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Discovery of the pancreatic basal cell: a new candidate for an adult stem cell emerges

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Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease and the seventh cause of cancer-related death worldwide.[1] Notably, clinical characteristics, response to chemotherapy and progression of PDAC can vary among patients. Thus, huge efforts on the molecular profiling of cancer specimens have been undertaken during the last decade. Large-scale gene expression studies defined two main PDAC subtypes with either a 'classical' or 'basal-like' transcriptional signature, with patients with the basal-like subtype having a significantly poorer overall survival.[2–4]

Basal cells are a cell type predominantly located in the basal layer of stratified and pseudostratified epithelia in several tissues, including the skin, oesophagus, lung and breast. Common basal cell markers include keratin5 (*KRT5*) and tumour protein P63 (*TP63*), a member of the *TP53* transcription factor family. In the pulmonary airway, the oesophagus and the mammary gland, basal cells serve as multipotent stem cells or progenitor-like cells which can give rise to organ-specific, terminally differentiated cells and thus have an important role in tissue regeneration on injury.[5 6]

Though basal cells have been found in several glandular organs, the pancreas is not among them. Despite the enormous advances in single-cell 'omics' technologies, no evidence has emerged of a pancreatic basal cell population; in fact, the existence of *any* sort of adult pancreas stem cell reservoir has long been debated. In the absence of a resident basal cell population, the basal-like subtype of PDAC has been widely believed to arise from tumour cell plasticity during progression.

In *Gut*, Martens *et al* combine a novel tissue processing method with high-resolution 3D imaging, an approach termed FLIP-IT, to discover a rare basal cell cohort in normal human pancreas specimens.[7] The identified cells were found in proximity to pancreatic duct cells and stained positive for widely accepted basal cell markers, such as ΔNp63, the ΔN isoform of TP63. Moreover, the basal cell cohort coexpresses GI stem cell markers, such as *Olfactomedin4* (*OLFM4*), suggesting a potential role as progenitor cell.

Importantly, the authors reveal that the number of ΔNp63-positive cells was significantly higher in chronic pancreatitis (CP), a risk factor for PDAC, as well as in PDAC samples.[7] The presence of a greater number of basal cells in pathological conditions is consistent with the stem or progenitor cell-like role they play in other tissues.[5 6] In PDAC, an intriguing possibility is that the pancreatic basal cell serves as a cell of origin for the basal-like PDAC subtype. To address this, performance of lineage-tracing experiments and genetic manipulation in mice would be the obvious choice. However, the authors found no evidence of a similar Δ*Np63*-expressing basal cell population in the mouse pancreas, even in CP or PDAC models, making their study in a progressive mouse model impossible.[7] This lack of similarity to the human condition also raises concerns regarding the usefulness of mouse models when studying certain aspects of pancreatic cancer development. Interestingly, in organoid cultures generated from larger murine pancreatic duct cells, the authors were able to generate ΔNp63-positive cells, suggesting that there may be conditions that give rise to basal cells in vivo as well. Initial analysis show that in both the murine organoid culture as well as human pancreas tissue, the identified basal cell population has a very low proliferative capacity.[7] Thus, it is likely that these cells rather arise through induced cellular plasticity rather than expansion of pre-existing ΔNp63 cells. With the ability to generate and culture a Δ*Np63*-expressing cell cohort in vitro, new avenues to dissect and identify regulatory networks emerge.

Prior to the discovery of a pancreatic basal cell population, the only plausible explanation for the evolution of a basal-like PDAC has been a classical-to-basal reprogramming of pancreatic cancer cells. Several lines of evidence point in this direction. In vitro studies confirm that ectopic expression of Δ*Np63* in pancreatic cancer cell lines induces a basal gene expression signature accompanied by a loss of factors that define classical cancer cell identity.[8 9] Although these studies clearly identify ΔNp63 as master regulator of the basal phenotype, the events and regulatory mechanisms that induce the expression of this transcription factor are also relatively unknown. Recently published data propose that an erosion of pancreas cell identity with the concomitant loss of the transcription factors GATA6, hepatocyte nuclear factor (HNF)1a and 4a (HNF4a) can drive the induction of Δ*Np63* and its dependent gene networks. However, the exact gene regulatory mechanisms remain elusive.[10] By combining histological analysis with whole-genome and RNA sequencing, Hayashi *et al* provide strong evidence for intratumoral heterogeneity, the coexistence of both subtypes within single PDAC samples. Moreover, based on their integrative analysis approach, the authors propose that PDAC evolves from a cancer progenitor cell, from which both classical and basal-like cells arise. Phylogenetic analyses mainly based on genetic alterations provide a clear indication for this scenario, making the existence of a classical-to-basal reprogramming in pancreatic cancer cells a likely phenomenon.[4] However, the discovery of a normal basal cell population adds another possible origin for the basal-like PDAC. Understanding the unique biology of the basal-like phenotype, whether intrinsic or acquired, will be crucial to targeting this especially deadly form of pancreatic cancer.

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