BioMed Research Journal
BMRJ, 5(1): 311-315
www.scitcentral.com

ISSN: 2578-8892

Review Article: Open Access

Epithelial Remodeling for the Endocrine Lineage

Stefanie Julia Willmann*

*Independent Researcher, Feldlistrasse 21, CH – 9000 St. Gallen, Switzerland

Received June 22, 2020; Accepted July 09, 2020; Published September 10, 2020

ABSTRACT

The pancreatic research community deeply deciphers the evolving pancreatic gland during embryogenesis. The challenge uncovers factors previously not described, which will further accelerate the understanding of pancreatic organ formation and especially of pancreatic lineage allocation into the acinar, ductal, and endocrine lineage. Thereby, the focus lies in the endocrine lineage, as the Islets of Langerhans evolve of this particular lineage. The review aims to introduce lineage allocation factors in the pancreas and compartmentalizes these specific factors to particular lineages as well as present orchestrated pathways in a comprehensive way.

Keywords: Pancreas, Islet of Langerhans, ß-cell, Signaling pathway, Transcription factor

Abbreviations: Ptf1a: Pancreas-specific factor 1 a; E: Embryonic stage; Pdx1: Pancreatic duodenal homeobox 1; Sox9: SRY-box 9; Nkx6.1: NK6 homeobox 1; Nkx6.2: NK6 homeobox 2; Pax6: Paired box 6; Cpa1: Carboxypeptidase 1; Nr5a2: Nuclear receptor subfamily 5 group A member 2; Isl1: islet 1; TF: Transcription Factor; PP: Pancreatic Polypeptide; Ngn3: Neurogenin 3; TCF7L2: TCF4; Wnt: Wingless; Mib1: mindbomb1

INTRODUCTION

As diabetes is a significant disease according to the WHO health report, and both diabetes type I and II means a decline in ß-cells and impairment of Insulin uptake, research is focusing on these specific ß-cells. The ß-cells allocate in the pancreas, which is a compound gland consisting of a heterogeneous cell population. Whereas the acinar cells secrete enzymes for lipid catalyzation, which are transported through the ductal system, the islet of Langerhans consist of the functionally essential ß-cells. As the Islet of Langerhans comprises more than the ß-cells, focusing on signalling and transcriptional network within ß–cell establishment will bring research further insights into factors mainly for these specific cell types. Regarding the developmental stages, when the endocrine cells derive, which give rise to ß-cells might be the best attempt to get to know the different factors of pancreas organogenesis. Thus, the factor controlling differentiation, expansion, and maintenance will help to improve protocols for *in vitro* and *in vivo* mimicking endocrine lineage formation. As a prospective therapeutic strategy replacing ß-cells will be more realistic, primarily as improvement of protocols will facilitate fate converting of pancreatic progenitors into functional ß-cells.

RESULTS

Transcription factor hierarchy orchestrates pancreatic organogenesis

Hepatic factors as a pancreas-specific factor (Ptf1a) although give rise to liver and pancreas, suggesting intrinsic and extrinsic signals which specify the fate for either lineage [1]. At E9.5, the lineage for the pancreas will be determined by co-expression of Ptf1a and pancreatic duodenal homeobox 1 (Pdx1) [2]. Nevertheless, Pdx1 is regarded as the entry point of the pancreas initiation [3]. The transcriptional hierarchy at this early stage reveals co-expression in line with Ptf1a/ Pdx1 of transcription factors as SRY-box 9 (Sox9), NK6 homeobox 1 (Nkx6.1) and NK6 homeobox 2 (Nkx6.2) [4-6] implicating that the diversity of the transcription factors will determine the different lineages of the pancreas. This phase of pancreatic budding is named as first transition phase (E9.5-12.5), including the first wave of Glucagon-positive cells as a consequence of paired box 6 (Pax6) expression [7]. Nevertheless, these Glucagon-positive cells will be diminished at later stages of pancreatic development. More importantly, the first transition phase initiates the secondary transition phase in which the lineages allocate to a specific pattern commonly declared as tip/trunk domain. Zhou et al. investigated the transcriptional network of pancreas development, showing that at the beginning of the secondary transition, specific accumulation of transcription factors determine a tip/trunk domain within the pancreas.

Corresponding author: Stefanie Julia Willmann, Feldlistrasse 21, CH-9000 St. Gallen, Switzerland, Tel: 0041 762 888 413; E-mail: SJWillmann@gmx.de

Citation: Willman SJ. (2020). Epithelial Remodeling for the Endocrine Lineage. BioMed Res J, 5(1): 311-315.

Interestingly, at this point, the epithelium of the pancreas is still multipotent, by means that all lineages can derive out of single cells within the pancreatic epithelium. This is in line with knockdowns of acinar determined TF as Ptf1a, Carboxypeptidase 1 (Cpa1), nuclear receptor subfamily 5 group A member 2 (Nr5a2)which will lead to hypoplasia and/ or failure in pancreas organogenesis [8-10] and marks out the multipotency of the pancreatic epithelium in the early embryonic stages (E). Furthermore, TF islet1 (isl1) is expressed within the epithelium and surrounding mesenchyme, changing in the secondary transition, specifically to the endocrine lineage in the epithelial cord [11] **(Figure 1)**.

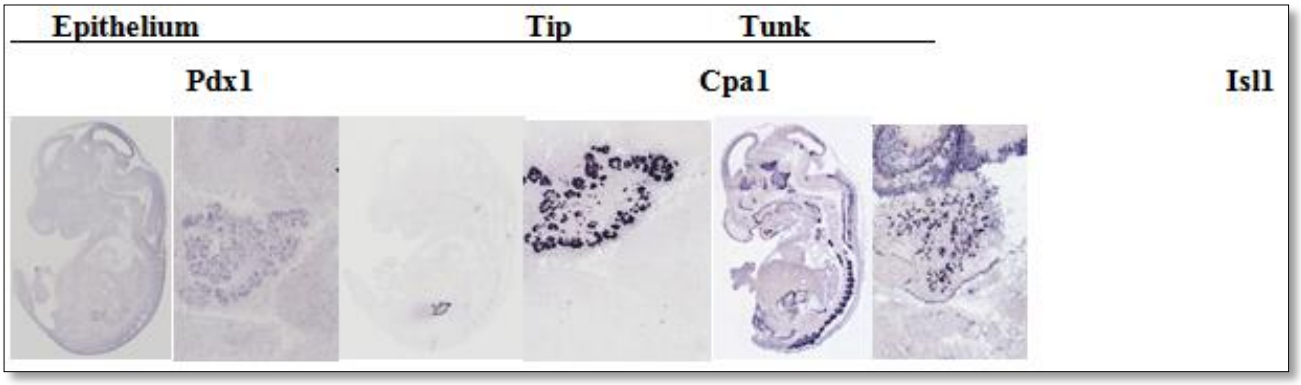

Figure 1. Genepaint*in silico in situ* patterns of Pdx1, Cpa1, and Isl1 at E14.5. Whole mount *in situ* and pancreas Zoom is indicating the mRNA expression of the selected genes. *Pdx1* represents the epithelium, whereas *Cpa1* illustrates the tip pattern and *Isl1* the typical trunk pattern. Mentioning that at E14.5, already lineage restriction is determined through tip/trunk pattern.

The epithelial cord represents the trunk domain, which is a model harbors the ductal progenitors and the endocrine progenitors. Whereas at the beginning of the secondary transition the tip domain is marked by Ptf1a/c-myc and Cpa1 and although Pdx1 expression, the trunk domain is characterized by the appearance of TF Sox9, Nkx6.1, Nkx6.2, and Mucin1 [12-15]. Implicating that within the trunk domain, the pool for the endocrine lineages resides as early and late endocrine progenitors are expressed in this specific region of the developing pancreas. Which factors trigger this process remains elusive as there plays, next to the TF, signaling cascades a role in the endocrine formation. The multipotency of the epithelium in the organogenesis of the pancreas might be a useful tool for research. Using these multipotent cells and applying different factors will bring further knowledge about signals and factors which determine the endocrine lineage.

DISCUSSION

Endocrine lineage formation remodelling epithelial cell organization

At the latest in the embpryonic stage, E13.5 multipotency of the epithelium will be disposed of, and cells are restricted to different lineages. As already mentioned above, exocrine specific factors play an essential role in pancreas formation, and here we will focus on the particular factors which drive the endocrine lineage. Described in **Figure 1**, the trunk pattern in the epithelium reflects an epithelial cord, which is represented by Sox9 expression. Within this cord-like structure location of the Ngn3-transient population represents the endocrine progenitors [16-18]. Mainly, lineage-tracing experiments implicated that Ngn3 is an essential helix-loop-helix transcription factor is necessary for the establishment of all endocrine cells as glucagon, insulin, somatostatin and pancreatic polypeptide (PP), which assemble into the islet of Langerhans earliest at E18.5 [16]. The latest attempts showed that Sox9 deficient mice show a severe reduction in endocrine progenitors marked by Ngn3, implicating that Sox9 acts upstream of the endocrine lineage [19].

Furthermore, Lynn and Seymour proposed a cell-autonomous role for Sox9 in Ngn3 induction, suggesting a negative feedback-loop for co-related expression of Sox9 and Ngn3 [19,13,20]. These results further determine the importance of Ngn3 as a final TF for the endocrine progenitor. Nevertheless, upstream TF as Sox9 and Pdx1, specifically in the duct regulates expression of endocrine precursor Ngn3. The signal cascade for the regulation of Ngn3 is still controversial, as there might be extrinsic and intrinsic signals affecting the proliferation of the endocrine lineage. Interestingly, signs from mesenchyme might not play a role in the endocrine formation. As the proximity of epithelium to the mesenchyme accelerates the exocrine fate, whereas missing contact of the epithelium to the mesenchyme leads to the endocrine lineage [21].

Pictet and Rutter already postulated in the 70's that these endocrine progenitors delaminate out of the epithelial sheet and cluster to precursor islet. This Delamination process accompanies alteration in contact with other cells. In the neuron crest system, delamination is well studied and

described as transcriptionally controlled by the Snail family of transcription factors [22].

In the process, the Snail family Zinc finger TF is involved and members of the Rho subfamily of GT Pases. Recently published by Rukstalis, Snail2/Slug is co-expressed with endocrine progenitor Ngn3 and still maintained in a subset of differentiated endocrine cells [23]. These results are suggesting at Epithelial-to mesenchymal-transition (EMT) of endocrine progenitors as they leave the ductal cord. In development, cancer cells and metastases EMT is well studied. In EMT, the epithelial cells remodel their polarity as they change from epithelial state to mesenchyme. The characteristic of epithelium is described as apical-basal polarity, including a polarized actin cytoskeleton. As cells vary to a mesenchymal state, polarity changes to front-rear and cell junction remodel as the cell moves out of the epithelial sheet. The Main TF of EMT are Snail2, Zeb, and Twist. Another hallmark of EMT is described as the switch of E-cadherin to N-cadherin. Loosening the epithelial character includes the down regulation of E-cadherin. Grapin-Botton already published that Ngn3 overexpression leads to endocrine differentiation [24].

Further work by Gouzi showed that E-cadherin is transcriptionally down regulated in endocrine precursors with Snail2 under the control of Ngn3. These results are suggesting that endocrine progenitors undergo delamination with at least partial EMT. Which mechanism in detail is focused on diabetes research, as it might help to trigger the endocrine commitment.
More interesting are the switches within the cells. What are the molecular cues which govern this reprogramming of epithelial, respective endodermal cells into endocrine cells? The latest paper by Kesavan suggests remodeling of Actin filament and centrosome separation in the formation of the early progenitors, especially in mitosis [25].

Signaling pathways in endocrine lineage formation

At the beginning of the development of the pancreas,Wnt-signaling plays an essential role. The canonical Wnt-/ß-Catenin pathway facilitates PTF1a expression and, thereby, pancreas formation [26]. At later stages non-canonical Wnt ligands as Wnt7b, Wnt5a and Wnt5b [27-29] are expressed within the pancreatic epithelium, suggesting activation of pathways which control cell fate and polarity during pancreas organogenesis [30] lately published by Rodriguez-Seguel Wnt5a facilitates Pdx1 expression. In zebra fish null-mutants of Wnt5a, the islets failed to organize correctly, implicating for Wnt5a a role in endocrine formation [28]. More interestingly, the LEF/TCF family member TCF7L2 (also named TCF4) as a member of the canonical Wntpathway is associated with T2D [31]. As further studies by Boj showed no effect on the endocrine development and outcome of the ß-cells, there remain questions of the Wnt-/ß-Catenin pathway in endocrine formation. By knowledge, β-catenin also associates with cadherin proteins at the cell surface, potentially stabilizing cell-cell interactions [32]. With this conclusion, there might be a role in the endocrine formation, at least in adult ß-cells, when cadherins affect the reorganization of cortical actin [33]. Other pathways that are involved in endocrine formation are Notch signaling, as inactivation of the Notch ligand Mindbomb 1 (Mib1) effects an decrease of multipotent progenitors and thereby a decrease in ductal and endocrine progenitors [34]. By other means indicating a role of Notch ligands in endocrine commitment [35]. These results are in line as published that Notch plays a role in duct formation [36] and thereby affecting the endocrine progenitors.

CONCLUSION

Next to the essential transcription factors for pancreatic organ development, signaling pathways such as the Wnt- and Notch pathways suggest to determine specific lineages within the pancreatic gland. Within the cell, a lineage allocation of a single cell might lead to a re-organization of filamentous structures, thereby affecting the localization of the different organelles. Until now, it is poorly understood how these complex interactions might lead to a specific lineage of *f.e.* endocrine progenitors [37]. The review summarizes previous literature of essential factors and signaling pathway in pancreatic organ development and thus will improve the understanding and further research attempts in this field.

REFERENCES

1. Jin K, Xiang M (2019) Transcription factor Ptf1a in development, diseases and reprogramming. Cell Mol Life Sci 76: 921-940.
2. Afelik S, Chen Y, Pieler T (2006) Combined ectopic expression of Pdx1 and Ptf1a/p48 results in the stable conversion of posterior endoderm into endocrine and exocrine pancreatic tissue. Genes Dev 20: 1441-1446.
3. Wang H, Maechler P, Laser BR, Hagenfeldt KA, Ishihara H, et al. (2001) Pdx1 level defines pancreatic gene expression pattern and cell lineage differentiation. J Biol Chem 276: 25279-25286.
4. McDonald E, Li J, Krishnamurthy M, Fellows GF, Goodyer CG, et al. (2012) SOX9 regulates endocrine cell differentiation during human fetal pancreas development. Int J Biochem Cell Biol 44: 72-83.
5. Donelanet W, Koya V, Li SW, Yang LJ (2010) Distinct regulation of hepatic nuclear factor 1alpha by NKX6.1 in pancreatic beta cells. J Biol Chem 285: 12181-12189.
6. Bonfanti P, Nobecourt E, Oshima M, Curiel OA, Laurysens V, et al. (2015) Ex vivo expansion and differentiation of human and mouse fetal pancreatic progenitors are modulated by epidermal growth factor. Stem Cells Dev 24: 1766-1778.
7. Sharon N, Vanderhooft J, Straubhaar J, Mueller J, Chawla R, et al. (2019) Wnt Signaling separates the

progenitor and endocrine compartments during pancreas development. Cell Rep 27: 2281-2291.

8. Kawaguchi Y, Cooper B, Gannon M, Ray M, MacDonald RJ, et al. (2002) The role of the transcriptional regulator Ptf1a in converting intestinal to pancreatic progenitors. Nat Genet 32: 128-134.
9. Krapp A, Knöfler M, Frutiger S, Hughes GJ, Hagenbüchle O, et al. (1996) The p48 DNA-binding subunit of transcription factor PTF1 is a new exocrine pancreas-specific basic helix-loop-helix protein. EMBO J 15: 4317-4329.
10. Liu T, Wang CY, Yu F, Gou SM, Wu HS, et al. (2007) In vitro pancreas duodenal homeobox-1 enhances the differentiation of pancreatic ductal epithelial cells into insulin-producing cells. World J Gastroenterol 13: 5232-5237.
11. Du A, Hunter CH, Murray J, Noble D, Cai CL, et al. (2009) Islet-1 is required for the maturation, proliferation and survival of the endocrine pancreas. Diabetes 58: 2059-2069.
12. Seymour PA, Freude KK, Tran MN, Mayes EE, Jensen J, et al. (2007) SOX9 is required for maintenance of the pancreatic progenitor cell pool. Proc Natl Acad Sci USA 104: 1865-1870.
13. Seymour PA, Freude KK, Dubois CL, Shih HP, Patel NA, et al. (2008) A dosage-dependent requirement for Sox9 in pancreatic endocrine cell formation. Dev Biol 323: 19-30.
14. Weir SB, Taneja M, Weir GC, Tatarkiewicz K, Song KH, et al. (2000) In vitro cultivation of human islets from expanded ductal tissue. Proc Natl Acad Sci USA 97: 7999-8004.
15. Schaffer AE, Taylor BL, Benthuysen JR, Liu J, Thorel F, et al. (2013) Nkx6.1 controls a gene regulatory network required for establishing and maintaining pancreatic Beta cell identity. PLoS Genet 9: e1003274.
16. Seymour PA, Shih HP, Patel NA, Freude KK, Xie R, et al. (2012) A Sox9/Fgf feed-forward loop maintains pancreatic organ identity. Development 139: 3363-3372.
17. Lynn FC, Smith SB, Wilson ME, Yang KY, Nekrep N, et al. (2007) Sox9 coordinates a transcriptional network in pancreatic progenitor cells. Proc Natl Acad Sci USA 104: 10500-10505.
18. Li Z, Manna P, Kobayashi H, Spilde T, Bhatia A, et al. (2004) Multifaceted pancreatic mesenchymal control of epithelial lineage selection. Dev Biol 269: 252-263.
19. Barrio MGD, Nieto MA (2002) Overexpression of snail family members highlights their ability to promote chick neural crest formation. Development 129: 1583-1593.
20. Rukstalis JM, Habener JF (2007) Snail2, a mediator of epithelial-mesenchymal transitions, expressed in progenitor cells of the developing endocrine pancreas. Gene Expr Patterns 7: 471-479.
21. Gouzi M, Kim YH, Katsumoto K, Johansson K, Grapin-Botton A (2011) Neurogenin3 initiates stepwise delamination of differentiating endocrine cells during pancreas development. Dev Dyn 240: 589-604.
22. Gradwohl G, Dierich A, LeMeur M, Guillemot F (2000) Neurogenin3 is required for the development of the four endocrine cell lineages of the pancreas. Proc Natl Acad Sci USA 97: 1607-1611.
23. Gu G, Dubauskaite J, Melton DA (2002) Direct evidence for the pancreatic lineage: NGN3+ cells are islet progenitors and are distinct from duct progenitors. Development 129: 2447-2457.
24. Villasenor A, Chong DC, Cleaver O (2008) Biphasic Ngn3 expression in the developing pancreas. Dev Dyn 237: 3270-3279.
25. Kesavan G, Sand FW, Greiner TU, Johansson JK, Kobberup S, et al. (2009) Cdc42-mediated tubulogenesis controls cell specification. Cell 139: 791-801.
26. Segue ER, Mah N, Naumann H, Pongrac IM, Esteban NC, et al. (2013) Mutually exclusive signaling signatures define the hepatic and pancreatic progenitor cell lineage divergence. Genes Dev 27: 1932-1946.
27. Afelik S, Rovira M (2017) Pancreatic β-cell regeneration: advances in understanding the genes and signaling pathways involved. Genome Med 9: 42.
28. Kim HJ, Schleiffarth JR, Jessurun J, Sumanas S, Petryk A, et al. (2005) Wnt5 signaling in vertebrate pancreas development. BMC Biol 3: 23.
29. Kanazawa A, Tsukada S, Sekine A, Tsunoda T, TakahashiA, et al. (2004) Association of the gene encoding wingless-type mammary tumor virus integration-site family member 5B (WNT5B) with type 2 diabetes. Am J Hum Genet 75: 832-843.
30. Moon RT, Campbell RM, Christian JL, McGrew LL, Shih J, et al. (1993) Xwnt-5A: A maternal Wnt that affects morphogenetic movements after overexpression in embryos of Xenopuslaevis. Development 119: 97-111.
31. Meigs JB, Manning AK, Fox CS, Florez JC, Li C, et al. (2007) Genome-wide association with diabetes-related traits in the Framingham Heart Study. BMC Med Genet Suppl 1 (Suppl 1): S16.

32. Nelson WJ, Nusse R (2004) Convergence of Wnt, beta-catenin, and cadherin pathways. Science 303: 1483-1487.

33. Mikami S, Katsube KI, Oya M, Ishida M, Mizuno R, et al. (2011) Expression of Snail and Slug in renal cell carcinoma: E-cadherin repressor Snail is associated with cancer invasion and prognosis. Lab Invest 91: 1443-1458.

34. Horn S, Kobberup S, Jørgensen MC, Kalisz M, Klein T, et al. (2012) Mind bomb 1 is required for pancreatic β-cell formation. Proc Natl Acad Sci USA 109: 7356-7361.

35. Murtaugh LC, Stanger BZ, Kwan KM, Melton DA (2003) Notch signaling controls multiple steps of pancreatic differentiation. Proc Natl Acad Sci USA 100: 14920-14925.

36. Greenwood AL, Li S, Jones K, Melton DA (2007) Notch signaling reveals developmental plasticity of Pax4(+) pancreatic endocrine progenitors and shunts them to a duct fate. Mech Dev 124: 97-107.

37. Zhang X, Rowan S, Yue Y, Heaney S, Pan Y, et al. (2006) Pax6 is regulated by Meis and Pbxhomeoproteins during pancreatic development. Dev Biol 300: 748-757.