Transcription factor Hoxb5 reprograms B cells into functional T lymphocytes

With the support by the National Natural Science Foundation of China, the research team led by Prof. Wang JinYong (王金勇) at Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences recently reported that transcription factor Hoxb5 reprograms B cells into functional T lymphocytes, which was published in *Nature Immunology* (2018, 19: 279—290).

Regeneration of functional T cells by reprogramming approach has been a central aim for regenerative medicine. The failure of mimicking thymus niches curbs the derivation of induced T cells from pluripotent stem cells (ESC/iPSC). Pro-B cells are widely used for reprogramming due to their abundant resource, natural genetic barcodes, and epigenetic plasticity. Attempts to convert B to T cells by silencing B lineage master genes have had limited success, in that it has not been possible to reconstitute the entire T lineage functionally, and in some instances, the manipulations increased cancer risk.

Wang and colleagues performed functional screening by an *in vivo* reprogramming platform and identified that Hoxb5, a transcription factor preferentially expressed in uncommitted hematopoietic stem/progenitors but absent in B cells and T cells, reprogrammed pro-B cells into early T lymphocyte progenitors (iETP) in irradiated animals. The reprogramming process started in bone marrow, forming ETP-like cell intermediates, and was completed in thymus, giving rise to functional iETP cells. The iETP cells were capable of differentiating into mature polyclonal iCD4SP and iCD8SP T cells in thymus, which showed a similar hierarchical pattern as their natural counterparts. The iT cells proliferated and secreted cytokines *in vitro* in response to stimuli. Further, the iT cells complemented the T-immune deficiency in Rag1$^{-/-}$ mice, which rejected allogeneic skin graft and formed adaptive immune memory. Mechanistically, Hoxb5 mediated the B cell fate-to-T cell fate conversion by repressing B cell master regulators, activating T cell regulators, and targeting chromatin modifiers and remodelers.

This study showed a rare example that a factor neither expressed in the initiating cell type nor in the terminal cell type could trigger complete cell fate change *in vivo*, revealing the complexity of cell fate regulation. This study provides an alternative approach to regenerate functional T cells for translational research.

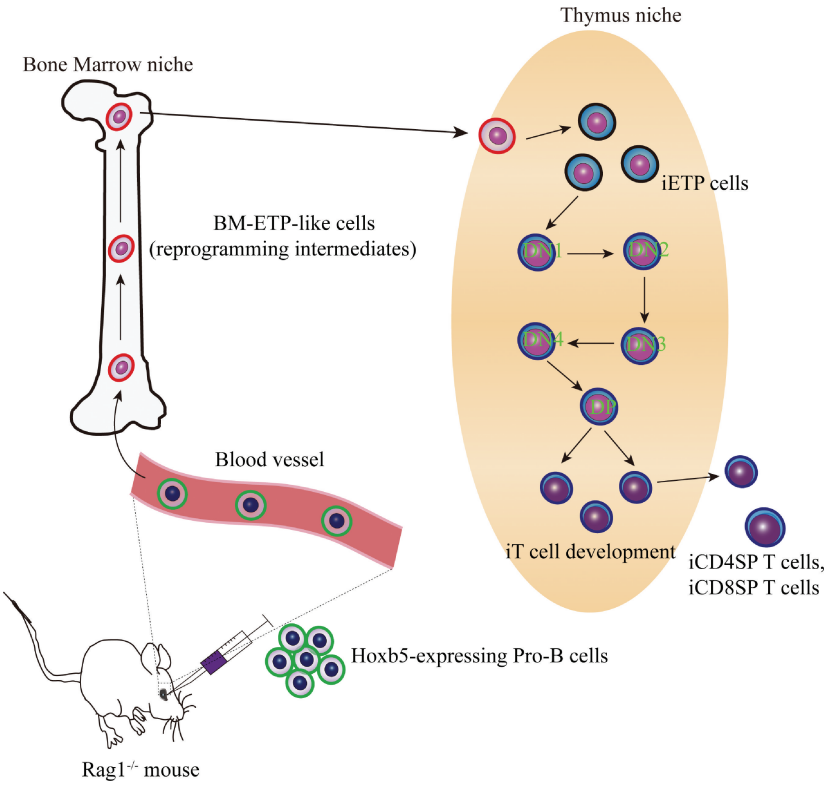

Figure Schematic diagram of B cell-to-T cell conversion induced by Hoxb5 *in vivo*.