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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Repurposing Tuft Cells to Suppress Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC), the most common form of pancreatic cancer, is a particularly deadly cancer, with a current 5-year survival rate of 10%.[1] This poor prognosis is due in part to late diagnosis, as patients usually present after the cancer has already spread locally or metastasized. Because so few cases of PDAC are detected in early stages, we have little information on factors that contribute to progression of this disease. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, new work by Hoffman et al[2] has identified novel mechanisms by which tuft cells inhibit cancer progression in the pancreas.

Tuft cells are specialized epithelial cells. They are thought to provide a mechanism of transepithelial communication, sensing luminal pathogens or toxins apically and then transmitting signals basolaterally to the underlying stroma. Unlike other epithelial tissues along the gastrointestinal (GI) tract, the pancreas has little contact with pathogens or toxins. It is not surprising, then, that the healthy mouse pancreas lacks tuft cells. However, recent studies have discovered that tuft cells arise in response to damage or neoplasia in the pancreas. The role of these tufts cells has been a mystery, but Hoffman et al have now discovered that tuft cells suppress specific inflammatory responses and limit the progression of pancreatic cancer.

Most of what is known of tuft cell function comes from other organs such as intestine and nasal passageways. Tuft cells in these tissues sense and signal via the gustatory signaling machinery. This machinery involves taste receptors coupled to α-gustducin (GNAT3). GNAT3 is critical for activating calcium efflux that triggers release of signaling molecules such as interleukin (IL)-25, eicosanoids, and acetylcholine from intracellular stores.[3] These signals then mediate immune cell activation, among other functions. Without GNAT3, this signaling pathway is compromised. Hoffman et al utilized this requirement for GNAT3 to dissect the function of tuft cells in pancreatic cancer. Genetic deletion of the *Gnat3* gene did not inhibit the development of tuft cells in pancreatic lesions but had very specific effects on inflammatory responses, both in the epithelium and in the underlying stroma. Surprisingly, loss of GNAT3 indirectly increased production of chemokines, including CXCL1 and CXCL2, by surrounding stromal and epithelial cells. This increase was accompanied by an increased number of granulocytic myeloid-derived suppressor cells (gMDSCs), which express CXCR2, the receptor for these chemokines. gMDSCs are known to promote tumorigenesis in mouse models of PDAC, and the CXCR2 level correlates with prognosis in human patients. Interestingly, the percentages of other inflammatory cells were largely unchanged by GNAT3 loss, indicating a very specific role for GNAT3-mediated signaling in pancreatic immune responses.

The increase in chemokines and gMDSCs correlated with functional consequences late in tumor progression. The $Kras^{G12D}$ mutation is well established to initiate pancreatic cancer in humans and mice, and in mice results in the rapid appearance of benign lesions accompanied by extensive fibrosis and inflammation. Loss of GNAT3 in *Kras*-mutant mice had no discernable effect on this early morphology, suggesting that tuft cell signaling does not influence tumor initiation. However, loss of GNAT3 had a profound effect on tumor progression. Mutation of *Kras* alone in the pancreas resulted in mostly benign lesions that only progressed to early, locally invasive PDAC in one-third of mice after 12 months. When combined with loss of GNAT3, two-thirds of *Kras*-mutant mice developed more aggressive PDAC between 8 and 12 months of age. Notably, a third of these cancers had progressed to metastatic disease, which did not occur without loss of GNAT3.

Another recently published study, by DelGiorno et al,[4] used genetic means to completely ablate tuft cells from mouse pancreas. They also found that loss of tuft cells promoted progression to PDAC. Investigating secreted products specific to tuft cells, they found that tuft cells secrete the eicosanoid PGD_2. Loss of PGD_2 production (via genetic deletion of a necessary synthase) accelerated tumor progression in *Kras*-mutant pancreas, supporting tuft cell production of PGD_2 as a mechanism of tumor suppression. Thus, 2 studies with different focuses identified signals produced by tuft cells (eicosanoids) and signals suppressed in responding cells (chemokines including CXCL1 and CXCL2) that impact tumor progression. It is intriguing to speculate that there may be a direct link between PGD_2 production by tuft cells and suppression of chemokines by surrounding cells, but that link remains to be explored. Another remaining question is whether tuft cells are responding to luminal sensing in neoplastic lesions and, if so, what they are sensing. Understanding the complete molecular pathway(s) by which tuft cells suppress tumor progression may uncover novel pathways that can be exploited pharmacologically to suppress pancreatic cancer in human patients.

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References

1. Cancer facts and figures 2020. Atlanta, GA: American Cancer Society, 2020.
2. Hoffman MT, Kemp SB, Salas-Escabillas DJ, Zhang Y, Steele NG, The S, Long D, Benitz S, Yan W,

Margolskee RF, Bednar F, Pasca di Magliano M, Wen H-J, Crawford HC. The gustatory sensory G-protein GNAT3 suppresses pancreatic cancer progression in mice. Cell Mol Gastroenterol Hepatol 2021:11:349–369.

3. Schneider C, O'Leary CE, Locksley RM. Regulation of immune responses by tuft cells. Nat Rev Immunol 2019; 19:584–593.
4. DelGiorno KE, Chung CY, Vavinskaya V, Maurer HC, Weiser Novak S, Lytle NK, Ma Z, Giraddi RR, Wang D, Fang L, Naeem RF, Andrade LR, Ali WH, Tseng H, Tsui C, Gubbala VB, Ridinger-Saison M, Ohmoto M, Erikson GA, O'Connor C, Shokhirev MN, Nah N, Urade Y, Matsumoto I, Kaech SM, Singh PK, Manor U, Olive KP, Wahl GM. Tuft cells inhibit pancreatic tumorigenesis in mice by producing prostaglandin D2. Gastroenterology 2020 Jul 24 [E-pub ahead of print].

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Conflicts of interest
The author discloses no conflicts.


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2352-345X
https://doi.org/10.1016/j.jcmgh.2020.09.009