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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

GEMMs Are a Gem When it Comes to Defining the Role of HIF2α in Mucinous Cystic Neoplasms

The most frequently diagnosed pancreatic malignancy is pancreatic ductal adenocarcinoma (PDA). Invasive PDA constitutes nearly 85% of pancreatic neoplasms, with a strong majority of the patients presenting with distal metastasis at the time of diagnosis, differentiating PDA as one of the most lethal cancers with a 5-year survival rate near 5%. Invasive PDA is dependent on a preceding proliferative and inflammatory pancreatitis events, most frequently pancreatic intraepithelial neoplasms (PanIN) formation with the less frequently observed precursor oncogenic event, mucinous cystic neoplasms (MCN). MCNs present as focal cystic masses composed of columnar, mucin-producing epithelium supported by ovarian-type stroma. This peculiar supporting stroma is a histologic hallmark for distinguishing MCN. The etiology and the cellular/molecular mechanisms driving MCN formation are understudied, most likely because of the paucity of *in vivo* model systems to mimic the human disease.

The dense desmoplasia and avascular nature typical of the PDA tumor microenvironment are likely contributors to another of its hallmark features, hypoxia. The pro-oncogenic hypoxic nature of the PDA tumor microenvironment results in the upregulation of a unique subset of genes, the hypoxia-inducible factors (HIF). These transcription factors (HIF1α, HIF2α, and HIF3α), during times of low oxygen, bind to hypoxia responsive elements in promotor regions and transcriptionally upregulate a gene program promoting tumorigenesis. Normoxic cells have adapted a means to post-translationally regulate the HIF proteins by targeting their degradation via association with the von Hippel-Lindau protein. In the context of oncogenic KRAS, deletion of HIF1α has been associated with increased primary tumor growth[1,2] and decreased metastasis[1] suggesting a context-dependent role for HIF1α in PDA development. However, much less is known about the contributions made by HIF2α. Limited evidence posits a role for HIF2α early in malignancy, primarily during PanIN transitioning, via engagement of the Wnt signaling pathway[3] or later in tumor progression by modulating the expression of E-cadherin through regulating Twist and promoting epithelial-mesenchymal transition.[4] Although there is preliminary evidence suggesting a role for the HIF transcription factors in PanIN and PDA progression, the molecular mechanisms driving preinvasive MCN formation during oxygen deprivation are only partially understood.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Schofield et al[5] implemented a complementary, 2-prong approach to reveal that homeostasis within the pancreas may depend on hypoxic signaling pathways. Generation and characterization of several novel murine strains that coupled expression of oncogenic KRAS with the constitutive expression or repression of HIF2α demonstrated a clear impact of the hypoxia signaling pathway in precursor chronic pancreatitis and MCN development. Significant progress in the field has been made by the pancreas specific expression of oncogenic KRAS either in the absence or presence of a mutant p53 allele. KPC (Pdx-Cre;$Kras^{+/LSL\text{-}G12D}$;$Trp53^{R172H}$) mice display full blown disease at a younger age, recapitulating many aspects of the human disease, including histopathologic similarities and metastasis to clinically relevant sites, such as liver and lungs.[6] In contrast, KC (Pdx-Cre;$Kras^{+/LSL\text{-}G12D}$) mice form precancerous PanINs with nearly 100% penetrance and are a strong model to investigate the events required early in the progression of disease.[7] Genetically engineered mouse models (GEMM), are available to study MCN by manipulation of the Smad4/Dpc4[8] or conditional deletion of Notch2[9] pathways, when in the context of oncogenic KRAS. A HIF2α conditional KC murine line has been previously generated[3] to examine one of the earliest events in KRAS-induced pancreatic neoplasia, the loss of von Hippel-Lindau and subsequence activation of the hypoxic pathway. Although these authors revealed a role for HIF2α in PanIN progression via modulation of the Wnt signaling pathway by maintaining appropriate levels of Smad4 and β-catenin, the role of HIF2α in MCN formation is unresolved.

To address this key gap, Schofield et al[5] revealed that mice generated with the pancreas-lineage-specific expression of the oxygen-stable form of HIF2α are born with histologically normal pancreata. However, by as early as 2 weeks of age, there is an increase in proliferative cells, onset of fibrosis, abundant immune cell infiltration, and a shift in the cytokine profile, all phenotypic hallmarks consistent with chronic pancreatitis. These markers are phenocopied upon HIF2α expression following the loss of the HIF regulatory protein von Hippel-Lindau. Thus, HIF2α mice recapitulate many aspects of human chronic pancreatitis including the molecular and histologic aspects, making them an exciting new experimental model. The inflammatory induction in these HIF2α mice predisposed them to formation of MCN following introduction of an oncogenic KRAS allele. These mice presented with a histologic and molecular phenotype that closely mimics human MCN disease, from the expression of CK19 on the flat cuboidal epithelial cells, to the formation of ovarian-type stroma and the activation of the Wnt signaling pathway.

The establishment of GEMMs has significantly advanced the understanding regarding the tumor microenvironment complexity and the diverse and multiple etiological triggers involved in the progression of pancreatic cancer. GEMMs closely mimic the genetic, pathophysiologic, and molecular aspects of the human disease making them ideal for the

characterization and validation of novel therapeutics. Additionally, GEMMs facilitate the understanding of the drivers of disease inception to the mechanisms behind disease progression and metastasis. Together, the GEMMs generated and characterized by Schofield et al[5] have used new state-of-the art model systems to characterize novel molecular insights into the progression of pancreatic cancer.

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