Involvement of Notch-HES signalings in T cell development.

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During development of nervous system in Drosophila, it is well-known that cell-cell interactions play a crucial role in specifying cell fate and this involves signalings through the transmembrane receptor Notch. Notch is widely conserved from flies to vertebrates and functions in a novel signal transduction pathway. Mammalian homologs of Notch have been identified and shown to be expressed not only in the nervous system but also in the hematopoietic-lymphoid organs including bone marrow and thymus.

In the thymus, developing T cells undergo a selection process based on the ability of their T cell antigen receptors (TCRs) to recognize MHC molecules expressed on thymic epithelial cells. The interaction between developing thymocytes and thymic epithelial cells promotes the survival of thymocytes and also affects the choice between the CD4 and CD8 T cell lineages. While it is clear that MHC recognition influences the choice, the mechanistic basis for this influence is not known.

HES-1 is a member of a family of a mammalian basic helix-loop-helix factor genes homologues to Drosophila hairy and Enhancer of split, and is suggested to be a direct target of Notch signaling pathway and acts as a negative regulator of neurogenesis. To investigate the role of Notch signaling in thymic development in the mouse by a loss-of-function analysis, we have examined mice targeted disruption of the HES-1 locus because Notch1 null mutation mice die by 9.5 days postcoitum when T cell development dose not occur. Surprisingly, the mice homozygous for the mutation exhibited thymus formation defects. Then, T cell development of HES-1 null mice was analyzed by co-culture of fetal liver cells with deoxyguanosine-treated fetal thymic lobs (FTOC). In FTOC of fetal liver cells from HES-1 null mice, reversion of the ratio $\alpha\beta$: $\gamma\delta$ T cells was observed after 2 weeks culture (normal mouse ; $\alpha\beta$ T cells 15%, $\gamma\delta$ T cells 5% : HES-1 null mice ; $\alpha\beta$ T cells 8%, $\gamma\delta$ T cells 15%). There was no significant difference in ratio CD4 : CD8 between normal and the mutation mice. However, more than 50% of CD8 T cells express $\gamma\delta$ TCR in FTOC of HES-1 null mice while most CD8 cells expressed $\alpha\beta$ TCR in normal mice. These results implicate Notch signaling pathway as a participant in the $\alpha\beta$ versus $\gamma\delta$ T cell lineage decision and suggest that $\gamma\delta$ T cell lineage is first fate of T cell development.

References

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