# ZEB1 expression by cDC1s is crucial for splenic macrophage numbers and splenic cDC1 and cDC2 phenotype.

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Splenic macrophages (mfs) develop from embryonic progenitors before birth and persist throughout adulthood with minimal input from circulating progenitors. Conversely, conventional Dendritic cells (cDCs) develop from lineage-committed BM derived progenitors (pre-cDCs) and exist in two main subtypes recently termed cDC1s and cDC2s. We have previously identified Zeb2 to be a transcription factor (TF) associated with pDC and cDC2 development. Here, we aimed to assess the role of its homolog, Zeb1, in cDC development using mice with a DC-specific loss of Zeb1 (CD11cCRExZeb1fl/fl). Unlike Zeb2, Zeb1 is expressed by at similar levels by both cDC1s and cDC2s. Analysis of CD11cCRExZeb1fl/fl mice revealed Zeb1 to be a major TF regulating the presence of both mfs and cDC1s in the spleen. Mice lacking Zeb1 in CD11c-expressing cells completely lack splenic mfs while also showing a significant reduction in cDC1s. Additionally, the phenotype of the cDC1s and cDC2s is augmented in these mice with the remaining cDC1s lacking CD8a expression and expressing CD103 compared with WT splenic cDC1s which lack CD103 expression and express CD8a. cDC2s displayed a decreased expression of CD11b and increased expression of ESAM. Automated unbiased analysis of the complete haematopoietic compartment of these mice using FlowSom also identified defects in multiple immune cell populations including T cells, B cells and NK cells. To examine if the effects seen in cDC1s were intrinsic or due to off-target effects of the CD11cCRE we utilised competitive BM chimeras. Analysis of these, BM chimeras, revealed that the effects of Zeb1 loss are dominant, also affecting WT cells in competitive BM chimeras. Thus, it was difficult to assess if the phenotype was indeed cell intrinsic or not. To overcome this, we crossed the Zeb1fl/fl mice to XCR1CRE mice to specifically remove Zeb1 from the cDC1s. This analysis revealed that the effects on cDC1s, cDC2s and splenic mfs result from the loss of Zeb1 specifically in cDC1s, highlighting that ZEB1 is required in cDC1s to maintain the other mononuclear phagocyte populations in the spleen. Using single cell RNA sequencing, we are currently investigating the mechanisms at play.
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