



# Fibroblast Growth Factor 10 in Pancreas Development and Pancreatic Cancer

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The tenacious prevalence of human pancreatic diseases such as diabetes mellitus and adenocarcinoma has prompted huge research interest in better understanding of pancreatic organogenesis. The plethora of signaling pathways involved in pancreas development is activated in a highly coordinated manner to assure unmitigated development and morphogenesis in vertebrates. Therefore, a complex mesenchymal–epithelial signaling network has been implicated to play a pivotal role in organogenesis through its interactions with other germ layers, specifically the endoderm. The Fibroblast Growth Factor Receptor FGFR2-IIIb splicing isoform (FGFR2b) and its high affinity ligand Fibroblast Growth Factor 10 (FGF10) are expressed in the epithelium and mesenchyme, respectively, and therefore are well positioned to transmit mesenchymal to epithelial signaling. FGF10 is a typical paracrine FGF and chiefly mediates biological responses by activating FGFR2b with heparin/heparan sulfate (HS) as cofactor. A substantial number of studies using genetically engineered mouse models have demonstrated an essential role of FGF10 in the development of many organs and tissues including the pancreas. During mouse embryonic development, FGF10 signaling is crucial for epithelial cell proliferation, maintenance of progenitor cell fate and branching morphogenesis in the pancreas. FGF10 is also implicated in pancreatic cancer, and that overexpression of FGFR2b is associated with metastatic invasion. A thorough understanding of FGF10 signaling machinery and its crosstalk with other pathways in development and pathological states may provide novel opportunities for pancreatic cancer targeted therapy and regenerative medicine.

**Keywords:** FGF10, FGFR2b, SOX9, pancreas development, pancreatic adenocarcinoma, mesenchyme, epithelium

## INTRODUCTION

The Fibroblast Growth Factor (FGF) family of peptides and the corresponding family of receptor tyrosine kinases (RTKs) collectively constitute one of the most adaptable, complex, and diverse growth factor signaling systems that are involved in many developmental and repair processes in virtually all vertebrate and invertebrate tissues and cells (Goetz and Mohammadi, 2013). Currently, the mammalian FGF nomenclature encompasses FGF1 to FGF23, comprising of secreted signaling proteins that transduce signals via their specific FGF receptors (FGFRs), and intracellular FGFs that

serve as cofactors for voltage-gated sodium channels. These ligands are divided and grouped into seven subfamilies based on phylogenetic analysis, sequence similarities, and function (Goetz et al., 2009; Ornitz and Itoh, 2015).

FGFR family of RTKs comprises of FGFR1, FGFR2, FGFR3, and FGFR4. As the name suggests, FGFRs bind to members of secreted FGFs along with the sequential formation of complexes with heparin/heparan sulfate (HS) cofactor-proteoglycans to propagate downstream signal transduction pathways, which include activation of PLC $\gamma$ , MAPK, AKT, and STAT cascades. At the cellular level, paracrine FGF-FGFR-HS signaling engages in vital roles in regulating cell proliferation, migration, survival, and differentiation during the development of the embryo (Kato and Sekine, 1999; Ornitz and Itoh, 2015).

FGF10, a FGF7 subfamily member, is a typical paracrine FGF and chiefly mediates its biological responses by activating FGFR2b. FGF10 is a potent morphogen and plays a crucial role in transmitting mesenchyme signaling to the epithelium. Genetic ablation of FGF10 in mice results in gross developmental defects characterized by agenesis and dysgenesis in a variety of organs and tissues highlighting an essential role of FGF10 signaling for the development of multiple organs including the pancreas (Bellusci et al., 1997; Bhushan et al., 2001; Itoh and Ohta, 2014). Although not as widely explored as in the development field, there is strong evidence suggesting that FGF10 is also involved in the pancreatic carcinogenesis (Nomura et al., 2008). Herein, we summarize the recent information about the involvement of FGF10 in pancreas development and diseases with a focus on pancreatic cancer.

## FGF10 SIGNALING MACHINERY

Alternative splicing of the extracellular IgIII loop of FGFR1-3 generates IIIb- and IIIc-variants of the receptors. Tissue- and cell-specific expression of these isoforms and modification in binding properties for the FGF ligands confer signaling specificity and functional diversity in regulating interactions in embryonic development, tissue homeostasis, repair, and cancer (Itoh and Ohta, 2014). FGFR2 generates two isoforms via alternative splicing, FGFR2b, predominantly expressed in epithelial cells and FGFR2c, chiefly expressed in mesenchymal cells. A distinct feature of the FGF7 subfamily is the preferential binding to their cognate receptor FGFR2b in a HS dependent manner in contrast to most other FGFs predominantly interacting with FGFR2c (Givol and Yayon, 1992; Orr-Urtreger et al., 1993; Lindahl et al., 1998; Holzmann et al., 2012).

Formation of the FGF10-FGFR2b-HS (2:2:2) ternary complex results in the phosphorylation of intracellular tyrosine residues in FGFRs (Figure 1A). Phosphorylated FGFRs activate FGFR substrate 2 $\alpha$ (FRS2 $\alpha$ ) and phospholipase C $\gamma$  (PLC $\gamma$ 1), which mediate cell motility (Zhang et al., 2006; Itoh and Ohta, 2014). FRS2 $\alpha$ , in turn, facilitates the activation of RAS-MAPK or PI3K-AKT and PLC $\gamma$  activates protein kinase C. The RAS-MAPK and PI3K-AKT pathways are predominantly involved in mitogenic cell responses or cell survival and are subjected to negative regulation by SPRY1 and SPRY2 (Tefft et al.,

2002; Zhang et al., 2006). These signaling cascades mediate a diverse range of biological outcomes that define FGF10/FGFR2b dependent signaling (Figure 1A). The spatiotemporal expression and activity of FGFs and FGFR isoforms is additionally enhanced by the diversity of HS structures, which are also involved in developmental processes, insinuating that tissue-specific HS regulates FGF signaling (Lindahl et al., 1998; Makarenkova et al., 2009).

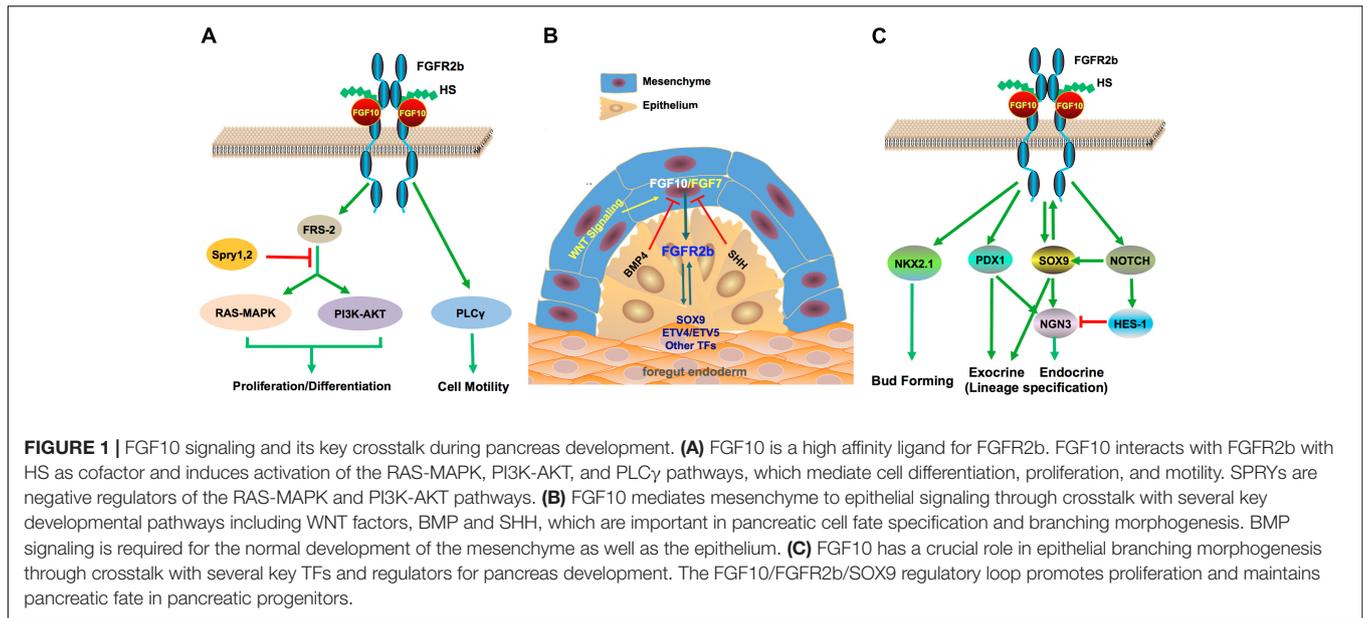
Interestingly, although FGF7 and FGF10 share a common receptor, expression in mesenchyme and the ability to promote proliferation of embryonic pancreatic epithelial cells *in vitro* (Ye et al., 2005), the phenotypes of their knockout mice are drastically different in that FGF7 null mice are born with no obvious abnormalities (Guo et al., 1996), whereas FGF10 knockout mice die at birth with major defects in multiple organs such as lung agenesis and pancreas dysgenesis (Min et al., 1998; Sekine et al., 1999; Ohuchi et al., 2000; Itoh and Ornitz, 2011). Based on a sophisticated quantitative proteomics approach, Francavilla et al. (2013) uncovered a fascinating ligand-dependent mechanism for the control of FGFR2b turnover and signaling outputs. FGF7 stimulation leads to FGFR2b degradation and, ultimately, cell proliferation, whereas FGF10 triggers additional phosphorylation on Y734 of FGFR2b leading to its recruitment of PI3K and SH3BP4 to promote receptor recycling and sustained signaling.

Zinkle and Mohammadi recently proposed a threshold model for RTK signaling specificity and cell fate determination (Makarenkova et al., 2009; Francavilla et al., 2013; Zinkle and Mohammadi, 2018). It is suggested that the intensity and duration of signaling via FGFR2b is dependent on the phosphorylation of Y734 within the kinase domain. Higher affinity of FGF10 for binding both FGFR2b and the co-receptor HS (Makarenkova et al., 2009) generates a more robust interaction than FGF7-FGFR2b dimers, therefore propagates more sustained MAPK signal that leads to cell proliferation and migration whilst FGF7 propagates a transient MAPK signal that leads to cell proliferation. It is conceivable that the difference in ligand-induced dimer stability distinguishes FGF7 from FGF10 on the choice and durability of intracellular pathways, which may well contribute to their functional discrepancies on branching morphogenesis during embryonic development.

## FGF10 IN PANCREAS DEVELOPMENT

The pancreas is an endoderm-derived glandular organ that partakes in the regulation of glucose homeostasis and nutrient uptake through the concerted functions of its endocrine and exocrine compartments, respectively (Edlund, 1999; Shih et al., 2013). Early mouse pancreas development has two characteristic periods: a primary transition (E9.5–12.5) that is characterized by rapid cell proliferation and histogenesis and a secondary transition (E12.5-birth) after rotation of the gut at E12.5 that is chiefly characterized by cytodifferentiation and formation of the significant intracellular organelles of the adult pancreatic cell (Pictet et al., 1972; Jorgensen et al., 2007; Benitez et al., 2012).

The mesenchyme is critical for the growth of all pancreatic lineages (Landsman et al., 2011). Reports indicate that FGF



signaling derived from the surrounding mesenchymal tissue is pivotal for the genesis of specific cellular domains (Hart et al., 2003; Zhou et al., 2007). FGF10, as a mesenchymal factor, has an indispensable role in ensuring the development of the pancreatic epithelium, which gives rise to the functional endocrine and exocrine cell types (Bhushan et al., 2001; Elghazi et al., 2002; Hart et al., 2003; Norgaard et al., 2003). To ascertain the role of FGF10 in pancreas development, Bhushan et al. (2001) demonstrated that FGF10 expressed from E9.5 until E11.5 in mice is vital for pancreas growth and differentiation of Pdx1<sup>+</sup> epithelial precursor cells. The absence of this mesenchymal protein led to pancreatic hypoplasia (Bhushan et al., 2001). Furthermore, the pancreata of *Fgfr2b*<sup>-/-</sup> mutant mice were smaller than the wild type littermates with pancreatic duct cell proliferation notably reduced (Miralles et al., 1999; Pulkkinen et al., 2003). FGF10 signaling predominantly targets the adjacent tissue due to its paracrine nature, hence in *Fgf10* null mutant mice, the pancreatic progenitor cells are diminished even before the onset of secondary transition. The few exocrine cells present do undergo differentiation and form acinar structures (Bhushan et al., 2001). Mice deficient in FGFR2b exhibit mild phenotypes comparable to the FGF10 null mice with differentiation of both pancreas compartments and consequent reduction of organ size (Miralles et al., 1999; Pulkkinen et al., 2003).

While many literature sources substantiate the role of FGF10 in epithelial development, the expression levels of the protein decrease to almost unperceivable levels at E13.5 in mice (Bhushan et al., 2001; Elghazi et al., 2002; Kobberup et al., 2010). Explant studies in mice involving pharmacological inhibition of FGF signaling proved that FGF10 is dispensable at later stages of gestation, implying that different epithelial cell types not only depend on FGF10 signals but also on other (same or distinct) mesenchymal factors (Greggio et al., 2013). Possibly, FGF10's primary role is vital for the initial stage of progenitor growth, then

might work in concert with other mesenchymal derived factors or signaling pathways.

## FGF10 CROSSTALK WITH OTHER SIGNALING PATHWAYS

The mesenchyme is a source of cell-extrinsic signals that promotes pancreatic specification, yet limits differentiation, so as to allow expansion of the pancreatic epithelium. Besides FGFs, other mesenchymal signals that promote growth of the pancreatic epithelium include WNT factors (Jonckheere et al., 2008), Retinoic Acid (RA) (Stafford et al., 2006), BMP (Ahnfelt-Ronne et al., 2010), and the TGF- $\beta$  pathway (Crisera et al., 2000; Figure 1B).

FGFs and WNT factors are known to act in synergy to promote proliferation in a variety of developmental systems (ten Berge et al., 2008; Afelik et al., 2015). Canonical WNT signaling is a mediator of epithelial to mesenchymal signaling, several WNT ligands plus frizzled (FRZ) receptors (e.g., WNT2b, WNT7b, and FRZ2-9) are expressed by both the mesenchyme and pancreatic epithelial cells during organogenesis (Heller et al., 2002; Afelik et al., 2015). Comparable phenotypes are observed between *Pdx1/Frz8CRD* (dominant-negative frizzled 8 receptor) and *Pdx1/Fgf10* null neonates revealing pancreatic hypoplasia, as early as E14, further implying a role for both signaling pathways in pancreatic growth (Papadopoulou and Edlund, 2005; Jonckheere et al., 2008).

RA signaling is also an indispensable mediator of mesenchymal function. In the lung, mesenchyme RA signaling has been implicated in the induction of FGF10 (Desai et al., 2004). Furthermore, absence of RA signaling leads to pancreatic hypoplasia (severe in the dorsal pancreas) (Martin et al., 2005). In an effort to produce functional  $\beta$  cells from endoderm derived human embryonic stem (hES) cells, Mfopou et al. (2010) exposed

these hES cells to noggin and RA, followed by FGF10 during early stage of induction, and successfully generated pancreatic cells, the majority of them are *Pdx1*<sup>+</sup> that coexpressed FOXA2, HNF6, and SOX9.

Unmitigated differentiation of the mesenchyme, which further ensures proper epithelial development, is reliant on many signaling molecules except members of the Hedgehog family from the early pancreatic niche (Kawahira et al., 2005). Ectopic expression of Sonic Hedgehog (SHH) in mice driven by the *Pdx1* promoter results in differentiation of the pancreatic mesenchyme into smooth muscle and the epithelium assumes an intestinal fate with the generation of few early endocrine cell types (Apelqvist et al., 1997). SHH is also implicated in repressing expression of *Fgf10* (Figure 1B; Bhushan et al., 2001).

## TRANSCRIPTION FACTORS IMPLICATED IN FGF10 SIGNALING

Genetic lineage tracing experiments have elucidated that cell clusters committed to adopting the pancreatic lineage express the transcription factor (TF) PDX1 (Pancreatic and duodenal homeobox 1) and PTF1a (Pancreas transcription factor 1). Ablation of either *Pdx1* or *Ptf1a* causes pancreatic agenesis or diabetes and wide gastro-duodenal deformations (Offield et al., 1996; Stoffers et al., 1997; Kawaguchi et al., 2002; Burlison et al., 2008; Fukuda et al., 2008).

After the establishment of the pancreatic anlage, a gene regulatory network is established with *Pdx1* at the focal apex in order to maintain pancreatic identity (Shih et al., 2015). PDX1 exhibits an extensive cross-regulation network between individual TFs and FGFs such as FGF10; however, sustentation of the pancreatic lineage requires high levels of PDX1 (Shih et al., 2015). Augmentation of PDX1 expression levels is supplemented by PTF1a, which binds to enhancer elements of PDX1 (Wiebe et al., 2007), whilst FGF10 is required to maintain the PDX1<sup>+</sup> expressing progenitor cell pool (Figure 1C; Bhushan et al., 2001).

Genetic lineage tracing has shown that multipotent progenitor cells (MPCs) can be similarly defined by several TFs such as SOX9, HNF6, NKX2.2, HNF1 $\beta$ , HES1, CAP1, and NKX6.1. At this juncture, MPCs not only have the potential to self-renew, but also can differentiate to form exocrine and endocrine progenitors with PDX1 functioning as the central node (Zhou et al., 2007; Pan and Wright, 2011; Seymour, 2014).

The SOX9 interacts with the FGF signaling pathway in concert with PDX1 to maintain both expansion (in a dosage-dependent manner) and organ identity of MPCs (Shih et al., 2013). SOX9 and PDX1 co-regulate the pancreatic versus intestinal lineage choice, ablation of both genes causes MPCs to embrace an alternative hepatic fate (Seymour et al., 2012; Shih et al., 2015). In mice, SOX9, FGFR2b, and FGF10 form a feed-forward expression loop; SOX9 cell-autonomously maintains FGFR2b expression, which in turn, augments its epithelial receptivity to FGF10, whilst FGF10 maintains SOX9 expression (Figure 1C). Hence nullification of any component in this loop leads to pancreatic hypoplasia and loss of both SOX9 plus FGFR2b

in FGF10-deficient MPCs leads to hepatic reprogramming (Seymour et al., 2012).

## FGF10 MEDIATES PANCREATIC CELL FATE

Spatial and temporal regulation of gene function is vital in the modeling of specialized cell types from a field of competent cells. FGF10 is known to maintain progenitor cells in an undifferentiated state to allow subsequent proliferation, ectopic expression results in a hyperplastic pancreas. Nascent emergent patterns of budding cells are additionally controlled by conserved developmental pathways such as the NOTCH signaling via lateral inhibition/specification in order to integrate terminal differentiation in FGF10 signaling. FGF10-positive progenitor cells express NOTCH1 and NOTCH2, the NOTCH-ligand genes JAG1 and JAG2, as well as the NOTCH target gene HES1 (Murtaugh et al., 2003; Norgaard et al., 2003; Miralles et al., 2006).

During the primary transition, NOTCH and FGF10 signaling are predominantly involved in restricting premature endocrine differentiation and maintenance of the progenitor state. Ablation of Notch target genes such as *Dll1* (Hrabe de Angelis et al., 1997), *Rbp-jk* (Fujikura et al., 2006), or *Hes1* (Jensen et al., 2000) results in an increase of NGN3<sup>+</sup> cells, leading to premature differentiation of the MPCs into glucagon<sup>+</sup>-cells (Apelqvist et al., 1999) and p57-expressing progenitor cells, which undergo premature cell cycle exit evident with the expression of a hypoplastic pancreas (Georgia et al., 2006). This phenotype is comparable to *Fgf10* and *Sox9* null mutant mice. HES1 is known to repress both the transcriptional activation of *Ngn3* and the cyclin kinase inhibitor *P57* (Figure 1C; Georgia et al., 2006).

SOX9 is a positive regulator of NGN3 in a dosage-dependent manner, and is expressed chiefly in trunk progenitor cells and its depletion results in the reduction of NGN3<sup>+</sup> cells. This suggests that there may exist a complicated but well-organized regulatory system involving FGF10, FGFR2b, NOTCH, HES1, SOX9, and NGN3 that controls endocrine differentiation and maintenance of progenitor cells (Miralles et al., 2006; Kobberup et al., 2010; Gouzi et al., 2011; Afelik and Jensen, 2013; Shih et al., 2015). It can be postulated that both FGF10 and NOTCH signaling pathways are critical for the establishment of two cell lineages:

- (i) NGN3<sup>+</sup> cells that form the early  $\alpha$ -cells.
- (ii) NGN3<sup>+</sup> that will remain proliferative and available to differentiate to other endocrine cell types (Apelqvist et al., 1999; Jensen et al., 2000; Miralles et al., 2006; Kobberup et al., 2010; Afelik and Jensen, 2013).

Ectopic expression of *Fgf10* from E10.5 to E13.5 leads to nearly complete loss of endocrine and ductal differentiation (Kobberup et al., 2010). This, in turn, favors the exocrine lineage because of the lack of competence to form the endocrine cell lineage. Furthermore, exocrine (acinar) differentiation has been observed to occur in FGF10 null mutant mice implying that FGF10

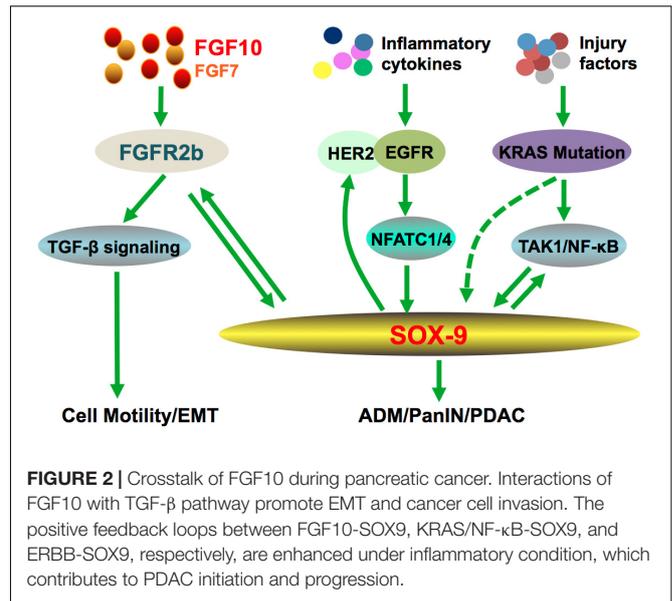
does not entirely control exocrine differentiation but rather it is permissive toward exocrine lineage fate (Miralles et al., 1999; Bhushan et al., 2001; Kobberup et al., 2010). This is observed with sustained expression of PTF1A in both *Fgf10*<sup>-/-</sup> mutant and wild type mice though reports have indicated that downstream effectors of FGF10, such as *Etv4* and *Etv5*, influence expression of PTF1A (Figure 1C; Dong et al., 2007; Kobberup et al., 2007, 2010).

Cellular proliferation and differentiation are mutually exclusive events; hence overexpression of FGF10 beyond the primary transition perturbs differentiation of endocrine and ductal cell types. At this stage, progenitor cells typically co-express PDX1, NKX6.1, and PTF1A, failure of endocrine cell formation leads to diabetes in mice (Hart et al., 2003; Petri et al., 2006; Kobberup et al., 2010). FGF10 signaling via FGFR2b is at the expense of endocrine cellular differentiation (Celli et al., 1998; Miralles et al., 1999; Pulkkinen et al., 2003). By understanding the exact timing of the competence window toward endocrine fate, FGF10 could be best exploited in cell-based therapeutic strategies to combat diabetes (Madsen and Serup, 2006).

## FGF10 -FGFR2B IN PANCREATIC DUCTAL ADENOCARCINOMA

Pancreatic ductal adenocarcinoma (PDAC) is the most common exocrine malignancy and represents one of the deadliest diseases with high mortality due to difficulties in its early diagnosis, metastasis and intrinsic resistance to conventional chemoradiotherapy. At a molecular level, cancer cells in PDAC are often characterized by mutations in the KRAS oncogene, SMAD4, and TP53. Several FGFs and FGFRs are expressed in stromal cells scattered around pancreatic cancer cells and their expression levels have been linked to increased cancer motility, proliferation and metastatic invasion (Kalluri and Zeisberg, 2006; Ying et al., 2016). FGF7 and 10 are both expressed in stromal cells surrounding cancer cells. Regardless of the high homology the latter induces cell migration and invasion whilst the former stimulates cell proliferation. FGF10-FGFR2b signaling induces the expression of type1-matrix metalloproteinase and *TGF-β1* genes (Nomura et al., 2008), these genes are related to cell motility (Friess et al., 1993; Seiki, 2003). Moreover, FGF10-FGFR2b signaling induced the secretion of TGF-β1, a crucial regulator of epithelial to mesenchymal transition (Figure 2; Moustakas and Heldin, 2007; Nomura et al., 2008).

A hallmark genetic alteration of PDAC is the high frequency mutation of KRAS. Numerous studies demonstrate that oncogenic KRAS mutations induce Acinar-to-ductal metaplasia (ADM), pancreatic intraepithelial neoplasia (PanIN), and eventually PDAC. Significantly, SOX9 is imperative for KRAS<sup>G12D</sup>-mediated ADM and PanIN formation (Kopp et al., 2012). A more recent study demonstrated that KRAS can independently induce SOX9 expression and promoted its nuclear translocation and transcriptional activity, which plays a positive role in the proliferation of PDAC cells (Zhou et al., 2018).



Our recent studies further showed that SOX9 could be induced by NFATC1 and NFATC4 in response to EGFR activation and pancreatitis, which promote ADM and PanIN (Chen et al., 2015; Hessmann et al., 2016). In a separate study, SOX9 is reported to stimulate expression of several members of the ERBB pathway, and is required for ERBB signaling activity to promote pancreatic tumorigenesis (Grimont et al., 2015). These studies further consolidate SOX9 as a central player in pancreatic adenocarcinoma via promoting ADM, particularly in the context of oncogenic KRAS and pancreatitis to accelerate development of premalignant lesions and PDAC (Figure 2). Therefore, three positive feedback loops have emerged from these studies (Figure 2): (1) FGF10/FGFR2/SOX9 inter-dependent expression is also present in a subset of PDAC patients (Seymour et al., 2012; O'Sullivan et al., 2017); (2) EGFR, via activation of NFATC1 and NFATC4, promotes SOX9 expression, whereas activated SOX9 stimulates ERBB2 protein expression (Chen et al., 2015; Grimont et al., 2015; Hessmann et al., 2016); (3) Oncogenic KRAS via TAK1/NF-κβ promotes SOX9 expression/activation, and SOX9 in turn enhances NF-κβ activity (Zhou et al., 2018). These findings open new perspectives for precision therapeutic strategies targeting specific cancer-driven signaling molecules such as ERBB2 or FGFR2.

## CONCLUSION AND PERSPECTIVE

Animal models lacking each of the secreted FGFs have been developed with diverse phenotypes ranging from mild abnormality in adult physiology to early embryonic lethality. Only three FGFs (FGF9, FGF10, and FGF18) upon knockout result in early postnatal lethality due to severe developmental defects in multiple organs. While *Fgf9* and *Fgf18* are essential for the development of mesenchymal components, numerous studies highlight FGF10 as an indispensable mesenchyme to epithelium signal required for the development of epithelial components

in multiple organs. Despite the interesting observations from previous reports, research on FGF10/FGFR2b in the pancreas is lagging behind compared to some other organs such as the lung. There remain some critical questions unanswered regarding how FGF/FGFR2b signaling influence acinar and ductal specification (e.g., further proliferation and differentiation from the progenitor cells), as well as its impact on the endocrine system remain largely unexplored. More elegant and specifically targeted genetic models allowing better spatiotemporal manipulation of gene expression will be essential to better address these questions. During both embryonic development and oncogenic process, FGF10 acquires the ability for unique crosstalk with other pathways as exemplified by its inter-dependent expression with SOX9, which may represent a key knot linking oncogenic KRAS, inflammation and other growth factor signaling. Understanding of FGF10 signaling machinery and its crosstalk with other pathways may provide novel opportunities for PDAC precision therapy and regenerative medicine.

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## AUTHOR CONTRIBUTIONS

RN, L-CD, JW, X-KL, and J-SZ conceived the study. RN and J-SZ wrote the manuscript. RN, L-CD, JW and J-SZ designed and drew the figures. J-SZ designed and edited the manuscript. J-SZ and X-KL supervised the study and acquired funding.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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