MedicalXpress

New immunotherapy targets misshapen protein in rare childhood brain cancer

December 4 2017

Children with an extremely deadly form of brain cancer might benefit from a new treatment that aims to direct an immune response against an abnormally shaped protein found exclusively on cancer cells, according to a new study led by UC San Francisco researchers.

The focus of the study, published online December 4, 2017 in the *Journal of Experimental Medicine*, is diffuse intrinsic pontine glioma (DIPG), an aggressive pediatric brain cancer. DIPG is rare—estimates suggest that about 300 new cases occur in the United States each year—but almost always fatal.

Because DIPG occurs in a difficult-to-access area of the brain stem that controls vital functions such as breathing, blood pressure, and heart rate, these tumors are almost impossible to remove surgically. Radiation therapy is the current standard treatment, but is rarely effective for long, according to Hideho Okada, MD, PhD, professor of neurological surgery and director of the Brain Tumor Immunotherapy Center at UCSF, and the senior author of the study.

"It is important to develop more innovative treatment approaches for childhood brain cancers, which now are the leading cause of cancer death in children. DIPG is a very deadly type of brain cancer, and not many children survive beyond 12 months from the time of diagnosis." said Okada, also a member of the Helen Diller Family Comprehensive Cancer Center (HDFCC) at UCSF and of the Parker Institute for Cancer Immunotherapy.

Okada, along with Sabine Mueller, MD, PhD, MAS, an assistant professor of clinical neurology at UCSF and a HDFCCC member, already are leading a phase I clinical trial in children with DIPG and closely related gliomas, in order to evaluate a new anti-tumor vaccine based on the new target identified by Okada's research group.

The new study's preclinical results also support the development of an immunotherapy treatment that is potentially more powerful than a simple vaccine, one in which some of the patient's own immune cells would be genetically engineered to recognize the molecular target, which is found on tumor cells in most cases of DIPG and related gliomas, but not on normal cells.

The immune system needs a boost to fight established tumors. Normally it can distinguish a healthy cell from a cell infected by invading pathogens by inspecting bits of molecules, called antigens, which cells display on their outer surface. Very early in life the immune system learns to tolerate rather than to attack cells displaying antigens made by the body's own cells. Because tumors arise from our own cells, the immune system is likely to tolerate rather than attack the cells of an established tumor.

The target of the new DIPG treatment is a "neoantigen." A neoantigen is a fragment of a protein made by a cancer cell that has an abnormal structure—and often an abnormal function—due to genetic mutation, a hallmark of cancer. Researchers are developing techniques to select neoantigens that they think will be the most likely to be seen and identified as foreign by the immune system, and they aim to develop immunotherapies to boost immune responses to tumor cells displaying these neoantigens.

Tumors often have a large variety of mutated proteins, but many of these proteins are too similar to normal antigens for the immune system to

recognize them as a threat. Even if the immune system can be coaxed to attack cells displaying a fragment of these mutant proteins, it might also learn to attack healthy cells displaying the protein's normal counterpart. In fact, autoimmunity is a risk for many patients given current immunotherapies, such as "checkpoint inhibitors," which release the brakes that prevent the immune system from attacking tumor cells.

The hope is that well-chosen neoantigens can be used to develop treatments that will more selectively and potently target tumors. Neoantigen-based treatments are still experimental, but many are in clinical trials.

The neoantigen Okada and colleagues worked with is a fragment of a protein called histone 3 variant 3. This protein is identically mutated in about 70 percent of cases of DIPG and results in abnormal control of gene activity in tumor cells. Earlier studies by other researchers found that when the mutation is present, it is present in all, or nearly all cells of the tumor.

"This may be an ideal case of a tumor neoantigen," Okada, said. "Most neoantigens in cancer are unique to individual patients, but this is one of very, very few examples of a shared, common neoantigen that may have the potential to be used in many patients."

The researchers used some of the latest computational techniques to predict that a specific fragment of the protein that includes the neoantigen would bind especially strongly to a protein called HLA A, which displays antigens for inspection by patrolling immune cells called T cells. The strength of this attachment ought to correspond to the likelihood that a neoantigen will be recognized as a threat by the immune system.

In laboratory experiments the researchers confirmed this prediction.

They found a strong affinity between the tumor neoantigen and a type of HLA A found in about 40 percent of DIPG patients. In contrast, they found no corresponding affinity between this HLA A type and non-mutated antigens from related proteins produced by healthy cells, suggesting that treatments based on this neoantigen should be specific to tumor cells only.

The goal of the neoantigen-containing vaccine now being tested in Okada and Mueller's clinical trial is to train the immune system's T cells to recognize the neoantigen in the vaccine, which should then trigger an immune response to tumor cells in the brain that display the same neoantigen, Okada said.

The new paper also demonstrates a promising, even more powerful form of treatment based on directly engineering patients' T cells to recognize the target neoantigen. Every T cell has a particular type of T cell receptor protein that can recognize a single antigen paired with an HLA protein. The scientists used T cells from patients with the HLA A type that bound tightly to the novel DIPG neoantigen to identify naturally arising T cell receptors that recognize the combination. They selected the best T cell receptor, cloned it into other T cells, and grew large numbers of these cells in the lab. They then demonstrated that these lab-grown T cells could effectively kill human glioma tumors grown in mice.

"We saw a significant reduction in tumor progression compared to control groups," said tumor immunologist Zinal Chheda, PhD, a postdoctoral fellow with Okada's lab and the co-lead author of the study. "The T cell receptor we selected for cloning has an affinity for the neoantigen that is in the range of what we see for antigens from viruses—orders of magnitude greater than what we generally see with neoantigens found on cancer cells."

More information: Zinal S. Chheda et al, Novel and shared

neoantigen derived from histone 3 variant H3.3K27M mutation for glioma T cell therapy, *The Journal of Experimental Medicine* (2017). DOI: 10.1084/jem.20171046