New model paves way for immune therapies against colorectal cancer

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Anna Capasso, M.D., and colleagues present a new humanized mouse model of colorectal cancer. Credit: University of Colorado Cancer Center

About 95 percent of colorectal cancers are considered "microsatellite stable" and very few of these cancers respond to immunotherapy, meaning that the vast majority of metastatic colorectal cancer patients are unable to benefit from medicines that activate the immune system against the disease - a strategy that has helped dramatically extend the lives of patients with related cancers. A study presented at American Association for Cancer Research (AACR) Annual Meeting 2017 describes a new "humanized mouse" model of colorectal cancer, allowing researchers to test new drugs and new drug combinations against the disease, potentially opening the door to immunotherapy for the larger, microsatellite-stable population of colorectal cancer patients.

"Traditionally, mice have had to be immunocompromised in order to engraft tumors. But you need the human immune system to be present in order to study human immunotherapies. With this new model, we found a way to have our cake and eat it too - to have colorectal cancer growing in a mouse with a human immune system," says Julie Lang, PhD, senior research associate at the CU Cancer Center and manager of the Humanized Mouse Core at the CU School of Medicine.

The challenge comes from the fact that the mouse immune system, by its nature, is predisposed to attack "foreign" tumor tissue, the same way a transplant patient's immune system might reject a donor organ. If researchers attempt to engraft a tumor into an immune-competent mouse, the mouse immune system will recognize and attack the tumor tissue before it can grow. The answer to making traditional mouse

models of cancer has been to eliminate the mouse immune system before engrafting a tumor.

This approach is all well and good when testing traditional medicines - for chemotherapies or targeted treatments designed to kill cancer cells directly, it doesn't really matter if the immune system is present or absent. But if the goal is to use the immune system to kill cancer, both the immune system and the cancer must be present (as Lang says above).

The answer to this challenge is the humanized mouse. Basically, in this strategy a human immune system is transplanted along with the human tumor into the mouse, so that now with this human-human match between immune system and tumor the immune system lets the tumor exist (until taught by medicines how to attack it).

In the current study, young mice were "humanized" by the introduction of human umbilical cord stem cells marked by the protein CD34. Then at 16 weeks, samples of colorectal cancer, obtained from human patients, were engrafted onto these humanized mice.

"It takes T cells a while to develop from these CD34 cells and so if you time it correctly to engraft the tumor after CD34 cells from umbilical cord blood are introduced but before T cells are mature, you can have a mouse in which the T cells accept and ignore tumor tissue," says first author Anna Capasso, MD, medical oncologist and postdoc at the CU School of Medicine.

The tumors grew in this model and when the researchers treated these tumors with the immunotherapy nivolumab, they saw what they would expect from a functional immune system activated against cancer: Treated tumors were smaller than tumors in an untreated control group. Nivolumab works by blocking the action of the protein PD1, which tumors use as a signal to deactivate the immune system - and in the mice

treated with nivolumab, the group found lower PD1 expression among other markers implying that the immune system had, in fact, successfully recognized and killed these cells.

"It's pretty exciting. We know we're on the right track - what we see in these models is what we would expect from a tumor treated in this way," says Capasso.

Now that the model has been validated, the group is turning its attention to utilizing the model for research and drug discovery.

"Several investigators have approached us with suggestions for combination therapies," Lang says. "What's interesting is that these include very different kinds of drugs, some that modulate the immune system, others that change the nature of tumor cells, and others that may simply be synergistic with immune therapies."

Currently, one of the most promising combinations seen in this model is that of immunotherapies targeting PD1 or PD-L1 along with drugs that inhibit the action of the gene MEK. Despite promise in laboratory and preclinical studies, MEK inhibitors have struggled to show clinical benefit. Forthcoming data demonstrates that modulating the immune system along with MEK inhibition may be more beneficial than either drug alone in microsatellite-stable metastatic colorectal cancer.

In addition to use by CU Cancer Center members, the group's humanized mouse model is available commercially, with information at the website of the Human Immunology and Immunotherapy Initiative of the University of Colorado School of Medicine.

The researchers also hope their model will help pick apart mechanisms that could lead to the design of new immunotherapies.

"It's as if research can extend either way from this model - forward toward translational research that can show the benefit of promising treatments, or back toward the bench where our lab work can help us discover mechanisms of the immune system that could influence the design of new drugs," Capasso says.

"With these mice we have the ability to look at immunotherapies for a variety of cancers in more depth," Lang says.

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