Early Studies Suggest a New Immune Checkpoint Target for Melanoma

Medications that block the PSGL-1 protein promote an anti-tumor immune response in people with melanoma.

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Checkpoint immunotherapies have revolutionized the way in which advanced melanoma is treated. Due to these and other new therapeutic options, patients are living longer, fuller lives than ever before despite advanced melanoma. However, up to 50% of patients don't respond or go on to develop resistance to even our latest approved therapies. Thankfully, researchers such as MRA-funded investigator Roberto Tinoco, PhD, are hard at work discovering the next checkpoint inhibitors capable of revving up the immune system and fighting melanoma.

The protein PSGL-1 has been known since 1993 and plays an important role in bringing white blood cells to areas of inflammation — a critical part of a normal immune response. In 2016, Dr. Tinoco — assistant professor of molecular biology and biochemistry at the University of California, Irvine — built upon this by discovering that PSGL-1 can also reduce the immune response when it is overexpressed, which can happen during chronic viral infection or in the presence of melanoma tumors.

"We found that excess PSGL-1 dampens T cell signaling and promotes T cell exhaustion in the body," says Dr. Tinoco. "Exhausted T Cells are associated with disease progression, treatment resistance, and metastasis — all things we don't want to see when it comes to melanoma."

Now, five years later, Dr. Tinoco and his team have shown that inhibiting this protein is not only possible, but that it may represent a new therapeutic approach to fighting melanoma. "Our lab has found that inhibiting the PSGL-1 protein may enhance and reinvigorate the immune response to melanoma," says Tinoco.

The immune system is a complex network of cells and proteins that defend the body against infection. It attacks foreign invaders, such as bacteria or viruses, and rogue cells that can cause us harm — such as cancer.

Melanoma and other cancers are often able to circumvent the immune system by releasing signals that turn it off. Checkpoint immunotherapies work to turn these switches back on, allowing the immune system to attack the cancer cells. Thus, these treatments are able to boost our immune response and allow it once again to attack melanoma.

“Checkpoint immunotherapies that target the proteins PD-1 and CTLA-4 have completely changed the way melanoma is treated, but we still need additional strategies to activate the immune system because not all patients are benefiting,” says Dr. Tinoco. “That’s why new immune system regulators, such as PSGL-1, are so exciting.”

In Dr. Tinoco’s research, he uses a variety of model systems to help him better understand the role of PSGL-1 in the anti-melanoma immune response. These models are used to test his core hypothesis — that inhibiting PSGL-1 improves tumor immune responses — and whether or not drugs can inhibit this pathway at any stage of disease. This robust modeling provides important insight into how future drugs could be customized for clinical use. “Not only do we need to prove that the absence of PSGL-1 suppresses melanoma, we want to know that people — who already have cancer — will benefit from inhibiting the protein.”

The team discovered that not only could they inhibit the PSGL-1 protein with medications, but that doing so promoted an anti-tumor immune response. “Basically, we demonstrated that blocking it creates a therapeutic benefit,” says Dr. Tinoco.

While Dr. Tinoco’s pre-clinical work is not immediately transferable to people, it offers an exciting proof of concept for future study. PSGL-1 is highly conserved, meaning that it has remained relatively unchanged despite evolution and is very similar in both people and in the types of models that Dr. Tinoco studies.

“We are also in an era of combination immunotherapy, so increasing the number of options available will give patients and doctors new tools at their disposal,” says Dr. Tinoco. “There is also real interest in how these could be combined with radiation, other checkpoint immunotherapies, or even chemotherapy agents.”

While cancer has always been a pressing personal concern to Dr. Tinoco, it wasn’t until he collaborated with senior melanoma scientist and two-time MRA-funded investigator Ze’ev Ronai that his professional interest in melanoma was sparked. “I was pursuing work in chronic viral studies and am now extending those studies to melanoma models. Bringing people together, from diverse backgrounds and experiences, is a true strength of MRA and its funding” says Dr. Tinoco.

“I want patients to know that as a scientist, I understand the importance of keeping the science moving forward. I understand what this work means to you and I take it seriously,” says Dr. Tinoco.

“As a scientist, I want patients to know that we are working every day to move science forward because we know what it represents to you. As someone who has lost family to cancer, this is a driving force for me and I take it very seriously,” says Dr. Tinoco. “I also want to say that this work would not have been possible without the support of MRA and the Denise and Michael Kellen Foundation who generously underwrote this grant award.”

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