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EMT factor Zeb1 depletion in dendritic cells enhances Helminth clearance in mice by increasing Th2 cell differentiation

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Abstract

Dendritic cells are professional antigen presenting cells that act as bridging link between innate and adaptive immune system. They are equipped with pathogen recognition receptors (PRR) to identify the pathogen associated molecular pattern (PAMPS) on any antigen. DCs elicit an immune response through polarizing T cells towards various subtypes like Th1, Th2 & Tregs. Though DC-T cell interaction has been widely studied, but how this single DC molecule amalgamate various transcriptional signals for translating the message to the T cells and induce diverse immunological responses still needs to be unraveled. Therefore to identify the role of transcription factor in immune programming we have targeted the largest member of TFs family, Zinc Finger Transcription Factors (ZF-TFs). Among various ZF-TFs we have narrowed our study to three interesting candidates Zeb1, Zeb2 and Zbtb10 based on their expression in DCs from an unpublished microarray data. Here in this study we have tried to understand the role of Zeb1, master regulator of EMT program in orchestrating DC responses. Zeb1 links the epithelial – mesenchymal transition and has been widely studied molecule in cancer biology. Except for the fact that it act as transcriptional repressor and represses IL2 gene promoter no other reports are available in immune biology, thereby rendering it a perfect candidate to be used for detailed characterization in dendritic cells. In our study, we found that Zeb1 depleted CD8α+DCs shows an increase in co-stimulatory marker like CD80 & CD86 whereas there is a decrease in MHC class I & II molecule. Thereafter at transcript & protein level we found decrease in pro-inflammatory & anti-inflammatory cytokine like IL6 & IL10 respectively, the bioactive form of IL12 i.e. IL12p70 which polarizes T cells towards Th1 response showed a significant decrease in bio-plex when compared with control CD8α+DCs. The regulatory markers which develop regulatory T cells like Pdl1, IL27 also showed decreasing trend in zeb1 depleted DCs. Thereafter we speculated that these Zeb1 perturbed DCs might be involved in default Th2 program. So, we looked into T-cell polarization by co-culture & MLR experiments which showed an increase in $GATA3^+$ T cells, a signature transcription factor for Th2 subtype along with higher levels of IL4, IL5 and IL13 Th2 cytokines. To evaluate the *in-vivo* function of Zeb1 knockdown (KD) cells we developed Helminth Polygyrus (*H.Poly*) disease model in mice, there we assessed for the worm load in intestine and egg count in the feces which showed a marked decrease in worm count and egg count in Zeb1 KD adoptive transfer mice as compared to control mice. The T cell response was examined through the draining lymph node (mesenteric lymph node) where we found significant increase in $GATA3^+$ T cells along with IL5 and IL13; this suggested that Zeb1 KD DCs polarize the T cells towards Th2 response which results in clearance of H. polygyrus in mice.

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