【Grant-in-Aid for Scientific Research(S)】

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Immune systems involved in the resolution of inflammation and tissue repair

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Research Project Number : 17H06175 Researcher Number : 90182815

Research Area : Basic Medicine Immunology

Keyword : Inflammation, Immune Signaling, Cytokine, Tolerance and Autoimmunity

【Purpose and Background of the Research】

Our group has investigated the mechanisms of promotion of inflammation by innate immune response within 7 days after onset of mouse experimental cerebral ischemia (cerebral infarction) model (Fig. 1). We discovered that infiltrating macrophages are activated by DAMPs (danger associate molecular patterns) such as peroxiredoxin derived from dead cells, and then release inflammatory cytokines during the acute phase within one day of onset of stroke. This contributes to expansion of the infarct lesion and deterioration of neurological symptoms. Then γδ T cells infiltrate 2 or 3 days after onset of stroke, and produce IL-17 that promotes deterioration of the disease state. On the other hand, we have also elucidated the mechanism of resolving inflammation. We identified the scavenger receptors for the clearance of DAMPs, and also macrophages which are involved in the termination of inflammation. Furthermore, we found that at the chronic phase of the stroke, a large amount of T cells accumulate in the brain. In this study, we aim to elucidate the significance of repairing macrophages and brain infiltrated T cells for resolution of inflammation and tissue repair and to identify factors that define these processes.

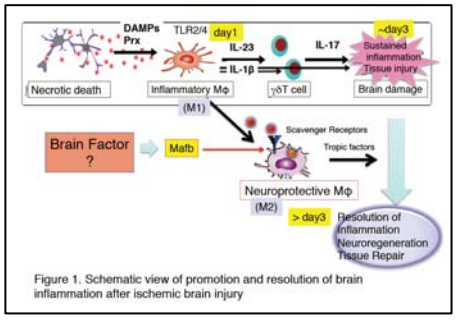

Figure 1. Schematic view of promotion and resolution of brain inflammation after ischemic brain injury

【Research Methods】

(1)Identification of the brain factor that induces repairing macrophages; It is considered that macrophages have an activity to induce expression of Igf1 and Msr1 in the brain. We will purify the factors from brain extract and examine whether this factor can induce repairing macrophages. We also search a master regulator for the generation of reparing macrophages by the RNA-seq technology.

(2) Elucidation of the mechanism of amplification and infiltration of T cells at the chronic phase of cerebral infarction; Most of CD4 positive T cells infiltrated into the brain of cerebral infarcted mice were Th1 and regulatory T (Treg) cells. In order to clarify the significance of each cell, activation of astrocytes, glial scar formation, and improvement of neurologic symptoms will be examined using IFNγ-deficient mice and Treg-depleted mice. We also analyze the chemokine-chemokine receptor and T cell receptor of infiltrated T cells and clarify the mechanism of infiltration and amplification of T cells into the brain.

(3) Elucidation of the relationship between T cells and microglia, astrocytes; We establish a co-culture system of T cells, microglia and astrocytes *in vitro* and elucidate the molecular mechanism by which T cells control these cells.

(4) Elucidation of the significance of T cells in other tissue injuries; We will investigate whether the repair mechanism in T cell tissue damage revealed in this study also applies to other chronic inflammatory systems such as myocardial infarction model and Alzheimer model.

【Expected Research Achievements and Scientific Significance】

Although inflammation has been often considered in relation to tissue injury, however, inflammation is also important for the initiation of tissue repair. In particular, there is in a dynamic equilibrium state including the acquired immune system during chronic stage of inflammation. The inflammatory processes leading from "removal of damaged cells" to "tissue repair" will be clarified by our research. Furthermore, new cells and soluble factors which are involved in these processes will be identified. Our goal is the development of new therapies for tissue injuries at the chronic phase including brain stroke.

【Publications Relevant to the Project】

Shichita T, Yoshimura A et al. Peroxiredoxin family proteins are key initiators of post-ischemic inflammation in the brain ***Nature Medicine*** 2012 Jun;18(6):911-917.

Shichita T, Ito M, Yoshimura A.et al. MAFB prevents excess inflammation after ischemic stroke by accelerating clearance of damage signals through MSR1. ***Nat Med.*** 2017 Jun;23(6):723-732

【Term of Project】 FY2017-2021

【Budget Allocation】 158, 300 Thousand Yen

【Homepage Address and Other Contact Information】 http://new2.immunoreg.jp