The Role of TGF- β in Gastrointestinal Cancers

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Abstract

Transforming growth factor-beta (TGF- β) is a multifunctional cytokines of biologically active peptides. Recently years, the TGF- β was confirmed highly expressed in various types of human digestive system tumors. With the improvement of medical technology, the cure rate of early-stage tumor is obviously improved, but that of middle- and advanced-stage tumors is still very low with poor prognosis. Therefore, it is important to explore a new targets, and increase the cure rate of malignant tumors and improve the life quality of patients. People have found that the tumor microenvironment (TME) can influence the tumors growth and evolution. The TME constituents such as pH, leukocytes, cytokines, extracellular matrix and humor, and contribute to the tumor cell proliferation, invasion and metastasis. There is plenty of evidence that TGF- β and their signaling play an important role in cell differentiation, inflammatory response, immunologic function and carcinogenesis in gastrointestinal cancers. The aims of this review is to provide a comprehensive view of TGF- β and its receptors and their function in the physiological and pathology mechanisms of the gastrointestinal cancers.

Keywords: Gastrointestinal cancers; TGF- β ; TGF- β signaling; Oncotherapy; Tumor microenvironment

Introduction

Transforming growth factor- β (TGF- β) signalling travels from the membrane and promote the cell development and progress. Moreover, in the tumor cells the TGF- β -related cytokines contribute to the cell proliferation, differentiation [1,2]. A large number of studies have shown that TGF- β involved in the regulation of tumor microenvironment (TME) and effect on tumor cell the growth [3-7]. Especially *in vivo* models of esophagus, stomach, colon, liver and pancreas cancers. All kinds of cancer belong to the Gastrointestinal cancer. Currently, the incidence, mortality and tendency of various malignant tumors is increasing. Further, those malignant tumors already became the serious illness of health of current and minatory people [8-12]. The dysregulation of TGF- β signaling was reported associated with the occurrence and development of gastrointestinal cancers [13-16]. In this review, we discuss TGF- β whose function has been related to cancer development or progression. Furthermore, we mention cases whether pharmacological modulation of the TGF- β points would be used a new target for cancer treatment.

Literature Review

TGF- β superfamily

The transforming growth factor beta family mainly includes transforming growth factor subfamily, activin and bone morphogenetic proteins (BMPs), etc [17]. More than 30 TGF- β superfamily members have been found so far (Figure 1), and their main roles include regulation of cell proliferation and differentiation, participation in embryonic development, promotion of extracellular matrix (ECM) formation and inhibition of immune response [17,18].

TGF- β was firstly found to be expressed in sarcoma virus-transformed mouse fibroblasts [19], consisting of two identical peptide chains with a molecular weight of 25 kDa [20]. There are five subtypes of TGF- β found at present, of which TGF- β 1, TGF- β 2 and TGF- β 3 are mainly expressed in mammals, and TGF β 4-5 occur in birds and amphibians [21]. Among them, TGF- β 1 occupies the highest proportion (>90%) with the strongest activity [22]. The human TGF- β 1 gene is localized on chromosome 19q3 [23] and contains 7 exons totally [24].

The nucleotide sequence is highly homologous across species (>98%) [25]. The encoded precursor molecule C has nine conserved cysteines (Cys) [26]. In recent years, multiple studies demonstrated the role of TGF- β in the occurrence and development of various cancers including gastrointestinal cancers [4].

TGF- β receptor

Transforming growth factor beta type receptors (TGF- β R) are mainly expressed on the surface of cell membrane, and high affinity binding protein for TGF- β , which belong to serine and threonine kinase receptor family [27]. These receptors can be divided into 3 groups

Figure 1: Schematic representation of the TGF- β superfamily. There are four major groups of TGF- β family members, TGF- β s, activins/inhibins, bone morphogenetic proteins (BMPs) and growth differentiation factors (GDFs), are represented.

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Figure 2: Schematic representation the role of TGF- β signaling pathway. The TGF- β pathway activities were regulated by the the ligands with extracellular matrices. TGF- β signals through a heterotetrameric receptor complex composed of two type I and two type II transmembrane receptor subunits with serine/threonine kinase domains. After the binding, both the type II receptor (TGF- β RII) and the type I receptor (TGF- β RI) were phosphorylated. The TGF- β is classically admitted that TGF- β s, activins, via the Smad2 and Smad3. Further, the Smad1, Smad5, and Smad8 were activated by the BMPs and GDFs. Besides the Smad-dependent pathway, TGF- β can activate a number of Smad-independent signaling pathways, including PI3K/Akt, p38, JNK, and ERK in a different cell type. In addition, TGF- β can induce nuclear factor- κ B (NF- κ B) signaling for inflammatory response. All those pathways contribute to the transcription of different targeted genes and promote the tumor cell proliferation, the immune response, tumor metastasis and angiogenesis.

Figure 3: Liver damage and inflammation-related activation of hepatic stellate cells (HSC), and further to liver cancer. The HSC were activated after the liver injury and hepatocyte damage. Then the activated HSC contribute to tissue repair by secreting large amounts of TGF- β . In HCC, TGF- β plays a dual role. In the early stage, it can be as a suppressor inhibit tumor growth. With the development of HCC development, at later stages of disease TGF- β switches to a promoter leading to metastasis.

according to their size and function. T β RI can also be termed activin receptor like kinase with a molecular weight of 53 kDa. Its structure is divided into four parts, namely signal peptide, hydrophilic extracellular region with a large number of Cys, transmembrane region, and cytoplasmic domain made up of kinase region and GS region. The GS region, which is highly conserved and responsible for intracellular signal initiation, localizes between the transmembrane region and the protein kinase domain of T β RI. T β RII has a molecular weight of 70-85 kDa, with a serine/threonine rich tail in the carboxyl end and without GS region. As a constitutively active kinase, upon ligand binding T β RII recruits T β RI into a heteromeric complex and activates T β RI by phosphorylating it in the GS region. The activated T β RI transmits the signal into nucleus via phosphorylation of Smad proteins to modulate gene transcription [28]. T β RIII, with a molecular weight of 250-350

kDa, can indirectly modulate ligand binding to receptors, and may not be involved in intracellular signaling [2]. Because the expression pattern of TGF- β superfamily has spatiotemporal specificity [17], and the condition or environment is different, the role is different, its receptors and many related signal molecules such as Smad and PI3K have become a hot spot in cancer research.

TGF- β and their signaling pathway

As a signaling molecule, TGF- β has a variety of biological functions, and participates in many physiological and pathological processes like cell proliferation, migration, differentiation, apoptosis, and EMT of tumor cells [1] (Figure 2). Normally, exogenous TGF- β binds to specific TGF- β receptors on the cell membrane and activates a variety of cellular signaling molecules that regulate downstream signaling

pathways (MAPK, Smad, PI3K, etc.), further the transcription of target gene, mRNA translation and protein synthesis [29]. Among them, the TGF- β /Smad signaling pathway is one of the most important signaling pathways [30]. The key to the transduction of the TGF- β /Smad signaling pathway is the Smad-mediated transmission of extracellular signals into the cell [30]. According to the different functions of smad protein family, Smad signaling pathway can be divided into three subtypes. Class I is receptor-regulated Smads (R-Smads), including Smad 1-3, 5, 8/9; class II is common-mediator Smads (Co-Smads), such as Smad 4; class III is inhibitory Smads (Anti-Smads), including Smad 6,7 [31]. Different signaling pathways play different roles in different tumors, such as the overexpression of Smad4 in gastric cancer and colorectal cancer can inhibit tumor progression [32,33], whereas the overexpression of Smad7 in gastric carcinoma can promote the progress of gastric cancer [34], but inhibit the invasion and metastasis of colorectal cancer in some cases [35].

Discussion

TGF- β and gastrointestinal/esophageal cancer

We know that, the incidence of the cancer of the esophagus was suspected to be pretty high. The current therapy is mainly surgical treatment, but the postoperative survival rate is very low. The formation of esophageal cancer is very complicated, the main causes of which include several aspects, like the diet containing large amounts of nitrosamines and mycotoxins, living environment and genetic factors, etc [12]. The development of esophageal cancer is accompanied by activation of a large number of oncogenes (*H-ras*, *C-myc* and *hst-1*) and inactivation of tumor suppressor genes (*Rb*, *p53*) [36-39]. The invasion and metastasis of esophageal cancer are the main causes of death in patients with esophageal cancer, and the most important biological feature is EMT [40]. EMT is a biological phenomenon in which epithelial cells lose their epithelial properties and then turn into mesenchymal cells [41]. The role of TGF- β signaling in esophageal cancer has recently been elucidated.

The miR-17/20a was confirmed as a suppressor and inhibiting the esophageal squamous cell carcinoma (ESCC) cell migration and invasion via activation of TGF- β /ITGB6 pathway [42]. It was shown that there was a correlation between TGF- β and EMT in ESCC [43]. TGF- β can induce EMT via a complicated nuclear reprogramming involving a set of EMT-associated transcription factors (Snail, Slug, Twist, etc.) [44]. The inhibition of TGF- β receptor can also significantly inhibit the development of EMT and the proliferation and migration of ESCC [43]. Meanwhile, researchers also found that TGF- β levels in the blood of patients with esophageal cancer are higher than normal population, which means TGF- β is upregulated in esophageal cancer [45]. These results further confirmed the high expression of TGF- β may be an important factor contributing to the development and metastasis of esophageal cancer. Therefore, to clarify the mechanism of TGF- β and its receptor in esophageal cancer can provide a new approach for the clinical treatment.

TGF- β and gastric cancer

Gastric cancer (GC) is one kind of malignancies, with high morbidity and mortality, and ranks among the top leading causes of cancer mortality. Now the current state of treatment for GC showing a less optimistic prospect [9,46]. How to completely cure gastric cancer has always been a common goal in medical community. However, the development of gastric cancer is not accomplished overnight, but it is a multi-step and multi-factor process. Under normal conditions, gastric

epithelial cells maintain a dynamic balance between proliferation and apoptosis. Once the balance is broken down, it will promote the secretion of several growth factors such as epidermal growth factor (EGF), TGF- β , and further promote the activation of some oncogenes in gastric cancer under the long-term effects of these growth factors. Epidemiology also showed that the TGF- β level in patients' serum was correlated with the clinical stages, pathological grade and survival rate [47]. It was also reported that TGF- β 1 can promote the invasion and metastasis, and participate in the early development of gastric cancer, and induce the EMT of gastric cancer cells [48,49]. Mutations in T β RII have been implicated in gastric carcinogenesis possibly via alternation of the growth control effect of TGF- β [50]. Studies have also confirmed that the occurrence, development, invasion and metastasis of gastric cancer are related to the low expression of Smad4 and the high expression of Smad7 [51].

TGF- β and hepatocellular carcinomas

Hepatocellular carcinoma (HCC) is a major public health threat due to increased incidence, late diagnosis and limited treatment options. HCC can be divided into many types with different ability of invasion and metastasis. Although the 5-year survival rate of HCC has been greatly improved after surgical treatment, the pathogenesis has not been fully defined [52]. It has been shown that growth factors including EGF and TGF play an important role in the development and progression of HCC [14,53], thus have attracted widespread attention. Studies found that TGF- β plays a dual role in HCC development [14] (Figure 3). On the one hand, it can act as a tumor suppressor factor to inhibit tumor growth by inhibiting cell cycle and inducing cell apoptosis in the early stage of carcinogenesis. Im et al. found that knockout of T β RII in the diethylnitrosamine-induced mouse liver cancer model increased the incidence of HCC [54], which indirectly reflects the tumor suppressor role of T β RII. On the other hand, as a cancer promoting factor in the late stage of carcinogenesis, TGF- β could destroy cell adhesion, promote the expression of extracellular matrix, block intercellular immune response, promote angiogenesis, induce cancer cell migration and invasion, ultimately lead to invasion and transfer to other normal organs.

The transgenic mice overexpressing TGF- β 1 in the liver are more likely to develop spontaneous or diethylnitrosamine-induced liver cancer. At the same time, TGF- β pathway is one of the key signals in the progression of liver cancer, which can regulate the proliferation, apoptosis, invasion, migration and differentiation of HCC cells [14]. The kinase inhibitor of TGF- β receptor, LY2109761, can block the TGF- β /Smad signaling pathway, reduce Smad2 phosphorylation, upregulate the expression of E-Cadherin, and promote the invasion and metastasis of HCC cells [55,56]. The expression of Neuropilin-2 is upregulated and plays a significant role in tumor cell migration by TGF- β /Smad signaling in HCC [57]. Different HCC cell lines have been shown to own different sensitivity to TGF- β . Cell lines with transcriptional Smad3 activity responded to the TGF- β cytostatic program, whereas those with disturbed TGF- β /Smad3 signaling were blunted to TGF- β -dependent cytostasis [58]. One recent study further showed that lncRNA-ATB, a long noncoding RNA, is involved in the EMT and invasion in HCC [59]. Therefore, to investigate the regulatory mechanism of TGF- β in HCC is expected to make it a potential new target for the treatment of HCC.

TGF- β and colorectal cancer

Colorectal cancer is the third most common malignant tumor, and its etiology and pathogenesis are not fully understood. The

epidemiology of colorectal cancer showed that the incidence of colorectal cancer is increasing rapidly, especially in the economically developed areas. And the risk of colorectal cancer is greatly increased in people over the age of 50 [8].

It was also found that the incidence of colorectal cancer may have genetic susceptibility and closely relate to the TGF- β gene polymorphism 509C/T [60]. There is a significant difference in colony cancer between people in different races and different regions. The T allele may increase the risk of colorectal cancer in individuals by promoting the high expression of TGF- β 1 [61]. It was reported that the expression of TGF- β is related to the differentiation degree, pathological stage and tumor size of colorectal cancer. In addition, TGF- β /Smad signaling pathway is implicated in the occurrence and development of colorectal cancer [13]. Mutation or deletion of Smad2 may promote the proliferation, invasion and metastasis of colorectal cancer. Smad3 inactivation can promote the proliferation of colorectal cancer cells. However, overexpression of Smad4 can induce apoptosis of colorectal cancer cells and activated Smad7 promotes apoptosis by inhibiting the activity of NF- κ B. Specially, Smad7 can also in turn act on the T β RI, making it unable to be phosphorylated hence inhibiting signal transduction. Smad8 is activated by BMPs pathway and then enters the nucleus and combines with DNA binding protein like Smad4 so as to promote the occurrence and development of colorectal cancer at the early stage.

Furthermore, transforming growth factor- β -induced (TGF β I), a secretory protein induced by TGF- β , is upregulated in colorectal cancer patients with Dukes' C and D stages, or with lymph node metastasis or distant metastasis, implying a role in the progression of colorectal cancers [62]. Ma et al. also reported that TGF β I overexpression was more frequent in high-grade (Stages III and IV) colon tumors than in low-grade (Stages I and II) tumors [63]. Importantly, multiple colorectal cancers escape the tumor-suppressor effects of TGF- β signaling and become resistant to TGF- β -induced growth arrest [64]. Targeting carcinoembryonic antigen (CEA), which enhances the metastatic potential of cancer cells, restored the inhibitory effects of TGF- β on the proliferation of colorectal cancer cell lines with high level of CEA [65]. Recently, TGF- β plays an increasingly important role in the clinical diagnosis and evaluation of colorectal cancer and the monitoring of objects with high risk of postoperative recurrence. This will be of great importance for the development of new drugs against colorectal cancer.

TGF- β and pancreatic cancer

In recent years, the proportion of pancreatic cancer in malignant tumors is growing. The cause has not yet fully elucidated, making it difficult to treat [11]. It has been shown that 90% of pancreatic cancers are related to mutations in the twelfth codon of the *K-ras* gene [66]. Researches also point out that the TGF- β plays an important role in the development and progression of pancreatic cancer [15]. Compared with that in the normal pancreatic tissues and chronic pancreatitis tissues, the expression of TGF- β in pancreatic cancers is upregulated, which has an important link with the clinical staging of pancreatic cancer. In addition, the positive rate of TGF- β in stage III and IV pancreatic cancers is obviously higher than that in stage I and II. Both T β R1 and T β R2 are present and increased in majority of pancreatic cancers [67]. TGF- β blockade can decrease the metabolic changes and improve survival in a murine model of pancreatic cancer cachexi [68]. Therefore, overexpression of TGF- β promotes the development and metastasis of pancreatic cancer. However, accumulated evidence shows that TGF- β plays a similarly paradoxical role in pancreatic

cancer as in HCC. At the early stage of pancreatic cancer, TGF- β could inhibit the proliferation of cancer cells by restraining the function of proto-oncogene *c-myc*. While at the later stage of tumor invasion and metastasis, TGF- β gradually loses the growth inhibitory effect, and switches to promote the occurrence, invasion and metastasis of pancreatic tumor through altered expression of ECM components, stimulation of angiogenesis, and immunosuppression, etc [69].

As a novel therapeutic approach, TGF- β as well as many related pathways has been extensively investigated, and various genes and molecules have been identified as important factors in pancreatic cancer progression. Response gene to complement-32 (RGC-32) has been shown to be a potential novel metastasis promoting gene in pancreatic cancer and mediate the TGF- β -induced EMT and migration in human pancreatic cancer cell line BxPC-3 [70]. Rac1 could switch the TGF- β 1 signaling from tumor suppression to tumor promotion outcome by antagonistically regulating Smad2 and Smad3 activation in pancreatic ductal adenocarcinoma cells [71]. A recent study showed that retinoblastoma 1 dysfunction confers TGF- β to activate known oncogenic signaling and upregulate Wnt7b, and promote pancreatic cancer cell invasion [72]. Furthermore, TGF- β -based therapeutic strategies for pancreatic cancer are promising and under development, which is beneficial for patients with this cancer.

Conclusion

In summary, TGF- β is expressed in majority of gastrointestinal cancers, which has confirmed as an important role in digestive system tumors. Therefore, to further exploration of the relationship between TGF- β signaling and digestive tumors, it is not difficult to foresee that TGF- β and its receptors may provide more clues and diagnosis and treatment pathways for the targeted therapy of gastrointestinal cancers.

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