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Review Article

Transforming Growth Factor Beta 1 Pathway in Pancreatic Ductal Adenocarcinoma

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Abstract

Pancreatic ductal adenocarcinoma (PDAC), a type of pancreatic cancer, is a highly fatal malignant disease with one of the poorest prognoses with rising incidence. The poor clinical outcomes are due to the limitation of the current therapeutic interventions and insufficient understanding of the pathogenesis for PDAC. For optimal treatments for patients with PDAC, the pathogenesis of the disease must be elucidated as the understanding of the mechanism can potentially lead to innovative therapies. Transforming growth factor beta (TGF-B) pathway is a cytokine-mediated signaling pathway that plays a critical role in various physiological and pathological processes, including wound healing, cell proliferation, organ fibrosis, immunosuppression, and tumorigenesis. However, TGF-B pathway's role in initiation and prognosis of pancreatic cancer has been controversial since there were multiple reports with conflicting results of pro- and anti-cancer. In this review, we aim to summarize the roles of TGF-B in physiology as well as the potential key pathways by which TGF-B1 modulates the progression of PDAC.

Introduction

Pancreatic cancer is the third leading cause of cancer death in the United States [1]. With poor prognosis, patients with pancreatic cancer are usually diagnosed when the cancer is already metastatic, affecting other organs, such as liver and lungs [2,3]. Being one of the most fatal cancer types, pancreatic cancer has a 5-year survival rate of less than 10% (all the stages combined) [4,5].

The tumor can arise in 3 different areas: head, body, and tail of the pancreas [6]. When the tumor forms in the head of the pancreas, it is called pancreatic ductal adenocarcinoma (PDAC) [6]. PDAC is very common type of pancreatic cancer, accounting for more than 90% of all pancreatic cancer [7]. PDAC is associated with cholestatic symptoms, such as jaundice, abdominal pain, and weight loss [8].

PDAC also comes with severe morbidities. Several complications like cardiovascular and other adverse events, such as strokes, cardiorespiratory distress, pneumonia, thrombosis, psychological disturbances, and metabolic dysfunction follow after the pancreatic resection surgery, one of the treatment options [9]. Other complications of the surgery may include weight loss and poor nutritional status [10].

For the standard treatment of PDAC, chemotherapy, surgery, radiation, and targeted therapy are available options despite its limitation of unguaranteed improvement in survival [11]. Therefore, currently, the most effective treatment is by far is surgical resection [11]. However, at the time of diagnosis, only 20% of pancreatic cancer is resectable [12]. Therefore, majority of the patients lean towards treatment with gemcitabine (GEM), a chemotherapy medication [13]. Over the last 5 years, there were new chemotherapeutic options provided, but many of these were simply combinations of other chemotherapeutics and inhibitors with GEM [14]. One big limitation of the current therapies is that these therapies can only be used on selected patient groups because of the severe drug toxicities and patient withdrawal issues. In addition, combination therapies, such as the GEM-Erlotinib combination, are only available to patients with certain genes mutated [13].

Although these therapies have lengthened the lives of a few patients, the current standard treatment is far from the ideal treatment as there has been no improvement in the overall 5-year survival rate over the past few years [15]. Another major limitation for pancreatic cancer is its late prognosis. In fact, albeit the new diagnostic and therapeutic methods, the overall pancreatic cancer prognosis rate has not made much progress in the past 20 years [16].

In order to provide prognosis for PDAC, in-depth understanding in the pathogenesis of pancreatic cancer is necessary. For cancer to form and grow, multiple genes undergo genetic changes: oncogenes become activated and tumor suppressors become inactivated [17]. Ras oncogene was found to be activated in more than 90% of the pancreatic cancers [18]. In fact, 80-90% of the pancreatic cancers were found to have point mutations on the same areas: codons 12, 13, and 61 in K-ras [18]. The point mutations lead to the constitutively active Ras [19]. The activated Ras ultimately lead to uncontrolled cell growth through binding to the GTP and sending stimulation signals down the signaling cascade [19]. In addition to the Ras oncogene, it has been discovered that Notch and COX-2 genes also play a significant role in the progression of pancreatic cancer. When the Notch protein is activated through binding with its ligands, it releases intracellular Notch which locates itself to the nucleus [19]. Then, the intracellular Notch interacts with the transcriptional factors,

regulating the expression of target genes19. COX-2 was found to be over-expressed in 47-66% of pancreatic cancers [20]. Additionally, Ras mutation and COX-2 level has a positive correlation because when the Ras is activated, it leads to an increased level of stability for the COX-2 mRNA, which would eventually lead to overexpression in COX-2 [19]. In addition to Ras, Notch, and COX-2, there are other oncogenes such as Akt-2 gene which is amplified in 10-15% of pancreatic cancers and Myb gene which is amplified in 10% of pancreatic cancers [19].

Another key pathway by which cancers initiate and progress is through inactivation of tumor suppressors. Some of the tumor suppressor genes targeted in pancreatic cancer are p16, p53, PTEN, and SMAD4 [19]. p53 is well known for its role in the cell cycle. When p53 binds to the p21WAF1 promoter, it leads to cell arrest at G1 phase as the production of p21WAF1 leads to negative regulation of cyclin D1 and CDK2 [19]. Therefore, the inactivation of p53 can lead to uncontrolled cell growth and an increase in cell survival [19]. In fact, 50% of pancreatic cancers have p53 inactivated [21].

When mutations accumulate, pancreatic cancer forms too. Some of the most common mutations for pancreatic adenocarcinoma include KRAS, TP53, CDKN2A, SMAD4, BRCA1, and BRCA2 [22]. The one most common genetic abnormality would be the mutation in KRAS2 oncogene as it is present in 90-95% of the pancreatic cancers [23].

Chronic inflammation is known to play a pivotal role in cancer formation24. Constant inflammation can cause damage in the DNA which can ultimately lead to mutations that ultimately develop cancer [24]. However, pancreatic cancer is a heterogenous disease with potentially multiple pathways involved. Therefore, the exact etiology and pathways are yet to be discovered. TGF-B1 is a well-known pathway which has been extensively studied in other physiology and pathology. Supported by several clinical and scientific findings, TGF-B1 pathway has been emerging as a critical pathway for pancreatic cancer. The role of TGF-B1 has been implicated in the pathogenesis of PDAC. For example, through genomic analyses of PDAC, it has been discovered that TBF-B is modified in 60% of the clinical cases [25]. This data shows that TGF-B plays a considerable role in the PDAC tumor growth.

In this paper, through discussing more information on the roles and the pathways of TGF-B1 in pancreatic cancer, tumor-micro environment, immunotherapy, fibrosis in PDAC, angiogenesis, epithelial-mesenchymal transition, and cancer therapy, we aim to make the distinction between the two seemingly self-contradictory roles of TGF-B1 (tumor-promoting role and tumor-suppressing role) in pancreatic cancer more clear [26]. Through a clearer distinction, improved therapy methods may be provided to raise the survival rate for pancreatic cancer patients of different stages.

TGF-B1 Signaling

TGF-B1 was first discovered in 1978 by De Larco and Todaro [27]. Some of TGF-B1's significant roles of regulating biological processes include immune regulation, inflammation, embryonic development, adult stem cell differentiation, and so on [28]. Since TGF-B1 plays multiple pivotal roles, its absence or malfunction can potentially lead to human diseases such as cancer, developmental defects, fibrosis, and cardiovascular diseases [29].

TGF-B1 signaling pathways can be mainly categorized into two groups: SMAD (canonical) pathways and non-SMAD (non-canonical) pathways [30]. The SMAD pathway involves the SMAD proteins and cofactors such as SMAD-2, SMAD-3, and SMAD-4 [26]. On the other hand, non-SMAD pathways such as the Erk and JNK/p38 pathway don't involve the SMAD proteins [30]. The activation of both pathways happens only in the presence of the functional receptor complexes [30]. These complexes are formed when the heterotetrametric complexes made of TGF-B type I (TGFβRI) and type II receptors (TGFβRII) are bounded with the dimeric ligands (Figure 1) [26]. Without the presence of the TGF-B, the TGF-B receptor complexes are usually dimerized, far in proximity [26].

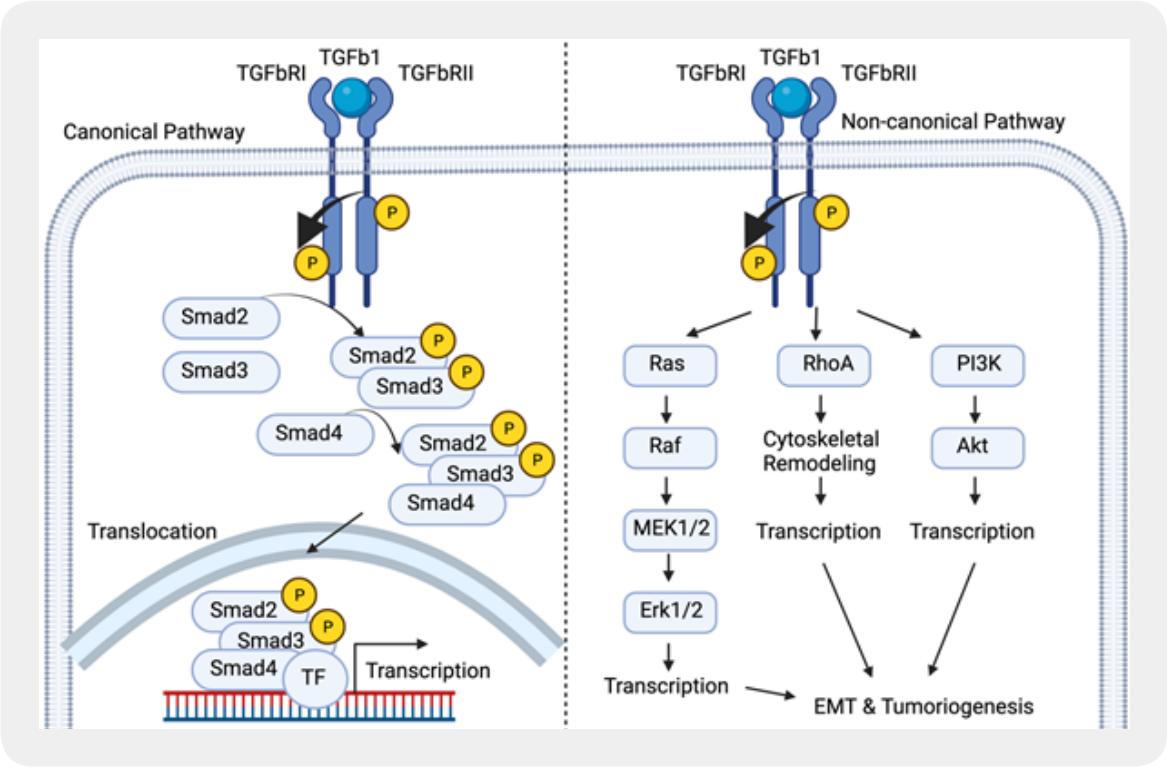

Figure 1: *SMAD and non-SMAD Signaling Pathways of TGF-B1. Extracellular TGF-B1 binds to the TGF-B receptors. Upon binding, TGF-BR1 is phosphorylated which leads to phosphorylation of the down-stream signaling proteins, such as Smad2 and Smad3. The phosphorylated Smad2 and Smad3 form a complex with Smad4 which leads to translocation into a nucleus. This complex binds to the binding site of the Smad complex in the promotor region in the target genes activating gene transcription (canonical pathway). For non-canonical pathway, binding of TGFb1 leads to phosphorylation of TGFbR1 and activation of downstream proteins, including Ras, RhoA, and PI3K. Activation of these proteins further propagated following their own pathway altering the cytoskeletal structure of the cells and affecting gene transcription (non-canonical pathway).*

In the SMAD pathway, the functional receptor complexes phosphorylate the SMAD-2 and SMAD-3 proteins by attaching a phosphate group to it (Figure 1) [26]. The SMAD-2 and SMAD-3 proteins are then joined by the co-factor SMAD-4 to from a heterotrimer [26]. This complex enters the nucleus of the

cell and binds with the promotor regions on the TGF-B target genes to transcribe and ultimately express those genes [26].

In contrast, the non-SMAD, or non-canonical, pathways function in a different way than the SMAD, or canonical, pathways (Figure 1). An example of a SMAD-independent pathway is the Erk MAPK pathway [31]. In this pathway, the presence of the TGF-B leads to the phosphorylation of tyrosine on either the type I/II receptors or on Shc [31]. Then the phosphorylated tyrosine is responsible for bringing on Grb2 and Sos [31]. The MAPK cascades which include MEK and Erk is then activated when Grb2 and Sos proteins activate Ras to its GTP-bound states which leads it to bind to Raf. When Erk 1/2 is activated, it has two functions: through the phosphorylation of R-SMADs, inhibit the R-SMAD activities or regulate the target gene transcription inside the nucleus [31].

Erk is an important protein mediator associated with multiple functions [31]. When Erk is activated, it is capable of mediating epithelial to mesenchymal transition, also known as EMT [32]. In addition, it can regulate the SMAD proteins by phosphorylating the receptor activated SMADs, making them available for the SMAD phosphorylation cascade [31]. Lastly, Erk can lead to the regulation of gene expression by having interactions in conjunction with SMADs [31].

Another non-SMAD pathway is the JNK/p38 pathway [31]. This pathway begins when the TGF-B receptors interact with TRAF6 to create K63-link poly-ubiquitin chains on TRAF6 [31]. The polyubiquitinated TRAF6 then activates TAK1 which allows the activation of downstream JNK/p38 which include the MAP kinase kinases (MKKs) like MKK4 and MKK3/6 [31]. JNK is activated by MKK4, while p38 is activated by MKK3/6 [31]. When JNK and p38 are activated, they control the activities of the transcription factors through working in conjunction with SMADs to regulate apoptosis and EMT [31]. Similar to Erk's association with several functions, JNK/p38 activation also has multiple functions such as TGF-B-induced apoptosis and TGF-B-induced EMT [31]. Another notable part of JNK/p38 activation is that it works in conjunction with the canonical pathways to regulate cellular responses [31].

TGF-B1 and Pancreatic Cancer

TGF-B1 plays dual roles in cancer [26]. In the first few stages of pancreatic cancer, TGF-B plays a positive role of a tumor suppressor by blocking cell cycle progression and increasing the amount of apoptosis [26]. TGF-B can block the growth of the cancer through increasing thrombospondin-1 and decreasing VEGF [26].

On the contrary, in the more advanced stages of pancreatic cancer, TGF-B's role drastically changes to a tumor promoter, helping the cancer grow [26]. While reducing the anti-tumor immune responses, it helps increase angiogenesis and produce stromal activation [26]. The overexpressed TGF-B ligands help promote epithelial-to-mesenchymal transition (EMT) which can help with the metastasis and the growth of the cancer [26].

In pancreatic cancer, the overexpression of TGF-B leads to negative outcomes such as higher tumor stages, shorter patient survival rate, progression of the disease, and metastasis [26]. Although TGF-B may have

countless unfavorable effects on the pancreatic cancer, deletion of these components may lead to even more critical issues in the pancreatic cancer progression [30]. It has been detected the pancreatic cancer leads to loss of function or mutations created in TGF-B receptor 1, TGF-B receptor 2, SMAD-2, SMAD-4 genes [26]. In fact, 4-7% of the pancreatic cancer patients have TGF-B receptor 1 mutated, while 2% of the patients have TGF-B receptor 2 mutated [26]. Moreover, it has been discovered that more than half, 60%, of the pancreatic cancer has the absence of 18q21 protein [26]. This protein is responsible for harboring the SMAD-4 gene which is a central mediator of the TGF-b signaling as it operates as the cofactor in the SMAD pathways [26]. In addition, the mutations in SMAD-4 that leads to the loss of normal signaling function can promote malignant transformation of pancreatic duct cells [26].

TGF-B1 and Tumor-Microenvironment

Tumor-microenvironment indicates the area surrounding the tumor [32]. This includes the nearby blood vessels, immune cells, fibroblasts, signaling molecules, and the extracellular matrix [32]. The tumor has a tremendous effect on its surround microenvironment [32]. The microenvironment can impact the tumor progression greatly by influencing, for example, the rate of metastasis [32].

The presence of TGF-B can vastly alter the tumor-microenvironment. In the microenvironment, the TGF-B is first secreted in order to control proliferation and inhibit cancer progression [33]. However, as time passes, the TGF-B is used by the cancer cells to help the progression of cancer [33]. The TGF-B creates a tumor microenvironment that is helpful for tumor growth and its metastasis [34].

Immune cells, a major components of tumor microenvironment, is heavily affected by TGF-B. TGF-B shows immunosuppressive effects on the immune system, making cancer cell recognition harder [34]. For instance, when the TGF-B is present in the tumor microenvironment, T-cell proliferation is reduced, leading to a decreased amount of their function and limitations of the matured T helper cells [35,36]. To add on, in this tumor microenvironment, the N2 neutrophil phenotype is induced by the TGF-B, increasing the amount of inflammatory cytokines [37]. Lastly, when a high amount of TGF-B is present, it can lead to the apoptosis of B cells and inhibit the maturation of natural killer cells [38]. These immunosuppressive effects of TGF-B all add up and allows the tumor to grow [33]. Not only that, but it also acts as an obstacle to immunotherapy [33].

TGF-B1 and Immunotherapy

Immunotherapy is a cancer treatment in which the immune system fights against the cancer using immune-checkpoint blockade (ICB) and chimeric antigen receptor T (CAR-T) cell therapy [39]. Cancer immunotherapy has brought significant changes. For instance, even patients who had advanced cancers that didn't respond to traditional cancer treatment options had significant prognosis after having anti-PD-1, PD-L1, or CTLA-4 antibodies infused in their body [40].

In a study conducted by Mariathasan *et al.*, it was discovered that when a combine treatment of both PD-L1 and TGF-B is used, it leads to an increase in CD8+ T cells and tumor reduction [41]. When the treatments

were performed separately, the results were ineffective, but in the combined treatment, there was a complete response rate of 70% [41]. Similar results were shown in another study conducted by Tauriello et al. where the combined treatment of galunisertib and antibodies targeting PD-L1 was far more effective than the single treatment of just the antibodies targeting PD-L1 [42]. The effects of this combined therapy also included rise in the tumor CD8+ T cell amount and tumor regression [42]. There are two clinical trials to examine the therapeutic potential of TGFb1 pathway as a combined therapy against solid tumors including PDAC: 1) galunisertib, a TGFbR1 inhibitor, with durvalumab, a check-point inhibitor, and 2) regorafenib, an inhibitor of TGFb1 downstream pathway and angiogenesis, with nivolumab, another check-point inhibitor (Table 1). Current clinical trials show a trend of having a target mechanism that inhibits TGF-B (Table 1). This shows that as of right now, there are more opinions that TGF-B1 promotes the growth of cancer, instead of inhibiting the growth (Table 1). In order to halt the growth of the cancer, clinical trials are being conducted in a way of inhibiting the TGF-B1 cytokine (Table 1).

Table 1: *Clinical Trials Related to PDAC and TGF-B*

Status	Study Title	Interventions (Drug)	Clinical Trial Identifier (https://clinicaltrials.gov/)	Target Mechanism
Not yet recruiting	Study of Efficacy and Safety of NIS793 in Combination With Standard of Care (SOC) Chemotherapy in First-line Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC)	NIS793 +/- combination with gemcitabine/nab-paclitaxel	NCT04935359	Anti-TGFb1
Recruiting	PF-06952229 Treatment in Adult Patients With Advanced Solid Tumors	PF-06952229 Enzalutamide	NCT03685591	TGFbR1 inhibitor
Completed	A Study of Galunisertib (LY2157299) and Durvalumab (MEDI4736) in Participants With Metastatic Pancreatic Cancer	Galunisertib Durvalumab	NCT02734160	TGFbR1 inhibitor; Immunotherapy
Recruiting	A Trial to Learn Whether Regorafenib in Combination With Nivolumab Can Improve Tumor Responses and How Safe it is for Participants With Solid Tumors	Regorafenib (Stivarga, BAY73-4506) Nivolumab (Opdivo)	NCT04704154	Indirect TGFb1 pathway inhibitor; angiogenesis; Immunotherapy
Completed	Safety and Tolerability of AP 12009, Administered I.V. in Patients With Advanced Tumors Known to Overproduce TGF-beta-2	AP 12009	NCT00844064	Anti-sense oligonucleotide for TGFb2

TGF-B's role is also shown prominent in immunotherapy. According to Ming O. Li and colleagues, when TGF-B is inhibited in the CD4+ T cells, cancer cell hypoxia and death in further avascular regions [43]. This leads to the slower cancer progression in models that are resistant to immune checkpoints [44]. Current research shows that a new generation of cancer immunotherapy that builds off the blockage of TGF-B in CD4+ T cells will be introduced [43,44]. This type of immunotherapy will ultimately limit the cancer growth through various factors such as eliminating the nutrient supply for the tumor, reshaping tumor vascular system, and so on [43,44].

TGF-B1 and Fibrosis

Fibrosis is the abnormal accumulation of extracellular matrix in the tissue that leads to the destruction of the normal shape and function [45]. It usually causes chronic inflammation [45]. Inflammation isn't always bad; in the beginning stages, inflammation may, in fact, be beneficial to the reparative mechanism [45]. However, in the later stages when the inflammation has lasted, it may lead to prolonged production of fibrogenic growth factors like chemokines and cytokines [46]. One of mediators involving fibrosis is TGF-B [45]. When the TGF-B is upregulated, it activates various fibrotic diseases and induces the fibroblast phenotypes [45].

There are two types of TGF-B pathways associated with fibrosis: canonical and noncanonical [26]. It has been more prominently known through abundant experiments that the canonical ALK5/SMAD3 pathway is associated with the fibrosis in many tissues [45]. However, there are some evidences that points to the noncanonical TGF-B signaling playing a role in affecting the fibrotic conditions too [45].

Fibrosis is one of the hallmarks of cancer [47]. In fact, up to 20% of the cancers are related to continued inflammation fibrosis [48]. It can be said that upregulation of TGF-B can possibly lead to cancer because when TGF-B is upregulated, it activates fibroblast phenotypes like chronic inflammation that will ultimately cause fibrosis [48]. Chronic fibrosis predisposes the development of cancer because inflammation causes the creation of non-healing wounds [49]. In a case of a tissue injury in the setting of chronic inflammation, the tissue will not be able to heal properly and be transformed into a tissue with fibrotic phenotype [50]. This will lead to effects on epithelial cell differentiation, epithelial proliferation, and epithelial mesenchymal transition [48]. This "non-healing wound" will later ultimately cause cancer-associated fibrosis, which will lead to the creation of malignant tumor, cancer [48].

The involvement of TGF-B in the fibrotic tissues shows that the TGF-B pathways may be a therapeutic target for the treatment of patients who have diseases that can lead to fibrosis such as PDAC [45]. Some methods to inhibit TGF-B would be the administration of anti-TGF-B neutralizing antibodies and the small molecule TBR kinase inhibitors [45]. Since SMAD-3 pathway plays a significant role in TGF-B-regulated fibrosis, usage of endogenous inhibitors to inhibit SMAD-3 may be an option as well [45]. As it has been proven that TGF-B is a key regulator of fibrosis, methods as such listed above may be possible treatment options for PDAC patients.

TGF-B1 and Angiogenesis

Angiogenesis, which can happen during wound healing, tumor growth, or embryonic development, is the formation of capillaries spreading out from preexisting blood vessels [51]. TGF-B1 plays a major role in modulating this process [51]. TGF-B1 also helps induce cell apoptosis which means that it plays an opposing role of VEGF, another modulator of angiogenesis that protects the cells from apoptosis [52]. The role of apoptosis is significant during angiogenesis because without apoptosis, abnormal vessels can form uncontrollably [53]. To add on, apoptosis can also help with capillary morphogenesis both *in vitro* and *in vivo* [54].

TGF-B1 initiates angiogenesis *in vivo* not directly, but through increasing the level of expression angiogenic factors such as VEGF [55]. However, some studies have indicated that TGF-B1 may in fact have direct effects on angiogenesis [51]. For instance, in the mouse embryogenesis, the expression of TGF-B1 receptor I (ALK1) is restricted in the endothelial cells while it is at high level rates in sites of active angiogenesis [51]. The mutations of TGF-B1 receptor I in mice can lead to mid-gestation mouse embryo death from angiogenesis, which is a similar effect observed in genetic deficiency of TGF-B1 [56]. Likewise, when mutations of ALK1 happen in humans, it can cause hereditary hemorrhagic telangiectasia [51]. Hereditary hemorrhagic telangiectasia is a condition where there are capillary bed (angiogenesis) missing in some of the vascular areas [51].

TGF-B1 affects the level of angiogenesis. Angiogenesis may not necessarily play a crucial role in the formation of cancer, but it plays a pivotal role in the progression of cancer [57]. Angiogenesis controls the growth because if the tumor desires to grow larger, blood supply is necessary [58]. This blood can be supplied through angiogenesis [51]. VEGF and TGF-B1 both control angiogenesis separately, but when they are co-existing and interacting together, it has been found that TGF-B1 increases the level of expression of VEGF, leading to a higher level of endothelial cell apoptosis [59]. To conclude, the presence of TGF-B1 affects the angiogenesis and the apoptosis both tremendously.

TGF-B1 and EMT

Tissue fibrosis and cancer metastasis is significantly associated with epithelial-mesenchymal transition (EMT), a process in which the polarized epithelial cells change into apolarized cells that can move around freely [60]. However, EMT is not an abnormal process that is exclusive in cancerous cells [60]. In fact, EMT is a necessary process for embryogenesis and tissue morphogenesis and can even be helpful in healing and repairing tissue damage [61]. Reinitiations of EMT can change its role and make it have invasive and metastatic phenotypes, leading to the development of carcinomas64. EMT especially specializes in the metastatic growth as it allows the cancerous cells to become highly motile [61]. *In vivo*, overexpression of TGF-B1 was sufficient to induce EMT, suggesting that TGF-B1 is critical for EMT promotion [61].

As explained previously, TGF-B is a suppressor of cell growth, especially for the cells of epithelial, hematopoietic, and endothelial origins [62]. TGF-B stimulates both cell invasion and metastasis [61]. Metastatic phenotypes are highly associated with their ability to undergo EMT because during EMT, the

epithelial cells lose their polarity and become more migrative [60,61]. This property allows the cancerous cells to migrate to other parts of the body, creating malignant tumors in those areas as well [61].

Conclusion

TGF-B pathway is a potent signaling pathway affecting multiple physiological and pathological processes including wound healing, fibrosis, cell migration, proliferation, and immune system. This cytokine may contribute to the progression of the cancer via multiple potential mechanisms, such as EMT, angiogenesis, immunosuppression, and modulation of tumor-microenvironment. Given the importance of this pathway over cellular and physiological processes, the exact mechanism and the significance of TGF-B1 to PDAC should be explored in the future. Such exploration will open a path to inventions of drugs and therapies related to TGF-B pathway, which will aid in increasing the survival rate of the pancreatic patients.

Conflict of Interest

There is no conflict of interest reported by the authors of this manuscript.

Contributions

JK designed this review paper; GK and JK contributed to this work by writing the manuscript.

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