A key role for microRNAs in the development and functional differentiation of γδ T cell subsets

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The ability of murine γδ T cells to rapidly produce the pro-inflammatory cytokines interleukin-17 (IL-17) or interferon-γ (IFN-γ) underlies their crucial roles in several (patho)physiological contexts. This capacity stems from a complex process of 'developmental pre-programming' in the thymus, after which a large fraction of γδ T cells migrate to peripheral sites already committed to producing either IL-17 or IFN-γ. To globally address the role of microRNAs in effector γδ T cell differentiation, we established a double reporter IL-17-GFP:IFN-γ-YFP mouse strain and isolated pure IL-17$^+$ and IFN-γ$^+$ γδ T cell populations from peripheral lymphoid organs to perform small RNA-sequencing. This allowed us to identify distinct microRNA signatures associated with cytokine expression in γδ T cells, from which we selected ten candidate microRNAs differentially expressed between IL-17$^+$ and IFN-γ$^+$ γδ T cells to functionally study further. Our results indicate that while some microRNAs, such as miR-128-3p and miR181a-5p, regulate γδ T cell development in the thymus, other candidates, including miR-7a-5p, miR-139-5p, miR-322-5p and miR-450b-3p, modulate peripheral γδ T cell effector functions. Furthermore, using a miR-181a deficient mouse model, we have demonstrated that miR-181a, highly expressed in immature γδ T cell subsets in the thymus, shifts the *in vivo* IL-17/IFN-γ balance towards the IL-17 pathway in the neonatal thymus, which is further maintained in the periphery during adult life. These data demonstrate the impact of microRNAs on the development, differentiation and functional identity of effector γδ T cell subsets, which may open new avenues for their manipulation in disease settings.