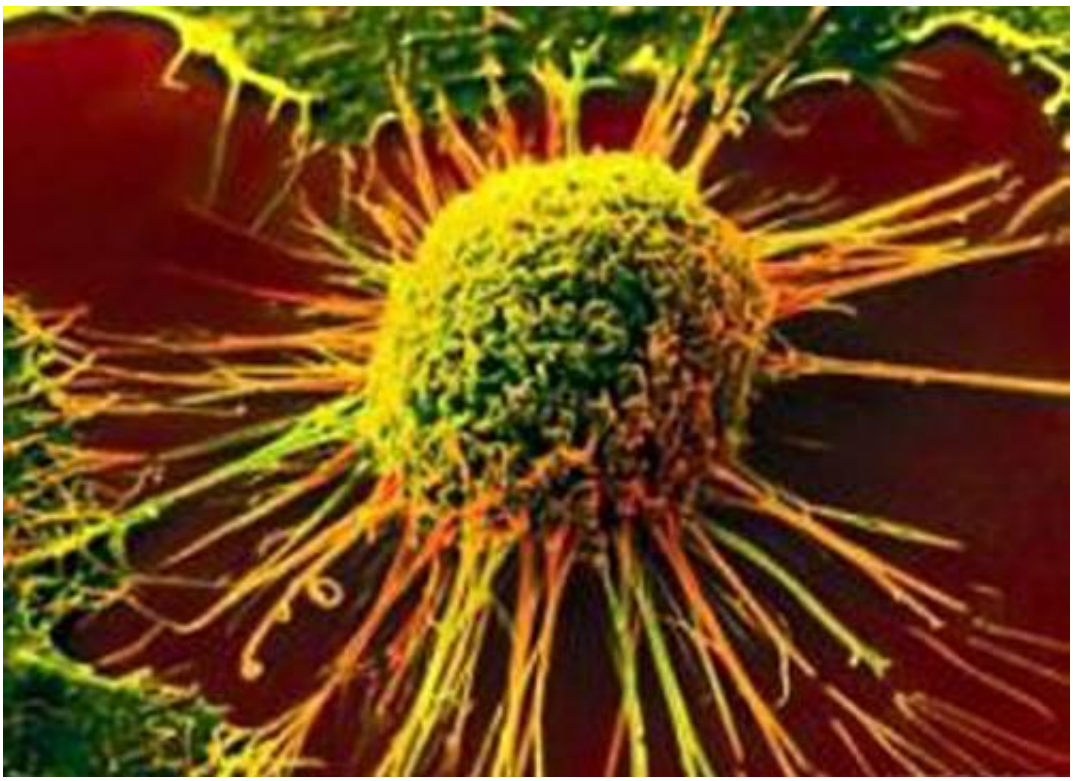
Medical Xpress

Splicing alterations that cause resistance to CD19 CAR T-cell therapy identified

October 29 2015



Bottom Line: Resistance to CD19 CAR T-cell therapy, a type of immunotherapy that yields long-lasting remissions in many patients with B-cell leukemia, can be caused by CD19 splicing alterations, leading to loss of certain parts of the CD19 protein that are recognized by the CAR T cells.

Journal in Which the Study was Published: *Cancer Discovery*, a journal of the American Association for Cancer Research

Author: Andrei Thomas-Tikhonenko, PhD, professor of pathology and laboratory medicine and pediatrics at the Perelman School of Medicine at the University of Pennsylvania, and chief of the Division of Experimental Pathology at the Children's Hospital of Philadelphia

Background: "Developed by Carl June, MD, and his colleagues at the University of Pennsylvania, CTL019 [CD19 CAR T-cell therapy] is based on the idea that the patient's own immune cells can be taken out of the body, grown in petri dishes, and altered in such a way that when returned to the bloodstream, they would kill several types of blood cancers, such as leukemias and lymphomas," said Thomas-Tikhonenko.

Although this therapy has resulted in exceptional treatment outcomes in clinical trials for pediatric patients with aggressive leukemias, about 10 to 20 percent of them see their leukemias come back after a few months, Thomas-Tikhonenko added. "Some of them can be successfully retreated, but in others a more pernicious kind of leukemia may emerge, which no longer responds to CTL019. This is because for CTL019 to work, leukemic cells need to present on their surface the target protein called CD19. In resistant leukemias, it just didn't seem to be there," he explained.

How the Study Was Conducted: To understand the mechanism of resistance, Thomas-Tikhonenko; a senior scientist from his lab, Elena Sotillo, PhD; and colleagues studied multiple tumor samples from four pediatric patients with leukemia collected before they were treated with CTL019 and/or after they developed resistance to therapy.

Results: First, the researchers found that in some cases, one of the two copies of the gene coding for CD19 and located on chromosome 16 was

deleted, and the other copy was damaged as a result of mutations in coding areas of the CD19 gene, most frequently in exon 2. However, they also learned that in the very same cases, by a process known as alternative splicing, exons 2, 5, and 6 were frequently skipped, making mutations in exon 2 largely irrelevant.

The researchers then conducted a series of experiments to understand the impact gene splicing might have on the production of CD19 protein. They found that the deletion of exons 5 and 6 resulted in premature termination of the protein and that the deletion of exon 2 resulted in the production of a modified version of CD19, which was more stable than its standard version. The shortened protein was functional and could perform many of the tasks that CD19 is known to handle.

The importance of exon skipping for resistance to CTL019 cannot be overstated, Thomas-Tikhonenko explained. "Without exons 5 and 6, the CD19 protein has no way of being retained on the cell surface. The case of missing exon 2 is more complex. Although the resultant protein can make it to the cell surface, albeit not very efficiently, it can no longer be recognized by CTL019," he said.

Designing new immunotherapeutics that can recognize the shortened version of CD19 is one approach to tackle resistance to CTL019, he added.

Author Comment: Thomas-Tikhonenko said,"Our goal was to figure out how the CD19 protein manages to vanish and whether it is gone for good or whether it could, under certain circumstances, be coaxed back. Our initial finding from this study was that in most cases the CD19 genetic code was not irretrievably lost. We also discovered that the CD19 protein was still being made, but as a shorter version, which escapes detection by the immune system."

"I think there are several lessons to be learned from our work. First, alternative splicing could be a potent built-in mechanism of resistance, and it might be better to target proteins that, unlike CD19, are not prone to exon skipping. Second, it might be important to preselect patients for CTL019 and similar therapies and make sure that the alternatively spliced CD19 variants are not already present in their leukemias. If they are, resistance could develop very quickly. Third, patients, too, can benefit from this information, because it would allow them to be matched with the best possible treatments, which is what precision medicine is all about," Thomas-Tikhonenko said.

"The most rewarding part of leading this study was to assemble in one room, on a monthly basis, great scientists coming from very different backgrounds and watch them find a common language—that of translational science," he added.

Study Limitations: A limitation of this study is the relatively small number of samples analyzed thus far, which might have prevented the researchers from identifying additional mechanisms of resistance, he added.

Provided by American Association for Cancer Research

Citation: Splicing alterations that cause resistance to CD19 CAR T-cell therapy identified (2015, October 29) retrieved 5 May 2024 from https://medicalxpress.com/news/2015-10-splicing-resistance-cd19-car-t-cell.html