New lipid nanoparticle-mRNA therapy combats melanoma in mouse models

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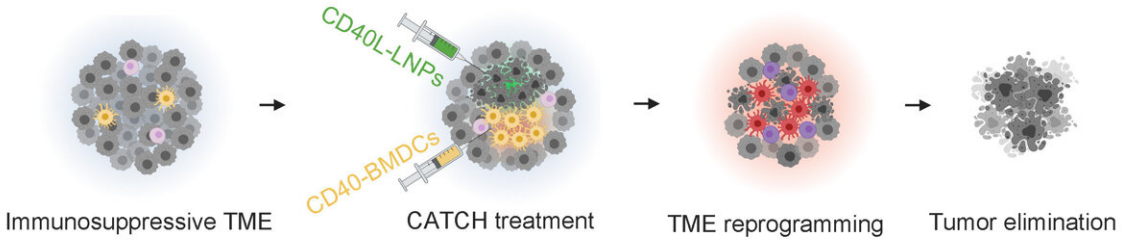

Illustration of the closing of the cancer-immunity cycle by integrating lipid nanoparticle-mRNA formulations and cell therapy (CATCH). Credit: Dong et al., Nature Nanotechnology

Investigators at the Icahn School of Medicine at Mount Sinai have designed an innovative RNA-based strategy to activate dendritic cells—which play a key role in immune response—that eradicated tumors and prevented their recurrence in mouse models of melanoma.

The findings, which suggest that the approach has the potential to be effective against tumors that have already spread to other parts of the body and against different cancer types, were reported in the July 27 issue of *Nature Nanotechnology*.

Cancer cells employ strategies to switch off various stages of the cancer-

immunity cycle, the process by which dendritic cells educate T cells to kill cancer cells. This immunosuppressive environment that impedes activation of cancer-killing T cells allows tumors to grow, say the researchers.

"Most approaches to boost this critical role of dendritic cells—or adoptive cell therapies—aim to increase the activation signals provided to dendritic cells when specific molecules on their surface bind to tumor cells. However, these have not been as successful in clinical trials as hoped. This is because tumors have a tendency to evolve in different ways to switch off each stage of the cancer-immunity cycle," says Yizhou Dong, Ph.D., corresponding author of the study.

The researchers named their approach CATCH. As part of the regimen, the researchers used new types of lipid nanoparticles to deliver two mRNA therapeutics—a process similar to that used successfully for COVID-19 vaccines—to ensure the dendritic cells were sufficiently activated to enhance the cancer-immunity cycle in established tumors.

Using multiple bioassays to gain insights on the effects of the CATCH regimen on different types of immune cells, the researchers showed that their strategy not only reactivated the cycle but also removed obstacles at other stages. This caused a change in the tumor's microenvironment, shifting it from having cell types that weaken T cells' ability to fight cancer to having cell types that actually support and enhance their ability to fight tumors.

Beyond the positive findings in mouse models of melanoma, the researchers conducted further tests to evaluate the effectiveness of the CATCH regimen in restarting the cancer immunity cycle more broadly. Their investigations revealed encouraging results, as the regimen reduced tumors in mouse models of B cell lymphoma by 83%. They also tested it in mouse models of breast cancer, where approximately half of the mice

favorably responded.

Next, the researchers plan feasibility and safety testing for using the CATCH regimen in early-phase clinical trials for patients.

"Dendritic cells have been a key focus for the development of new cancer therapies as these cells organize the cancer-immunity cycle. In theory, the CATCH regimen using this particular RNA-based technology has the potential to provide a much more effective approach for using dendritic cells for cancer immunotherapy to treat a wide range of solid tumors," says Brian Brown, Ph.D., Director of the Icahn Genomics Institute and Associate Director of the Marc and Jennifer Lipschultz Precision Immunology Institute at Icahn Mount Sinai.

The paper is titled "Close the Cancer-Immunity Cycle by integrating lipid nanoparticle-mRNA formulations and dendritic cell therapy."

More information: Close the Cancer-Immunity Cycle by integrating lipid nanoparticle-mRNA formulations and dendritic cell therapy, *Nature Nanotechnology* (2023). DOI: 10.1038/s41565-023-01453-9. www.nature.com/articles/s41565-023-01453-9

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