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Scientists breach brain barriers to attack tumors

16 January 2020 | News

Researchers have found a novel way to circumvent the brain's natural defenses when they're counterproductive by slipping immune system rescuers through the fortresses' drainage system



The brain is a sort of fortress, equipped with barriers designed to keep out dangerous pathogens. But protection comes at a cost: These barriers interfere with the immune system when faced with dire threats such glioblastoma, a deadly brain tumor for which there are few effective treatments. Yale researchers have found a novel way to circumvent the brain's natural

defenses when they're counterproductive by slipping immune system rescuers through the fortresses' drainage system.

"People had thought there was very little the immune system could do to combat brain tumors," said senior corresponding author Akiko Iwasaki. "There has been no way for glioblastoma patients to benefit from immunotherapy."

Iwasaki is the Waldemar Von Zedtwitz Professor of Immunobiology and professor of molecular, cellular, and developmental biology and an investigator for the Howard Hughes Medical Institute in the US.

While the brain itself has no direct way for disposing of cellular waste, tiny vessels lining the interior of the skull collect tissue waste and dispose of it through the body's lymphatic system, which filters toxins and waste from the body. It is this disposal system that researchers exploited in the new study.

These vessels form shortly after birth, spurred in part by the gene known as vascular endothelial growth factor C, or VEGF-C.

Yale's Jean-Leon Thomas, associate professor of neurology at Yale and senior co-corresponding author of the paper, wondered whether VEGF-C might increase immune response if lymphatic drainage was increased. And lead author Eric Song, a student working in Iwasaki's lab, wanted to see if VEGF-C could specifically be used to increase the immune system's surveillance of glioblastoma tumors. Together, the team investigated whether introducing VEGF-C through this drainage system would specifically target brain tumors.

The team introduced VEGF C into the cerebrospinal fluid of mice with glioblastoma and observed an increased level of T cell response to tumors in the brain. When combined with immune system checkpoint inhibitors commonly used in immunotherapy, the VEGF-C treatment significantly extended survival of the mice. In other words, the introduction of VEGF-C, in conjunction with cancer immunotherapy drugs, was apparently sufficient to target brain tumors.

"These results are remarkable," Iwasaki said. "We would like to bring this treatment to glioblastoma patients. The prognosis with current therapies of surgery and chemotherapy is still so bleak."

The study was primarily funded by the Howard Hughes Medical Institute and the National Institutes of Health.

Other Yale authors are Tianyang Mao, Huiping Dong, Ligia Simoes,Braga Boisserand, and Marcus Bosenberg. Salli Antila and Kari Alitalo of the University of Helsinki are also authors.