Making Combination Therapies for Melanoma Safer and More Effective

At Melanoma Research Alliance's 2021 Scientific Treat, scientists discussed enhancing anti-tumor immune response of combination therapies.

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Every general knows that the best way to successfully win a war is to deploy multiple weapons with different targets. This strategy was first used in cancer to conquer childhood leukemias with combination chemotherapy and now is being put to the test in melanoma by combining multiple checkpoint inhibitors, as well as combining checkpoint inhibitors with targeted BRAF and MEK inhibition or other agents. At MRA's 2021 Scientific Retreat, several researchers reported from such innovative frontlines. They recounted the current thinking on combination therapy for melanoma and ways to enhance the anti-tumor immune response using promising new immune targets, as well as strategies aimed at modulating the gut microbiome.

During his MRA Scientific Retreat opening keynote lecture, 2019 Nobel Laureate William Kaelin, Jr., of Dana-Farber Cancer Institute, pointed out that many melanoma patients treated with BRAF/MEK targeted therapy initially respond, only to relapse later due to drug resistance. This resistance stems from combining drugs that block the same target or multiple targets in the same cellular signaling pathway. This not only increases the risk of toxic reactions, but also revs up the evolutionary pressure for tumor cells to escape the effects of these drugs. Such pressure prompts molecular changes inside tumor cells that enable them to elude the effects of these drugs. Underlining the challenge clinicians and researchers face in fighting melanoma and other cancers with such drugs, Kaelin said, "If you strike at the king, you must kill him."

To overcome such resistance, Kaelin suggested combining drugs with distinct and independent mechanisms of action. That way, "There is a low probability of any one [tumor] cell being resistant to three non-cross-resistant drugs. The trick is to make the math work for and not against you so you can potentially win," Kaelin said.

This approach has already proven effective for kidney cancer, Kaelin noted, and is starting to be applied to melanoma. For example, early-stage trials targeting BRAF/ MEK inhibition with CDK4/6 inhibitors. "Hopefully we can someday look back at kidney cancer and melanoma and be able to say that with the development of combinations, we were able to find cures for these diseases," Kaelin concluded.

Using “Smart” Technologies to Boost Anti-Tumor Immunity

To foster more effective combination immunotherapies, a number of researchers are focusing on aspects of the immune system that work independently from those targeted by currently approved melanoma checkpoint inhibitors, such as ipilimumab, nivolumab, and pembrolizumab. Up to 50% of patients do not durably respond to these therapies, and researchers believe that by targeting additional pathways involved in an anti-tumor immune response, such combination therapy will become more effective in the long term to more patients.

One MRA-funded researcher, John Wilson of Vanderbilt University, is designing innovative nanotechnology to access a new and previously unreachable immune target within the cell. Currently approved immunotherapies use antibodies that target molecules called receptors that stick out from the surface of a cell. These receptors easily come into contact with medications circulating in the bloodstream. It is much more difficult, if not impossible, for antibodies and many other promising drug candidates to penetrate cell membranes, and access the molecules within them. These molecules include a “growing arsenal of promising intracellular therapeutic targets that have enormous potential, but require a strategy to provide open access to them,” pointed out Wilson.

To provide that access, Wilson’s lab, which has expertise in chemistry, materials science, and immune-engineering, designed smart nanoparticles (NPs) that mimic the way some viruses enter cells. The researchers designed NPs so they are engulfed by the cell membrane of tumor and immune cells. And, once inside these membranes, a change in acidity triggers the NPs to release their active drug component, where it binds with its target. When loaded with a drug cargo that can stimulate the immune system, the NPs trigger molecular signaling that causes immune cells to activate and expand in number, so that they infiltrate into and kill tumor cells.

Wilson found that their approach resulted in significant therapeutic benefit in multiple mouse models, and that his NPs greatly enhanced anti-tumor immune responses when combined with checkpoint immunotherapy. This experimental combination inflamed a previously dormant immune response to the tumors, significantly boosting complete response rates in a mouse model of melanoma and increasing survival without causing any serious side effects. Wilson also coupled his NP technology to personalized cancer vaccines aimed at stimulating an anti- tumor immune response. The particles were small enough that they easily penetrated cells in the lymph nodes, where they enhanced the immune response there, and showed good efficacy in a mouse model of melanoma when combined with checkpoint immunotherapy. “Our smart NPs offer a platform for cancer vaccine delivery and have a number of other potential advantages as a drug carrier platform that we are actively exploring,” Wilson concluded.

The Scoop is in the Poop

Perhaps, a less technical solution to improving responses to checkpoint inhibitors may be to alter

the microbes in our gut, Jennifer Wargo of University of Texas MD Anderson Cancer Center reported. She noted these microbes, and the foreign proteins they produce, stimulate the immune system to better kill tumors. She found that the more diverse gut microbes are in a patient, including those with melanoma, the better their response to checkpoint immunotherapy. Having certain types of microbes in the gut were also linked to better responses in melanoma patients treated with checkpoint immunotherapy. “The scoop is in the poop,” she said, adding, “You are what you eat!”

But even those patients with favorable microbes in their gut responded better to treatment when they were also on a high fiber diet. “It’s not enough to have a good microbiome signature, but you also have to feed it the right things,” Wargo stressed. She found that eating a high-fiber diet was linked to greater progression-free survival in melanoma patients treated with checkpoint immunotherapy. Mouse studies then suggested that the greater responses and survival seen in patients with a high fiber diet was due to heightened activation of immune cells. This boost in immune activity can happen in a remarkably short period of time in response to changes in diet. Wargo is currently working with other investigators at MD Anderson Cancer Center (Dr. Jennifer McQuade and Dr. Carrie Daniel-MacDougall) to interrogate the impact of dietary intervention with fiber and other strategies in patients with melanoma (NCT03950635).

Building on Wargo’s findings, researchers recently experimented with transplanting stool from melanoma patients who responded to checkpoint immunotherapy into patients with metastatic melanoma in which the treatment was unsuccessful — a treatment called fecal microbiome transplantation (FMT). Wargo collaborated in one study in which clinical responses were observed in three of ten patients treated with FMT followed by anti-PD1 immunotherapy. In another study published at the same time, six of 15 patients derived clinical benefit. These results suggest that FMTs may modulate the gut microbiota in such a way as to allow patients who previously did not respond to benefit from checkpoint immunotherapy.

FMTs might also reduce certain side effects, what researchers call adverse reactions, to checkpoint immunotherapies. When patients undergoing immunotherapy developed the all-too common side effect colitis, and were treated with FMTs from healthy donors, the colitis resolved, even though it previously did not respond to steroids or other drugs intended to suppress it, Wargo reported.

Given the role that microbes play in shaping the response to cancer immunotherapies, Wargo worried that antibiotics might hamper that response. Her collaborator Dr. Laurence Zitvogel found that to be true for a number of lung cancer patients given antibiotics prior to being treated. “Those patients receiving antibiotics had dramatically worse response to therapy and worse survival,” Wargo said. She is pursuing a clinical study to further examine these preliminary results.

“There’s still a tremendous amount to be learned, but the future is looking quite bright,” Wargo concluded.
