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Fibroblast Growth Factors and Pancreas Organogenesis

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Abstract—Fibroblast growth factors (FGFs) are growth factors that regulate many important biological processes, including proliferation and differentiation of embryonic cells during organogenesis. In this review, we have summarized current information about the role of FGFs in pancreas organogenesis. The pancreas organogenesis is a complex process, which involves constant signaling from mesenchymal tissue and activation of various genes regulating particular stages thus determining specification of progenitor cells. Changes in the FGF/FGFR signaling pathway during this process result in incorrect activation of master genes, leading to different pathologies in pancreas development. Understanding the full picture about the role of FGFs in pancreas development will help better understanding of their role in other pathologies of the pancres, including carcinogenesis.

Keywords: growth factors, pancreas, master genes, organogenesis, pancreatic tumors

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INTRODUCTION

The pancreas is a vital organ consisting of two spatially separated and functionally different parts: the exocrine and endocrine ones. Traditionally, the exocrine part of the pancreas includes compartments responsible for synthesis, secretion, and transport of digestive proenzymes. The exocrine secretory part of the pancreas is consists of polarized secretory acinar cells forming the acini. The hierarchically organized system of the pancreatic ducts provides ensures transport of acinar cell secretion products into the duodenum and neutralization of gastric juice by bicarbonate ions produced by ductal epithelial cells (Fig. 1). The endocrine part of the pancreas is organized into compact cell clusters disseminated along the length of the pancreas and known as islets of Langerhans. The islets of Langerhans contain five types of hormone-secreting cells: α-cells producing glucagon, β-cells producing insulin, δ-cells producing somatostatin, ε-cells producing ghrelin, and PP-cells secreting pancreatic polypeptide. Hormones of the pancreatic islets are involved in regulation of the metabolism of many organs and control of carbohydrate homeostasis of the body [1–3].

During embryogenesis, the pancreas is formed from ectodermal cells of the posterior part of the foregut of the primitive gut tube (Fig. 1). The pancreas develops from two buds (dorsal and ventral), which are formed during protrusion of ectoderm cells into the surrounding embryonic mesenchyme. In mice, the dorsal bud becomes morphologically prominent on day 9 of embryonic development (E9, dpc, days post coitum). The ventral pancreatic bud begins to form later (E9.5) than the dorsal bud and has a slightly different development program. On day 10 of mouse development (E10) and on day 30–33 of human development, the embryonic pancreas consists of paired buds that contain rapidly dividing multipotent pancreatic progenitor cells. In pancreatic buds formation of the first ducts begins with formation of microcavities followed by subsequent initiation of their fusion. On day 12 of the mouse development, the pancreatic buds begin to fuse with formation of a single organ, in man this process occurs during days 37–43 of development. Starting from stage E14 of mouse embryo development, active branching and remodeling of ducts are initiated and accompanied by differentiation of acinar cells, formation of a pool of bipotent progenitor cells, and initiation of delamination of endocrine progenitor cells. Growth and final maturation of the exocrine and endocrine parts of the pancreas gland occur in the postnatal period. The entire embryonic organogenesis of the pancreas occurs as a constant process of interaction between the growing epithelium of the gland and the surrounding cells of the embryonic mesenchyme. Numerous mesenchymal factors, such as retinoic acid, various BMPs (bone morphogenetic proteins [4]), ligands interacting with Notch and Wnt/b-catenin signaling pathways, play a decisive role both in the induction of early pancreatic buds of the primary gut and in maintaining the right balance between proliferation of pancreatic progenitor

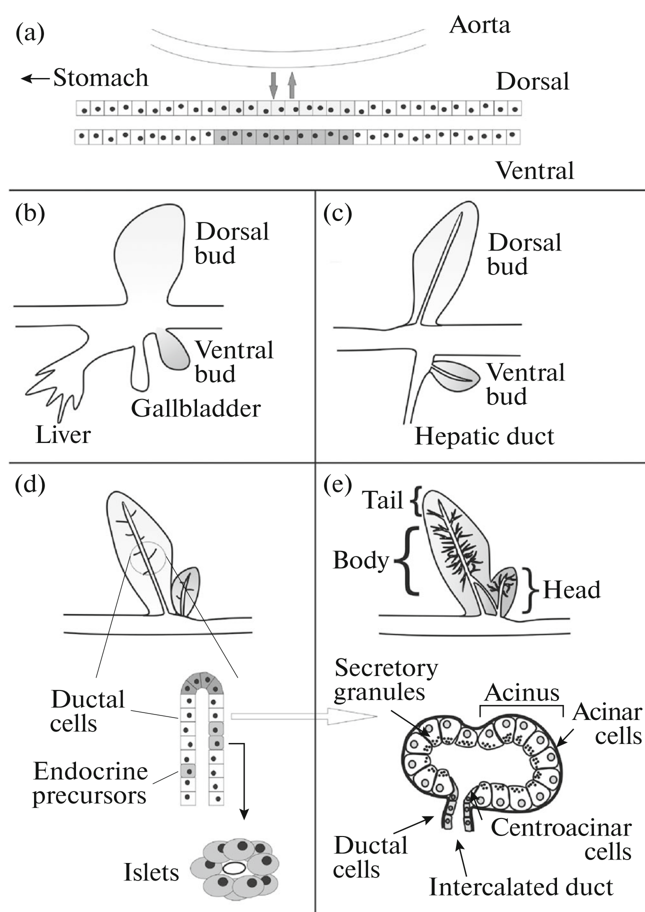

Fig. 1. Stages of pancreas formation. (a) Mutually potentiating interaction between the gut tube endoderm and aorta. E8.5, 29 dpc; (b) formation of outgrowths E9.5, 30 dpc; (c) epithelial formation E10.5, 34 dpc; (d) branching of ducts E12, 38 dpc; (e) final maturation, formation of acini, migration of endocrine cells to islets. E14, 47 dpc [66].

cells and the directed differentiation of these cells into the exocrine and endocrine gland tissue. Among these factors proteins of the fibroblast growth factor (FGF) family, particularly, FGF-1, FGF-2, FGF-4, FGF-7, and FGF-10, play an important role. In addition to participation in pancreas organogenesis, FGF proteins act as important signaling molecules involved in carcinogenesis and pancreatic cancer tumor progression [5–7]. This review focuses on the role of FGF family proteins in the development of the pancreas.

1. A BRIEF OVERVIEW OF THE FGF/FGFR SIGNALING PATHWAY

The general characteristics of the FGF/FGFR signaling pathway and the role of FGF factors in carcinogenesis we have considered earlier [8]. Briefly, the FGF growth factor family includes 23 proteins (Fig. 2). They are subdivided into three groups: paracrine (FGFs 1–10, 16–20, 22); endocrine (FGFs 15, 19, 21, 23), and intracrine (FGFs 11–14). Presumably, their functional differences are associated with their different structures.

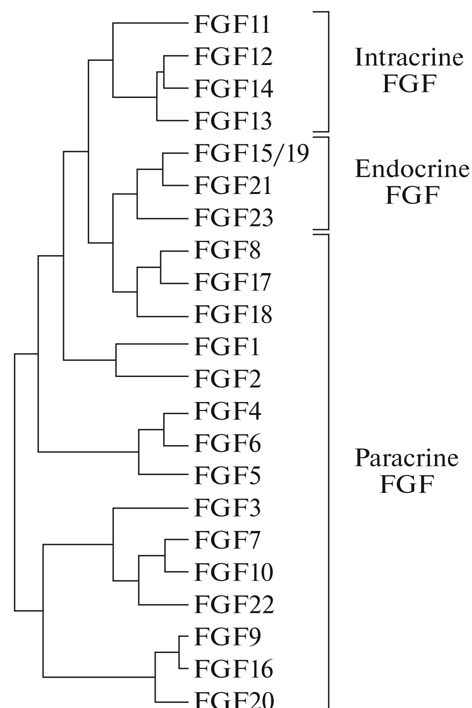

Fig. 2. FGF families [67].

The paracrine factors, which include factors FGFs 1–10, FGFs 16–20, and FGF22, contain the heparin-binding site and the N-terminal signal sequence. They are secreted into the intercellular space, bind to extracellular matrix proteins and act mainly on the nearest target cells.

The endocrine properties of proteins from the FGF19 group (FGF19/15, FGF21, FGF23) are attributed to the absence of the heparin-binding site. They are secreted from the cell, do not retain in the extracellular matrix, and much more quickly enter the bloodstream.

The intracrine factors, including FGF11, FGF12, FGF13, and FGF14, do not contain a signal sequence and bind weakly to the membrane receptors of FGFR. Their main targets are intracellular receptors.

1.1. FGF, Involved in Pancreas Organogenesis

The process of forming the acinus and islet of Langerhans in the pancreas includes three stages (Fig. 1). In mice, the first stage consists in determination and proliferation of progenitor cells and appearance of the first glucagon-producing cells (alpha cells) on E9.5 and E12.5 [9]. The second stage occurs from E13.5 to E15.5, during this period all five hormone-producing cell lines, appear (as well as amylase-secreting acinar cells appear on the apical part of the embry-

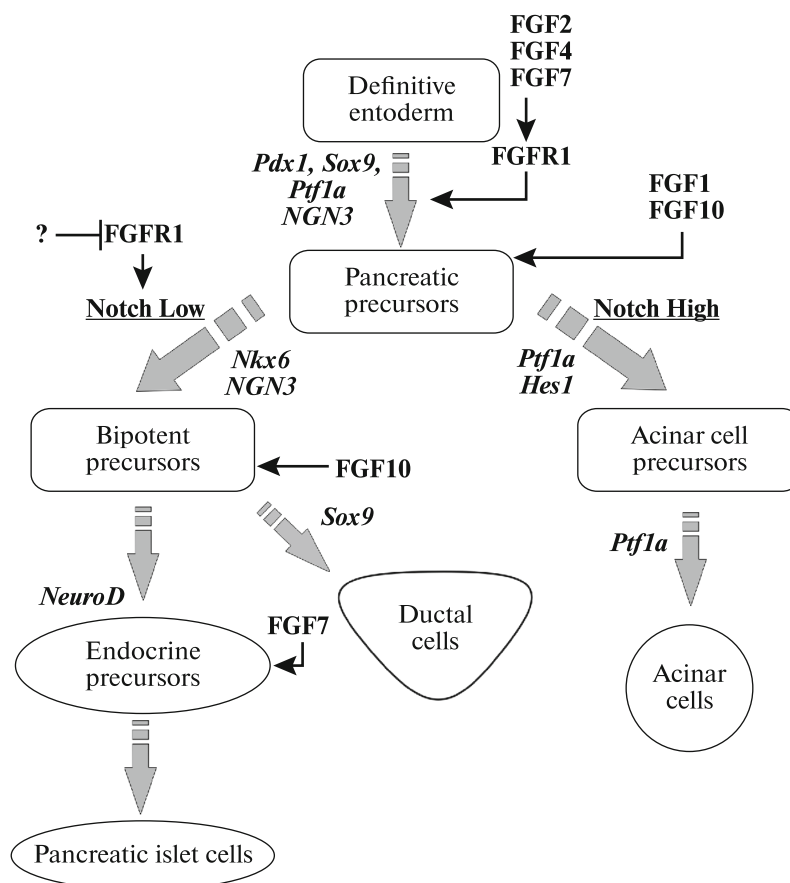

Fig. 3. Differentiation of pancreatic exocrine and endocrine RV cells. The activity of master gene regulators at each stage and the proposed effect of FGF factors secreted from the mesenchyme [56].

onic ducts) [10]. The third stage occurs between E16.5 and E19. During this period, the endocrine cells separate and migrate to the forming islets, while the acinar cells continue to divide [11].

Specific transcription factors control pancreatic determination of endoderm cells to pancreatic progenitors and then into cells of certain exocrine and endocrine lineages (Fig. 3). All the pancreatic cells originate from early progenitor cells, which are characterized by expression of the *Pdx1* gene [12]. After completion of the differentiation process, the high *Pdx1* gene expression remains only in β-cells, where it participates in regulation of the transcription activity of the insulin gene. The progenitor cells express *Sox9* and *Ptf1a* (also known as *P48*). In the adult organ, *Sox9* expression is limited only to a small number of ductal and centroacinar cells, while *Ptf1a* is expressed only in mature acinar cells [13].

During the whole period of pancreatogenesis, the activity of genes, the master regulators of development [14], and transcription factors determining cell growth and differentiation, is controlled by complex interactions of various protein factors secreted by the adjacent mesenchyme. These include numerous growth factors of the FGF family; in the context of pancreas development the following FGFs are especially important: FGF1, FGF2, FGF4, FGF7, and FGF10. They will be considered below. Some information about other FGFs, which have not been considered in this review (e.g. FGF5, FGF8, FGF9, FGF11, FGF18, and FGF23), is available in the literature (e.g. [15]). Different expression levels of these factors are observed in the pancreas at various stages of its formation. However, their participation cannot be denominated as strictly obligatory. Their role is often limited by additional stimulation or inhibition of proliferation of early progenitor cells. In the case of insufficient secretion they are usually replaced by other FGFs, thus avoiding serious disturbances in the development of the pancreas. Most of these additional FGFs involved in the formation of the pancreas lack any dominant physiological effect on a particular type of cells. Almost all of them are able to exert different effects on different types of cells in the developing pancreas [16, 17].

Below we consider known experimental data on the functional activity of various FGFs in the process of embryogenesis of the pancreas.

1.1.1. FGF1. This polyfunctional acidic protein is synthesized in many types of cells, including cells in the embryonic mesenchyme, fibroblasts and endothelial cells of adult pancreas. FGF1 is the only ligand capable of binding to all types of FGFR receptors and their isoforms [8]. The FGF1 protein (like FGF2) lacks a classical signal sequence and therefore its secretion occurs via an alternative pathway that does not involve the Golgi apparatus. It is known that FGF1 is able to induce and support division of multipotent pancreatic progenitor cells, and also to stimulate the development of exocrine tissue. There is evidence for the presence of a nuclear localization signal in the FGF1 protein sequence, and the importance of this amino acid sequence for the functioning of the protein, since its removal leads to attenuation of the mitogenic effect of FGF1 [18, 19].

1.1.2. FGF2. This basic FGF protein shares 55% sequence identity with FGF1. There are four different forms of the FGF2 protein, which are formed due to the use of alternative start points of FGF2 mRNA translation [20] and differ in their molecular masses (18 kDa, 22.5 kDa, 23.1 kDa, and 24.2 kDa). During embryogenesis, FGF2 is secreted from cardiac mesoderm cells; it sets patterns for the formation of adjacent multipotent ventral intestinal endoderm and determines organogenesis of the liver or lungs. The signal is transduced mainly through the IIIc isoform of the FGFR1, 2, and 3 receptors; however this protein can also bind to the FGFR1-IIIb and FGFR4 receptors but with low affinity [8]. FGF2 plays an inductive role in the formation of the dorsal bud of the pancreas during embryonic development. Induction of the ventral pancreatic bud may occur in the absence of cardiac mesoderm and FGF2 [21].

FGF2 is able to induce differentiation of gut endoderm cells in several directions, depending on its concentration. For example, low concentrations of FGF2 determine the hepatic differentiation lineage, while medium and high concentrations induce formation of pancreatic and pulmonary cell lineages [22]. It has been shown that the induction of PDX1+ progenitor cells is partially dependent on the FGF2-mediated activation of the MAPK signaling pathway. It is also assumed that FGF2 influences the activation of the *NKX6.1* gene; the latter suggests FGF2 involvement in the formation of mature β-cells of the pancreas. In this regard, it should be noted that in different tissues the effect of FGF2 on the growth and differentiation of cells can be different. For example, isolated brain multipotent stem cells demonstrate unlimited division in the presence of FGF2, but they do not enter into differentiation. After FGF2 removal from the culture medium, the stem cells differentiate into neuronal or glial cell types [23–26].

It is possible that the main mechanism of the FGF2 effect on the process of early organogenesis of the pancreas consists in inhibition of the Hedgehog (Hh) signaling pathway in the ectodermal cells of the posterior part of the foregut of the primitive gut tube. Inhibition of the expression of the Sonic hedgehog (Shh) endodermal factor by the combined action of mesenchymal ActivinB and FGF2 is important for regionalization of the dorsal part of the primary gut, from which the dorsal pancreatic bud is later formed [27, 28]. Reduced content of endodermal Shh leads to an increase in the expression of genes encoding the transcription factors Pdx1, Isl1, and Pax6. These are the main factors for subsequent cell differentiation and expression of genes required for normal development of the pancreas [29]. The interaction between the dorsal aorta tissue, cardiac mesoderm, and endoderm may influence subsequent interaction between the mesenchyme and the epithelium of the pancreatic primordia [30, 31].

1.1.3. FGF4. This factor is expressed in close proximity to the posterior endoderm in the gastrula and in embryos during early somitogenesis (from day 21 of embryonic development). Transduction of the FGF4 signal mainly occurs via the cell receptors FGFR1IIIc and FGFR2IIIc [8], and to a lesser extent via FGFR3IIIc and FGFR4. It was believed that FGF4 possessed the activity crucial for regulation of the gut ectoderm pattern formation. For example, studies on chick embryos have shown that in a concentration-dependent manner FGF4 stimulates expression of the posterior endoderm markers, and inhibits expression of such marker genes of the anterior endoderm, as *Hex1* and *Nkx2.1* [32, 33].

However, certain evidence exists that FGF4 alone cannot induce pre-pancreatic endoderm. Experiments with Activin A-induced human hESC and mouse mESC cells revealed that FGF4 was unable to induce the *PDX1* gene and had no influence on expression of the anterior and posterior gut markers, regardless of its concentration. This led to the conclusion that FGF4 could not be involved in primary gut pattern determination during organogenesis. Combined treatment of hESC and mESC cells with FGF4 cells and retinoic acid resulted in *PDX1* mRNA expression observed on day 12 of stimulation. This effect was also confirmed at the protein level. These experiments also revealed an increase in survival of stimulated cells. Treatment of the same cells with retinoic acid with simultaneous blockade of the FGF signaling pathway revealed a lower level of *PDX1* mRNA. Based on these results it has been concluded that the main role of the FGF4 protein consists in partial support of the retinoic acid effect and an increased survival of anterior gut endoderm PDX1+ cells [15, 32].

Experimental increase of FGF4 expression in the developing pancreas results in formation of an unformed cyst with a large number of ductal and acinar cells instead of the normal organ. The number of endocrine cells in these mice was reduced; instead of organized islets, these cells were randomly distributed

in the surrounding epithelium. These results may indicate that FGF4 either can specifically function as a growth factor for the ductal cells (with simultaneous suppressing other developmental lineages), or that it mainly affects the adjacent mesenchyme. In this case, all the observed effects are the result of an abnormal response of mesenchymal cells to the increased signal of FGF4 [15].

1.1.4. FGF7. FGF7 is a growth factor, synthesized by fibroblasts, which exhibits mitogenic activity only towards epithelial cells, and does not affect the proliferation of fibroblasts and endothelial cells. The latter explains its alternative name as keratinocyte growth factor (KGF). FGF7 is secreted by the mesenchymal cells of the pancreas; binding to the FGFR2-IIIb receptor, it simultaneously influences the process of pancreatogenesis in several directions [34]. Like other FGF factors, FGF7 induces proliferation of epithelial cells. However, this effect is not specific and is not limited to the development of pancreatic epithelial cell lineage. The mitogenic effect of FGF7 on ductal and β-cells is weaker, as compared to FGF1 and FGF2. The other important feature of FGF7 is its effect on definitive endoderm cells that results in activation of *Pdx1* expression, and several other markers of pancreatic progenitor cells: *Hnf6, Nkx6.1, P48* [35]. The effect of FGF7 on cell differentiation at later stages remains unclear. Studies, performed on induced PDX1-positive mESC, have shown that a combination of FGF7, GLP-1 (glucagon-like peptide 1), and nicotinamide has driven their differentiation to acinar cells secreting amylase, carboxypeptidase A, and chymotrypsinogen B [36]. On the other hand, certain evidence exists that FGF7 in vivo causes proliferation of ductal cells. Moreover, it has been shown that FGF7 can also positively influence in vivo the amount of islet β-cells due to activation in the duct cell Glut 2, the transcription target of PDX1, followed by their direct differentiation into β-cells (or possibly with the presence of a dedifferentiation step) [37]. It should be noted that FGF7 is not a factor that is essential for the normal functioning of the pancreas, as in mice with the inactivated gene encoding this protein, offspring without metabolic defects still appears [18, 38–41].

1.1.5. FGF10. A primary structure of this factor is close to FGF7 and this similarity can explain the proliferative effect of FGF10 towards keratinocytes. However, unlike FGF7, FGF10 at high concentrations is able to exhibit mitogenic activity towards fibroblasts. FGF10 is characterized by higher affinity to heparin than FGF7 and this results in significant differences in functional properties of these proteins. For example, FGF10 is mainly associated with the extracellular matrix where it is bound to heparan sulfate proteoglycans, while FGF7 diffuses more freely in the intercellular space. The effect of FGF10 is concentrated on a narrow epithelial/mesenchymal interface; this causes growth and elongation of the pre-pancreatic bud. FGF7 influences the entire length of the pre-pancreatic bud and this leads to its branching [42]. The latter explains why heparin inhibits mitogenic activity of FGF7 and causes a 5–10-fold increase in FGF10 activity. Like FGF7, FGF10 is expressed mainly in mesenchymal cells of the pancreas [43, 44].

FGF10 is an important growth factor involved in formation of the pancreas and influencing proliferation of epithelial cells. FGF10 participates in several stages of development of the pancreas, mainly in the transition from the definitive endoderm to the stage of pancreatic progenitor cell formation. The critically important role of FGF10 for pancreatogenesis is confirmed by the fact that mice with genetic knockout of the *FGF10* gene are characterized by pancreatic dysgenesis [45]. FGF10 plays a dual role during embryonic development: it can promote maintenance of pancreatic progenitor cells in an undifferentiated state and to trigger a proliferative signal. During normal development of the pancreas, FGF10 is predominantly expressed in the mesenchyme and in the course of organ formation the quantitative ratio of the mesenchymal and epithelial tissues is shifted toward the epithelial tissue. Consequently, at the late stages of organ formation, the FGF10 concentration may be insufficient for inhibition of differentiation and stimulation of proliferation, and this finally results in activation of the differentiation process [24, 46].

The main mechanism by which FGF10 influences the progenitor cells in the pancreatic epithelium is the activation of the master gene *Sox9* [47]. The transcription factor Sox9 is a specific marker and a supporting factor of multipotent progenitor cells during organogenesis of the pancreas and other organs. During the early stages of pancreas organogenesis, the *Sox9* gene is expressed in all epithelial cells [48]. Targeted inactivation of Sox9 results in significant hypoplasia of the pancreas due to a decrease in the pool of progenitor cells. Based on these data it has been suggested that Sox9 supports pancreatic progenitor cells, by stimulating their proliferation, survival, and maintaining them in an undifferentiated state [49]. Being secreted in the pancreatic mesenchyme, FGF10 binds to the membrane receptor FGFR2-IIIb. Activation of the receptor triggers a signaling pathway, which finally activates Sox9 expression. Sox9 activates synthesis of factors that support proliferation and an undifferentiated state, cell survival and their commitment to the pancreatic developmental lineage, and also increases the number of FGFR2b receptors on the cell membrane. The latter increases cell sensitivity to FGF10, thus forming a loop of positive feedback. Impairments in FGF10 signal transduction, decreased expression of Sox9 and FGFR2-IIIb have a significant impact on cell commitment and give rise to onset of alternative differentiation programs, such as the hepatic differentiation lineage [50–52].

FGF10 may also be needed to support the specific expression of the *Ptf1a* gene for the pancreatic progen-

Table 1. The role of components of the FGF/FGFR signaling pathway in pancreas organogenesis and pathological changes associated with their abnormalities

	The role in pancreas organogenesis	Pathology associated with impaired functioning
FGF1	Induction of progenitor cell proliferation [18]	Tissue hypoplasia [18]
FGF2	Induction of progenitor cell proliferation [21, 29]	Tissue hypoplasia [26]
FGF4	Induction of ductal cell proliferation [32]	Impaired morphology [15]
FGF7	Induction of progenitor cell proliferation [35]	Tissue hypoplasia, hyperplasia of ductal tissue [37]
FGF10	Induction of progenitor cell proliferation [46]	Tissue hypoplasia and/or organ dysgenesis [45]
FGFR1		–
FGFR2	Formation of the exocrine part of the pancreas [41]	Pancreatic epithelial dysplasia [41]
FGFR3		Tissue hyperplasia [53]

itor cells (Fig. 3). Ectopic expression of FGF10 in the pancreatic epithelium results in organ hyperplasia characterized by an increase in the number of Pdx1+/Nkx6.1+ progenitor cells and impaired differentiation of endocrine and exocrine cells [45, 53].

The effects of each component of the FGF/FGFR signaling pathway in the pancreas organogenesis pathologies associated with up-regulation or down-regulation of each of them are shown in Table 1.

2. INTERACTIONS BETWEEN FGFR AND NOTCH SIGNALING PATHWAYS

The Notch signaling pathway plays a critical role by controlling processes of division or differentiation of progenitor cells [54]. The final result of the induction of the Notch signaling pathway consists in activation of the *Hes1* gene encoding a transcriptional repressor, which suppresses activity of the *NGN3* gene. Activation of the Notch signaling pathway, activation of the *Hes1* gene, and suppression of the *NGN3* gene shift the determination of pancreatic progenitor cells towards the pre-acinar cells (Fig. 3). In the case of Notch (and, therefore *Hes1*) suppression activation of *NGN3* occurs, which determines the differentiation towards the bipotent progenitor cells. FGF10 functioning is also associated with the Notch signaling pathway [55]. It has been shown that the action of FGF10 on cells is accompanied by activation of Notch pathway components in them. Several scenarios have been proposed for the mechanism underlying interactions between two pathways. One of them exploits recognized relationship between FGF10 and the Lunatic Fringe (LFNG) protein. LFNG is known for its ability to enhance Notch signaling. This is confirmed by the fact that the maximum level of LFNG expression in cells during mouse pancreatogenesis is observed between the embryogenesis stages E12 and E16, when maximal expression of pancreatic mesenchyme FGF10 occurs [55].

An alternative point of view consists in the assumption of the existence of a signaling cascade containing the Sox9 protein as an intermediate link. It is based on the Sox9 control of expression of many number of transcription factors, including Ngn3; the latter activates expression of the Notch ligand Delta, which binds to the Notch receptor [56]. Binding of the Delta ligand leads to subsequent proteolytic cleavage of the receptor; this is accompanied by release of a fragment of the intracellular domain, which is then translocated into the nucleus where it acts on target genes. Activation of the Notch receptor enhances *Hes1* expression, which in turn inhibits expression of *Ngn3*, resulted in maintenance of cells in the proliferatively embryonic state. On the contrary, when the Notch signaling is suppressed, Ngn3 is activated, and subsequent differentiation occurs in endocrine progenitor cells [57, 58].

It has been noted [59] that the *NGN3* expression is in antiphase with the activity of FGFR1 and PDX1. It is possible that FGFR1 has a significant impact on the process of cell differentiation. The proposed mechanism of this effect is as follows (Fig. 3) [59]. In definitive endoderm cells, activation of the FGFR1 receptor directly or indirectly (through intermediate factors) leads to increased *PDX1* transcription; this determines specification of the cells in the primary pancreatic progenitors. Inactivation of the receptor is accompanied by a decrease in *PDX1* expression and an increase in *NGN3* expression thus limiting direction of differentiation to bipotent progenitor cells. During the late stages of endocrine cell maturation, the *PDX1* gene is reactivated, as it is needed for the transcriptional activation of the insulin gene during β-cells differentiation. However, it remains unknown, whether this effect occurs due to reactivation of the FGFR1 signaling pathway.

The proposed interaction between FGF/FGFR and Wnt/β-catenin signaling pathways as one of the possible mechanisms that determine pancreas organogenesis needs experimental evidence [60]. Wnt signaling molecules are secreted proteins that are able to bind to the transmembrane Frizzled receptors. This leads to a cascade of interactions between cytoplasmic molecules, stabilization and accumulation of β-catenin, its subsequent translocation into the nucleus, where it is capable of controlling the target genes.

During pancreas organogenesis, the Wnt/β-catenin signaling pathway is active only from the moment of endoderm formation to differentiation of exocrine and endocrine cells [61]. According to the latest results, activation of the Wnt signaling pathway is important for proliferation of precursors of endocrine and acinar cells. The suggestion about possible interrelationship between the FGF and Wnt signaling pathways in the pancreatic progenitor cells is based on the experimental demonstration of β-catenin activation induced by FGF10 binding to FGFR2b in spatially close liver precursor cells [62, 63].

CONCLUSIONS

Summarizing known effects of FGF factors that are expressed during formation of the pancreas, it is reasonable to suggest that the main effects of these factors are manifested during the initial stages of organogenesis. Growth factors, including several proteins of the FGF family secreted from the cardiac mesenchyme and dorsal aorta, are crucial for activation of master genes, the regulators of the pancreatic development program, such as *Sox9, Pdx1, Ptf1a*, and although for manifestation of other important effects, such as support for the undifferentiated states and acceleration of cell division. In most cases, altered expression of these growth factors has a significant impact on the overall organization of the pancreas, leading to significant organ hypoplasia, dysgenesis, or hyperplasia in cases of insufficient effects of the effectors limiting division and triggering differentiation. During later stages of pancreas formation, FGF factors preferentially support proliferation of the pool of undifferentiated pancreatic cells [64, 65]. Thus, despite the accumulated knowledge, additional studies are required to obtain an integral picture of the participation of FGF and their receptors in the regulatory network that determines pancreas development. Obtaining such information will make it possible to determine more accurately the targets of therapeutic effects in various pathologies of the pancreas.

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