【Grant-in-Aid for Transformative Research Areas（B）】

Section III

Title of Project： **Integrated elucidation of inflammatory tissue-resilience and tissue damage-entropy; Creation of innovative science for resolution of inflammation**

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【Purpose of the Research Project】

Tissues, which are damaged by various causes, including infection with harmful pathogens or ischemic injury, demonstrate the “tissue resilience function” to resume their normal state to maintain organ homeostasis. Resolution of inflammation is characterized as self-limiting processes: clearance of the infiltrated inflammatory cells and restoration of damaged tissues. Meanwhile, ex-inflamed tissues store “inflammatory memories”, diverse biological information derived from the inflammation, and particularly, the accumulation of “pathological inflammatory memories”. The deposition of inflammation-generated factors, which we termed “tissue damage entropy”, leads to flare-ups or prolongation of inflammation as well as irreversible remodeling and subsequent tissue dysfunction. The next generation of therapies for intractable diseases will need to focus on how to restore better functioning tissues by means of successful elimination of “inflammatory memories” and correction of “tissue damage entropy”. To achieve this purpose, an integrated understanding of the mechanisms of tissue resilience, especially during the resolution of inflammation, is required; however, it is difficult to grasp the whole picture of the machinery of tissue resilience because various biological systems, such as the immune system and the nervous system, are interconnected in a multilayered fashion.

In this research area, we will elucidate the biological responses of physiological tissue resilience and inflammatory memory during the resolution of inflammation. Furthermore, we will revisit the pathogenesis of chronic inflammation from our distinctive perspective such as inflammatory tissue resilience, pathological inflammatory memory and tissue damage entropy, through which we aim to create a new discipline related to the resolution of inflammation.

【Content of the Research Project】

In this Research Area, we will target (A) inflammatory memory, (B) inflammatory tissue resilience, and (C) tissue damage entropy. For these three themes, the following will be elucidated within the research period (Figure 1).

Group A "Inflammatory memory and resolution of inflammation": Kiyoshi Hirahara (Chiba University) aims to elucidate the mechanisms through which “inflammatory memory” is induced and maintained in the local inflammatory tissue. To this end, we will investigate how tissue-resident memory T (T_{RM}) cells are induced and maintained *in vivo*. Group B "Inflammatory tissue resilience and convergence of inflammation": Satoko Arai (The University of Tokyo) aims to elucidate the molecular mechanisms that define inflammatory tissue resilience, focusing on the molecular machinery underlying the removal of dead cells and dead cell-derived pathogenic self-materials from inflammatory tissue by investigating the roles of macrophages including tissue-resident macrophages, inflammatory monocytes, and in particular restorative macrophages that emerge in resolution phase, in regulation of inflammatory tissue resilience. Group C "Tissue damage entropy and resolution of inflammation": Yohei Mikami (Keio University) aims to elucidate how tissue damage entropy is increased by the acquisition of tissue resident cell diversity. The aim of this research is to identify the specific cell populations responsible for increasing tissue damage entropy using a comprehensive gene expression analysis of various cell populations, including the resident stromal cells.

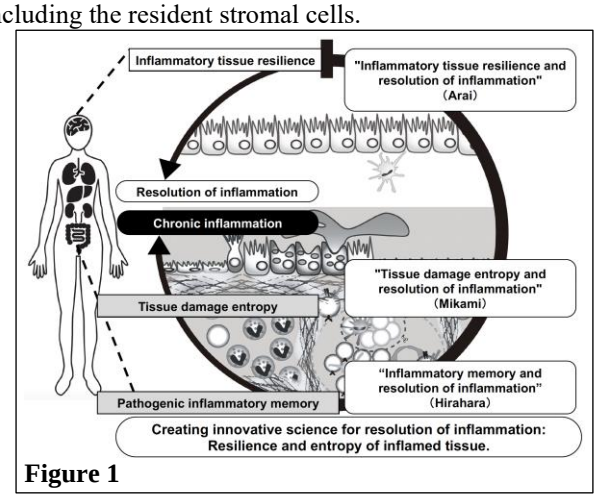

Figure 1

【Expected Research Achievements and Scientific Significance】

We aim to create an innovative science for "resolution of inflammation" that will enable us to understand tissue resilience mechanisms as a multidimensional biological homeostatic system conserved in all living species. We will establish the molecular basis of the resolution of inflammation by investigating inflammatory tissue resilience mechanisms. Furthermore, we aim to elucidate the pathogenesis of various intractable diseases by developing "clinical inflammation resolution science".

【Key Words】

Inflammatory tissue resilience; Resuming the normal state of damaged tissue to maintain organ homeostasis

【Term of Project】 FY2021-2023

【Budget Allocation】 105,000 Thousand Yen

【Homepage Address and Other Contact Information】

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