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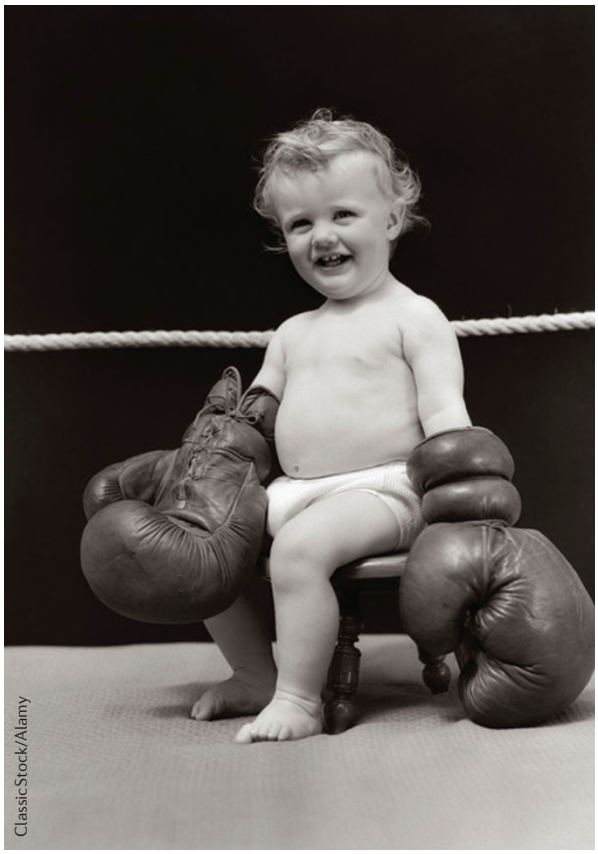
NEONATAL IMMUNITY

Babies' T cells can fight

> "CXCL8 production could be induced in purified CD4$^+$ T cells"

The immune system of newborn babies is relatively unexplored, but now, a study published in *Nature Medicine* shows that a substantial number of CD4$^+$ T cells from human newborns respond to activation by expressing high levels of CXC-chemokine ligand 8 (CXCL8; also known as IL-8), whereas this is not true for adults.

Gibbons *et al.* took weekly blood samples from 2–5-week-old premature babies born between 23–30 weeks gestation. Similar to previous studies, they found that CD4$^+$ T cells from preterm babies produced lower levels of interferon-γ (IFNγ) in response to stimulation with phorbol 12-myristate 13-acetate (PMA) and ionomycin compared with CD4$^+$ T cells from adults. By contrast, up to 50% of the preterm CD4$^+$ T cells showed increased levels of intracellular CXCL8 in response to stimulation. This finding was not specific to preterm babies, as stimulated CD4$^+$ T cells from the blood of term babies showed a similar increase in levels of CXCL8. Of note, neonatal CD4$^+$ T cells more commonly produced CXCL8 than tumour necrosis factor — which was previously considered to be the most common effector cytokine produced by these cells — and CXCL8 was hitherto regarded as an innate immune cytokine mainly produced by myeloid or epithelial cells. Further analysis confirmed that substantial CXCL8 production is a signature of immature neonatal CD4$^+$ T cells.



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Next, the authors found that CXCL8 production could be induced in purified CD4$^+$ T cells from cord blood after 24 hours of stimulation with antibodies that activate the T cell receptor (TCR) and the co-stimulatory molecule CD28. Furthermore, they found that combining the TCR-activating antibody with a Toll-like receptor 5 (TLR5) ligand or a TLR2 ligand increased CXCL8 production in neonatal CD4$^+$ T cells, whereas this had no impact on adult CD4$^+$ T cells. This result emphasizes the fundamental functional differences between the infant and adult immune systems.

Spontaneous cytokine production by CD4$^+$ T cells is rarely detected in blood samples from adults with an infection. However, Gibbons *et al.* identified a small population of CD4$^+$ T cells that constitutively expressed CXCL8 in blood from a preterm infant with suspected sepsis. Interestingly, in a few infants, increased levels of CXCL8 upon stimulation also coincided with and/or preceded a transient increase in levels of C-reactive protein (CRP), which suggests that the babies had an ongoing infection. Indeed, these babies were later diagnosed with *Escherichia coli* or *Staphylococcus aureus* septicaemia.

Finally, the authors found that CXCL8 enhanced IFNγ expression in γδ T cells, which are considered to be important producers of effector cytokines in newborns. This result, together with the fact that CXCL8 can activate human neutrophils, led the authors to suggest that the production of CXCL8 is a pro-inflammatory immunoprotective function of neonatal T cells, which counters the view that early life T cells are anti-inflammatory.

This newly identified neonatal T cell effector function may underlie inflammatory pathologies such as necrotizing enterocolitis, and could potentially be targeted to improve the care of preterm babies and for vaccine development.

Elisabeth Kugelberg

ORIGINAL RESEARCH PAPER Gibbons, D. *et al.* Interleukin-8 (CXCL8) production is a signatory T cell effector function of human newborn infants. *Nature Med.* http://dx.doi.org/10.1038/nm.3670 (2014)