cell adhesion molecules, and then improve the invasiveness of cancer cells, creating a favorable microenvironment for tumor growth and metastasis (18). At the same time, TGF-β1 can induce apoptosis of normal cells around cancer cells and thereby eliminate their inhibitory effect on tumor growth.

TGF-β1 in the Late Stage of Tumor

In the late stage of tumors, TGF-β1 becomes a tumor-promoting factor and plays an important role in the process of tumor metastasis (19). Immunostaining analysis showed that the metastasis of breast cancer, oral cancer and esophageal cancer were all related to the expression of TGF-β1 (20). About 40% of breast cancer patients are positive for TGF-β gene, especially those with negative estrogen receptor and lung metastases (21). The mechanism of TGF-β-induced lung metastasis of breast cancer is that the Smad signaling pathway acts on the angiopoietin-like protein 4 (ANGPTL4) gene in situ, making cancer cells leave the breast and invade the pulmonary capillary wall (22). The fenestrated capillaries of bone marrow are not affected by ANGPTL4 activity, which may explain why TGF-β can directly induce lung metastasis of breast cancer but not bone metastasis. The genes related to bone metastasis of breast cancer are IL-11, CXCR4, MMP-1, PTHrP and VEGF, and these genes are all regulated by TGF-β signal transduction pathway (23). Micalizzi et al. showed that Six1 may be the key factor that mediates the transformation of TGF-β1 from inhibiting the growth of breast cancer to promoting its growth (24). Six1 is misexpressed in many tumors and is closely related to tumor progression. However, the mechanism of how it affects the TGF-β1 pathway remains unclear. In vivo experiments showed that inhibition of TGF-β1 and β3 integrin can significantly reduce the incidence of lymph node metastasis of lung cancer (25).

TGF-β1 and Epithelial-Mesenchymal Transition

Epithelial-mesenchymal transition (EMT) is a biological process in which epithelial cells transform into mesenchymal phenotype cells (26). It is not only the basic process of individual development but also the characteristic of tumorigenesis. Through EMT, epithelial cells lose cell polarity, lose epithelial phenotypes such as connection with basement membrane, and simultaneously gain higher abilities such as migration and invasion, anti-apoptosis, and degradation of extracellular matrix. Studies have shown that TGF-β1 is an important regulator in the process of epithelial-mesenchymal transition (27, 28). The metastasis of breast cancer is related to epithelial-mesenchymal transition, and the elasticity coefficient of breast cancer tissue matrix is about 10 times that of normal breast tissue (29). TGF-β enhances these biomechanical responses by stimulating the expression and secretion of some components of the extracellular matrix. The formation of this specific breast tumor microenvironment promotes the distant metastasis of cancer cells, which indicates poor prognosis of patients (30). Normal mouse mammary epithelial cells treated with TGF-β changed from cuboidal to spindle-shaped, accompanied by decreased expression of epithelial cell markers and increased expression of mesenchymal cell markers, that is, epithelial-mesenchymal transition occurred. Clinical data show that the expression of TGF-β1 in breast cancer patients is closely related to cancer-associated fibroblasts (31). Recent studies have shown that TGF-β1 is recognized as the most effective inducer of fibroblast transformation into cancer-associated fibroblasts (32). TGF-β1 can promote epithelial-mesenchymal transition by down-regulating TP53INP1 through miR-155 (33).

At present, mouse mammary epithelial cells (MECs) are

the most used cell line to study TGF-β1-induced EMT, because these MECs exhibit EMT appearance 36 hours after being treated with TGF-β1, which is a classic Smad pathway and Smad-independent pathway such as ERK1/2 and p38 MAPK pathway (34). While maintaining the sustained activity of TβRI, enhancing the expression of Smad3 and Smad4 can improve the EMT response (35). The transcription factors that regulate EMT through the Smad pathway mainly include Snail, Slug, Twist, Cripto-1, FOXC2 and Six1 (36). Activation of Smad2/3 in MECs can induce the expression of nuclear HMGA2, which in turn can promote EMT by stimulating the expression of Snail1, Snail2, Slug, Twist and inhibiting the expression of ID2 (37). TGF-β1-mediated formation of Snail Smad3/4 complex can inhibit the expression of E-cadherin in mammary epithelial cells (38). E-cadherin is lost during EMT and later in tumors. Recent studies have shown that TIP30 protein can reduce the EMT induced by TGF-β1, thereby delaying the metastasis of esophageal cancer (39). Meanwhile, TGF-β1 inhibitors are being used in clinical trials as inhibitors of cancer progression (40). Studies have also shown that TGF-β can induce cells to express cell surface markers related to tumor stem cells, which are highly homologous to bone marrow mesenchymal stem cells (41, 42).

TGF-β1 and Immune Cells in the Tumor Microenvironment

It is well known that regulatory T cells can suppress the anti-tumor immunity of cytotoxic T cells, such as CD8+, CD4+ effector T cells (43). Recently, intratumoral regulatory B cells have also received attention. TGF-β1 in the tumor microenvironment is mainly derived from regulatory T cells. However, some thought that TGF-β1 may also come from tumor stromal cells, together with epidermal growth factor, fibroblast growth factor, hepatocyte growth factor and insulin growth factor, it forms part of the tumor microenvironment (44).

TGF-β1 in the tumor microenvironment has a significant impact on the anti-tumor activity of T cells. In the presence of exogenous IL-2 and IL-4, TGF-β1 can regulate the growth of T cells, usually promoting proliferation. TGF-β1 can also inhibit T cell-mediated tumor rejection (45). TGF-β1 can cause host macrophages to become inhibitors of CD4+ T cell proliferation. It was recently demonstrated that CD4+ and CD25+ regulatory T cell populations are the major source of TGF-β1 (46). And TGF-β1 also plays a key role in inducing the differentiation of regulatory T cell subsets like CD4+, CD25+, Foxp3+ (47). TGF-β1 can inhibit the differentiation of cytotoxic T cells and the lysis of cancer cells mediated by cytotoxic T cells (48). In addition, TGF-β1 can also prevent the expression of granzyme A, granzyme B and perforin, and the expression of granzyme B is directly related to the Smad transcription factor (49). It has been reported that TGF-β1 has the function of suppressing the effects of NK cells and neutrophils, thereby leading to tumor progression (50). Increased levels of TGF-β1 and IL-6 have the effect of promoting inflammation and gastric cancer progression (51). TGF-β1 has also been shown to suppress the expression of cell populations MHC I and MHC II. Decreased expression of MHC I in tumor cells reduces tumor cell lysis by NK cells, thereby accelerating tumor growth and metastasis (52).

TGF-β1 and Carcinoembryonic Antigen

Carcinoembryonic antigen (CEA) is a classic broad-spectrum tumor marker, which can reflect the existence of a variety of tumors and is of great significance to the progression and prognosis of colorectal cancer, breast cancer and lung cancer. Carcinoembryonic antigen can not only bind to its specific CEA receptor, but also bind to the receptor of TGF-β1 to participate in the induction of immune tolerance of malignant tissues (53). Although the assertion that CEA binding to TGF-β receptors will have adverse effects has not been confirmed (54), TGF-β may have the property of promoting cancer development by mimicking CEA through CEA receptors (55). It was boldly speculated that CEA combined with TGF-β receptor induced NF-κB pathway. It has also been suggested that NF-κB is a key factor in the oncogenic transformation of breast cancer, a fact that makes endocrine therapy of human breast cancer cells may present other complications, such as the generation of intrinsic and acquired drug resistance (56, 57).

It is worth mentioning that the target gene of the Smad pathway initiated by TGF-β receptor is CEA-related cell adhesion molecule 5, and the secretion of CEA caused by it is the mechanism of gastric cancer cell proliferation (58). Then, whether there is synergy between CEA and TGF-β signaling cascade will be the direction of future research.

TGF-β1 and Cancer Cell Apoptosis

There are few studies on the relationship between TGF-β and cancer cell apoptosis, and its ability to induce cancer cell apoptosis is still unclear. Studies have shown that through the TGF-β1/Smad3 signaling pathway to induce apoptosis and promote the occurrence of pulmonary fibrosis (59, 60). It has been reported that TGF-β1 can inhibit the growth of human ovarian cancer cells in vitro, but the mechanism is unknown. In vitro experiments showed that TGF-β1 significantly inhibited the growth of multi-lineage endometrial cancer cells in a time-dependent manner and prevented cells from stagnating in G phase (61). TGF-β1 significantly down-regulated Bcl-2, up-regulated the expression of Bax, Smad7 and PAI-1, and promoted cell apoptosis (62); transfection of Smad4 significantly enhanced the anti-tumor effect of TGF-β1 (63, 64). Moreover, TGF-β can increase the expression of death-associated protease (DAPK) in liver cancer cells through Smad-dependent and Smad-independent pathways (65). Other apoptosis-related genes affected by the TGF-β pathway include DAXX, FAS, BIM and GADD45 (66). The final targets of TGF-β-induced apoptosis are pro-apoptotic proteases and some members of the BCL2 family (67). The physiological relevance of these genes needs to be demonstrated using experimental data in simulated in vivo systems.

Conclusion

TGF-β1 plays a pivotal role in the occurrence and development of tumors. When designing therapeutics to control tumor progression and metastasis, the direct effect of the cytokine TGF-β1 on tumor cells, i.e., modulating the interaction between tumor cells and immune cells, must be considered. Currently, some anti-TGF-β1 therapeutic agents are being developed, which may be used as a new way to improve the overall survival rate.■

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