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Special Issue: Singularity Biology and Beyond

Commentary and Perspective (Invited)

Elucidating molecular and cellular mechanisms of singularity phenomena in immunology

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Many of the immune-related events such as pathogen elimination, tissue destruction in autoimmune patients, and tumor eradication through immunotherapy do not progress gradually; rather, they often happen suddenly with involvement from a very limited number of immune cells. In the "Singularity Biology" research project supported by the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) as scientific research on innovative areas, such sudden events are considered as "singularity" phenomena [1], and a variety of groups investigated the molecular and cellular mechanisms of singularity phenomena in immunology.

Our group investigated the roles of co-receptors and immune microenvironment in the regulation of rare T cells reactive to self-tissues and tumors. First, we demonstrated that self-reactive $CD8^+$ T cells in non-obese diabetic mice go through four activation phases and PD-1, an inhibitory co-receptor, strongly attenuates the transition from the second to the third phase, where effector functions are acquired [2]. Next, we found that T cell receptor (TCR) signal strength required for the induction of genes varies across different genes, and PD-1 preferentially inhibits the induction of genes that require stronger TCR signal [3]. We further demonstrated that PD-1 inhibits the expression of TCR-inducible genes efficiently when the affinity of TCR to antigen is low [4]. In addition, we found that PD-1 function is restricted at the activation phase of T cells for the optimal induction of T cell responses [5,6]. We also revealed the establishment of immuno-suppressive microenvironment in tumors and draining lymph nodes during the early phase of tumor development, which attenuates the proliferation of tumor-specific T cells and tumor eradication. These results strongly suggest that inhibitory co-receptors and immune microenvironment play crucial roles in the occurrence of singularity phenomena [7,8].

The group lead by Masahiro Ono (Kumamoto University and Imperial College London) aimed to identify and analyze the rare and unique T cells that are at the bifurcation point in T cell activation and differentiation by analyzing the spatiotemporal dynamics of T cell responses [9,10]. Shinya Tanaka (Kyushu University) tried to develop a novel sensor to monitor the dynamics of self-reactive T cells in the murine model of lupus erythematosus [11]. Minako Ito (Kyushu University) investigated the immune response that regulates the expansion of rare cells that play a key role (i.e., singularity cells) in the development of neurodegenerative diseases [12]. Shunsuke Chikuma (Keio University) focused on the epitope spreading to determine the point of no return for the establishment of autoimmune symptoms. Shinichiro Kato (Nagoya University) aimed to identify a singularity cancer cell(s) that instigates resistance to cancer immunotherapy by establishing a novel RNA-expressed barcode technology. Naotoshi Nakamura (Osaka University) aimed to identify outlier immune cells from a set of imaging data and reveal their functional significance using extreme value statistics. Jun Arii (Kobe University) tried to identify and characterize cells that trigger the onset of viral encephalitis that infrequently occurs in herpes virus infection [13]. Yusuke Ohba and Yoichiro Fujioka (Hokkaido University) aimed to identify and characterize singularity cells in viral infection to elucidate the mode of infection in the real world [14]. Yuhei Maruzuru (The University

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of Tokyo) tried to establish the concept that the viral production from infected cells is regulated digitally using omics-based analysis and imaging technology [15].

As described in the beginning, many of the immune-related events can be considered as singularity phenomenon in which a very limited number of cells play a critical role. Continued interdisciplinary investigations are needed for the identification and characterization of such singularity cells, ultimately leading to a comprehensive understanding of the molecular and cellular mechanisms underlying singularity phenomena in immunology.

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