Roles of Runx Transcription Factors In Immune System Development

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Runx transcription factors complexes, which acts as heterodimer of Runx and Cbfβ proteins, are evolutionally conserved transcriptional regulators that play numerous roles during development of multiple hematopoietic cells. Mammal Cbfβ gene generates two RNA splice variants, Cbfβ1 and Cbfβ2, each of which harbors distinct C-terminal amino acid sequences. Our study using mouse strains lacking either Cbfβ1 or Cbfβ2 reveals that Cbfβ2 had unique function in generation of primary and secondary lymphoid tissues in part by endowing tissue-homing capacity to hematopoietic-lineage cells. For instance, Runx/Cbfβ2 complexes are essential for induction of CCR9 chemokine receptor in pre-thymic fetal liver thymocyte progenitors via activating cell type-specific enhancers. Thus, C-terminal sequences of Cbfβ protein serves as a regulatory module to diverse Runx complexes function. Given that Runx proteins contain an evolutionarily conserved penta-peptide sequences, VWRPY, at the C-terminal end, we address whether the VWRPY motif play any regulatory roles for Runx complexes function by replacing the last Tyrosine (Y) to Tryptophan (W) in murine Runx3 protein. Homozygous Runx3WRPW/WRPW mutant mice show severe reduction of CD8+ T cell, NK cells, Langerhans cells, gut γδT cells and group 1 and 3 innate lymphoid cell (ILC1/3). In addition, was also observed in Runx3WRPW/WRPW mice lack second lymphoid tissues, which was observed by attenuated Runx1 function rather than Runx3 deficiency. Along with intermediate phenotype observed in heterozygous Runx3+/WRPW mice, Runx3WRPW mutant protein is likely to act as a dominant negative form that interfere with not only Runx3 but also some Runx1 function.