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The gods of human T cell development

T cells are the component of the immune system required for recognizing and targeting pathogens and tumor cells. Because each T cell recognizes a different pathogen, the challenge of T cell development is to create a pool of T cells that is highly diverse and can target any pathogen we might encounter. In addition to the complexity of a generating a diverse lymphocyte repertoire, developing T cells receive signals that dictate whether they will become $CD4^+$ T cells, which direct the adaptive immune response, or $CD8^+$ T cells, which directly mediate destruction of virus-infected cells and tumor cells. Within the $CD4^+$ population, some cells differentiate into regulatory T (Treg) cells, which suppress the immune response and maintain homeostasis. During these cell fate decisions, T cells receive signals through multiple receptors and the signals are coordinated through the expression and activation of transcription factors. Dysregulation of the transcription factors can cause the developing T cells to become leukemic.

A family of transcription factors critical for the regulation of cell fate decisions is the Ikaros family, which includes five members: Ikaros, Helios, Aiolos, Eos, and Pegasus. Each family member can associate with itself or each other family member to form a dimer. Dimerization is essential for the ability of Ikaros family members to function. For this reason, it is critical that we understand how the expression of each Ikaros family member changes during T cell development. Changes in one family member alters the ratio of each family member to each other, thereby affecting the nature of the dimers formed and the function of the Ikaros family.

In our recent papers, we defined the pattern of Ikaros expression at each stage of human T cell development. Human T cell development has not been as thoroughly described as murine T cell development, so we first needed to identify the developmental stages at which major checkpoints occur. A major checkpoint during T cell development is the expression of T cell receptor (TCR) β chain, one of two proteins required for antigen recognition. This step occurs during the transition from the $CD4^-CD8^-$ double negative (DN) developmental stage to the $CD4^+CD8^+$ double positive (DP) developmental stage. Passage through this checkpoint is associated with a transient increase in the expression of Ikaros, Aiolos, and Helios. Of these, the greatest increase was observed with Helios and only the increase in Aiolos protein levels persisted through the next stages.

The next developmental checkpoint is positive selection, which occurs after TCRa is expressed. Our in-depth analysis of human T cell development showed that this checkpoint could be found in a developmental stage after the DP stage. Cells undergoing positive selection decrease their expression of CD4 to become transitional single positive (TSP) $CD8^+$ thymocytes. At the TSP stage, cells also undergo lineage commitment, in which the decision to become $CD4^+$ or $CD8^+$ T cells occurs. At positive selection and lineage commitment, there was another transient increase in the expression of Ikaros, Helios, and Aiolos. Aiolos levels continued to increase as cells matured, while Ikaros and Helios levels declined with continued maturation, except for the small population of cells that are destined to become Treg cells; Treg cells maintain high Helios expression.

In summary, we defined the stages of human T cell development in more detail than has been previously reported. At each major developmental checkpoint, the relative expression of each Ikaros family member changes in a manner that would likely lead to altered dimer composition within the cell.

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Publications

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