Is It Working? Imaging the Immune Response in Melanoma

Researchers are developing better tools to help determine as early as possible whether melanoma tumors are responding to immunotherapies.

March 14, 2019 By Melanoma Research Alliance

We are fortunate to now have effective immunotherapies for many patients facing melanoma. However, we also know that these treatments can sometimes cause serious side effects, like diabetes and colitis. In order to help mitigate the risk of these side effects — often called adverse events — researchers are developing better tools to help determine who should receive immunotherapies, and of those patients who do, determining as early as possible whether their tumors are responding.

MRA-funded investigators are hard at work solving this problem. At the 2019 MRA Scientific Retreat three researchers presented on their efforts to develop novel imaging techniques to better predict treatment response. While each approach is different, together they represent an important field of study that will improve the way we treat patients with melanoma.

Llamas Lend a Hand

Immune responses to tumors are always changing. According to MRA Established Investigator Hiddle Ploegh of Boston Children's Hospital, to truly understand this dynamic relationship, it's crucial to image the immune cells of live animals to see how they interact with tumors over long periods. To do this, he enlisted the help of llamas, who have unusually small antibodies that can be easily modified and attached to an imaging agent for PET (positive electron tomography) scans such that they seek out and light up specific components of the immune system in tumors.

Using such "nanobodies" in mice with melanoma, Ploegh has been able to distinguish when pseudo-progression of tumor may in fact be a response to immunotherapy. He has also shown that one of the earliest responses to these treatments is the infiltration of killer T cells throughout the tumor, whereas non-responders show a more varied distribution, much of which occurs in outlying regions of the tumor. "In responder animals, the tumor is penetrated to the core by CD8 [killer T] cells, but in non-responders there isn't that full penetration," said Ploegh. He also found that responders have a massive increase in a molecule that attracts immune cells and can help them hone in on tumors.

Ploegh has developed human versions of his mouse nanobodies that are ready to be tested in the

clinical setting and can be used to image key immune cells in both the tumor and lymph nodes with great sensitivity. He also developed a nanobody that can be used to detect melanoma metastases. “Our approach is ready for translation to the clinic. We just need an industrial partner to make it good to go,” Ploegh concluded.

Borrowing Lessons from Breast Cancer

In previous investigations, Sean Bendall of Stanford University used imaging techniques such as mass spectrometry—a way to separate and weigh all the micro-components of a sample—to track immune responses to breast cancer from preserved slices of tumors. Now, he is applying these same techniques to melanoma.

Bendall combined the mass spectrometer’s ability to detect minute quantities of specific substances with single-cell imaging to reveal patterns in howimmune cells infiltrate breast tumors. He found two distinct patterns in the samples: either the infiltrating immune cells appeared scattered amidst tumor cells, or they appeared in concentrated clusters. “In one, the immune cells looked like grains of sand in the tumor, while within the concentrated clusters, it was more like islands of immune cells in the tumor,” he said, stressing, “Not all immune infiltration is equal—it’s not just a matter of getting immune cells into tumors, but how they are infiltrated.”

Bendall found those patients whose tumors showed infiltration with a concentrated cluster pattern were more likely to survive. He also found this compartmentalized response pattern was found throughout an entire tumor, regardless of where the sample was taken. He next plans to apply this imaging technique to see whether there are distinct differences in immune infiltration in melanoma tumors between those who respond to immunotherapies compared to those who do not respond. “We expect our data will help us understand why we get responses in some patients and not in others,” Bendall said.

Following the Stars

MRA Established Investigator Janis Taube took to the stars to approach the same problem, using traditional fluorescent staining of tumor slices, but in a novel way. Instead of staining for just a few cell types, Taube uses up to 28 different stains “for the basic roll call of immune cells present and also lymphoid structures, tumor cells, and new vasculature,” she said. That staining combined with an innovative stacking technique enables her to simultaneously view dozens of parameters. Because of the large data sets generated by this technique, she then uses sophisticated tools, processes, and algorithms borrowed from astronomers to analyze her results so she can superimpose and make sense of one set of findings on top of another. The millions of cells activated during an immune response is indeed a microcosm akin to the flashing stars that blanket the sky.

“We have used the astronomy experience to generate high-quality, three-dimensional maps of the local interactions between melanoma and immune cells that will provide critical insights,” Taube said.

Because each tumor slide is linked to patient information such as survival and response to immune

therapy, researchers can use this information to help determine what features in pre-treatment biopsies predict response to therapy. “We’ve taken what we’ve learned in terms of imaging the whole sky to image whole tissue sections and are starting to drill down to individual cells and subcellular structures and patterns in data that can resolve even more structures. Our goal is to have a perfect prediction that match patients to appropriate the therapy,” said Taube. Read more about Taube’s work here.

What’s Next?

These three researchers, who presented at the 2019 MRA Scientific Retreat, highlight just some of the ways MRA-funded investigators are trying to understand how best to measure and monitor response to immunotherapy in melanoma patients. Several additional MRA-funded researchers are also tackling this problem, and as these new technologies move towards the clinic, doctors will be able to better monitor treatment effectiveness and have improved decision making capabilities about if and when to switch treatment approaches.

This post was originally published by the Melanoma Research Alliance. It is republished with permission.
