IL-17 polarization of MAIT cells is derived from the activation of two different pathways

We have read with interest the report by Wang et al. [1] showing that MAIT cells are numerically reduced and phenotypically and functionally altered in peripheral blood and salivary glands (SG) of patients with primary Sjögren’s Syndrome (pSS) [1]. The altered function of MAIT cells in pSS SG might lead to the dysregulation of the local immune responses, triggering autoimmune damage of the glandular tissue and development of sicca symptoms. Although Wang et al. showed a lower level of MAIT-cell activation with reduced expression of CD69 and CD154 (CD40L) and a lower production of TNF and IFN-γ, a precise functional characterization of MAIT cells in pSS patients is still missing [1].

Considering the established role of IL-7 and IL-23 in pSS pathogenesis [2–4] and given that their receptors are expressed on MAIT cells surface, we have assessed the functional in vitro responses of isolated MAIT cells to IL-7 and IL-23. For this purpose, we enrolled 16 pSS patients (15 female, mean age 45 ± 12 years, mean disease duration 28 ± 12 months, EULAR Sjögren’s syndrome disease activity index mean 6, range 0–45) and 14, aged and sex-matched subjects with nonspecific chronic sialoadenitis as controls. MAIT cells were analyzed by flow cytometry and RT-PCR and isolated from PBMCs and salivary glands mononuclear cells (as previously described) [5] of patients and controls by FACS aria cell sorter. Since the majority of MAIT cells are CD8+ cells [6], with very low frequencies of double negative CD4/CD8 MAIT cells, we confined our analysis to the CD8+ fraction.
According to Banovic and colleagues, flow cytometry analyses showed a significant reduction of MAIT cells in the peripheral blood (Fig. 1A–B), and was accompanied by an enrichment of IL-17 polarized MAIT cells in pSS SG (Fig. 1C). In vitro IL-7 and IL-23 stimulation of MAIT cells induced a significant IL-17 overexpression only in pSS patients (Fig. 2A–B). Changes in STAT3, HIF1a, and RORc transcript levels were also evaluated by RT-PCR after IL-7 and IL-23 stimulation. Interestingly, IL-7 and IL-23 resulted in a different modulation of STAT3, HIF1alpha, and RORc. IL-7 stimulation induced a significant STAT3 and HIF1alpha upregulation with no relevant modulation of RORc (Fig. 2C). Conversely, IL-23 stimulation significantly induced RORc overexpression not affecting STAT3 and/or HIF1alpha expression (Fig. 2D). These findings seem to indicate that in pSS, both IL-23 and IL-7 are capable to promote IL-17 polarization of MAIT cells. We also provide evidence that different molecular pathways might be activated by IL-7 and IL-23, selectively involving RORc or STAT3/HIF1alpha expression. Taken together, our results confirm the potential role of MAIT cells in pSS pathogenesis and, for the first time, link IL-7 and IL-23 to the IL-17 polarization of MAIT cells in these patients.

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References


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