Reviving exhausted T cells to tackle immunotherapy-resistant cancers

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Jennifer Hope, Ph.D. and Linda Bradley, Ph.D. Credit: Jennifer Hope, Ph.D. and Linda Bradley, Ph.D.

When the cells of our immune system are under constant stress due to cancer or other chronic diseases, the T cells of the immune system shut down in a process called T cell exhaustion. Without active T cells, which kill tumor cells, it's impossible for our bodies to fight back against

cancer. One of the biggest goals of immunotherapy is to reverse T cell exhaustion to boost the immune system's ability to destroy cancerous cells.

Researchers at Sanford Burnham Prebys studying melanoma have found a new way to make this happen. Their approach, described in Cell Reports, can reduce T cell exhaustion even in tumors that are resistant to clinically approved immunotherapies. It can also help T cells from becoming exhausted.

"Slowing or reversing T cell exhaustion is a huge focus in cancer research, and many researchers are working on different ways to accomplish this," says first author Jennifer Hope, Ph.D., who completed this research as a postdoctoral researcher at Sanford Burnham Prebys and is now an assistant professor at Drexel University. "This new approach could be a viable treatment on its own, but it also has tremendous potential to work synergistically with existing therapies."

Although there are established immunotherapies that target T cell exhaustion, the new approach is unique in that it targets several different aspects of the process at once. This means that it could help people overcome resistance to various anti-cancer immunotherapies that are currently available.

"One of the foundational ideas of modern cancer treatment is not relying on a single therapy, since this can cause the cancer to become resistant to that treatment," says senior author Linda Bradley, Ph.D., a professor in the Cancer Metabolism and Microenvironment Program at Sanford Burnham Prebys. "The more tools at our disposal to slow down or reverse T cell exhaustion in different ways, the better chance we have of improving precision medicine and helping more people with cancer benefit from immunotherapy."

Their approach hinges on a protein called PSGL-1, which is found in most blood cells. By studying mice with a genetic deficiency in PSGL-1, the researchers determined that this protein helps facilitate T cell exhaustion, a major roadblock to effective anti-cancer immunity.

The researchers then used an antibody to block the activity of PGSL-1 in mice with immunotherapy-resistant melanoma. They found that targeting PSGL-1 slowed the process of T cell exhaustion and helped exhausted T cells switch back into functioning T cells. These two effects significantly reduced tumor growth in the mice.

"One of the things that makes this approach unique compared to existing immunotherapies is that it directly alters the way T cells become exhausted and helps them regain their function," says Hope. "I think this is going to be crucial in terms of its translational potential."

The researchers were also able to replicate this effect in mice with mesothelioma, suggesting that the approach could be applicable to a wide range of cancers. Although the treatment they used in this study is not yet suited for clinical use in humans, the overall approach of using antibodies or recombinant proteins for immunotherapy is well established. This means that translating these results for people with cancer may just be a matter of time and testing.

"Once we've done all the necessary science, this could be really valuable, or even lifesaving, for a lot of people with cancers that are resistant to current treatments," says Bradley. "We still have a long way to go, but I'm optimistic that we're onto something game-changing here."

More information: Jennifer L. Hope et al, PSGL-1 attenuates early TCR signaling to suppress CD8+ T cell progenitor differentiation and elicit terminal CD8+ T cell exhaustion, *Cell Reports* (2023). DOI: 10.1016/j.celrep.2023.112436

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