Source of p53-reactive T cells: Peripheral blood from patients with metastatic solid tumors

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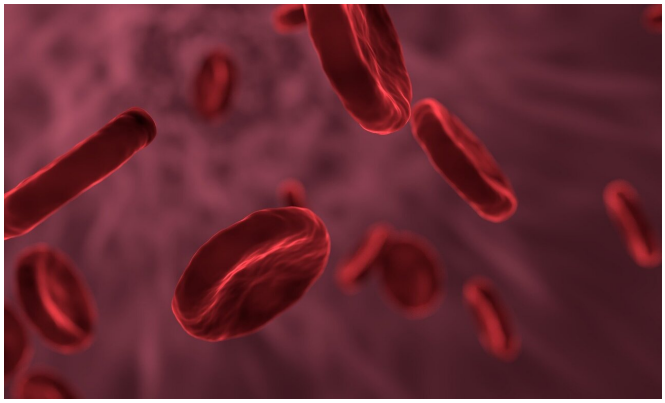

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T cells targeting p53 hotspot mutations can be harvested from peripheral blood of patients with metastatic solid epithelial cancers, according to results published in *Clinical Cancer Research*, a journal of the American Association for Cancer Research.

This finding could facilitate the development of adoptive cell therapy for solid epithelial tumors with p53 mutations.

"Solid epithelial cancers accounted for approximately 90 percent of the 600,000 cancer-related deaths in the United States last year," said Steven Rosenberg, MD, Ph.D., chief of the Surgery Branch at the National Cancer Institute's Center for Cancer Research and a pioneer in adoptive cell therapy. "Our goal is to apply adoptive cell therapy to treat these cancers." While adoptive cell therapy has shown success for the treatment of melanoma and some blood and bone marrow cancers, the treatment of solid epithelial cancers with this therapy has been challenging, explained Rosenberg.

Successful adoptive cell therapy for solid epithelial cancers relies on the selective recognition of cancer-specific mutations by T cells. "Approximately half of all human cancers contain mutations in the p53 protein. These mutations do not exist in normal cells, which means that they could be selectively targeted without affecting normal cells," said Rosenberg. "Accordingly, we have put significant effort into identifying T cells that can recognize common p53 mutations in solid cancers."

Another advantage to targeting p53 mutations is that they appear to be essential for a cancer to maintain malignancy, explained Rosenberg. Therefore, it is less likely that the cancer cells will lose the mutation and become resistant to the therapy.

A study published earlier this year—led by Rosenberg and colleagues Parisa Malekzadeh, MD, and Drew Deniger, Ph.D.—identified p53-targeting T cells by examining the immune cells found inside of tumors. "This was a very important finding in the development of immunotherapy for solid epithelial cancers," said Rosenberg. "However, the problem with finding T cells in the tumor is that it requires major surgery to resect the tumor. We were interested in determining if we could identify p53-targeted T cells from peripheral blood instead."

In this study, Rosenberg and colleagues isolated peripheral blood cells from nine patients with tumors that had p53 mutations. Since the frequency of T cells in peripheral blood is about 0.1 percent of the frequency within the tumor, the authors developed an in vitro stimulation method to expand the number of T cells to a level that was detectable in their assays.

The expanded T cells were then tested in cell cultures for reactivity to mutant p53. Peripheral blood T cells from five of the nine patients were reactive for mutant p53 in cell cultures. All five of these patients also had p53-reactive T cells within their tumors, while the four patients without p53-reactive T cells in peripheral blood lacked p53-reactive T cells within their tumors.

The p53-reactive T cells were selective for mutated p53 and were not reactive against normal p53 in these experiments.

"Our results indicate that an obstacle to performing adoptive cell therapy, which is the need to resect tumors with surgical procedures to obtain T cells, may not be necessary," said Rosenberg. "In theory, we could do a blood draw and then identify and expand reactive T cells using techniques similar to those used in this study. These findings bring us closer to the practical application of targeting common cancer mutations, such as those in p53."

Since these experiments were performed using cell cultures, clinical studies are needed to determine if any T cells isolated from peripheral blood or from the tumor would be effective against p53-mutated solid tumors in patients.

In addition, future studies from Rosenberg and colleagues will examine ways to improve the identification and expansion of T cells from peripheral blood and to overcome obstacles within the tumor. Furthermore, Rosenberg and colleagues are interested in developing "off-the-shelf" reagents to target p53 mutations. "In theory, we could have T cell receptors that recognize p53 mutations readily available to put into patients' cells, which would help expedite the process for adoptive cell therapy," explained Rosenberg.

More information: Parisa Malekzadeh et al. Neoantigen screening identifies broad TP53 mutant immunogenicity in patients with epithelial cancers, *Journal of Clinical Investigation* (2019). DOI: 10.1172/JCI123791