



miR-31: the double-edged sword of CD8 T lymphocytes

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MicroRNAs (miRNAs) are small regulatory molecules that control gene expression. During the immune response, both initiation and resolution of the response must be tightly regulated to achieve a successful clearance of the infectious agent, avoiding excessive activation that could be detrimental for the host. T cell activation comprises a plethora of signaling pathways that promote expansion and differentiation of the T cell repertoire into effector and memory cells. Moreover, T cells can become exhausted and even dysfunctional under certain circumstances. However, the precise mechanisms that control these processes are only starting to be elucidated. Not surprisingly, microRNAs have important roles in the control of T cell biology and function.

The ablation of the miRNA-producing enzyme Dicer can impact both the CD8 T cell development and effector function (1-3). Moreover, several miRNAs have been described to be regulated in CD8 T cells playing important roles in their biology (4,5). Additionally, upon T cell activation, global miRNA regulation of gene expression changes dramatically due to different processes like argonaute proteins degradation (6), shortening of mRNA targets 3'UTR (7) and even post-transcriptional non templated uridylation of miRNAs (8). In the recently published work in *Nature Immunology* by Moffett and colleagues (9), miR-31 function in CD8 T cells is uncovered for the first time. Authors describe that the expression of miR-31 is highly increased during CD8 T cell activation being controlled by nuclear factor of activated T cells (NFAT). Moreover, they show the implication of this miRNA in limiting CD8 T cell function that ultimately causes the inability of the host to resolve the chronic phase of lymphocytic choriomeningitis

virus (LCMV) clone 13 infection (9).

After already a quarter of a century of miRNA research, mRNA target prediction and validation are still very challenging subjects. The difficulties are originated mainly by the incomplete matching of sequences between miRNA seed sequence and the target mRNA 3'UTR (10). In their study, Moffett *et al.* use two approaches to experimentally predict the miR-31 mRNA targets (9). First they identify its direct targets by comparing mRNA expression of control and miR-31 overexpressing cells by microarrays and subsequent validation by 3'UTR luciferase reporter assays. Secondly, they use miR-31 deficient mice to assess the gene expression changes in the absence of this miRNA by RNA sequencing and validation by qPCR and flow cytometry. Interestingly, *in silico* study by ingenuity pathway analysis of the targets identified in the first approach, leads them to type I interferon (IFN) pathway. Accordingly, they then study the T cell function of miR-31 deficient cells finding that T cell dysfunction is decreased and T cell effector molecules increased in the miR-31 deficient cells in an IFN- β treatment dependent fashion. The main target of miR-31 responsible for this effect is the phosphatase Ppp6c that would have been inhibiting type I IFN signaling otherwise. The consequences of this signaling modulation is linked to the differential expression of genes related to T cell dysfunction that impact on the CD8 T cell capacity to deal with infection (*Figure 1*).

Although miRNA levels can change very rapidly upon T cell activation (9,11,12), the actual impact of these changes in the levels of the proteins regulated by miRNAs is often delayed in time. Target proteins half lives as well

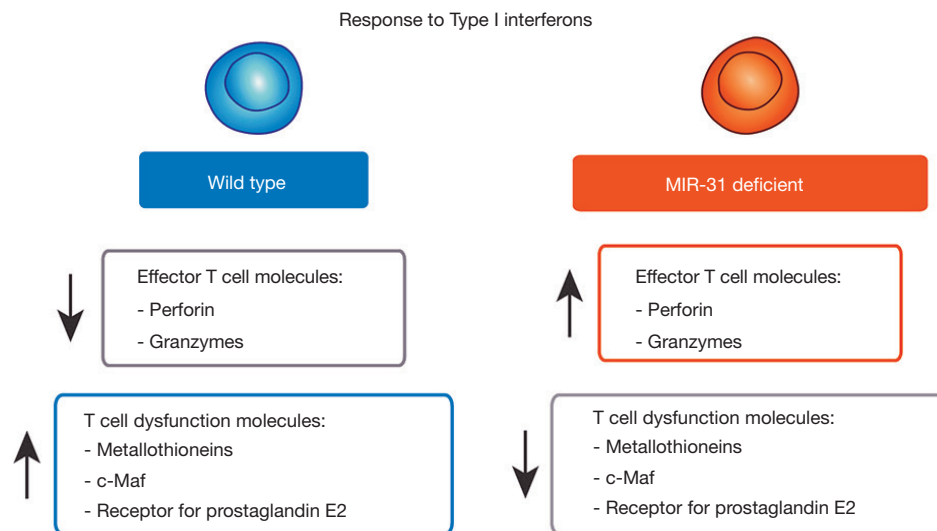


Figure 1 Response to Type I interferons. Wild type and miR-31 deficient CD8 T cells differ in their T cell effector programs after stimulation with type I IFN. IFN, interferon.

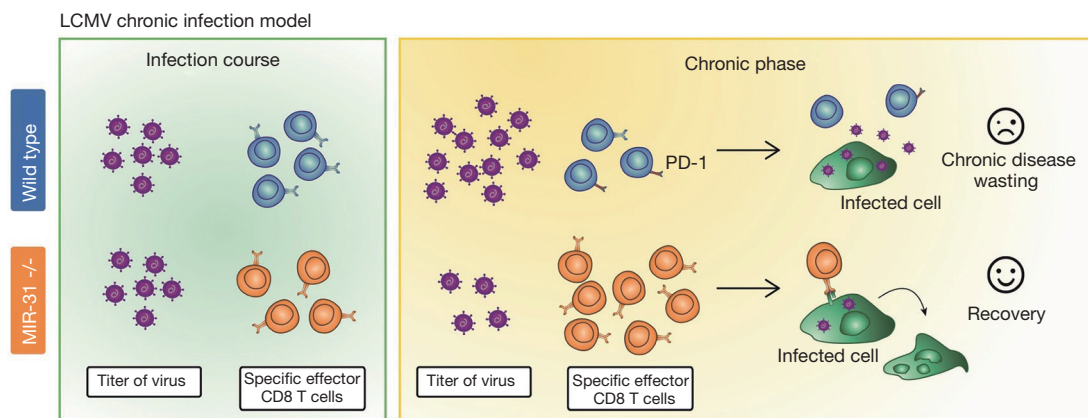


Figure 2 Chronic-LCMV-infection model. Initial course of LCMV infection on miR-31 deficient mice does not differ from wild type. However, at later time points miR-31 deficient mice recover faster, presenting less titer of virus and more CD8 T cells specific for the virus while wild types fail to recover and undergo a chronic disease. LCMV, lymphocytic choriomeningitis virus.

as transcription rates of both mRNA and miRNA are variable parameters that influence the time when the outcome of miRNA levels changes will be evident. The study by Moffett *et al.* represents a nice *in vivo* example of the delay of miRNA effect. Since miR-31 is induced very rapidly after T cell activation, it would be expectable that its deficiency would affect the acute infection of influenza virus or LCMV. However, the difference between wild type and deficient mice starts to be evident only at the chronic phase of LCMV infection (9) (Figure 2). These findings also confirm that miRNA-driven regulation comprises very

intricate spatiotemporal regulatory networks.

During viral chronic infection, the absence of miR-31 helps CD8 T cells to mount a more efficient response and prevents them to be exhausted as wild types. This poses an intriguing question that remains unsolved: why would the host upregulate this miRNA during infection if it is not beneficial but detrimental in this context? The most plausible explanation is that miR-31 probably represents a mechanism to prevent excessive T cell response in other situations which in this particular case has turned against the host.

Collectively, the findings by Moffett and coworkers

uncovered a relevant mechanism of control of T cell dysfunction that could be interpreted beyond the context of infection. T cell dysfunction and exhaustion is a common feature of cancer that is often promoted by the tumor itself. The identification of miR-31 as a target to prevent this CD8 T cell aberrant behavior opens important new avenues that would be worth it to explore in order to develop new therapeutic approaches against tumors. Conversely, promoting a less efficient immune response is the goal of autoimmunity treatment that could be potentially be accomplished by boosting miR-31 expression specially in diseases dependent on type I IFN signaling like systemic lupus erythematosus or multiple sclerosis (13) among others.

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Footnote

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