Asian Transplantation Week 2023

Nov. 15(Wed)~18(Sat), 2023
Conrad Seoul, Korea

Submission No.: PG07-9329
Session : Postgraduate Course 7 (Basic)
Date & Time, Place : November 16 (Thu), 13:00-14:30, Room 6F-1
Session Title : Newly emerging immune cells

CD8+ regulatory T cells

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CD8$^+$ regulatory T cells From Mice to Humans: Uncovering Novel Insights into CD8$^+$ regulatory T cells The identification of regulatory CD8$^+$ T cells that suppress pathological immune responses has been a long-standing goal of immunological research. The idea of regulatory CD8$^+$ T cells originated from a study examining Qa-1-dependent T cell-T cell suppressive interactions in a mouse model of experimental autoimmune encephalomyelitis. Further investigations using Qa-1 KO mouse revealed that Qa-1-dependent regulatory CD8$^+$ T cells could be identified by their CD122^{hi}Ly49$^+$phenotype. In this mouse model, the expansion of pathogenic follicular helper T (T_{FH}) cells and the development of systemic lupus erythematosus (SLE)-like features were observed. CD122^{hi}Ly49$^+$CD8$^+$ T cells were identified as crucial regulators of hyper-activated Qa-1-expressing T_{FH} cells. Additionally, interleukin-15 (IL-15) has been shown to have a significant role in supporting the development and function of CD122^{hi}Ly49$^+$CD8$^+$ T cells. Molecular mechanisms behind the regulation of CD8$^+$ T cells also have been explored. The modulation of CD122^{hi}Ly49$^+$CD8$^+$ T cells is governed by several molecular mechanisms, including the necessity of TGF-β signal-induced Helios for sustaining their stable suppressive functions and role of Eomes in their homing ability within follicular regions. Mouse Ly49 receptors share several fundamental characteristics with human inhibitory NK receptor known as killer-cell immunoglobulin-like receptors (KIRs) in terms of binding to MHC-I and delivering inhibitory signals via immunoreceptor tyrosine-based inhibitory motifs (ITIMs). Recent studies have revealed the role of KIR-expressing CD8$^+$ T cells in humans as the human equivalent of mouse Ly49$^+$CD8$^+$ regulatory T cells. KIR$^+$CD45RA$^+$CD8$^+$ T lymphocytes were shown to suppress the proliferation of KIR-NKG2A typical CD8$^+$ T cells in a dose dependent manner. In addition, KIR$^+$CD8$^+$ T cells have been found to suppress pathogenic CD4$^+$ T cell responses in patients with autoimmune diseases such as celiac disease, multiple sclerosis and SLE, as well as in individuals infected with the influenza virus or SARS-CoV-2. Specific subsets of KIR-expressing CD8 T cells, such as CD161$^-$CD56$^+$CD8$^+$ T cells, can exert regulatory functions through NK receptors independently of TCR engagement. I will provide a comprehensive summary of the current understanding of the biology regulatory CD8$^+$ T cells and discuss their role in human disease and explore their potential therapeutic applications.