MicroRNA-mediated post-transcriptional regulation of peripheral γδ T cell effector functions

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γδ T cells are unconventional lymphocytes able to rapidly produce large quantities of interleukin-17A (IL-17A) or interferon- γ (IFNγ), which often have major effects on the pathophysiology of diseases such as cancer or infections. Yet, we do not fully understand how the thymic-derived effector γδ T cell subsets making either IL-17A ($γδ^{17}$ cells) or IFNγ ($γδ^{IFN}$ cells) are activated and function in peripheral tissues. Here, we established an *Il17a-GFP:Ifng-YFP* double-reporter mouse strain to analyse at unprecedented depth the microRNA transcriptomes of pure $γδ^{17}$ versus $γδ^{IFN}$ cell populations from peripheral lymph nodes, and uncover new mechanisms of miRNA-mediated post-transcriptional regulation of γδ T cell effector functions. We found 103 differentially expressed microRNAs between $γδ^{17}$ and $γδ^{IFN}$ cells, from which we selected 10 candidates likely to target members of the transcriptional networks underlying IL-17A of IFN-γ production, to test their effects on γδ T cell differentiation or effector functions. Retroviral gain-of-function approaches *in vitro* highlighted a plethora of context-dependent microRNA-specific effects on the differentiation or expansion of $γδ^{17}$ or $γδ^{IFN}$ cells, and respective cytokine production. Furthermore, a detailed analysis of each candidate miRNA expression throughout ontogeny showed that in some cases it was imprinted in the thymus, whereas in others it was peripherally induced. This led to the observation that miR-181a-5p, highly expressed in early thymic γδ T cell subsets, favours thymic $γδ^{17}$ cell commitment, while conversely promoting peripheral $γδ^{IFN}$ activation and proliferation in response to TCR stimulation *in vitro* and upon malaria infection *in vivo*. On the contrary, we found miR-128-3p to act as a peripheral regulator of IFN-γ, preventing aberrant IFN-γ production upon TCR stimulation. These findings unravel a new layer of regulation of γδ T cell effector functions, which we are further characterizing with additional molecular assays.