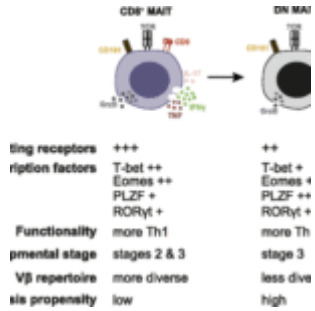
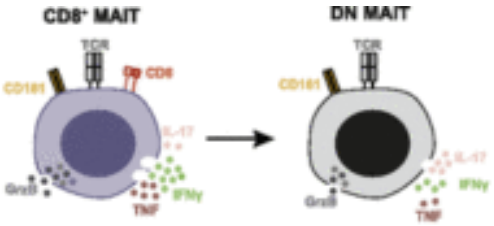
Are CD8+ and DN MAIT cells distinct populations ?





Co-activating receptors	+++	++
Transcription factors	T-bet ++ Eomes ++ PLZF + RORγt +	T-bet + Eomes + PLZF ++ RORγt ++ (mucosa)
Functionality	more Th1	more Th17
Developmental stage	stages 2 & 3	stage 3
Vβ repertoire	more diverse	less diverse
Apoptosis propensity	low	high

Properties and relationship of the main MAIT cell subsets. (Source: [Dias *et al., 2018* PNAS])

Mucosal associated invariant T (MAIT) cells are MHC class I-like restricted T cells, that recognise bacterial riboflavin metabolites. Studies have shown that MAIT cells can be activated either a MR1-dependent manner or MR1-independent manner via IL-12/IL-18 activation. Upon activation they can produce pro-inflammatory cytokines (IFN-□, IL-17) and cytotoxic molecules. In adulthood circulating (non-thymus) MAIT cells predominantly express CD8α, however a subset of CD4-CD8- (double negative, DN) MAIT cells have also be detected and characterised. Whether these two phenotypes represents truly distinct functional MAIT subsets is unclear.

Study by Dias *et al.,* aimed to determine the difference in transcriptional, activation and functional capacity of CD8+ and DN MAIT cells. They defined MAIT cells as $CD161^{hi}TRAV\text{-}1\text{-}2^{+}$ MR1-tetramer+ T cells. CD8+ MAIT cells expressed higher levels of activation markers (CD9, CD27, NKG2D, PD-1), functional (IFN-□, TNF) and cytotoxic markers (granzyme B, granulysin, perforin) than DN MAIT cells. Suggesting that CD8+ MAIT cells are more responsive and functional than DN cells, this was further demonstrated by increased expression of T-bet, Eomes and up-regulation of pro-inflammatory (mRNA) transcripts in CD8+ MAIT cells than DN MAIT cells. Surprisingly, DN MAIT cells detected in tissue expressed higher levels of PLZF, ROR□t and Helios than CD8+ MAIT cells, however this did not translate to significantly higher levels of IL-17 production compared with CD8+ MAIT cells.

How do DN MAIT cells form?

Three stages of MAIT cell development in the thymus have been characterised. DN MAIT cells first appear in the 3^{rd} stage of MAIT cell development, however at very low frequencies and are observed at significantly more abundant levels in circulation (blood). Upon *in vitro* activation by antigen and in long term cell culture assays CD8+ MAIT cells down regulated expression of CD8 resulting in increased proportion of DN MAIT cells. This down regulation occurred in an MR-1 dependent manner, suggesting that a proportion of DN MAIT cells differentiate from CD8+ MAIT cells.

In summary findings by Dias *et al.,* defined CD8+ and DN MAIT cells as two distinct populations, where DN MAIT cells are more differentiated and less functional than CD8+ MAIT cells. They also showed that DN MAIT cells can be derived from CD8+ MAIT cells, elucidating why they are observed at increased proportions in circulation during adulthood than during thymic development.

Journal Article: Dias *et al.*, 2018., The CD4–CD8– MAIT cell subpopulation is a functionally distinct subset developmentally related to the main CD8+ MAIT cell pool. PNAS

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