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T-cell sensitivity: A microRNA regulates the sensitivity of the T-cell receptor

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T cells must change their T-cell receptor sensitivity towards antigen during development to allow delivery of positive-selection signals in the thymus while avoiding activation of mature T cells by self-antigens. In a striking new study, Chen and colleagues reveal that a microRNA whose expression is regulated during T-cell development controls changes in T-cell antigen receptor (TCR) sensitivity during T-cell maturation.

In healthy immune systems, immune responses are mounted against foreign antigens but not endogenous self-antigens. For T cells, this paradigm is established during a highly regulated developmental process that occurs in the thymus. During thymic development, the T-cell antigen receptor (TCR) samples a broad array of self-peptides presented in major histocompatibility complex (MHC) molecules on the surface of antigen-presenting cells. The selection of the developing thymocytes has a 'Goldilocks' quality; only those cells whose TCR's affinity for self is 'just right' survive to populate the periphery.[1] T cells with no affinity for self die by neglect; those with high affinity for self die through negative selection. Those that are 'just right' are positively selected and populate the peripheral lymphoid organs. However, this raises a conundrum. All positively selected T cells must react with self-antigens to survive; thus, how can negative selection rid the mature repertoire of all autoreactive T cells? T-cell responsiveness to specific ligands must change during the development of the cell to permit deletion of immature autoreactive thymocytes and prevent autoreactivity in the mature repertoire. Indeed, maturation in the thymus is accompanied by substantial changes in the cell's responsiveness to TCR ligation so that mature peripheral lymphocytes are less responsive to low-affinity ligands than are thymocytes undergoing selection. This change in the sensitivity of the TCR shifts the mature T-cell repertoire from self- to foreign responsiveness.

How does the T cell developmentally regulate its sensitivity? In a paper recently published in *Cell*, Li, Davis, Chen and their Stanford colleagues suggest that TCR sensitivity is controlled by developmental changes in the expression of microRNAs.[2] Micro-RNAs are ~22-nucleotide non-coding RNAs that control cellular and developmental processes by modulating epigenetic events or post-transcriptional gene silencing. Micro-RNAs control gene expression through recognition and binding of target sequences in the 3′untranslated regions of mRNAs that leads to target mRNA degradation or translational repression.

The current manuscript focused on one particular microRNA, miR-181a, which is limited to the hematopoietic system and can influence the differentiation of T and B cells.[3] Li and colleagues found that mIR-181a expression is dynamically regulated during T-cell development. Specifically, expression of the microRNA was significantly higher in unselected, immature 'double positive' DP cells – which are more sensitive to low-affinity peptide–MHC complexes – than in more mature selected T cells. This suggested that mIR-181a might be involved in the developmental alteration of TCR sensitivity.

Overexpression of miR-181a in mature T cells resulted in a substantial increase in the sensitivity to both low-affinity and high-affinity peptide–MHC complexes with enhanced intracellular calcium flux and production of the cytokine, interleukin-2. In contrast, inhibiting expression of miR-181a in immature developing thymocytes impaired their selection.

T-cell receptor signaling and T-cell activation are mediated by a cascade of phosphorylation and dephosphorylation events. Li and her colleagues hypothesized that miR-181a might enhance T-cell sensitivity by controlling the expression of negative regulatory tyrosine and serine phosphatases. Computational analysis of candidate genes identified a number of phosphatase genes with potential mIR-181a pairing sites; protein levels of the phosphatases SHP-2, PTPN22, DUSP5 and DUSP6 were reduced by overexpression of mIR-181a.

Interestingly, Neilson, Sharp and their colleagues at MIT took a distinct approach to catalog the expression of microRNAs during thymic development and also showed that miR-181a was enriched in immature thymocytes.[4] However, they identified a different set of target genes, including the anti-apoptotic protein, Bcl-2, and the cell surface regulator, CD69.

What are the implications for this work? First, is the concrete observation that a differentially expressed microRNA acts as a ‘rheostat’ controlling the developmental sensitivity of the T-cell antigen receptor. Second, this work shows that the microRNA pathway offers a multitarget mechanism for coordinate regulation of the T-cell developmental program – altering sensitivity of the TCR, which changes at different stages, as well as expression of other proteins such as Bcl-2 and CD69 that are developmentally regulated.

Are there therapeutic applications for these observations? There are two obvious clinical scenarios where alteration of TCR sensitivity would have utility. The expression level of mIR-181a is relatively low in mature, peripheral T cells. However, decreasing the expression of miR-181a may decrease the responsiveness of the autoreactive T cells that cause diseases such as type I diabetes mellitus and multiple sclerosis. More relevant may be the contrasting application to tumor immunotherapy. The immune response to tumors is compromised by failure to mount immune responses to tumor antigens perceived as self-antigens. Targeted expression of miR-181a in tumor-specific T cells should enhance their sensitivity to tumor antigens and improve the efficacy of tumor immunotherapy. As more data about the regulation of the immune response by microRNAs are obtained, we look forward to such clinical trials.

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