CHARACTERIZING TSPO EXPRESSION AND RADIOLIGAND-BINDING IN THE CENTRAL NERVOUS SYSTEM AND PERIPHERAL BLOOD IN NEUROINFLAMMATORY DISEASE

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ABSTRACT

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) that is a leading non-traumatic cause of disability in young adults. The 18 kDa Translocator Protein (TSPO) is a mitochondrial protein and positron emission tomography (PET)-imaging target that is highly upregulated in MS brain lesions and may potentially represent both an inflammatory biomarker and a therapeutic target for the monitoring and treatment of MS. However, its pathological significance is not well understood. While experimental autoimmune encephalomyelitis (EAE) in the common marmoset is a well-established primate model of MS, TSPO expression in this model has not yet been studied. Moreover, the comparison of TSPO expression and PET radioligand signal in inflammatory conditions has been limited by the lack of suitable unfixed pathological samples for concurrent measurement of protein expression and radioligand-binding.

In this thesis, I seek to characterize patterns of TSPO expression in fixed CNS tissues from EAE marmosets using multiplex immunofluorescence and directly compare TSPO protein expression measured by flow cytometry with radioligand-binding signal in the peripheral blood of healthy donors and MS patients. Through these studies, I have established that marmoset EAE recapitulates temporal and cellular patterns of TSPO expression seen in MS, rendering it a suitable model for the study of human disease that may give insight into the pathological significance of TSPO in immune dysregulation. Furthermore, I have found TSPO expression in the peripheral blood of MS patients to be significantly increased, suggesting TSPO to be a useful peripheral biomarker of CNS disease. However, I found that radioligand-binding by second-generation PET radioligand PBR28 is paradoxically decreased in the peripheral blood of MS patients, implying that the clinical utility of PBR28 may be limited, likely by conformational changes occurring in inflammation. Collectively, these results allow us to better interpret the pathological significance of TSPO expression and TSPO-radioligand binding in the CNS and peripheral blood in neuroinflammatory disease.