New Models for Testing Melanoma Drugs and Vaccines

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Before experimental drugs and vaccines can ever be tested in people, they must first be studied in animal models of the disease. Such models allow researchers to investigate scientific questions that they cannot answer using people due to unknown risks. These models help researchers to better understand how melanoma forms and progresses, and what happens during treatment response and resistance. Fortunately, melanoma researchers have several experimental animal models from which to choose, each with its own advantages and disadvantages. Because these models are still far from perfect, some investigators have opted to tinker with them so that they more closely mimic certain melanoma subtypes or so they enable a better understanding of how the immune system interacts with tumor cells and tumor vaccines. A few of these novel animal models and what they can reveal were highlighted at the 2019 MRA Scientific Retreat.

But First, What's a Model?

Models are powerful tools that help make things easier to understand. In medical research, models help researchers to advance science without subjecting people to possible therapies without reasonable expectation that the benefit of the treatment will outweigh the risks. Specifically in melanoma, researchers use a variety of models, including cell lines, computer simulations, mouse models, zebrafish, and other techniques to determine what agents make sense to advance forward.

NINJA Mice Reveal Anti-Tumor Immunity

Nikhil Joshi of Yale University reported on his NINJA mice that he and his colleagues genetically engineered to activate production of novel tumor-specific proteins, called neoantigens. He aims to use the mice to better understand the balance between tolerance (T cell non-response to tumors) and the anti-cancer immune response over time and in different tissues. In melanoma and other cancers, tumor neoantigens play an important role in driving T cell killing of tumors in patients taking immunotherapy. NINJA mice will help reveal to researchers why some cancers, such as melanoma, tend to respond to immunotherapies, while others don't, and why some tumors, depending on their surroundings, are seemingly better tolerated by the immune system than others.

Joshi suspects that an immune response to tumors might depend on where in the body it occurs. Other studies have found some parts of the body tolerate novel proteins, meaning they are less likely to prompt an immune response to them. For example, liver transplants are less likely to provoke an immune response than other types of tissue transplants. Joshi verified this with his NINJA mice. “In the liver, when we turn on the production of a tumor neoantigen, we don’t get much of an immune response and a lot of the T cells [needed to destroy tumor cells] we see there look exhausted and nonfunctional, unlike those we see in the skin

when we turn on the neoantigen,” Joshi said. This suggests that T cells in the skin are more primed to “see” neoantigens, and that may explain, at least in part, why melanoma is more likely to respond to cancer immunotherapies than cancers arising in other sites of the body, he added.

Joshi also wants to use the NINJA mice to explore what regulates the natural immune response to melanoma tumors, that is, the killing of tumor cells by T cells that happens in the absence of treatment and can keep small numbers of cancer cells from growing into a larger tumor at the primary site or prevents micrometastases from growing into larger tumor masses. “We want to understand why immune cells ultimately stop functioning, which we think leads to metastatic disease,” Joshi stressed.

Mouse Models for Cancer Vaccines
To better predict an immune response to personalized melanoma vaccines, Nina Bhardwaj of the Icahn School of Medicine at Mount Sinai has modified mice so that they have all the major components of a human immune system. This will allow the researchers to study tumor cells taken from patients in mice with an intact immune system – something that isn’t possible in normal mice because the mouse immune system rejects any human cells it sees, similar to organ rejection.

The researchers ‘humanize’ the mice by destroying these animals’ own immune systems with radiation, and then injecting human stem cells derived from patient blood samples into their bone marrow. These stem cells can then generate all the key components of the human immune system. Bhardwaj next plans to make humanized mice using stem cells taken from melanoma patients and then inject the fragments of the patient’s tumor into these mice. Using these mice, Bhardwaj plans to study the effectiveness of tumor vaccines and tease apart the immune responses they generate. By first testing personalized tumor vaccines in these mouse ‘patient avatars,’ Bhardwaj and her colleagues hope to one day be able to select the specific components of the vaccine that elicit the strongest immune response and then use that to fine tune personalized vaccines for cancer patients.

Zebrafish Reveal Promising Compounds for Difficult-to-Treat Melanoma Subtype
Researchers are also developing novel animal models to better predict effective drug combinations in subtypes of melanoma that traditionally do not respond to current therapies. To better understand how to treat melanomas that have a mutation in the gene NF-1, a particularly aggressive and treatment-resistant genetic subtype, A. Thomas Look of Dana-Farber Cancer Institute and his colleagues created zebrafish with this subtype of melanoma. Zebrafish, which are smaller than a nickel in size, are a favored model for some cancer researchers because they have

translucent skin, so the growth or shrinkage of tumors is easily visible. They also have a short life cycle compared to mice, making rapid genetic manipulation feasible.

Thomas is using the NF-1 mutant zebrafish to understand and predict molecular pathways that cause resistance to drugs. Better understanding this could suggest combination therapies that are more likely to cause a durable response to treatment. For example, Thomas' studies found the need to simultaneously inhibit two proteins (MCL-1, BCL-2) that work together to promote the survival of melanoma cells. When these two inhibitors were combined with another drug (rapamyacin) that slowed the growth of tumors, they dramatically prolonged survival of the NF-1 zebrafish by killing off melanoma cells. This three-pronged attack also killed NF-1 human melanoma cells grown in culture. "This subtype of melanoma is likely to respond to this treatment strategy," Thomas said, as well as perhaps other molecular melanoma subtypes. He suggested the three-agent treatment be tested in mouse melanoma models to better understand its clinical potential.

Together, these studies demonstrate the importance of model optimization to discover new treatments and understand the complex dynamics of tumor-immune cell interaction.

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