

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

Biological Sciences (Medicine, dentistry, and pharmacy)



Title of Project : Identification of Cellular Signaling Mechanism that regulates inflammation and tissue repairing

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Research Area : Basic Medicine Immunology

Keyword : Inflammation, Immune regulation, Signal Transduction

【Purpose and Background of the Research】

The immune system proceeds through the balance between positive and negative signals, which is necessary for maintaining homeostasis. There is a flexibility between these signals, and the strength of immune reactions determines the balance. Such homeostasis and plasticity are maintained by cytokines and growth factors, and breakdown of the balance causes immune diseases, such as allergy, inflammatory disease and autoimmune diseases (Fig.1). The aim of this study is defining the molecular mechanisms that supports the balance between pro- and anti-inflammatory systems. We will also develop new therapeutic method for such immunological disorders. We will discover new signals and cytokines that promotes inflammation as well as anti-inflammation and tissue repair.

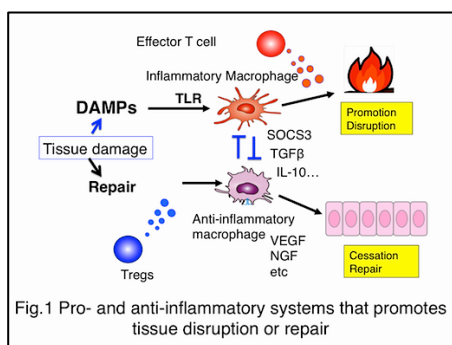


Fig.1 Pro- and anti-inflammatory systems that promotes tissue disruption or repair

【Research Methods】

We will try to analyze interaction of molecules and cells from the point of view of immune balance between pro-inflammatory and anti-inflammatory signals. We will establish a paradigm that can be extended to other fields. (1) We will define the molecular mechanism of interaction between pro-inflammatory signals (eg. NF-kB, STAT1) and anti-inflammatory signals (eg. IL-10-STAT3 and TGF-beta-Smad and PGE2-cAMP) by using epigenetic analysis (2) Immune balance in the brain and intestine will be analyzed in vivo by using various reporter mice. We will define cells that produce and receive cytokines. (3) We will find new factors that promotes resolution of inflammation and tissue repair. Role of these factors will be clarified using in vivo disease models.

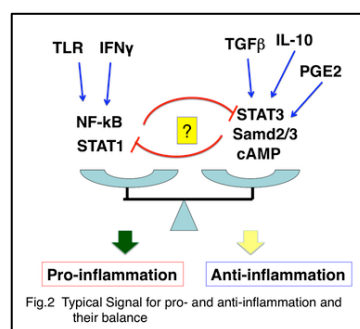


Fig.2 Typical Signal for pro- and anti-inflammation and their balance

【Expected Research Achievements and Scientific Significance】

Recent progress in this field clarified the factors and signals that promotes inflammation. However, mechanisms of anti-inflammation, resolution of inflammation and tissue repair are still largely known. In addition, relationship between immune balance and tissue repairing has not been clarified. Our goal is define the molecular mechanisms that making balance between pro- and anti-inflammation. Our study will promote our understanding of immune regulation and will be extended to develop novel therapeutics for acute tissue damaging diseases.

【Publications Relevant to the Project】

- Sekiya T, Yoshimura A. et al. Nr4a receptors are essential for thymic regulatory T cell development and immune homeostasis. *Nature Immunol.* 2013 2013 Jan 20;14(3):230-7.
- Hasegawa E, Yoshimura A et al. IL-23 Independent Induction of IL-17 from $\gamma\delta$ T Cells and Innate Lymphoid Cels Promotes Experimental Intraocular Neovascularization. *J Immunol.* 2013 Feb 15;190(4):1778-87.
- 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):911-7.

【Term of Project】 FY2013-2017

【Budget Allocation】 147, 600 Thousand Yen

【Homepage Address and Other Contact Information】

<http://new.immunoreg.jp/>