Exploiting fungal mechanisms to breach the blood–brain barrier

Dr Angela Gelli is a professor in the department of Pharmacology at the University of California, Davis, where she is the principal investigator at the Gelli Lab, as well as a founder and president of NanoCERE Technologies. Her research focuses on the pathogenesis of a fungus called Cryptococcus neoformans, which can cross the blood–brain barrier (BBB) and is the leading cause of fungal brain infections. Dr Gelli’s research has exciting implications for the delivery of drugs into the brain to treat a variety of neurological diseases.

Dr Gelli’s work focuses on Cryptococcus neoformans, a fungal infection capable of causing brain damage and death due to its ability to cross the blood–brain barrier. The brain protects itself from foreign and toxic bodies by having a tight wall between the brain and the blood surrounding it, called the brain endothelium, or blood–brain barrier (BBB). C. neoformans is important because it can cross this barrier, often causing devastating brain disease.

The fungus causes meningoencephalitis, a form of fungal meningitis, which worldwide infects approximately one million people and causes around 600,000 deaths per year. It predominantly infects people with already impaired immunity, such as those who are HIV-positive. The disease is fatal in the absence of treatment but occasionally even after successful treatment neurological deficits can remain. This is thought to be because of the permanent change caused to the BBB following a breach.

CROSSING THE WALL

There are two main mechanisms by which foreign (fungal) bodies can cross the BBB:

1. The ‘Trojan Horse’ mechanism, whereby cells passively migrate across the barrier inside white blood cells; and secondly, the transcellular mechanism, which allows the active internalisation of cells by triggering receptors in the endothelium.

C. neoformans uses the second, transcellular mechanism by causing changes in protein expression. In order to gain access to the central nervous system (CNS), the fungus engages the endothelial cells that form the barrier to the brain, damaging vital parts of the cell structure and causing their irreversible decline. This compromises the integrity of the BBB as a whole, which partly explains why those who have recovered from infection can experience neurological sequelae and a more permeable BBB.

THE SMUGGLER

Gelli’s work has shown that C. neoformans crosses the BBB by means of a metalloprotease called Mpr1 that is secreted by the fungus. Metalloproteases are enzymes that degrade proteins, and Mpr1 is part of a family called fungyalysins produced by some fungi.

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Mpr1 works by promoting attachment to the surface of endothelial cells by changing the physical characteristics of the C. neoformans–endothelium interface. In an active, receptor-mediated process, Mpr1 stimulates the formation of strand-like protrusions on the endothelium surface called microrills, which act almost like Velcro to enhance the adhesion of C. neoformans on the endothelium.

The precise mechanism by which C. neoformans crosses the BBB is not yet clear, however, it is the crucial role that Mpr1 plays in facilitating migration across the BBB.

In vitro and in vivo studies by Gelli’s team showed that strains of C. neoformans that did not express the metalloprotease could not cross the BBB, demonstrating its importance in breaching the endothelium and gaining access to the CNS.

Furthermore, the team also engineered a non-pathogenic form of yeast that could cross the BBB purely by getting it to express Mpr1.

WHAT C. NEOFORMANS CAN HELP CURE BRAIN CANCER

Exploiting this new information about how C. neoformans crosses the BBB may also be key to developing novel platform technologies for the delivery of drugs that can treat other neurological diseases. Prime examples of such diseases are aggressive forms of brain cancer such as glioblastoma, the most common form of brain cancer in children, which currently has a mortality rate of around 80%. Most chemotherapy drugs are severely limited by their inability to cross the BBB and while new models of glioblastoma in mice, before examining the activity of these nanocarriers, this time laden with drugs to treat tumours, in a mouse model of glioblastoma.

They hope to test the ability of Mpr1 to facilitate the internalisation of neurological drugs into the brain using in vivo and in vitro techniques, following three research aims. They will first create a recombinant version of Mpr1 which can effectively penetrate the endothelium. Then they aim to track nanocarriers in vivo to determine the presence of the BBB and in vivo models of glioblastoma, before examining the activity of these nanocarriers, this time laden with drugs to treat tumours, in a mouse model of glioblastoma.

The dire need for a mechanism to get neurological drugs into the brain to treat life-threatening diseases makes Gelli’s work exceedingly important. The team hope that the Mpr1-mediated pathway is just one of many that will unearth and can apply to a variety of neurological diseases. Hopefully they will be able to revolutionise chemotherapy and drastically improve clinical outcomes.