Acinar-to-Ductal Metaplasia and Transcription Factors Involved

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Pancreatic acinar-to-ductal metaplasia (ADM) is a cellular process in which the differentiated pancreatic acinar cells transform into duct-like cells. This process can occur as a result of cellular injury or inflammation in the pancreas. While ADM is a reversible process allowing pancreatic acinar regeneration, persistent inflammation or injury can lead to the development of pancreatic intraepithelial neoplasia (PanIN), which is a common precancerous lesion that precedes pancreatic ductal adenocarcinoma (PDAC).

Keywords: acinar-to-ductal metaplasia (ADM) ; pancreatic intraepithelial neoplasia (PanIN) ; pancreatic ductal adenocarcinoma (PDAC)

1. Introduction

The pancreas composed of endocrine and exocrine components is an important organ for the regulation of food digestion and blood glucose balance. In human or mouse pancreas, exocrine cells account for more than 90% of the organ. Acinar cells, the main component of exocrine tissue, are polarized epithelial cells that are responsible for the production of digestive enzymes, including amylase, protease, lipase and trypsin. Terminally differentiated, secretory acinar cells are normally post-mitotic and store zymogen granules filled with these enzymes that are secreted by exocytosis. Digestive enzymes are transported in a network of ducts that discharge pancreatic juices into the duodenum. Ductal cells are responsible for producing and secreting bicarbonate ions that neutralize the acidic contents of the stomach as they enter the small intestine.

Pancreatic tissue homeostasis is a regular process of cellular renewal. The homeostatic balance in pancreas is critical for its normal functions and is disturbed during tissue injury, inflammation and tumorigenesis. Acinar-to-ductal metaplasia (ADM) is a process that corresponds to pancreatic acinar cells dedifferentiating into ductal-like cells. During ADM, the acinar cells lose their characteristic shape and function and adopt a ductal-like cell morphology. The process involves changes in the expression of genes that control cell differentiation, proliferation, and survival. It shows the ability of acinar cells to adapt to the genetic and environmental pressure. However, the exocrine cellular plasticity within the pancreas is exploited in tumorigenesis, with metaplastic, dedifferentiation and trans-differentiation processes leading to the development of pancreatic intraepithelial neoplasia (PanIN).

Pancreatic Ductal Adenocarcinoma (PDAC) is the fourth leading cause of cancer-related deaths worldwide. The projection of incidence in 2030 indicates that PDAC will become the second most prevalent cause of cancer-related death [1]. As PDAC is often diagnosed at an advanced stage, the 5-year survival rate is very low, less than 10%. Pancreatic intraepithelial neoplasia (PanIN) refers to the most frequent PDAC precursor lesions. These microscopic noninvasive epithelial preneoplastic lesions that are not detectable in humans by radiological examination exhibit varying mucin levels and degrees of cytologic atypia [2]. With oncogenic genetic insults and/or sustained environmental stress, ADM can lead to PanIN, preceding PDAC.

2. Acinar-to-Ductal Metaplasia (ADM) and Transcription Factors Involved

Metaplasia is a reversible change in which one differentiated cell type is replaced by another cell type. This process can occur in response to various stimuli, such as chronic inflammation or cellular injury. The metaplasia of pancreatic acinar cells manifests their ability to adapt to the genetic and environmental pressure they encounter. Many studies have shown the crucial role of acinar cells in post-injury pancreatic regeneration [3][4][5]. During this process, acinar cells undergo ADM —which is the traditionally used terminology—by losing their mature and functional characteristics as well as undergoing a morphological and transcriptional transformation into ductal-like cells with embryonic progenitor properties [6][7][8]. Like pancreatic progenitor cells, ADM cells are proliferative, whereas mature acinar and ductal cells are largely mitotically

quiescent. ADM cannot be considered as a trans-differentiation event corresponding to direct conversion from acinar to ductal cells, as acinar cells dedifferentiate into an embryonic progenitor-like phenotype and differentiate into duct-like cells. The terminology of metaplasia, trans-differentiation and dedifferentiation is a matter of debate [9]. Recently, the term paligenosis, described as the biological process of converting a mature cell into a regenerative cell, was also proposed [10]. In the context of ADM, acinar cell reprogramming can englobe the different terminologies. ADM appears to be a protective mechanism that temporarily reduces extensive tissue damage caused by excessive pancreatic secretion of digestive enzymes. The damaged tissue may return to normal if the stimulus causing metaplasia is removed. Metaplasia, however, can progress to dysplasia and tumors if the stimuli that promote it persist.

The process is evolutionarily conserved as it happens in rodents (references below) and humans [11][12][13][14][15]. ADM was demonstrated with the use of genetically engineered mouse models (GEMMs) (references below) and in vitro in 3D cell culture with mouse and human primary acinar cells [16].

Morphologically, zymogene granules are gradually lost by acinar cells, which show a reduced apical cytoplasm while the lumen of the acini increases. Acinar cells lose polarity and acquire a cuboidal–columnar morphology resembling ductal precursors of the embryonic pancreas. During this process, ADM structures composed of both acinar and duct-like cells can be observed. In the later stages, ADM structures are composed only of duct-like cells, making them difficult to distinguish from pancreatic branched ducts.

The expression of acinar-specific transcription factors including Ptf1a, Mist1 and Nr5a2 is reduced, as well as the expression of digestive enzymes such as carboxypeptidase and amylase, leading to a gradual loss of digestive enzyme synthesis and secretory functions. During pancreas development, Ptf1a is required for the maintenance of multipotent progenitor cells (MPC) [17][18]. After E12.5, Ptf1a expression is restricted to the tip of the pancreatic epithelium adopting an acinar fate, while the cells in the trunk become restricted to a ductal or endocrine fate [19]. Ptf1a is required for maintenance of acinar cell identity by forming a complex network regulating acinar cell-specific digestive enzyme genes [6][20][21][22]. Loss of Ptf1a in acinar cells is sufficient to induce ADM and potentiate inflammation [23][24]. Mist1, restricted to acinar cells throughout development and in adult tissue [25], is a key regulator of acinar cell function, proliferation and identity maintenance [25][26]. Mist1 plays a protective role in ADM. Inhibition of Mist1 aggravated ADM [27][28][29], whereas forced expression of Mist1 significantly attenuated ADM [30]. Nr5a2, a member of the nuclear receptor family of ligand-activated transcription factors, maintains the secretory functions of acinar cells and is a key regulator of acinar cell plasticity. Loss of Nr5a2 accelerates the ADM process, and it was shown that Nr5a2 is required for maintenance of acinar identity and re-establishment of acinar fate during regeneration [31].

Co-expression of acinar markers and duct markers is used to detect ADM. The co-expression of various digestive enzymes is not completely lost in acinar cells during ADM and there is a concomitant upregulated expression of the duct markers including Sox9 [32], Hnf1b [33][34], Hnf6 [35], Pdx1 [36], CA19–9 [37], CAII [38], CD133 [39], and osteopontin [40].

The transcription factors Hnf1b, Hnf6, Pdx1 and Sox9 are known to play critical roles in the development and differentiation of pancreatic cells [41][42]. Hnf1b is a key member of the transcription factor network implicated in pancreatic MPCs' control. *Hnf1b* deficiency in embryos leads to pancreas agenesis, showing that Hnf1b is required for pancreas morphogenesis and regional specification of the gut [43]. The sequential activation of Hnf1b, Hnf6 and Pdx1 controls the differentiation of endodermal cells into MPCs [44]. Hnf1b was shown to regulate MPC proliferation, survival and differentiation [45] and was found upregulated in ADM [11][15][22][46][47]. The transcription factor Pdx1 is essential for the specification and differentiation of MPC into endocrine and exocrine cell types. After pancreatic morphogenesis, Pdx1 is required for maintaining the identity and function of mature beta cells. Pdx1 was shown to be up-regulated in human and murine ADM, and persistent expression of Pdx1 in the pancreas causes ADM through Stat3 activation [36]. Sox9 is expressed in pancreatic MPC at E9.5 and is required for proliferation and survival of MPCs [48]. Hnf6 is also expressed in MPCs [49]. In normal adult pancreas, Sox9 and Hnf6 expression is restricted to the duct lineage. *Sox9* and *Hnf6* are up-regulated in human and mouse models of ADM and their overexpression in acinar cells leads to ADM. They are required for repression of acinar genes, for ADM-associated changes in cell polarity and for activation of ductal genes in acinar cells [35]. In order to study to what extent dedifferentiated acini differ from native duct cells and which genes are uniquely regulating acinar cell dedifferentiation, lineage tracing experiments and RNA sequencing were performed with human pancreatic exocrine acinar and duct cells. MECOM, regulated by Sox9, was identified as a transcription factor unique to dedifferentiated acinar cells, critical to maintain cell adhesion and to suppress acinar cell death by permitting cellular dedifferentiation [14].

If the stimuli causing ADM is removed, the acinar tissue is regenerated, and these duct-like progenitor cells formed by ADM proliferate and redifferentiate into acinar cells to replenish the damaged organ.

References

1. Rahib, L.; Smith, B.D.; Aizenberg, R.; Rosenzweig, A.B.; Fleshman, J.M.; Matrisian, L.M. Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States. Cancer Res. 2014, 74, 2913–2921.
2. Matsuda, Y.; Furukawa, T.; Yachida, S.; Nishimura, M.; Seki, A.; Nonaka, K.; Aida, J.; Takubo, K.; Ishiwata, T.; Kimura, W.; et al. The Prevalence and Clinicopathological Characteristics of High-Grade Pancreatic Intraepithelial Neoplasia: Autopsy Study Evaluating the Entire Pancreatic Parenchyma. Pancreas 2017, 46, 658–664.
3. Puri, S.; Folias, A.E.; Hebrok, M. Plasticity and Dedifferentiation within the Pancreas: Development, Homeostasis, and Disease. Cell Stem. Cell 2015, 16, 18–31.
4. Stanger, B.Z.; Hebrok, M. Control of Cell Identity in Pancreas Development and Regeneration. Gastroenterology 2013, 144, 1170–1179.
5. Mills, J.C.; Sansom, O.J. Reserve Stem Cells: Differentiated Cells Reprogram to Fuel Repair, Metaplasia, and Neoplasia in the Adult Gastrointestinal Tract. Sci. Signal. 2015, 8, re8.
6. Pan, F.C.; Bankaitis, E.D.; Boyer, D.; Xu, X.; Van de Casteele, M.; Magnuson, M.A.; Heimberg, H.; Wright, C.V.E. Spatiotemporal Patterns of Multipotentiality in Ptf1a-Expressing Cells during Pancreas Organogenesis and Injury-Induced Facultative Restoration. Development 2013, 140, 751–764.
7. Murtaugh, L.C.; Keefe, M.D. Regeneration and Repair of the Exocrine Pancreas. Annu. Rev. Physiol. 2015, 77, 229–249.
8. Jensen, J.N.; Cameron, E.; Garay, M.V.R.; Starkey, T.W.; Gianani, R.; Jensen, J. Recapitulation of Elements of Embryonic Development in Adult Mouse Pancreatic Regeneration. Gastroenterology 2005, 128, 728–741.
9. Mills, J.C.; Stanger, B.Z.; Sander, M. Nomenclature for Cellular Plasticity: Are the Terms as Plastic as the Cells Themselves? EMBO J. 2019, 38, e103148.
10. Willet, S.G.; Lewis, M.A.; Miao, Z.-F.; Liu, D.; Radyk, M.D.; Cunningham, R.L.; Burclaff, J.; Sibbel, G.; Lo, H.-Y.G.; Blanc, V.; et al. Regenerative Proliferation of Differentiated Cells by MTORC1-Dependent Paligenosis. EMBO J. 2018, 37, e98311.
11. Houbracken, I.; de Waele, E.; Lardon, J.; Ling, Z.; Heimberg, H.; Rooman, I.; Bouwens, L. Lineage Tracing Evidence for Transdifferentiation of Acinar to Duct Cells and Plasticity of Human Pancreas. Gastroenterology 2011, 141, 731–741.e4.
12. Baldan, J.; Houbracken, I.; Rooman, I.; Bouwens, L. Adult Human Pancreatic Acinar Cells Dedifferentiate into an Embryonic Progenitor-like State in 3D Suspension Culture. Sci. Rep. 2019, 9, 4040.
13. Liu, J.; Akanuma, N.; Liu, C.; Naji, A.; Halff, G.A.; Washburn, W.K.; Sun, L.; Wang, P. TGF-B1 Promotes Acinar to Ductal Metaplasia of Human Pancreatic Acinar Cells. Sci. Rep. 2016, 6, 30904.
14. Backx, E.; Wauters, E.; Baldan, J.; Van Bulck, M.; Michiels, E.; Heremans, Y.; De Paep, D.L.; Kurokawa, M.; Goyama, S.; Bouwens, L.; et al. MECOM Permits Pancreatic Acinar Cell Dedifferentiation Avoiding Cell Death under Stress Conditions. Cell Death Differ. 2021, 28, 2601–2615.
15. Jiang, J.; Hakimjavadi, H.; Bray, J.K.; Perkins, C.; Gosling, A.; da Silva, L.; Bulut, G.; Ali, J.; Setiawan, V.W.; Campbell-Thompson, M.; et al. Transcriptional Profile of Human Pancreatic Acinar Ductal Metaplasia. Gastro. Hep. Adv. 2023, 2, 532–543.
16. Paoli, C.; Carrer, A. Organotypic Culture of Acinar Cells for the Study of Pancreatic Cancer Initiation. Cancers 2020, 12, 2606.
17. Kawaguchi, Y.; Cooper, B.; Gannon, M.; Ray, M.; MacDonald, R.J.; Wright, C.V.E. The Role of the Transcriptional Regulator Ptf1a in Converting Intestinal to Pancreatic Progenitors. Nat. Genet. 2002, 32, 128–134.
18. Masui, T.; Long, Q.; Beres, T.M.; Magnuson, M.A.; MacDonald, R.J. Early Pancreatic Development Requires the Vertebrate Suppressor of Hairless (RBPJ) in the PTF1 BHLH Complex. Genes Dev. 2007, 21, 2629–2643.
19. Schaffer, A.E.; Freude, K.K.; Nelson, S.B.; Sander, M. Nkx6 Transcription Factors and Ptf1a Function as Antagonistic Lineage Determinants in Multipotent Pancreatic Progenitors. Dev. Cell 2010, 18, 1022–1029.
20. Rose, S.D.; Swift, G.H.; Peyton, M.J.; Hammer, R.E.; MacDonald, R.J. The Role of PTF1-P48 in Pancreatic Acinar Gene Expression. J. Biol. Chem. 2001, 276, 44018–44026.
21. Rodolosse, A.; Chalaux, E.; Adell, T.; Hagège, H.; Skoudy, A.; Real, F.X. PTF1alpha/P48 Transcription Factor Couples Proliferation and Differentiation in the Exocrine Pancreas . Gastroenterology 2004, 127, 937–949.

22. Jiang, M.; Azevedo-Pouly, A.C.; Deering, T.G.; Hoang, C.Q.; DiRenzo, D.; Hess, D.A.; Konieczny, S.F.; Swift, G.H.; MacDonald, R.J. MIST1 and PTF1 Collaborate in Feed-Forward Regulatory Loops That Maintain the Pancreatic Acinar Phenotype in Adult Mice. Mol. Cell Biol. 2016, 36, 2945–2955.

23. Hoang, C.Q.; Hale, M.A.; Azevedo-Pouly, A.C.; Elsässer, H.P.; Deering, T.G.; Willet, S.G.; Pan, F.C.; Magnuson, M.A.; Wright, C.V.E.; Swift, G.H.; et al. Transcriptional Maintenance of Pancreatic Acinar Identity, Differentiation, and Homeostasis by PTF1A. Mol. Cell Biol. 2016, 36, 3033–3047.

24. Krah, N.M.; De La O, J.-P.; Swift, G.H.; Hoang, C.Q.; Willet, S.G.; Chen Pan, F.; Cash, G.M.; Bronner, M.P.; Wright, C.V.; MacDonald, R.J.; et al. The Acinar Differentiation Determinant PTF1A Inhibits Initiation of Pancreatic Ductal Adenocarcinoma. Elife 2015, 4, e07125.

25. Pin, C.L.; Rukstalis, J.M.; Johnson, C.; Konieczny, S.F. The BHLH Transcription Factor Mist1 Is Required to Maintain Exocrine Pancreas Cell Organization and Acinar Cell Identity. J. Cell Biol. 2001, 155, 519–530.

26. Direnzo, D.; Hess, D.A.; Damsz, B.; Hallett, J.E.; Marshall, B.; Goswami, C.; Liu, Y.; Deering, T.; Macdonald, R.J.; Konieczny, S.F. Induced Mist1 Expression Promotes Remodeling of Mouse Pancreatic Acinar Cells. Gastroenterology 2012, 143, 469–480.

27. Zhu, L.; Tran, T.; Rukstalis, J.M.; Sun, P.; Damsz, B.; Konieczny, S.F. Inhibition of Mist1 Homodimer Formation Induces Pancreatic Acinar-to-Ductal Metaplasia. Mol. Cell Biol. 2004, 24, 2673–2681.

28. Kowalik, A.S.; Johnson, C.L.; Chadi, S.A.; Weston, J.Y.; Fazio, E.N.; Pin, C.L. Mice Lacking the Transcription Factor Mist1 Exhibit an Altered Stress Response and Increased Sensitivity to Caerulein-Induced Pancreatitis. Am. J. Physiol. Gastrointest. Liver Physiol. 2007, 292, G1123–G1132.

29. Shi, G.; Zhu, L.; Sun, Y.; Bettencourt, R.; Damsz, B.; Hruban, R.H.; Konieczny, S.F. Loss of the Acinar-Restricted Transcription Factor Mist1 Accelerates Kras-Induced Pancreatic Intraepithelial Neoplasia. Gastroenterology 2009, 136, 1368–1378.

30. Shi, G.; DiRenzo, D.; Qu, C.; Barney, D.; Miley, D.; Konieczny, S.F. Maintenance of Acinar Cell Organization Is Critical to Preventing Kras-Induced Acinar-Ductal Metaplasia. Oncogene 2013, 32, 1950–1958.

31. von Figura, G.; Morris, J.P.; Wright, C.V.E.; Hebrok, M. Nr5a2 Maintains Acinar Cell Differentiation and Constrains Oncogenic Kras-Mediated Pancreatic Neoplastic Initiation. Gut 2014, 63, 656–664.

32. Kopp, J.L.; Dubois, C.L.; Schaffer, A.E.; Hao, E.; Shih, H.P.; Seymour, P.A.; Ma, J.; Sander, M. Sox9+ Ductal Cells Are Multipotent Progenitors throughout Development but Do Not Produce New Endocrine Cells in the Normal or Injured Adult Pancreas. Development 2011, 138, 653–665.

33. Quilichini, E.; Fabre, M.; Dirami, T.; Stedman, A.; De Vas, M.; Ozguc, O.; Pasek, R.C.; Cereghini, S.; Morillon, L.; Guerra, C.; et al. Pancreatic Ductal Deletion of Hnf1b Disrupts Exocrine Homeostasis, Leads to Pancreatitis, and Facilitates Tumorigenesis. Cell Mol. Gastroenterol. Hepatol. 2019, 8, 487–511.

34. Roy, N.; Hebrok, M. Regulation of Cellular Identity in Cancer. Dev. Cell 2015, 35, 674–684.

35. Prévot, P.-P.; Simion, A.; Grimont, A.; Colletti, M.; Khalaileh, A.; Van den Steen, G.; Sempoux, C.; Xu, X.; Roelants, V.; Hald, J.; et al. Role of the Ductal Transcription Factors HNF6 and Sox9 in Pancreatic Acinar-to-Ductal Metaplasia. Gut 2012, 61, 1723–1732.

36. Miyatsuka, T.; Kaneto, H.; Shiraiwa, T.; Matsuoka, T.; Yamamoto, K.; Kato, K.; Nakamura, Y.; Akira, S.; Takeda, K.; Kajimoto, Y.; et al. Persistent Expression of PDX-1 in the Pancreas Causes Acinar-to-Ductal Metaplasia through Stat3 Activation. Genes Dev. 2006, 20, 1435–1440.

37. Gmyr, V.; Belaich, S.; Muharram, G.; Lukowiak, B.; Vandewalle, B.; Pattou, F.; Kerr-Conte, J. Rapid Purification of Human Ductal Cells from Human Pancreatic Fractions with Surface Antibody CA19-9. Biochem. Biophys. Res. Commun. 2004, 320, 27–33.

38. Inada, A.; Nienaber, C.; Fonseca, S.; Bonner-Weir, S. Timing and Expression Pattern of Carbonic Anhydrase II in Pancreas. Dev. Dyn. 2006, 235, 1571–1577.

39. Zhang, F.; Ma, D.; Liu, T.; Liu, Y.H.; Guo, J.; Song, J.; Wu, Q.; Pan, Y.; Zhang, Y.; Guo, C.; et al. Expansion and Maintenance of CD133-Expressing Pancreatic Ductal Epithelial Cells by Inhibition of TGF-β Signaling. Stem. Cells Dev. 2019, 28, 1236–1252.

40. Kilic, G.; Wang, J.; Sosa-Pineda, B. Osteopontin Is a Novel Marker of Pancreatic Ductal Tissues and of Undifferentiated Pancreatic Precursors in Mice. Dev. Dyn. 2006, 235, 1659–1667.

41. Pan, F.C.; Wright, C. Pancreas Organogenesis: From Bud to Plexus to Gland. Dev. Dyn. 2011, 240, 530–565.

42. Shih, H.P.; Wang, A.; Sander, M. Pancreas Organogenesis: From Lineage Determination to Morphogenesis. Annu. Rev. Cell Dev. Biol. 2013, 29, 81–105.

43. Haumaitre, C.; Barbacci, E.; Jenny, M.; Ott, M.O.; Gradwohl, G.; Cereghini, S. Lack of TCF2/VHNF1 in Mice Leads to Pancreas Agenesis. Proc. Natl. Acad. Sci. USA 2005, 102, 1490–1495.
44. Poll, A.V.; Pierreux, C.E.; Lokmane, L.; Haumaitre, C.; Achouri, Y.; Jacquemin, P.; Rousseau, G.G.; Cereghini, S.; Lemaigre, F.P. A VHNF1/TCF2-HNF6 Cascade Regulates the Transcription Factor Network That Controls Generation of Pancreatic Precursor Cells. Diabetes 2006, 55, 61–69.
45. De Vas, M.G.; Kopp, J.L.; Heliot, C.; Sander, M.; Cereghini, S.; Haumaitre, C. Hnf1b Controls Pancreas Morphogenesis and the Generation of Ngn3+ Endocrine Progenitors. Development 2015, 142, 871–882.
46. Pinho, A.V.; Rooman, I.; Reichert, M.; De Medts, N.; Bouwens, L.; Rustgi, A.K.; Real, F.X. Adult Pancreatic Acinar Cells Dedifferentiate to an Embryonic Progenitor Phenotype with Concomitant Activation of a Senescence Programme That Is Present in Chronic Pancreatitis. Gut 2011, 60, 958–966.
47. Chuvin, N.; Vincent, D.F.; Pommier, R.M.; Alcaraz, L.B.; Gout, J.; Caligaris, C.; Yacoub, K.; Cardot, V.; Roger, E.; Kaniewski, B.; et al. Acinar-to-Ductal Metaplasia Induced by Transforming Growth Factor Beta Facilitates KRASG12D-Driven Pancreatic Tumorigenesis. Cell Mol. Gastroenterol. Hepatol. 2017, 4, 263–282.
48. Seymour, P.A.; Freude, K.K.; Tran, M.N.; Mayes, E.E.; Jensen, J.; Kist, R.; Scherer, G.; Sander, M. SOX9 Is Required for Maintenance of the Pancreatic Progenitor Cell Pool. Proc. Natl. Acad. Sci. USA 2007, 104, 1865–1870.
49. Pierreux, C.E.; Poll, A.V.; Kemp, C.R.; Clotman, F.; Maestro, M.A.; Cordi, S.; Ferrer, J.; Leyns, L.; Rousseau, G.G.; Lemaigre, F.P. The Transcription Factor Hepatocyte Nuclear Factor-6 Controls the Development of Pancreatic Ducts in the Mouse. Gastroenterology 2006, 130, 532–541.