Nanoparticles Take Immunotherapy in New Direction

Fred Hutchinson scientist to use nanoparticles to reprogram macrophages to tackle brain tumors

June 15, 2018 By Sabrina Richards

Fan Zhang, PhD, a postdoctoral fellow in the laboratory of Matthias Stephan, MD, PhD, in Fred Hutchinson Cancer Research Center's Clinical Research Division, is using nanoparticles to take immunotherapy in a new direction. The American Brain Tumor Association awarded Zhang $100,000 to develop nanoparticles that can be used to reprogram tumor-infiltrating macrophages, a type of immune cell that eats cellular debris and diseased cells, to attack the cancer that surrounds them.

The strategy hinges on the dual nature of macrophages, Zhang explained. These cells are capable of both stimulating and suppressing inflammation. Macrophages recognize and engulf diseased cells such as cancer cells while also sending signals to other immune cells that trigger them to fight disease. Indeed, during a tumor's early days, the macrophages that make their way in are spoiling for a fight.

"But as the tumors start to grow, they secrete effectors that affect the macrophage cells and polarize them into a type of cell that's trying to help the tumors to grow," Zhang said. These macrophages also support tumors by counteracting the activity of other immune cells, such as T cells, that could try to kill cancer cells.

Zhang aims to use nanoparticles to flip macrophages from tumor supporters to tumor antagonists. The tiny particles are made up of bundles of reprogramming instructions, called mRNA, wrapped in strings of amino acids. He plans to inject the nanoparticles directly into tumors. To make sure the nanoparticles reach macrophages — and only macrophages — they will be studded with proteins that specifically target them to this cell type.

Each type of macrophage relies on different proteins, known as transcription factors, to coordinate the right set of genes that allow them to suppress or boost immune function. These nanoparticles will carry specific mRNA for building the transcription factors on which immune-enhancing macrophages rely.

Working with Hutch colleague Eric Holland, MD, PhD, Zhang will test this strategy in a mouse model of glioblastoma, a type of brain cancer. Glioblastoma is an ideal testing ground for a

macrophage-based cancer immunotherapy. While very few T cells make their way into the brain or brain tumors, as much as 30 percent of cells in a glioblastoma may be various types of macrophages.

“It’s a great opportunity for us to use this as a way to fight against the tumor cells,” Zhang said. Other scientists testing T-cell immunotherapies find that even those T cells that make it past the blood-brain barrier don’t penetrate far into tumors.

The support from the ABTA will allow him to see whether his macrophage-reprogramming strategy can cause brain tumor regression, and monitor for potential neurotoxic side effects. Other systemic approaches to suppress tumor-supporting macrophages affect the macrophages throughout the body and disrupt immune function; because Zhang’s approach is localized to macrophages within tumors, it will avoid system-wide side effects.

Zhang also will examine how tumor regression occurs. Though macrophages can kill tumors directly, he expects that much of their power will come from stimulating other immune cells. This could be good news for current immunotherapies.

“By polarizing macrophages, we could make it easier for current immunotherapies, such as T-cell immunotherapies [or checkpoint inhibitors], to work,” Zhang said.

He’s currently envisioning using reprogrammed macrophages as part of a combination immunotherapy, and he hopes to someday bring the strategy to the clinic. And, the method is eminently flexible: change the targeting ligand attached to the nanoparticles’ surface, and they can be directed to a new cell type. Change the mRNA inside, and change what the target cells do.

“It really extends the application to a lot of different areas, not only limited to cancer,” Zhang said.

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