Abstract:

Display of thousands of self-antigens in the thymus is fundamental for the establishment of central tolerance as its failure can lead to the development of autoimmunity. Medullary thymic epithelial cells (mTECs) and thymic dendritic cells (DCs) constitute essential populations of antigen presenting cells (APCs) which present these self-antigens to developing T cells. While mTECs produce and present antigens in self-autonomous manner, DCs can hijack mTEC-derived antigens by the process of cooperative antigen transfer (CAT). It is well found that CAT is essential for working central tolerance, however, the overall heterogeneity of thymic APCs participating in CAT remains unclear. Using transgenic mouse models and multicolor flow cytometry analysis, we determined that APCs involved in CAT are exclusively of $CD11c^+$ phenotype. Within these cells, we identified previously unrecognized $CX3CR1^+$ subset of migratory DCs (mDCs) exhibiting monocyte/macrophage markers. These $CX3CR1^+$ mDCs are more efficient in CAT than their $CX3CR1^-$ counterparts and reveal robust antigen presenting properties with the capability to present CAT-acquired antigen. Genetic ablation of $CX3CR1^+$ mDCs resulted in increased cellularity of $CD8^+$ and $CD4^+$ thymocytes, indicating importance of this mDC subset for negative selection of self-reactive T cell clones. In addition, for the very first time, we visualized CAT *in vitro* by using fluorescence microscopy. While further work is required to formally prove the role of $CX3CR1^+$ mDCs in thymic T cell selection processes, our work, in a broad sense, provides a comprehensive analysis of the contribution of distinct subsets of thymic cells to CAT and shows an experimental platform for the assessment of functional relevance of various smaller DC subsets in establishment of central immune tolerance.

Key words:

central tolerance, mTEC, dendritic cell, cooperative antigen transfer, CX3CR1, transgenic mouse