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Cutting the Edge of β-Cells – WNT Pathway Thrives Lineage Segregation in Pancreatic Organogenesis

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Abstract

Lately Revealed by Genome-wide association studies (GWAS) the association of TCF7L2 and Type 2 Diabetes (T2D) which implicates underlying mechanism of this Wingless (WNT) pathway effector gene in pancreatic ß-cell development. Also, further research linking TCF7L2 to T2D and impaired ß-cell mass accomplished by insulin secretory malfunction, shed light on the regulatory function of this particular canonical WNT pathway member. Thus, highlighting the fact that indeed Dishevelled (DEL) regulates as a scaffold protein in canonical and non-canonical WNT regulatory pathway components. Fairly is understood in the process of canonical and non-canonical WNT signaling, except that DEL acts through transmembrane domains of co-/receptors as Frizzled (FZ) and Low-density lipoprotein receptor-related protein 5 (LRP5). Well described in the context of regulatory mechanism is the canonical WNT signaling pathway, resulting in stabilization/activation of functional ß-catenin in line with accumulation in a multi-protein complex at the specifically located membrane surface. Contrary the absence of WNT signaling components determines the destabilization/degradation of ß-catenin. Thus, either supporting junctional complexes of neighboring cells for the formation of the epithelial cell sheet or by degradation initiate cell differentiation/segregation within the epithelial sheet. Also, the non-canonical WNT signaling pathway suggests to be part of the intracellular trafficking vesicular network and thereby regulate cytoskeletal control and polarization, respective migration of a specific subset of cells. Mainly, these processes are undertaken by non-canonical pathway divisions as the Planar Cell Polarity (PCP) and calcium (Ca^{2+}) pathway. We will focus in this review on common highlights of WNT pathway components in pancreatic organogenesis in the secondary transition as the different lineages of the pancreas segregate. Also, further dissecting the various WNT ligands and core components at this specific stage in the mesenchyme and epithelium will enable putative mechanism regarding tissue remodeling and tubulogenesis in line with lineage differentiation of the pancreatic gland.

Keywords: Pancreas; Endocrine; Exocrine; Islets of langerhans; WNT

Abbreviations

ARP 2/3: Actin Related Protein 2/3; CELSR: Cadherin EGF LAG Seven-Pass G-Type Receptor; EMT: Epithelial to Mesenchymal Transition; FRP: Frizzled Related Protein; FZ: Frizzled, GSIS: Glucose Stimulated Insulin Secretion; GWAS: Genome Wide Association Study; LRP5: Low Density Lipoprotein Receptor Related Protein 5; M: *Mus musculus*; mRNA: Messenger Ribo Nucleic Acid; PCPL: Planar Cell Polarity; SFRP: Secret Frizzled Related Protein; T2D: Type 2 Diabetes; DEL: Dishevelled; TCF7L2: Transcription Factor 7-Like 2; WASP N: WNT-Activating Small Molecule Potentiator; WNT: Wingless; XS: *Xenopus laevis*

Introduction

The WNT signaling pathway core components play an essential role in the formation of the pancreas. In the *Mus musculus* as mFRP1 and mFRP2 with homologs in human termed as hFRP1b and hFRP2 are capable of binding to WNT and reveal expression in the pancreatic epithelium, as well in respect to hFRP2 a diverse subset of organs like heart, muscle, and adipose tissue reflects protein expression. These results are implicating a potential role of the WNT pathway in the classical disease pattern of obesity and thereby of metabolic diseases as diabetes [1]. Lately published by Leimeister, sFRP2 is expressed in the embryonic organogenesis with up to 2 days in line with subsequent expression in the mesenchyme and a diverse subset of epithelial-derived organs. Also, sFRP1 and four expression correlates to sFRP2 but remains mutually exclusive suggesting a distinct role of the WNT pathway core components in the pancreatic organogenesis as the different lineages segregate [2]. However, sFRP4 as WNT antagonist implicates that it may not control glucose homeostasis and β-cell mass in mice [3]. Furthermore, model organism as *Xenopus laevis* XsFRP5 knockdown affects both, the canonical and non-canonical WNT pathway. Pancreatic hypoplasia in line with an enlargement of the stomach is observed for the XsFRP5 knockdown as well as the knockdown of Wnt2b. Contrary results are obtained in sFRP deficient mice as on the one hand metabolic phenotypes revealed a diverse phenotype in Glucose-stimulated Insulin secretion (GSIS) as these experimental approaches preliminary suggest a role of sFRP5 as a negative regulator of glucose metabolism [4]. An essential role in the specification of the ventral pancreas and the exocrine tissue of the pancreas will be determined more precise in on-going experiments [5]. Interestingly, Heller et al. recapitulated WNT expression within the adult pancreas in regard of the exocrine and endocrine tissue and could detect all 10 FZ receptors in the pancreatic epithelium. Whereas FZ1-7 specified by in situ hybridization localizes in the adult Islets of Langerhans, contrary FZ 1, 4-5 are detected in the exocrine gland compartment [1]. In the WNT pathway components, FRP is the antagonist to the diverse subfamily of WNT proteins as Wnt5a, which in loss of function studies by morpholinos revealed defects in

endocrine progenitors emerging the ductal cord-like structure in the secondary transition as the different lineages segregate. These results, suggesting a dosage-dependent effect in endocrine lineage commitment [6]. In addition, WNT 5a ligand FRP5 inhibition leads to improved glucose metabolism and pancreatic insulin-cell migration proven by loss-of-function studies in mice [7].

Essential for the maturation of the adult Islet of Langerhans suggests being WNT 2b, 3, 4, 5a, 7b, 10a and 14 as these mRNA are classified in purified Islets of Langerhans [1]. Lately published by Willmann et al., the pancreatic epithelium in the secondary transition contains WNT family members as WNT 1, 3a, 5a, 6, 10a, 10b [8]. These transcriptional expression data implicates that a specific subset of these WNT mRNAs is to be expressed lineage specific, either endocrine or exocrine. Also, Wnt7b appears to be essential for the outgrowth of both lineages, as loss-and gain of function studies, in particular, described either adverse effects of the entire outcome of the pancreas and failed tubulogenesis. Interestingly, the pancreatic mesenchyme remains competent to respond to Wnt7b ligands, leading to the result that cell differentiation might not occur in the surrounding tissue of the pancreatic region as early as the lineages segregate [9]. In addition, polymorphism in Wnt5b is already shown to be associated with the risk of T2D. Whereas Wnt9a impairs exocrine proliferation through a regulatory function on the WNT effector gene Tcf7l2 [9]. It is to note that canonical WNT -effector gene ß-catenin deficient mice results in a loss of the exocrine pancreatic compartment, contrary this may have no effect on the endocrine lineage [10,11]. Interestingly, the non-canonical Ca^{2+} pathway is directly connected to the canonical pathway via ß-catenin; both pathways are implicated in endocrine lineage formation [10]. On a cellular level, vesicular trafficking and thereby remodeling including lineage segregation suggests being specifically direct the endocrine lineage transition of the inherited ductal cells. This might hint that during remodeling, the specific localization of the protein complex on the apical surface membrane shifts to an intracellular receptive basal localization [12-14].

Taken this hypothesis of endocrine lineage segregation, the non-canonical WNT pathway in regards of PCP and Ca^{2+} will play a putative role along with the mechanism of epithelial-to-mesenchymal transition (EMT). Thus, cell-cell interactions as apico-basal polarity are important in the pancreatic organogenesis and in the secondary transition as the different lineages segregate. The core PCP proteins CELSR2 and 3 are expressed in the ductal cord in the secondary transition; loss-of-function studies revealed a decrease in the impact of differentiated endocrine cells in the precursor Islets of Langerhans [15].This is pointing to the general role of the PCP pathway in the process of lineage segregation. The factor β-catenin, together with α-catenin promotes cell-cell contacts in the pancreatic gland but appears to be downregulated in the endocrine precursor cells [8]. The mechanism of EMT is clearly described in this context as cells loose the established polarity complex in regard of apical-basal polarity and enter a mesenchymal state, likely described with the establishment of filipodia [16]. Thereby, in the nucleus, β-catenin activates transcription of WNT/β-catenin target genes as c-myc which in turn regulates a subset of WNT ligands [17]. Mainly, the organization of the actin cytoskeleton is depending on localization and protein-interactions of actin filament nucleating proteins and implicates transcriptionally regulated by the subset of the different protein-interactors. The N-WNT-activating small molecule potentiator (N-WASP), Actin-related Protein 2/3 (ARP2/3) complex are specifically oriented at junctional complexes, nevertheless, are redirected to cell leading edges in the remodeling of the polarity complexes to a mesenchymal state. In the protein family of WASP, WASP-1- enhances canonical WNT/β-catenin and thereby implicates to sequester a transition into the mesenchymal state [18]. Thus, N-WASP mediates an interaction between the ARPp2/3 complex and G-protein Cell Division Cycle 42 (CDC42) [19]. Kesavan et al. published the landmark study on CDC42/N-WASP, which lead to the result that endocrine lineage segregation is highly enhanced under the perspective of loss of the apical-basal polarity complex, contrary constantly active CDC42 inhibits cell delamination and differentiation [20,21]. These preliminary results pointing to a fine tuned spatio-temporal mechanism in the regulation of cellular trafficking and polarity establishment within lineage commitment of the inherited ductal cells to endocrine progenitors. Further insights into the player of this specific process and exocytotic function of proteins and transport within the Ca^{2+} pathway will finally lead to the in vitro derived β-cell and highlight current findings (Figure 1).

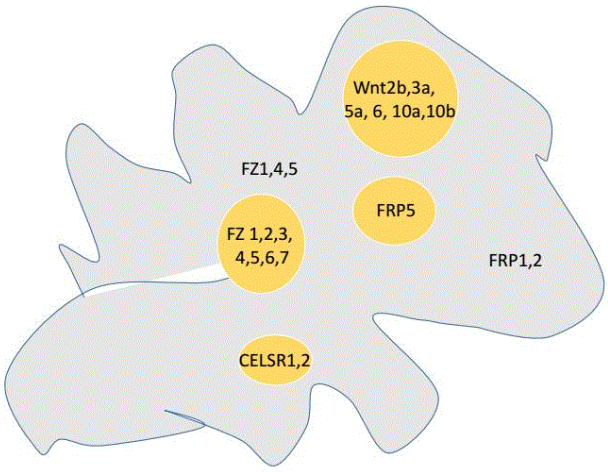

Figure 1: Pancreatic gland including the different WNT core pathway members a described above in the text, The FZ1, 4, 5 are outlined in the literature in the exocrine pancreas whereas FZ1.2, 3, 4, 5, 6, 7 and CELSR1, 2 in the adult Islets of Langerhans. FRP1 and 2 reflect by the literature exocrine expression, and FRP5 is described in the context of the Islets of Langerhans. WNT ligands expressed in the adult Islets of Langerhans are WNT 2b, 3a, 5a, 6, 10a, 10b which reflects endocrine mRNA expression in the pancreatic organogenesis during secondary transition.

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