Pancreatic Cancer

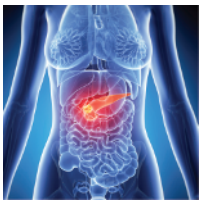
Major Finding: The mycobiome influences cancer progression in mouse models of pancreatic ductal adenocarcinoma.

Concept: Cancer-promoting fungi were more common in human pancreatic tumors than in healthy pancreata.

Impact: This work uncovers a role for the mycobiome in pancreatic cancer and outlines a possible mechanism.

PANCREATIC FUNGAL COMMUNITIES ARE LINKED TO PANCREATIC CANCER

Recently, it has been shown that the pancreatic microbiome is a contributor to pathogenesis in pancreatic ductal adenocarcinoma (PDAC). Building on this unexpected finding, Aykut, Pushalkar, and colleagues discovered a role for the mycobiome (the fungal version of the microbiome) in PDAC. Experiments in mice indicated that fungi could migrate to the pancreas within 30 minutes of oral administration, demonstrating that it is possible for gut fungi to colonize the pancreas. Although the mycobiomes of wild-type mice and mice genetically predisposed to pancreatic cancer were similar at first, they differed at 30 weeks, and PDAC tumors exhibited an increase in intratumoral fungi. Similar results were seen in patients; notably, the mycobiomes of pancreata from patients with PDAC differed substantially from those of healthy pancreata. Further, several experiments provided preliminary evidence for a causal relationship between components of the pancreatic mycobiome and PDAC pathogenesis. Mycobiome ablation or treatment with the antifungal agent amphotericin B in two mouse PDAC models protected against PDAC progression and potentiated gemcitabine-based chemotherapy. Following amphotericin B treatment, repopulation with one fungal species found more commonly in PDAC tumors than in normal tissue (*Malassezia globosa*) accelerated the growth of PDAC tumors, whereas this was not the case with other commensal fungal species. Deletion of the gene encoding the mannose-binding lectin MBL, a protein that activates the lectin pathway of the complement cascade upon recognition of pathogenic fungi, protected against PDAC tumor development in the mice, as did deletion of the gene encoding complement component 3 (C3). These results indicate a previously unknown, MBL–C3 dependent role for the pancreatic mycobiome in PDAC, providing a basis for further work that may uncover disease biomarkers or aid in the development of new therapies. ■



Aykut B, Pushalkar S, Chen R, Li Q, Abengozar R, Kim JI, et al. The fungal mycobiome promotes pancreatic oncogenesis via activation of MBL. Nature 2019;574:264–7.

Lung Cancer

Major Finding: In mouse pulmonary neuroepithelial bodies, few stem cells per cluster proliferate upon lung injury.

Concept: NOTCH signaling triggered deprogramming of the stem cells, whereas Rb and p53 prevented proliferation.

Impact: Pulmonary neuroepithelial stem cells may be the progenitors of small-cell lung cancer cells.

RARE NEUROEPITHELIAL STEM CELLS MAY UNDERLIE SMALL-CELL LUNG CANCER

Pulmonary neuroendocrine cells, which sense airway status and signal to other lung cells as well as the brain, rarely, if ever, divide under normal circumstances. However, following injury to the lung epithelium, pulmonary neuroepithelial cells proliferate to repair the damaged tissue. In mice, Ouadah and colleagues found that in each pulmonary neuroepithelial body (NEB), a cluster of around 20 to 30 cells, two to four cells proliferated in response to injury caused by naphthalene ablation, with each parental cell yielding one to three daughter cells. The neuroepithelial cells that proliferated upon injury, which the authors called NE^{stem}, represented a unique subpopulation of the original NEB. In rare cases, lung injury also appeared to cause outward migration of some neuroendocrine cells toward the injured region. Neuroendocrine outgrowths derived from a single cell were able to restore injured portions of the lung epithelium. Single-cell mRNA-sequencing experiments revealed that neuroendocrine cells undergoing reprogramming exhibited specific activation of the NOTCH pathway, which is involved in cell-fate decisions. Further experiments showed that NOTCH signaling following lung injury triggered deprogramming of neuroendocrine cells, and NOTCH signaling was also able to cause deprogramming under normal conditions. Additionally, *Notch2* expression was a marker of the NE^{stem} state, and was inherited asymmetrically among daughter cells, allowing maintenance of a pool of NE^{stem} cells. The cell-cycle proteins Rb and p53 prevented NE^{stem} proliferation in the absence of injury and curtailed dispersal and reprogramming signals in NEBs following injury, allowing restoration of quiescence after injury. Given that Rb and p53 are almost uniformly inactivated in small-cell lung cancer (SCLC) and that there is some prior evidence that pulmonary neuroendocrine cells initiate SCLC, these findings suggest that NE^{stem} cells may be the progenitors of SCLC and provide a possible mechanism by which SCLC development from NE^{stem} cells may occur. ■

Ouadah Y, Rojas ER, Riordan DP, Capostagno S, Kuo CS, Krasnow MA, et al. Rare pulmonary neuroendocrine cells are stem cells regulated by Rb, p53, and Notch. Cell 2019;179:403–16.