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TGIF1-Twist1 axis in pancreatic ductal adenocarcinoma

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ABSTRACT

TG-interacting factor 1 (TGIF1) exerts inhibitory effects on transforming growth factor-beta (TGF-β) signaling by suppressing Smad signaling pathway at multiple levels. TGIF1 activity is important for normal embryogenesis and organogenesis, yet its dysregulation can culminate in tumorigenesis. For instance, increased expression of TGIF1 correlates with poor prognosis in triple-negative breast cancer patients, and enforced expression of TGIF1 facilitates Wnt-driven mammary tumorigenesis, suggesting that TGIF1 might function as an oncoprotein. Quite surprisingly, TGIF1 has recently been shown to function as a tumor suppressor in pancreatic ductal adenocarcinoma (PDAC), possibly owing to its ability to antagonize the pro-malignant transcription factor Twist1. In this article, we will briefly elaborate on the biological and clinical significance of the unique tumor-suppressive function of TGIF1 and its functional interaction with Twist1 in the context of PDAC pathogenesis and progression.

Contents

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an extremely aggressive tumor and a leading cause of cancer-associated related death [1]. More than 85% of pancreatic cancers are PDAC, and less than 7% of patients with PDAC have a 5-years survival rate [2]. PDAC arise from pancreatic acinar cells or their common progenitor [3]. Early stages of pancreatic tumors are usually symptom-free, and the tumor becomes clinically apparent once cells have invaded the adjacent tissues or metastasize to distant organs. Therefore, most of the patients who present with pancreatic cancer symptoms frequently present advanced stages of the disease. The liver, peritoneum, lungs, and bones are the most common sites for pancreatic tumor metastasis [4]. To make the situation worse for the patients, PDAC does not respond well to conventional chemotherapy and radiotherapy [5]. A two-fold increase in the number of PDAC cases and subsequent death is predicted in the USA and worldwide in the next ten years [6,7]. In addition, both obesity and type 2 diabetes are predisposing factors for PDAC [8,9], highlighting the fact that other major life-threatening conditions could contribute to the rising prevalence of PDAC.

The pancreatic intraepithelial neoplasia (PanIN), with activating mutations in the *KRAS* proto-oncogene, usually leads to the formation of more than 90% of PDACs [3,10]. The *KRAS* activating muta-

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tions are key early genetic markers of the genesis of PDAC, while the subsequent accumulation of inactivating mutations in several tumor suppressor genes (e.g., *p16INK4A*, *TP53*, and *SMAD4*) are related to tumor progression and late-stage metastasis [3,11]. Genetically, inducing the expression of the most prevalent oncogenic mutation in Kras ($Kras^{G12D}$) in mouse pancreas leads to the formation of PanINs that occasionally progress to an invasive PDAC phenotype with a very prolonged latency period, suggesting a key role of KRAS in the initiation of human PDAC [12,13]. Interestingly, combining $Kras^{G12D}$ expression with genetic inactivation of the tumor suppressor *Smad4*, which encodes for an essential component of the canonical transforming growth factor-beta (TGF-β) signaling pathway, led to a dramatic acceleration of PDAC, highlighting the importance of this pathway in restricting PDAC progression [11].

2. Dichotomous roles of TGF-β signaling in cancer

Canonical TGF-β signaling is initiated by the interaction of the ligand with two transmembrane receptors called type I (TβRI) and type II (TβRII) [14,15]. The TβRII is constitutively active while the TβRI is inactive in the absence of ligand, [16]. TGF-β binding allows the formation of an oligomeric complex in which TβRII phosphorylates TβRI, leading to the activation of its kinase activity. The activated TβRI then phosphorylates Smad2 and Smad3, which subsequently form a complex with Smad4, and the complexes translocate into the nucleus to regulate the expression of TGF-β genes through interacting with transcriptional cofactors or transcriptional corepressors [15,17]. As for the roles of TGF-β pathways in tumorigenesis, reduced signaling through the "loss of function" mutations of TβRII has been detected in a significant number of colorectal and gastric carcinomas with microsatellite instability [18]. Impaired TGF-β signaling due to the deletion of *SMAD4* is also detected in 16–25% of colorectal cancer and up to 50% in PDAC [19]. Quite paradoxically, sustained activation of TGF-β can exacerbate tumor progression rather than exerting tumor-suppressive effects. For instance, increased expression of TGF-β has been shown to be associated with poor prognosis and decreased survival in colorectal cancer patients [20,21]. Other studies have shown that TGF-β-mediated angiogenesis could also enhance tumor growth [22,23]. Thus, the TGF-β pathway appears to have both anti- and pro-tumorigenic functions [24]. In the early stage of tumorigenesis, activation of TGF-β signaling can induce cell cycle arrest and apoptotic cell death, while in the later stages, TGF-β activation can promote tumor progression, invasion and metastasis by facilitating the epithelial-to-mesenchymal transition (EMT) as well as increasing cancer cell motility [25,26]. These opposing functions during the different stages of tumorigenesis are known as the "TGF-β paradox" [27]. Recently, we have shown that sustained activation of TGF-β signaling through the deletion of the *Tgif1* gene promotes the progression of PDAC, shedding new mechanistic insight into how TGF-β signaling can exert its bimodal function in this aggressive malignancy [28].

3. Role of TGIF1 in the progression of PDAC

TGIF1 is a suppressor of TGF-β signaling, acting primarily either by preventing Smad2 phosphorylation [29] or by facilitating the ubiquitin-dependent degradation of Smad2 [30] (Fig. 1). TGIF1 maintains cellular homeostasis by influencing cell differentiation and proliferation [31,32]. Mutations in the human *TGIF1* gene are associated with holoprosencephaly, a congenital developmental anomaly of the forebrain [33]. In direct support of the role of TGIF1 in holopresencephaly, ablating the mouse *Tgif1* gene resulted in a defective brain development phenotype with features reminiscent of holoprosencephaly [34]. Besides its role in development, TGIF1 has been shown to play oncogenic roles in a wide variety of human hematological and solid malignancies. For instance, in myeloge-

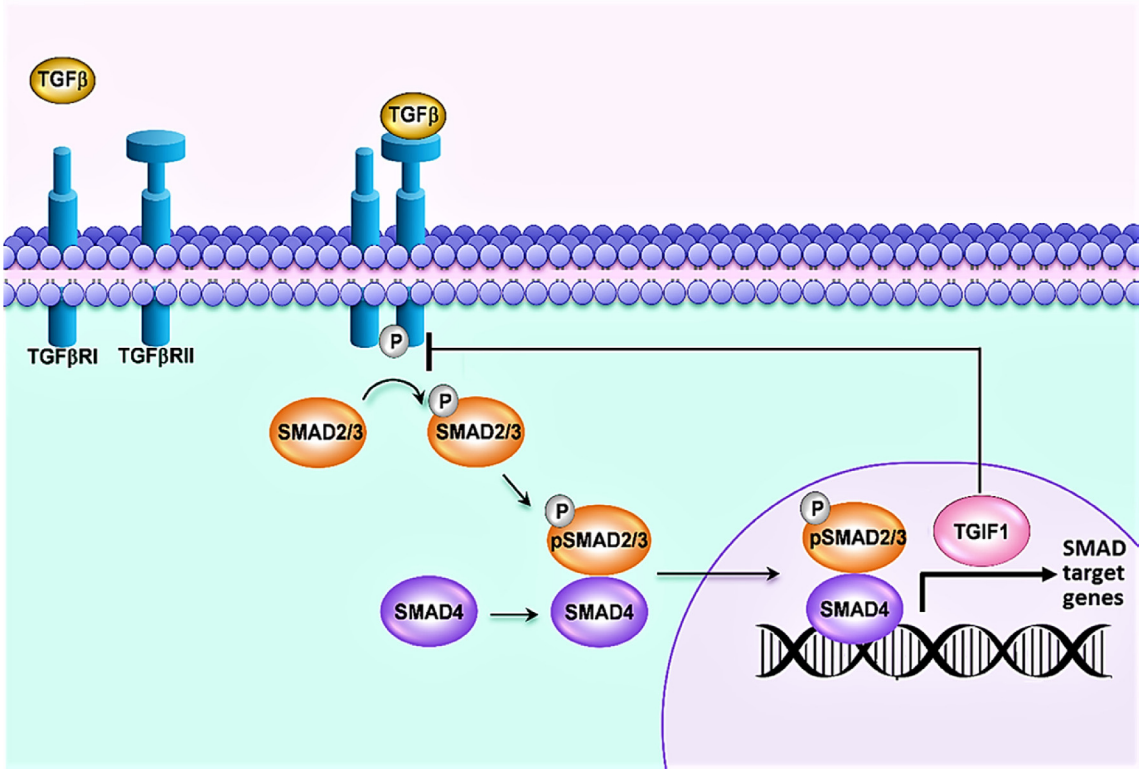

Fig. 1. Simplified diagram showing canonical TGF-β signaling. Note TGIF1 exerts an antagonistic effect on TGF-β signaling.

nous leukemia, an association between TGIF1 expression and poor patient outcomes was noted [35]. In similar lines of study, *TGIF1* gene overexpression is correlated with poor survival in urinary tract urothelial carcinoma and triple-negative breast cancer [36,37]. Moreover, constitutive TGIF1 protein stabilization occurs in promyelocytic leukemia initiated by the oncogenic fusion protein PML-RARα [32], providing strong indications that TGIF1 function to promote tumorigenesis. TGIF1 is deemed to contribute to tumorigenesis through the suppression of the TGF-β cytostatic program, which is known to orchestrate cell cycle arrest and apoptotic cell death in many cell systems [38].

Perhaps unexpectedly, we found that genetic inactivation of *Tgif1* in mice accelerated $Kras^{G12D}$-driven PDAC, suggesting that TGIF1 might also have a dual role in tumorigenesis, as does TGF-β signaling [39]. Mice with global *Tgif1* knockout alone did not show any major pancreatic structural or functional changes. Similarly, targeted ablation of *Tgif1* in pancreatic progenitor cells did not result in any pancreatic defects. Even though targeted pancreatic deletion of *Tgif1* caused an elevated TGF-β/Smad signaling, none of the $Tgif1^{KO}$ mice developed pancreatic neoplasms in the 18-month follow up period, indicating that activation of TGF-β signaling does not play a major role in pancreas biology and function [39]. Similar results were reported by a separate group, showing no pancreatic developmental defects or pancreatic tumor formation in mice with targeted pancreatic deletion of *Tgif1* [40]. Consistent with the absence of no obvious histological changes between the wild-type and mutant mice, the glucose tolerance tests were similar, indicating that TGIF1 is dispensable for pancreas development and physiology [40].

As discussed earlier, the expression of $Kras^{G12D}$ in mice leads to the development of PanINs that eventually progress to PDAC after a long latency period, typically within 8 to 12 months of age. Despite having no effect on the pancreas in a wild-type background, we found that ablating *Tgif1* from these mutant mice accelerated the onset of PDAC formation and progression, as gauged by the dramatic decrease in survival of mice, which rarely exceed two months [39]. What was also interesting is the observation that *Tgif1* inactivation in $Kras^{G12D}$-bearing mice also bolstered the metastatic behaviors of PDAC, providing us with a powerful tool to investigate mechanistic paradigms of PDAC metastasis [39], which remain poorly understood. Again, these results were independently validated by a separate group, which demonstrated using similar genetic approaches, that TGIF1 deficiency in the pancreas is enough to accelerate PDAC in cooperation with $Kras^{G12D}$ [40]. Given the sustained activation of TGF-β signaling in these mice, it is likely that combined Kras and TGF-β activation synergistically promotes pancreatic tumorigenesis with increased metastatic potentials, therefore resulting in reduced survival. It is also worth restating that the inactivation of TGF-β signaling through genetic deletion of *Smad4* also facilitates $Kras^{G12D}$-driven PDAC, which fits well with the dichotomous role of TGF-β signaling as both tumor suppressor and tumor promoter, depending on the stage of tumor progression. Given these similarities in phenotypes following TGIF1 or Smad4 inactivation, it would be interesting to investigate whether TGIF1 and Smad4 converge to regulate biological processes, whether pro- or anti-tumorigenic, that are instrumental to PDAC progression. Regardless, the available experimental data indicate that the underlying mechanisms of TGIF1-mediated PDAC are partly driven by Twist1 [39].

4. Functional interaction between TGIF1 and Twist1 in PDAC

Twist1 is a pro-malignant transcription factor that plays important role in tumor invasion and metastasis in a wide variety of human malignancies, including PDAC [41]. Twist was first detected in Drosophila [42], and subsequently Twist isoforms were identified in humans and mice [43,44]. Twist1 is important for regulating the activity of genes that are essential for embryogenesis and organogenesis [44–46]. Mutation of the human *TWIST1* gene resulted in craniosynostosis (premature closure of the sutures between the bones of the skull), as detected in the patients with Saethre-Chotzen syndrome [47]. Increased expression of Twist1 has been shown to be associated with various human malignant tumors, including PDAC [41,48]. Recently, the induction of Twist1 in muscle progenitor cells has been demonstrated to drive muscle cachexia during the progression of PDAC [49,50]. One of the possible mechanisms of PDAC-induced muscle cachexia is through the tumor-derived Activin A, which acts on the skeletal muscle cells to increase the expression of Twist1, in turn inducing the expression of the muscle-specific ubiquitin ligases (MuRF1 and Atrogin1) to drive muscle protein degradation and subsequent muscle cachexia in PDAC [49,50]. These studies highlight that Twist1 plays a dual role in PDAC, acting in the tumor to orchestrate invasion and metastasis, and in muscle to orchestrate PDAC-associated muscle cachexia.

Endogenous interaction between TGIF1 and Twist1 has been detected in pancreatic extracts of wild-type mice, and as expected, no such interaction was found in pancreatic extracts obtained from *Tgif1* null mice [39]. Ablating *Tgif1* resulted in an increased abundance of the Twist1 protein, while forced expression of TGIF1 reduced the levels of endogenous Twist1 protein and mRNA. Of note, the TGIF1-Twist1 interaction seemed to be independent of TGF-β signaling [39]. Interestingly, Twist1 can induce its own expression, and such auto-transcriptional activity could be blocked by TGIF1. Furthermore, strong binding of endogenous TGIF1 to the Twist1 promoter has been detected both in vitro and in vivo. Based on these and other findings, it appears likely that TGIF1 acts as a direct transcriptional repressor for the *Twist1* gene.

Earlier studies have shown that Twist1 promotes tumorigenesis by inducing cell invasion and metastasis, possibly through creating a microenvironment for EMT [51–54]. A molecular hallmark of EMT is manifested by the loss of E-cadherin expression [55]. Twist1 is thought to reduce the expression of E-cadherin, which leads to disassembly of the epithelial cell–cell interaction to help in cell invasion and migration. Twist1-induced suppression of E-cadherin expression could be blunted by inducing the expression of TGIF1, and this phenomenon is associated with reduced PDAC metastasis [39]. Collectively, these observations implicate TGIF1 as a novel tumor suppressor gene in PDAC, likely functioning through suppression of Twist1 to restrain PDAC progression and metastasis.

In addition to promoting tumor invasion and metastasis, Twist1 could also help in the growth of various human tumors by modulating the functions of several tumor suppressors and oncogenic signaling pathways [48,56]. For instance, Twist1 has been found to directly suppress the expression of the tumor suppressor p16Ink4A, thereby allowing tumor cells to escape cell senescence, which is essential for tumorigenesis in $Kras^{G12D}$ mutant mice [48]. Consistent with this notion, genetically inactivating *Twist1* in $Kras^{G12D}$ mice completely blocked the PDAC phenotype [39]. Twist1 inactivation in $Kras^{G12D}$ mice with targeted pancreatic deletion of *Tgif1* resulted in increased expression of Cadherin-1 and p16Ink4A, concurring with concomitantly decreased expression of the mesenchymal marker Vimentin [39]. The underlying mechanism of how and why TGIF1 inactivation accelerates $Kras^{G12D}$-induced progression of PDAC appeared to be linked directly to Twist1 hyperactivation. In the absence of TGIF1, sustained Twist1 occurs and ultimately promotes tumor growth, invasion, and metastasis to increase the overall mortality in PDAC. In patients with PDAC patients, a 3-fold higher level of Twist1 has been detected in tumor tissues as compared to the healthy normal tis-

sues [57], further supporting the oncogenic role of Twist1 in human PDAC.

Most of the tumor cells utilize aerobic glycolysis to induce uncontrolled proliferation and perhaps evade cell death. Unlike normal cells, tumor cells preferentially metabolize glucose (glycolysis) instead of (mitochondrial) oxidative phosphorylation to generate energy, even when oxygen is sufficiently available, a phenomenon called aerobic glycolysis (Warburg effect) [58]. Warburg effect can create a tumor microenvironment favorable to cancer cell proliferation. The Warburg effect changes reactive oxygen species (ROS) production, and dysregulated ROS can influence cell signaling cascade by impacting phosphatase and tensin homolog (PTEN) and tyrosine phosphatases activities to create a mitogenic milieu for the tumor cells [59]. Of note, Twist1 is a regulator of aerobic glycolysis in PDAC. Using human pancreatic cancer cell lines, Twist1 has shown to transcriptionally regulate the expression of key glycolytic genes, such as GLUT1, HK2, ENO1, and PKM2 to promote the Warburg effect [60]. Whether TGIF1 functions to limit this pro-tumorigenic activity of Twist1 remains to be established. Besides promoting Twist1 activity, inactivation of TGIF1 could create a microenvironment for the generation of tumor-associated macrophages (TAMs), which in turn contribute to the growth of PDAC [40]. In fact, TGIF1 inactivation results in the increased production of certain cytokines and chemokines in the murine model of PDAC. Most notably, tumor cells produce colony-stimulating factor-1 (CSF-1), vascular endothelial growth factor (VEGF), C–C motif chemokine ligand 2 (CCL2), IL-4, IL-10, IL-13, and TGF-β among others. These factors can act as chemoattractant to recruit monocytes and eventually differentiate those cells into the M2-like macrophage phenotype [61]. In PDAC patients, a higher number of M2-like TAMs has been reported to be associated with metastasis and poor prognosis. In studies using CD68 as a pan-macrophage marker and CD204 as a marker for M2 macrophage, increased numbers of M2-phenotype macrophages were detected in patients with invasive PDAC, as compared to the patients with chronic pancreatitis [62]. Increased numbers of M2 macrophages correlated with the enlarged tumor size, metastatic behavior, and shortened survival of PDAC patients [62]. From a translational perspective, suppressing macrophage recruitment resulted in reduced hepatic metastasis in the experimental model of the pancreatic tumor [63], while enhancing macrophage phenotype towards an M2 phenotype resulted in an increased metastatic spreading [64]. Again, loss of TGIF1 function in PDAC could induce TAM polarization towards the M2-like macrophage phenotype to promote pancreatic tumorigenesis [40].

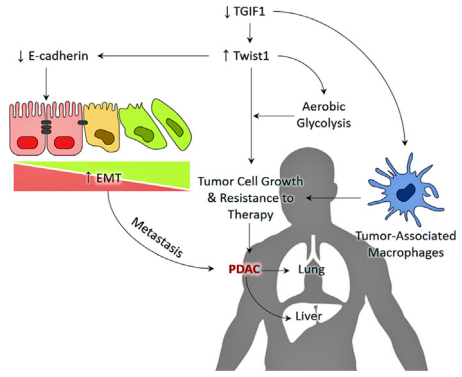

Fig. 2. Simplified diagram showing various cellular events that are mediated by the disruption of the TGIF1-Twist1 axis in the genesis of PDAC.

5. Conclusion

Recent studies from independent groups have convincingly shown that enhancing TGF-β signaling by inactivating *Tgif1* in the pancreatic epithelium resulted in a highly aggressive and metastatic PDAC phenotype in mice, partly mediated through facilitating Kras-driven tumorigenesis. Although there was no death in pancreatic deleted *Tgif1* mice during the entire observation period exceeding 18 months, all the $Kras^{G12D}$;$Tgif1^{KO}$ double mutant mice died within 19 weeks [39]. These results clearly suggest that enhanced TGF-β signaling, due to selective pancreatic inactivation of *Tgif1*, could not avert the genesis of PDAC, when Kras activity is normal. The available evidence implicates TGIF1 as a tumor suppressor in PDAC owing to its ability to inhibit the progression of Kras-initiated pancreatic tumor formation, possibly by inhibiting the formation of EMT and consequently minimizing metastasis (Fig. 2). The tumor suppressor effects of TGIF1 are partly exerted through antagonizing the pro-tumorigenic activity of Twist1, which is known to play key roles in malignant transformation and tumor progression and metastasis. Manipulating the TGIF1-Twist1 interaction and subsequent signaling might be a valid therapeutic target to reduce disease burden for the patients with PDAC. In this context, recent studies showed that inhibition of Twist1 activity by the small molecule JQ1 was able to restrain tumor growth in vivo [65], underscoring Twist1 as an attractive candidate target for anti-cancer therapy. Of particular relevance, JQ1 analogs are currently under clinical trials for a variety of malignancies, hinting at the possibility that targeting the TGIF1-Twist1 axis could hold promise for designing breakthrough therapeutic strategies with immediate clinical applicability in fatal PDAC.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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