Generation of T cells with diverse reactivity by regenerating thymic function

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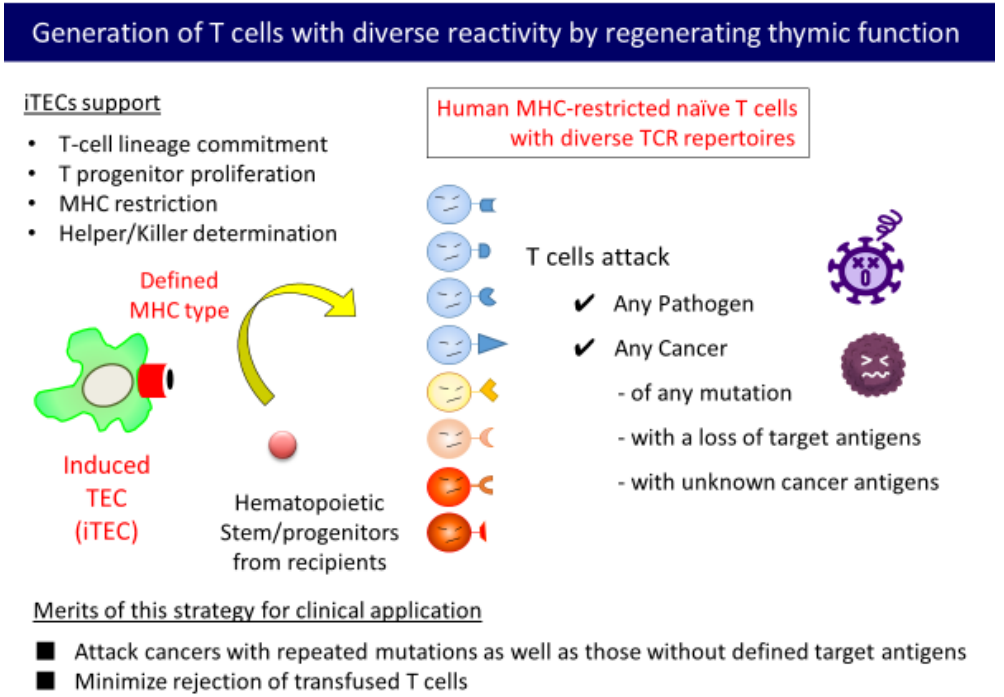
The regeneration of T cells that recognize antigens specifically expressed on cancers is an emerging form of immunotherapy. However, a frequent recurrence of tumors losing the expression of the target antigens by further mutations has compromised this strategy. T cells can theoretically react to any antigen by generating a highly diverse T-cell receptor (TCR) repertoire that can be only achieved during their differentiation in the thymus. The aim of this project is to regenerate thymic function by inducing thymic epithelial cells (TECs), which are indispensable stromal components for developing T cells and ensuring MHC restriction. As cellular sources, we will use human iPS cells, which are available from desired MHC haplotype donors, or human keratinocytes, which are easily available self-somatic cells and share similar biological properties as TECs. Using induced TECs (iTECs), we will establish a method to induce human T cells with a diverse TCR repertoire from primary hematopoietic stem/progenitor cells. This strategy could lead to significant advances in T-cell immunotherapies that reduce relapse and increase the number of patients who benefit from the immunotherapy. Furthermore, this strategy avoids the risks related to gene transduction in T cells and minimizes the rejection of transfused T cells in patients.



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