MicroRNA mediates CD8+ T cell dysfunction in chronic viral infection

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Editorial

Primary infections are generally cleared by antigen-specific effector T cells. As a result of clearance of primary infections, memory T cells are produced that are highly functional and provide a long-lasting protective immunity. In contrast, chronic viral infections often cause the development of dysfunctional T cells that respond to the antigen very poorly and are not sufficient to mount an efficient protective immune response. In case of chronic lymphocytic choriomeningitis virus (LCMV) infection in mice, some of the effector $CD8^+$ T cells get exhausted while others are deleted. Thus, a persistently high level of antigens caused $CD8^+$ T cells exhaustion or dysfunction [1-3]. In case of chronic viral infection, the exhausted $CD8^+$ T cells overexpress several inhibitory receptors and show altered expression of other genes involved in performing antiviral function efficiently [4].

MicroRNAs (miRNAs), a class of small non-coding RNAs, regulate the pattern of gene expression by translational repression and mRNA destabilization. Also, miRNAs play a critical role in the development of T cells as the conditional deletion of the key miRNA-biosynthetic enzyme Dicer during thymic T cell development markedly reduced CD8+ T cells in the periphery [5]. Moreover, the deletion of Dicer in mature $CD8^+$ T cells impaired the effector function of $CD8^+$ T cells *in vivo* [6]. There are several miRNAs involved in various stages of T cells development, differentiation, and involved in shaping effector and memory phenotypes of the cells. Also, the role of other miRNA is well documented in T cell receptors (TCRs) signaling and variety of cytokine production, which shapes the microenvironment either pro-inflammatory or anti-inflammatory.

Recently, Moffet HF et al. studied $CD8^+$ specific inhibitory role of miR-31 in chronic viral infection [7]. They observed that miR-31 and several other miRNAs were upregulated when a variety of immune cells (CD4, CD8 T cells, and NK cells) were stimulated with anti-CD3 and anti-CD28. Also, miR-31 expression is upregulated in effector and memory cell types. However, miR-31 expression was unaffected in case of B cells when stimulated with an antibody specific for immunoglobulin M and a CpG oligonucleotide. The authors argued that TCR-engaged upregulation of miR-31is mediated via calcium signaling and subsequent NFAT transcriptional activity in CD8+ T cells. Also, they identify several new target mRNAs (Psd4, Sh2d1a, Ilf3, Coro7, Rab1b, Stra13, Cdkn1a, and Ifi30) of miR-31 along with previously known targets (Ppp6c, Lats2, Oxsr1, Elavl1, and Stk40). Further, the authors showed that $CD8^+$ T cells from $Mir31^{-/-}$ mice respond strongly when stimulated with TCR engagement as the cells showed enhanced expression of mRNAs encoding T cell effector molecules, including perforin and several granzymes, as well as osteopontin than that of wild-type cells. Moreover, $Mir31^{-/-}$ mice infected with LCMV clone 13 (a clone causes a chronic infection) did not show any symptom of chronicity while wild-type mice did. In $Mir31^{-/-}$ mice viral titer was significantly reduced after the initial course of infection.

Gene-expression profile in $miR\text{-}31^{-/-}$ showed diminished expression of genes involved in T cell dysfunction, including c-Maf, the prostaglandin E2 receptor, and metallothioneins, and also enhanced T cell effector function. The author's findings suggested that the blocking of miR-31 might be having a therapeutic potential in chronic viral infections. The similar strategy can be envisaged to overcome tumor-infiltrating CD8 T cells dysfunction [7].

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