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Breaking Symbiosis in Tumor Microenvironment with Small Molecule

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Editorial

When I was asked to write 2-page editorial for Symbiosis Online Journal Immunology, I contemplated the meaning of symbiosis in immunology. The first thing that came up in my mind was the question how I can connect the symbiosis to drug development.

When I started postdoctoral work in the laboratory of Dr. Reinherz at Dana-Farber Cancer Institute, Harvard Medical School, I was fascinated with the beautiful tissue organization of thymus. Thymus is constituted with several irregular round-shape medulla surrounded by outer cortex. The outer cortex is densely packed with $CD4^+CD8^+$ double positive immature thymocytes but the inner medulla is filled with $CD4^+$ or $CD8^+$ single positive mature T cells. Thymic epithelial cells secrete several chemokines such as CXCL12, CCL19 and CCL21. These chemokines control thymocyte migration for the clear separation of developing thymocytes into different thymic compartment. My first question was why each animal has different shape and distribution of medulla. If thymic epithelial cell development is the first step for the construction of thymic architecture, I guessed that all the organisms should have a similar pattern in medulla distribution. The irregularity of medulla distribution suggested that thymic epithelial development is not dependent on epithelial cell alone but on the interaction with other cells such as developing thymocytes. When T cell development was induced with anti CD3ε antibody injection into the $TCR\beta^+$ $Rag2^{-/-}$ mice where thymus has only cortex and T cell development was blocked at $CD4^+$ $CD8^+$ double positive stage, T cell development was resumed temporarily and the medulla developed again promptly [1]. This result suggested that the interaction between epithelium and lymphocyte affects the development of both sides.

There are several examples for such interactions between immune cells and stromal compartment. In particular, the interaction between tumor cell and microenvironment controls cytokine production or suppresses immune systems for tumor survival. The interaction of LLPC (long lived plasma cells) or multiple myeloma cells with BMSC (bone marrow stromal cells) is essential for their proliferation. IL6 and BAFF from BMSC induce multiple myeloma cell profilieration [2]. DKK1 from myeloma cells inhibits osteoblast differentiation from mesenchymal cells and bone formation, providing more spaces to myeloma cells for expansion [3]. In melanoma tumor environment, CD8 T cell infiltration induces PD-L1, IDO and Treg cells which suppress immune response to tumor cells for melanoma cells to escape immune surveillance [4]. All together, these results suggest that the low efficacy of chemotherapy may be due to the tumor environment in part.

Recent advances in biologics field provided antibody-based drugs for tumor therapy by breaking immune tolerance to tumor. The strong anti-tumor efficacy of anti CTLA4 and PD1 antibodies (BMS-936558 and ipilimumab, respectively) implies that controlling tumor microenvironment would be a key issue in small molecule drug development, too [5,6]. Until now, most of target-specific small molecule drugs were developed based on the direct efficacy on tumor cells without considering the control of tumor environment. In near future, I hope that breaking symbiosis between tumor cells and tumor microenvironment would be one of main topics in this Symbiosis Online Journal Immunology.

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