How Pancreatic Cancer Survivors Shed Light on the Immune System

Most pancreatic cancer cells have relatively few mutations on their surface to attract the attention of cancer-killing immune T cells.

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Despite the best efforts of cancer researchers and clinicians, pancreatic cancer remains a highly lethal disease, with only 5% of patients surviving 5 years after their diagnosis. This is in part because pancreatic cancer cells have relatively few mutations, meaning fewer strange-looking proteins, or neoantigens, on their surface to attract the attention of cancer-killing immune T cells. This makes most pancreatic tumors “immune cold,” safe from detection by the body’s defense system.

At Memorial Sloan Kettering Cancer Center, Damon Runyon Clinical Investigator Vinod P. Balachandran, MD, and his colleagues study what makes the 5%, the rare long-term survivors, different. In survivors, Dr. Balachandran has found, T cells manage to infiltrate the tumors despite their scarce neoantigens. So what makes the neoantigens in survivors different? To answer this question, his team developed a measure of neoantigen “quality,” where high-quality neoantigens are those that elicit a T cell response.

By their measure, neoantigen quality is a factor of both its similarity to known antigens, which the immune system recognizes as foreign, and its difference from normal cells—the strangeness that attracts T cell attention. (Consider how an especially bright bird, if still identifiable as a bird, might make the easiest prey.) In tumors of patients who survive pancreatic cancer, the neoantigens are few but high-quality, like especially bright birds standing out in a forest. Classifying tumors with this measurement system could thus be used to predict prognosis.

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Five years later, Dr. Balachandran and his team have amassed more evidence that certain neoantigens play a key role in pancreatic cancer survival. Tracking the evolution of 70 pancreatic tumors over 10 years, the researchers found that long-term survivors develop more genetically homogenous tumors with fewer neoantigens. Returning to their neoantigen quality model, the team confirmed that the missing neoantigens were indeed the “high-quality” ones—indicating that the immune system “edits” out these neoantigens, allowing a smaller number of lower-quality antigens to dominate the tumor cell population. (Again, consider how predation might create a more homogeneous, dully colored population of birds.)

Together, these studies lend hope to the prospect of a neoantigen-based vaccine for pancreatic cancer. If researchers can determine which neoantigens stimulate the immune system, they may be able to use them to provoke an immune response in patients whose own antigens go unnoticed by T cells.

“Our finding provides more evidence that the immune system recognizes neoantigens in pancreatic cancer, and that we are on the right track in picking these neoantigens,” Dr. Balachandran says. “This could be useful for personalized vaccines for pancreatic cancer—which urgently needs better treatments—and other cancers as well.”

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