Unique features of IL-6 mediated germinal center responses to vaccines in neonatal mice

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The inability of neonates to develop CD4+Foxp3-CXCR5+PD-1+ T follicular helper (Tfh) cells contributes to their weak vaccine responses. Previously, we measured diminished Tfh and IgG responses when IL-6 was co-injected with a pneumococcal conjugate vaccine (PCV) in neonatal mice. This is in sharp contrast to adults, where IL-6 improves vaccine responses by expanding Tfh cells. In this study, we investigated the changes in IL-2 response in immunized neonates because recent reports suggest that in adult mice IL-6 promotes the expansion of Tfh cells by protecting them from IL-2 mediated suppression through the downregulation of IL-2Rβ expression on Tfh cells. Indeed, we found decreased IL-2Rβ expression on Tfh cells in IL-6 co-injected adult mice. In sharp contrast, co-injection of neonatal mice with PCV and IL-6 not only stimulated IL-2 production from CD4+ T cells but also significantly increased IL-2Rβ expression on Tfh cells. Reflecting the differences in IL-2Rβ expression on immunized adult vs neonatal mice Tfh cells, IL-2 stimulation increased phospho-STAT5+ Tfh cells in neonates and decreased in adults. Underscoring the detrimental role of IL-6 in neonates and in contrast to adult mice, PCV immunization of IL-6 KO neonatal mice resulted in increased Tfh generation accompanied by elevated antibody responses. Importantly, in the absence of IL-6, neonatal mice Tfh cell IL-2Rα and IL-2Rβ levels were decreased. We also observed that CpG containing PCV increased antibody responses in neonatal mice, which was accompanied by an increase in IL-21 producing Tfh frequency and a sharp decrease in IL-6Rα as well as IL-2Rα and IL-2Rβ levels on Tfh cells. The decrease in receptor levels translated into suppressed signaling because IL-6 and IL-2 stimulation resulted in diminished p-STAT3 and p-STAT5, respectively. These findings underscore age specific differences in IL-6 mediated vaccine responses and highlight the need to consider age related immunobiological differences in designing vaccines.