

Interleukin interrupted: A new strategy for the treatment of pancreatic cancer

Pancreatic cancer is an aggressively metastatic cancer with a high mortality rate, but the mechanisms underlying this aggression are not yet fully understood. In this issue, Wu et al. shed some light on this subject. They report that pancreatic cancer cells depend on IL-17B receptor (IL-17RB) signaling for maintenance of their malignant and metastatic properties. With pancreatic cancer slated to become the second leading cause of cancer death in the US by 2020, these findings are timely and important.

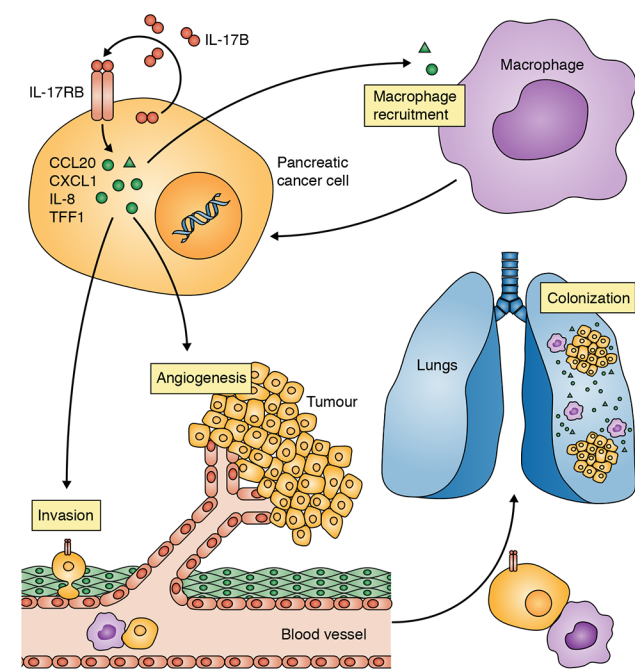
Perhaps even more than most cancers, pancreatic ductal adenocarcinoma is characterized by extremely robust interactions between malignant epithelial cells and the surrounding tumor microenvironment. Within this microenvironment, abundant extracellular matrix, activated fibroblasts, proinflammatory macrophages, and immunosuppressive myeloid and lymphoid elements all conspire to create a dense barrier to chemotherapeutic and immune assault.

Using both gain- and loss-of-function studies, Wu et al. show that IL-17B and IL-17RB potently support the anchorage-independent growth, invasion, tumorigenicity, and metastasis of human pancreatic cancer cells, mediated in part by downstream cytokine activation and macrophage recruitment. In addition to supporting the intrinsic malignancy of pancreatic cancer cells, the current report also implicates IL-17 signaling in the creation of a proinflammatory microenvironment. The authors

also demonstrate that treatment with a monoclonal antibody targeting IL-17RB extends survival in an orthotopic xenograft model. These results may have direct clinical relevance, as additional data suggest that high-level expression of IL-17RB is associated with shortened progression-free survival in patients with pancreatic cancer.

This study complements another recent report from McAllister et al. implicating hematopoietic-to-epithelial IL-17 signaling as a requisite driver of preinvasive pancreatic cancer. Together, these two studies suggest that IL-17 signaling is required during all stages of pancreatic cancer, from preinvasive inception to metastatic spread. Given the fact that clinical trials of IL-17 inhibition are already under way in a variety of proinflammatory conditions, including psoriasis and rheumatoid arthritis, these studies clearly set the stage for similar trials in patients with pancreatic cancer.

There are a number of unresolved issues and caveats with these studies. It is possible that protumorigenic IL-17 activity is confined to specific subsets of patients with pancreatic cancer, as the current study suggests that ~40% of pancreatic cancers display detectable IL-17RB expression as assessed by immunohistochemistry. In addition, some studies have suggested that IL-17 might exert antitumor effects in the context of vaccine-augmented immune responses; it is therefore possible that IL-17 signaling may exert opposing influences on pancreatic tumorigenesis in the context of variability in the host immune response.



Schematic diagram showing the central role of IL-17B-IL-17RB signaling in pancreatic cancer metastasis.

These caveats aside, this study contributes to the growing realization that interrupting IL-17 and other interleukins may soon become an important therapeutic option for an otherwise deadly disease.

McAllister, F., et al. 2014. *Cancer Cell*. 25:621-637.

Wu H-H. et al. 2015. *J. Exp. Med.* <http://dx.doi.org/10.1084/jem.20141702>.

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**Insight from
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The real thing: How to make human DC subsets



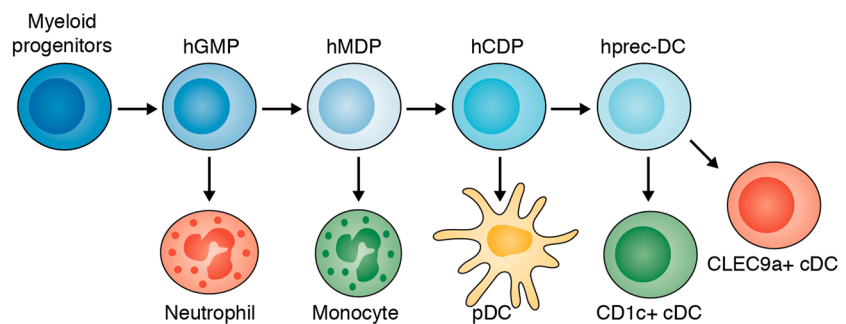
**Insight from
Frederic
Geissmann**

The developmental relationship between monocytes, dendritic cells (DCs), and macrophages has been well defined in mice, but human DC development is less well understood and has been hampered by the lack of a suitable culture system. Now, two papers published in this issue describe a novel *in vitro* culture system for human DC progenitors and the use of this system to elucidate the pathway of human DC development.

The extent to which mouse studies are useful to understand the human immune system is debatable. One expects—and observes—important similarities, but there are also differences in the way the building blocks of the immune system are assembled in different species of vertebrates that have evolved in different contexts and milieus, and with different lifespans. Laboratory mice, maintained as inbred strains under selected housing conditions, are amenable to controlled genetic studies. However, genetic and environmental variations are difficult to control in human studies, and experimental limitations make it difficult to assess whether "mouse" immunology "works" in humans.

The two studies in this issue, by Lee et al. and Breton et al., represent an important advance in the DC field. The work describes, at the population and single cell level, a hierarchy of human myeloid precursors that closely parallel the hierarchy in the mouse bone marrow and blood. The authors used a combination of technically impressive qualitative and quantitative approaches, including *in vitro* differentiation of human hematopoietic precursors cultured on a stromal cell line with defined sets of cytokines, *in vivo* "cultures" of human precursors in immunodeficient NOD-*scid* γ mice, and observational studies in humans. This allowed them to map out the development of monocytes, conventional DCs (cDCs), and plasmacytoid DCs (pDCs), and the sequential relationship between the different precursor populations. They showed that a granulocyte-monocyte-DC progenitor (hGMDP) develops into a monocyte-DC progenitor (hMDP), which itself differentiates into monocytes and into a common DC progenitor (hCDP) that produces the three major human DC subsets (CD1c⁺ cDCs, CD141⁺ cDCs, and pDCs). Furthermore, they report the identification of an immediate DC precursor (hpre-cDC) that originates from the hCDP, circulates in the human blood, and increases in response to plasma levels of the cytokine FLT3.

These results are a significant advance in the field. They illustrate the similarities between mice and humans regarding the development of monocytes, cDCs, and pDCs, and provide a guide—and experimental systems—to further interrogate the genetic and molecular control of human monocyte/DC development and their functions in disease. It is possible to imagine that DC-based therapy may benefit from knowledge of the "real thing."



Schematic of the developmental relationship between human monocytes, cDCs, and pDCs.

Breton, G., et al. 2015. *J. Exp. Med.* <http://dx.doi.org/10.1084/jem.20141441>.

Lee, J., et al. 2015. *J. Exp. Med.* <http://dx.doi.org/10.1084/jem.20141442>.

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