ABSTRACT

Student Sessions

1-SS-01 THE CRITICAL ROLES OF GINGIPAINS IN CELL MIGRATION AND INFLAMMATORY RESPONSES OF MICROGLIA THROUGH ACTIVATION OF PROTEASE-ACTIVATED RECEPTOR-2 (PAR-2)

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Despite a positive relationship between periodontitis and cognitive decline associated with Alzheimer's disease has been demonstrated, the precise mechanism by which periodontitis affects the cognitive functions remains unclear. Gingipains, cysteine proteases secreted by P. gingivalis, are known as important virulence factors of periodontal diseases. In this study, we have thus examined possible roles of gingipains in the cellular activation of microglia.
P. gingivalis infection significantly increased the expression levels of IL-6, TNF-α and iNOS mRNA and the cell migration of cultured microglia. PAR-2 expressed in cultured microglia was activated following infection. P. gingivalis infection-induced expression of pro-inflammatory mediators, cell migration and PAR-2 activation of cultured microglia were significantly inhibited by gingipain inhibitors and functional inhibition of PAR-2. Moreover, P. gingivalis infection-induced expression of pro-inflammatory mediators, the membrane ruffling and the cell migration were significantly inhibited by PI3K/Akt signaling pathway inhibitors. Furthermore, P. gingivalis-induced cell migration of microglia in gingipain-dependent manner was also observed in vivo.
These observations suggest that gingipains play critical roles in the inflammatory response and cell migration of microglia through the activation of PAR-2.

1-SS-02 IL-10 plays a pivotal role in anti-inflammatory effects of Rheum tanguticum in activated microglia

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In recent years, Chinese herbal medicine and Asian traditional medicine has attracted researcher renewed attention on their function in the central nervous system. We have previously reported that Ratanasampil, a traditional Tibetan medicine, improves memory and learning impairment caused by Aß accumulation in Alzheimer's disease model mice and also suppresses neuronal death induced by oxidative stress. Rheum tanguticum (Rt), another traditional Tibetan medicine, is also used as commercial drugs for it's anti-inflammatory, anti-microbial and anti-tumor properties. Therefore, the present study was conducted to investigate the anti-inflammatory effects of Rt in activated microglia.
The findings of the present study first show that Rt has anti-inflammatory effects in activated microglia through the production of IL-10, which suppresses NF-κB and STAT1 pathways. The present study further provides evidence that three components of Rt are responsible for the IL-10 production in microglia. It was also noted that Rt significantly increased the mean mRNA expression level of MEF2D, a potential transcription factor of IL-10 gene. Therefore, Rt is a possible pharmacological intervention against excessive inflammation-mediated neurodegenerative diseases, including Alzheimer's disease.

1-SS-03 Role of microglia rewiring corticospinal tract after brain injury

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Brain injury that results in an initial behavioral deficit is often followed by spontaneous recovery. We previously identified that reorganization of the corticospinal tract (CST) was crucial for functional recovery. However, intrinsic molecular mechanism underlying this recovery system has not yet been elucidated. Microglia, primary immune cells in the central nervous system (CNS), are known to have a neurotoxic role and contributes to neuronal degeneration. On the other hand, recent studies showed microglia protects CNS by clearing cell debris, suppressing inflammation, and promoting neurogenesis during CNS injury. In this study, we investigated whether microglia plays a role in compensatory neural circuit formation after traumatic brain injury. Our model exhibited sprouting CST fibres from the intact-side into the denervated side of the spinal cord compensating for the lost motor function. With PLX3397 (CSF-1 receptor inhibitor), microglia depletion was seen in the spinal cord. Moreover, we found that the number of sprouting fibres were increased in PLX3397-administrated mice and by the elimination of microglia enhanced motor functional recovery. These results suggest that microglia suppresses the compensatory neuronal circuit formation.

1-SS-04 Control of neurovascular unit development by Zic family zinc finger proteins

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Recent studies showed that the blood-brain-barrier is formed by a complex interactions among vascular endothelial cells, vascular pericytes and astrocytes and neurons. These cells are orderly placed in brain capillaries, and the structure is called as neurovascular unit. In a previous study, we showed that Zic family zinc finger proteins have critical roles in the development of the meningeal cell progenitors (Inoue et al., 2008). Since the vascular cells also derive from the meningeal cell progenitors, we focused the role of Zic proteins in the neurovascular unit development in mammalian brains. Zic1, Zic2 and Zic3 were selectively and differentially expressed in the neurovascular unit-constituting cells. In particular Zic2 was expressed in vascular endothelial and pericyte progenitors. We therefore established a conditional knockout system to eliminate the expression of Zic2 in cells derived from meningeal/vascular cell progenitors. The Zic2 conditional knockout mice showed significant change of the blood vessel marker expression. These results indicated that Zic2 regulates neurovascular unit development. The analysis is being extended to the neurovascular unit-related abnormalities of the other Zic mutant mice or their combined mutants.