A multimodal, translational approach to clarify the role of microglial dysfunction in schizophrenia

Virtual event held on 17th February 2021, 9:00-11:00 (GMT)

The objective of this JSPS London Seminar was to bring together expertise from the fields of PET imaging in clinical populations, cellular neuroscience, and animal models of chronic environmental stress and associated immune response to discuss the nature of microglial dysfunction in schizophrenia.

The Seminar followed the programme below.

09:00 Housekeeping, Professor Oliver Howes, King's College London
09:05 Opening remarks, Professor Nobuo Ueno, Director of JSPS London
09:10 1st presentation + Q&A, "A multimodal approach to study microglial dysfunction in patients with schizophrenia: the IRIS-iMG project", Dr Yuya Mizuno, King's College London
09:35 2nd presentation + Q&A, "Directly induced microglia-like (iMG) cells from peripheral blood as a dynamic translational research tool", Dr Takahiro Kato, Kyushu University
10:00 3rd presentation + Q&A, "Chronic stress-induced neuroinflammation and its relevance to mental illness", Professor Tomoyuki Furuyashiki, Kobe University
10:25 Panel discussion + Q&A
10:45 JSPS funding opportunities, Ms Polly Watson, International Programme Coordinator of JSPS London
10:55 Closing remarks, Professor Oliver Howes, King's College London
11:00 End of event

The first speaker, Dr Yuya Mizuno presented the ongoing Inflammatory Response in Schizophrenia (IRIS) study. This is a PET imaging study which aims to quantify microglial activation in the brains of patients with schizophrenia, and whether this can be targeted using the monoclonal antibody natalizumab. As a collaborative project within this study, the speaker is collecting blood samples which will enable collaborative iMG experiments with Dr Kato's group at Kyushu University, Japan. The collaborative project aims to combine *in vivo* markers of overall microglial activation (PET imaging), *in vitro* markers of dynamic microglial function (iMG), and inflammatory markers in the blood and cerebrospinal fluid to gain a holistic picture of microglial dysfunction in schizophrenia. The speaker presented results from his preliminary PET analysis indicating increased microglial activity in the temporal lobes of patients with schizophrenia compared to healthy controls.

The second speaker, Dr Takahiro A Kato presented the rationale for creating experimental models of microglia-like cells. The speaker then discussed the protocol which his group developed to generate induced microglia-like (iMG) cells from human peripheral blood mononuclear cells (PBMC). As presented by the speaker, these cells show dynamic functional characteristics consistent with microglia *in vitro*, and have

been used to examine abnormalities in the cellular response of microglia-like cells in a range of neurological and psychiatric disorders. The strengths and limitations of the iMG method in comparison to protocols which induce microglia-like cells from induced pluripotent stem cells (iPSC) were discussed. The need to examine the heterogeneity of iMG cells using single-cell analysis, and co-culturing of microglia-like cells with induced neurons and/or astrocytes to examine interactions between cell types were discussed as future directions for research.

The third speaker, Professor Tomoyuki Furuyashiki presented his research using the repeated social defeat stress paradigm, which highlights the pivotal role of innate immunity in the relationship between chronic stress and behavioral/emotional changes. Findings from the speaker's research and others have demonstrated that chronic stress induces microglial activation and stress-induced neural and behavioral changes. The speaker's group showed that chronic stress mobilizes leukocytes from the bone marrow, and a subset of these leukocytes infiltrates the brain and amplifies neuroinflammation and its neural consequences. The speaker discussed that such brain-periphery interaction of inflammation upon stress might explain the comorbidity of mental and physical symptoms in neuropsychiatric illnesses including schizophrenia.

The three presentations were followed by a panel discussion mediated by Professor Oliver Howes. Many interesting comments and questions were raised from the audience including suggestions to assess markers of blood-brain barrier permeability in the clinical study presented by Dr Mizuno, and the generalisability of Professor Furuyashiki's findings to other forms of chronic stress.

Finally, Ms Polly Watson shared information regarding various funding opportunities that JSPS offers.

Over 50 participants from the UK, Japan and elsewhere participated in this event. The full recording of the event can be accessed via the link below.
https://www.dropbox.com/s/91dvsn80wzkhlbv/JSPS%20London%20Seminar.mov?dl=0
-Dr Yuya Mizuno, King's College London.