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Overcoming the Barrier to the Brain: Repurposed Drug Gives Hope to Glioblastoma Patients

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Malignant brain tumors are among the most feared cancer types. Ninety percent of patients with glioblastoma, the deadliest form of malignant brain tumor, die within five years after diagnosis. Treatment is both difficult and painful, and can cause further brain damage and diminish the patient's quality of life. The standard treatment is surgical removal of the tumor along with radiation therapy and chemotherapy. Drugs that could be used as alternatives to the standard treatment do exist. However, they are ineffective due to the difficulty of delivering them to the brain. As a result, much of the recent research on brain disease treatment has focused on finding non-invasive ways to get therapeutic compounds into the brain without compromising normal brain functioning.

A closed door

Our brain is protected by a cellular barrier known as the blood-brain barrier. The difficulty in delivering therapeutic compounds to the brain lies partly in the existence of a blood-brain barrier protein known as P-glycoprotein, or P-gp. P-gp acts as a gatekeeper, allowing only essential nutrients to get into the brain while keeping toxic chemicals away. Although protective, P-gp is also a major obstacle to treating brain disorders such as glioblastoma, because it can block the entry of drugs that could otherwise be helpful to treat the disease. "P-gp is the bottleneck that blocks treatment of neurological conditions," says Dr. Margaret Bynoe, professor of Immunology in the Department of Microbiology and Immunology. Bynoe and her colleagues target P-gp as a way to open the blood-brain barrier and get therapeutic compounds into the brain.

Lexiscan is the key

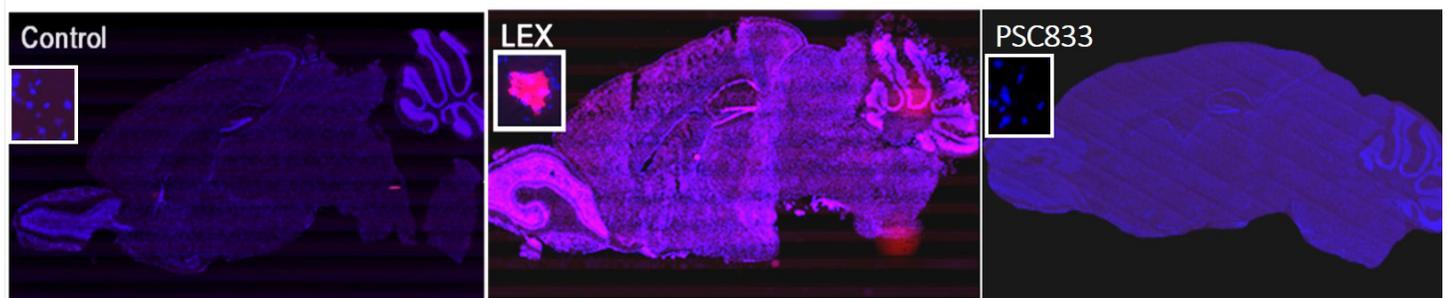
To do this, they use a drug called Lexiscan, an FDA-approved compound used clinically for diagnosing heart disease. Bynoe and her colleagues found that Lexiscan transiently opens the blood brain barrier in mice, and that administering therapeutic compounds along with Lexiscan increases the accumulation of those compounds in the brain. Lexiscan does this by reducing the activity of P-gp as well as by activating one of the receptors for a molecule known as adenosine.

Adenosine: Where it all began

The first clues to adenosine's involvement in opening of the blood brain barrier came from studies conducted by Bynoe's group in which blocking the receptor for adenosine prevented the migration of cells through the blood brain barrier. They observed the same results in mice that were engineered to be incapable of making adenosine. Bynoe and her colleagues then asked: "If lack of adenosine or blockade of the receptor for adenosine blocks cell migration through the blood brain barrier, how about activating the receptor?" This led Bynoe's group to experiments using 5'-N-ethylcarboxamide adenosine (NECA), a compound that can activate all four of the adenosine receptors. NECA increased the permeability of the blood brain barrier in mice and caused the accumulation of fluorescent dyes in the brain.

Of the four known receptors for adenosine, the A_{2A} receptor is highly present in the cells that form the blood brain barrier. “We heard of a drug that specifically targeted the A_{2A} receptor and that was already FDA-approved. I said let’s test it,” says Bynoe. “Our most exciting finding was that Lexiscan could simultaneously ablate P-gp as well as ablate the proteins that hold endothelial cells together.” This resulted in permeation of the blood brain barrier in a rapid but reversible manner.

The image below shows brain tissue sections from mice treated with Lexiscan and Epirubicin, a chemotherapeutic agent. Epirubicin, shown in red, entered the brain within 15 minutes of Lexiscan treatment (middle image). Blocking P-gp with PCS833 -a well-known inhibitor of P-gp currently in clinical trials-did not have the same effect (right image), indicating that Lexiscan is a much more powerful inhibitor. This experiment supported a role for Lexiscan in potentially reducing the activity of P-gp and simultaneously allowing the accumulation of therapeutic drugs in the brain.



Images of brain sections from mice showing the accumulation of the chemotherapeutic agent Epirubicin (middle image) inside the brain.

Bynoe’s findings have implications for the treatment of neurological diseases as well as a wide variety of cancers, not just those that affect the brain. Our kidney, liver, and gut use P-gp and therefore these findings can affect how we treat diseases that attack those organs. Moreover, P-gp is one of the reasons for therapy-resistant cancers. “Lexiscan not only holds promise for neurological diseases; we can also use it to treat pretty much every single resistant cancer on the face of the earth. That, to me, is even bigger than just being able to treat neurological diseases,” says Bynoe.

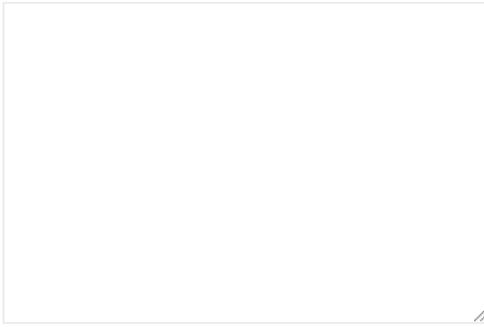
Currently, Bynoe is collaborating in two clinical trials conducted at Johns Hopkins Hospital and the National Institutes of Health where they have enrolled more than a dozen patients with glioblastoma. She has agreed to work with them to guide them and make suggestions based on her understanding of how Lexiscan works. They hope to use Lexiscan to deliver Temozolamide, a chemotherapeutic agent, in the brains of these patients in hopes that it will shrink the tumor and prolong their life. So far, some of the enrolled patients are already undergoing treatment. “To date, there hasn’t been a single patient that has survived glioblastoma,” says Bynoe. “I’m hoping that lives will be prolonged or even saved.”

-Luisa Torres, Postdoctoral Researcher in Microbiology & Immunology

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