Microbiota-associated myeloid TNF production dictates the balance between tolerogenic and protective neonatal pre-cDC1

Introduction: Induction of immune protection against pathogens is particularly crucial during the neonatal period dominated by anti-inflammatory and tolerance immunity. We have previously shown that precursors of type 1 conventional dendritic cells (pre-cDC1) are key players in this dynamic equilibrium thanks to their unique ability to secrete both pro- (IL12p40) and anti-inflammatory (IL10) cytokines.
Methods: C57BL/6, TNFM-KO, IL10reporter/GFP and antibiotics-treated neonates were analyzed by flow cytometry and RNA sequencing to evaluate the differentiation and function of pre-cDC1 during the first week of life at steady state and upon Listeria monocytogenes infection.
Results: We demonstrated that microbiota colonization promotes TNF secretion by splenic monocytes and macrophages during the first hours of life. This cytokine production is involved in the differentiation and function of neonatal pre-cDC1. Indeed, in the absence of myeloid TNF, splenic neonatal pre-cDC1 adopted a newly characterized regulatory phenotype, based on the expression of C1q and β-catenin that are correlated with their IL-10 production. We further demonstrated that during neonatal Listeria monocytogenes infection, microbiota-associated myeloid TNF production increased the ability of pre-cDC1 to induce protective CD8+ T cells responses, by favoring their IL12p40 secretion and inhibiting their IL10 production.
Conclusion: Early life environmental factors such as microbiota-associated myeloid TNF promote the adaptive T-cell response later in life by dictating the balance between neonatal tolerogenic and protective pre-cDC1.

Keywords : Neonates, pre-cDC1, Microbiota, TNF
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