Two genomic studies could yield more effective, less toxic immunotherapies

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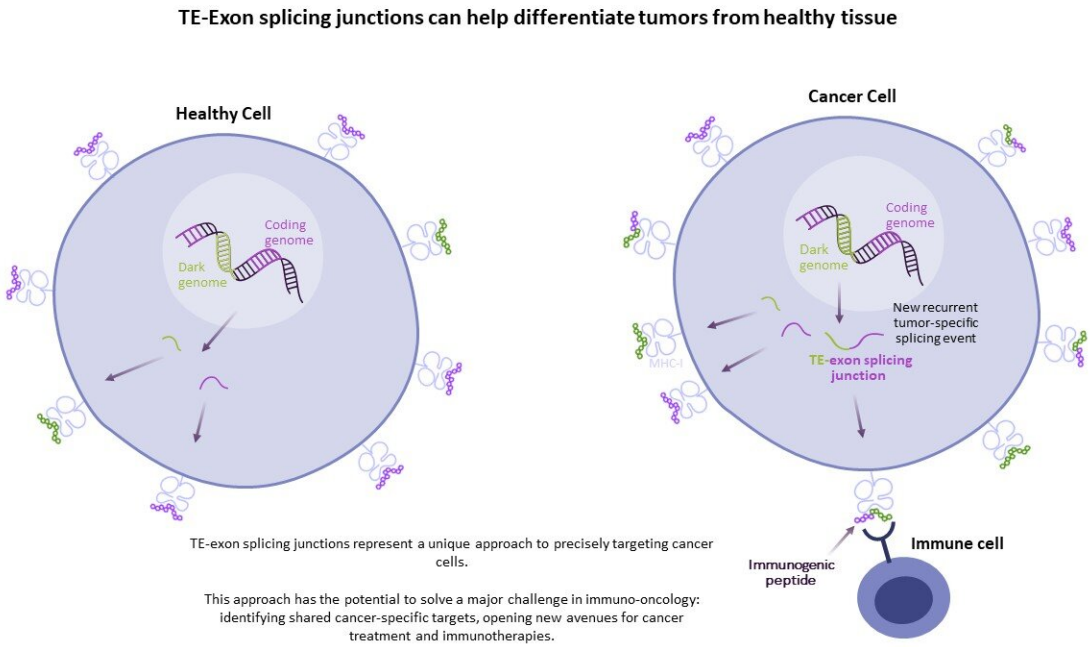

TE-Exon splicing junctions can help differentiate tumors from healthy tissue. Credit: Verge Scientific Communications / Antonela Merlotti / Marianne Burbage / Benjamin Sadacca

Mnemo Therapeutics, a biotechnology company developing transformational immunotherapies, has announced publication of two scientific studies developed at Institut Curie, its closest academic collaborator, in the journal *Science Immunology*. The publications reveal

TE-exon splicing junctions act as a source of novel recurrent, cancer-specific targets and have potential implications for developing more effective and less toxic immunotherapies. The findings presented further validate Mnemo's antigen discovery platform, which is a critical driver of the company's cell therapy pipeline.

The "grey genome," also known as the part of the dark genome that is annotated, transcribed and sometimes translated, accounts for approximately 45% of the total human genome. These genomic regions were historically disregarded because they are poorly understood; however, a recent growing body of evidence hints that probing the grey genome could expand the potential universe of previously unknown targets by identifying features that encode for cancer-specific targets that are both tumor-specific and shared by significant proportions of patients.

"Current cancer targets originate from a very small percentage of the human genome, leaving regions with potential oncology targets largely overlooked," said Robert LaCaze, CEO of Mnemo Therapeutics. "By mining the grey genome, the authors have uncovered an entirely new class of cancer antigens that are highly tumor-specific and recurrent in cancer patients. We are eager to not only better understand how these new tumor antigens synergize with our current pipeline, but also the ways they might be further leveraged as part of strategic partnerships to advance the broader immuno-oncology field."

In the first study, directed by Sebastian Amigorena, Ph.D., senior vice president, immunology, and scientific co-founder of Mnemo, CNRS Research Director and head of the Immune Responses and Cancer team (Institut Curie/Inserm) and Marianne Burbage, Ph.D., Inserm Researcher on the team, researchers identified a new family of antigens derived from non-canonical splicing junctions in mouse tumor cell lines.

These antigens prompt an immune response in tumor-bearing mice and successfully delayed tumor growth when these peptides were administered as prophylactic or therapeutic vaccines. Additionally, inactivation of Setdb1, a histone methyltransferase, resulted in increased expression of this family of antigens and tumor cell immunogenicity (the ability to trigger an immune response that stops tumor growth).

The second study, led by Amigorena and Joshua Waterfall, Ph.D., head of the Integrative Functional Genomics of Cancer team (Institut Curie/Inserm), specifically examined this family of antigens in non-small cell lung cancer (NSCLC) patient and healthy tissue samples. The team identified tumor-specific, non-canonical splicing junctions that generated immunogenic peptides in NSCLC patients, thus describing new a source of recurrent, tumor-specific antigens in NSCLC cancer patients.

"Identifying targets that are unique to cancer cells and absent from healthy tissue has been a major barrier to developing more successful immunotherapies," said Amigorena. "The collective findings advance our knowledge of tumor-specific antigens, unlocking new possibilities for the treatment of cancer not only in the cell therapy space, but across multiple approaches and modalities."

More information: Marianne Burbage et al, Epigenetically-controlled tumor antigens derived from splice junctions between exons and transposable elements, *Science Immunology* (2023). DOI: 10.1126/sciimmunol.abm6360.
www.science.org/doi/10.1126/sciimmunol.abm6360

Antonela Merlotti et al, Non-canonical splicing junctions between exons and transposable elements represent a source of immunogenic recurrent neo-antigens in lung cancer patients, *Science Immunology* (2023). DOI: 10.1126/sciimmunol.abm6359.

www.science.org/doi/10.1126/sciimmunol.abm6359

Provided by Institut Curie

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