Description of research

There are four main cell types in the brain: (a) neurons, which transmit and process information via electrical signals, (b) oligodendrocytes, which insulate neuronal processes called axons with fatty sheets called myelin to ensure fast and complete electrical signal transduction, (c) microglia, which provide defence against potential infections in the brain and, (d) astrocytes, which provide metabolic support for neurons and ensure their proper functioning, are involved in immune defence and maintain healthy microenvironment in the brain. These cells, and indeed all living cells, have a wide range of proteins called receptors on their surface, which are activated by signalling molecules. EBI2 is one such receptor that plays very important roles in the biology of immune cells, where it regulates antibody production to fight infections. Every receptor has its ligand, a molecule that activates the receptor when it binds to it. Receptors and their ligands are like locks and keys, only a specific key opens a specific lock. The EBI2 receptor's ligand (key) is an oxysterol 7 α,25HC.

Blood vessels in the brain are built differently than the blood vessels in the rest of the body. The main difference is that in the brain the blood vessels are not leaky and only certain molecules and cells can pass through this so called blood-brain barrier, which protects the brain from harmful substances, cells and microbes. This barrier is damaged in multiple sclerosis and as a result cells from the immune system, that usually do not have access to the brain, can enter and attack myelin formed by oligodendrocytes. The existing therapies for multiple sclerosis prevent the entry of these harmful cells from the blood vessels into the brain via the blood-brain barrier.

Project goal

This research aims to investigate whether EBI2 receptor (lock) and oxysterol 7α,25HC (key) are present specifically in the cells that form the blood vessels in the brain. We will investigate if the receptor (lock) or its ligand (key) are involved in the immune cells crossing from the blood into the brain via the blood-brain barrier. We will research whether there are differences in the amount of receptor and oxysterols in the blood vessels in people who have multiple sclerosis and whether bodily fluids taken from multiple sclerosis patients affect proteins in mouse brain tissue. We will also research disease-causing interactions between proteins in fluids taken from multiple sclerosis patients and compare them to protein interactions in fluids taken from healthy people.

Reasons for attempting this research topic

Our research so far has shown that EBI2 is present on the surface of brain cells that also form the blood vessels in the brain, namely astrocytes. We have discovered that EBI2 receptor plays important roles in the brain such as immune defence, cell movements, formation of myelin and many others. Importantly, research done by us and other groups suggests that EBI2 receptor and oxysterols are involved in multiple sclerosis disease processes. For instance, a study has found that EBI2 receptor is present at higher amounts in areas where myelin is lost in the brain of multiple sclerosis patients. Different study has found that the receptor is present at higher levels in blood lymphocytes that attack myelin in multiple sclerosis patients who take a certain multiple sclerosis therapy called natalizumab. The proposed research will allow us to further investigate the function of EBI2 receptor and oxysterols in multiple sclerosis disease processes.

Expected results

We expect to find that EBI2 receptor (lock) is present and oxysterol (key) is produced by the cells that form the blood vessels in the brain. We also hypothesise that EBI2 receptor and oxysterol are involved in immune cell crossing through the blood-brain barrier into the brain and that blocking the receptor or lowering the amount of oxysterol at the blood-vessels will reduce the number of immune cells entering the brain. Bodily fluids taken from multiple sclerosis patients will change the proteins present in mouse brain tissue. We also expect to find novel disease-causing interactions between proteins in bodily fluids taken from multiple sclerosis patients.

Implications of the research results

Findings resulting from this project are important because they will provide new facts on the role of EBI2 receptor in the brain and in multiple sclerosis and will possibly lead to a discovery of new disease processes, diagnostic markers and possibly even new treatment options in multiple sclerosis.