Creating a New Generation of Melanoma Models

Taking the guesswork out of melanoma treatment

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We all can remember the eruption that happened when our 1st grade science teacher combined vinegar and baking soda together to represent a volcano. In some ways, this is just like experiments that take place every day in the search for better treatments, and ultimately a cure, for melanoma. In both instances, the researcher uses models to represent systems and phenomena that would otherwise be difficult or unethical to touch, see, or manipulate. Models are powerful things and we use them every day to make things easier to understand. In science, modeling is an essential component of our scientific process.

In medical research, modeling allows us to advance science without subjecting people to possible therapies without reasonable expectation that the benefit of the treatment will outweigh the risks. In melanoma, researchers use cell lines, computer simulations, mouse models, and other techniques to determine what agents make sense to move into human trials. But, just like the baking soda and vinegar volcano example we talked about earlier—there are real limits to what we can learn from models because at the end of the day, models aren't perfect. Baking soda and vinegar cause quite the reaction, but they still don't equate to what goes on in a true volcano. The same is true in medical modeling.

In research, the adage goes: "models are models, but you have to start somewhere." We know that every model has limitations, for example cell lines don't have an immune system like people do—but we accept these limitations because the rubber has to meet the road somewhere. But, what if we could dramatically accelerate our research by just using better models? This is exactly what Dr. Meenhard Herlyn and Dr. Katherine L. Nathanson partnered together to find out.

In the first of two studies published in November, Dr. Herlyn who is the director of the Wistar Institute Melanoma Research Center and member of the MRA Grant Review Committee, created 462 patient-derived xenografts (PDX), representing a wide variety of melanoma subtypes and genetic aberrations. PDX are a special type of xenograft created by injecting a small amount of cancerous tissue taken directly from a patient into another species (generally mice) with the twist of adding in a human immune system. PDX are important models for melanoma researchers,

because they more closely represent what happens in real people with working immune systems than is possible using cell lines. And it may better predict what treatments may or may not work for individual patients.

In performing the studies, one thing that stood out was just how well melanoma cells were able to adjust to the new experimental conditions. Using a fine needle aspirate to transplant tumor tissue into a mouse, the implantation success rate for melanoma was over 90%, much higher than the rates for breast or prostate cancer, 20 and 10 percent respectively. “Melanoma is extraordinary. We found that it only takes 1-5 melanoma cells to induce a tumor,” says Herlyn. “The consequences of this are important because it means you can’t leave anything [when treating melanoma] or it will come back.”

This PDX collection isn’t notable just for its size. It features an extremely diverse representation of melanomas. It includes 57 PDX from tumors that are resistant to targeted therapy, 61 PDX from the tumors of people who responded to immunotherapy and an equal number of people who did not, and 31 PDX from brain metastasis. In addition to regular cutaneous melanoma, the collection also represents the three main subtypes of melanoma; acral, mucosal, and uveal too.

Dr. Nathanson, a geneticist by training, has collaborated with Dr. Herlyn for over 12 years. She serves as deputy director of the Abramson Cancer Center of the University of Pennsylvania – next door. In this companion study, she and her team took the hundreds of PDX created by Dr. Herlyn and used genome sequencing to analyze 108 genes that have been previously implicated in melanoma formation to identify which mutations and copy number changes they have. “If you want to use these PDX to facilitate the development of new drugs, in biological studies or in preclinical studies, you need to understand each one’s genetics and genomics,” said Nathanson. “Precision medicine – the idea that doctors should select treatments that are most likely to help patients based on a genetic understanding of their disease - can only happen when you have models that are good enough to be representative of the patient’s tumor and that’s what our sequencing does.”

Beyond being an important resource for the field, sequencing of DNA from PDXs, cell lines and biopsies provided new insights into the genetic landscape of rare subtypes of melanoma. For instance, Dr. Nathanson identified patterns of co-occurring mutations within some of these subtypes, which could lead to the identification of novel drug targets upon further study. Moreover, the researchers gained a better understanding of how tumors evolve genetically in response to treatments and also how tumors taken from the same individual can differ in the genetic alterations they acquire.

This massive undertaking was born out of a true collaborative spirit between doctors Herlyn and Nathanson and their teams. Although both teams have worked together across their institutions for years, this project really leveraged the combined expertise of both groups. In addition to the collaboration between the University of Pennsylvania and the Wistar Institute, eight institutions provided patient tumor samples needed to create the PDX. “You cannot underestimate the power of collaboration in science,” said Nathanson.

Today, this huge body of work gives researchers better tools for preclinical studies to facilitate drug development. Long term, this collection will help create and refine new therapies and combination of therapies with models that more closely represent melanoma in humans. It also makes the promise of precision medicine one step closer to reality for melanoma patients.

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