Delivering immunotherapy directly to brain tumors

August 29 2019

A new study led by Julia Ljubimova, MD, PhD, could help scientists develop immunotherapies for brain tumors. Credit: Cedars-Sinai

A new study gives insight into how immunotherapies, treatments that help the body's immune system fight cancer, might one day be delivered

directly to the brain in order to treat brain tumors.

The study, published this week on the peer-reviewed open access journal *Nature Communications*, demonstrated that a new type of nano-immunotherapy traversed the blood-brain barrier in laboratory mice, inducing a local immune response in brain tissue surrounding the tumors. The tumor cells stopped multiplying, and survival rates increased.

For patients with glioblastoma, the most common and also most deadly form of brain cancer, immunotherapies like this could hold the key to longer survival, said Julia Ljubimova, MD, Ph.D., senior author of the study and professor of Neurosurgery and Biomedical Sciences at Cedars-Sinai.

"This study showed a promising and exciting outcome," Ljubimova said. "Current clinically proven methods of brain cancer immunotherapy do not ensure that therapeutic drugs cross the blood-brain barrier. Although our findings were not made in humans, they bring us closer to developing a treatment that might effectively attack brain tumors with systematic drug administration."

Harnessing the power of the body's own immune system to attack tumors is a concept that has intrigued investigators for decades. Scientists have been studying ways to persuade the immune system to attack tumors in the same way that it attacks, for example, a virus.

While promising, this idea presents a few key challenges, especially when it comes to brain tumors. The environment of the brain can be hard to penetrate with drugs or other therapies. The blood-brain barrier, which the body uses to naturally block toxins and other harmful substances in the bloodstream from getting into the brain, can keep out potentially lifesaving treatments.

In addition, brain tumors seem to have the effect of suppressing their local immune systems. Tumors accumulate immunological guards such as T regulatory cells (Tregs) and special macrophages, which block the body's anti-cancer immune cells, protecting the tumor from attack, Ljubimova said. In order to allow tumor-killing immune cells to activate, investigators needed to find a way to arrest or deactivate the tumor-protecting Tregs and macrophages.

Other immunotherapies have been successful in triggering an immune response in the whole body, which can slow the growth of tumors and extend the life of patients, but this treatment is one of the first of its kind to demonstrate the activation of both whole body and local immune systems around the tumor in laboratory mice.

The immunotherapy tested in this study works by delivering checkpoint inhibitors, a type of antibody drug that can arrest and block Tregs and macrophages, so the tumor can't use them to block the incoming tumor-killing immune cells.

Those checkpoint inhibitors are attached with a biodegradable polymer to a protein or peptide that enables the drug to traverse the blood-brain barrier.

"The checkpoint inhibitors can then block the Tregs and macrophages, allowing the local immune cells to get activated and do their job-fight the tumor," Ljubimova said.

With the tumor-shielding cells blocked, immune cells like cytotoxic lymphocytes and microglial cells can then attack and destroy the cancer cells.

"Drug delivery is the major obstacle for the treatment of central nervous system diseases, including brain conditions," Ljubimova said. "The

horizon for treatment of brain cancer is getting clearer. We hope that by delivering multifunctional new-generation drugs through the blood-brain barrier, we can explore new therapies for many neurological conditions."

Ljubimova says that further tests are needed before this therapy can be tested in humans.

More information: Anna Galstyan et al, Blood–brain barrier permeable nano immunoconjugates induce local immune responses for glioma therapy, *Nature Communications* (2019). DOI: 10.1038/s41467-019-11719-3

Provided by Cedars-Sinai Medical Center