

Age-Dependent Trajectories of Antigen-Specific IL-17 and IL-22 Responses in Naïve T Cells

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ABSTRACT

T-cell responses in early life exhibit distinct characteristics that have mostly been studied under non-physiological conditions. In this study, we investigated the responses of naïve T cells to bacteria and fungi in newborns, infants, children and adults, with a particular focus on Th22- and Th17-like responses. Our results demonstrate that T cells from newborns and infants up to two years of age exhibit increased IL-22 expression and secretion in response to stimulation by fungi, such as *Candida albicans*, and bacteria, such as *Staphylococcus aureus*. In summary, pathogen-specific responses are characterized by Th17- and Th22-like responses, which are typical of newborns. Our data support the notion that pathogen responses follow an age-related trajectory up to the age of five, while distinct pathogen-specific differences persist.

METHODS

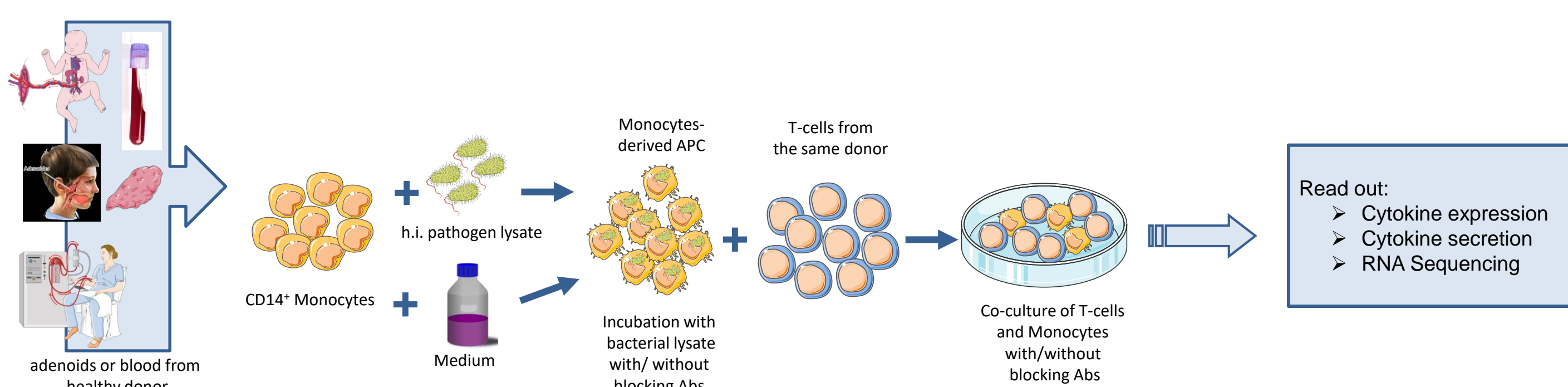


Fig. 1. Experimental Setup. To stimulate T-cells antigen-specifically, autologous CD14⁺ monocytes pulsed for 24h with lysates of heat inactivated (h.i.) *S. aureus* or *C. albicans* were used. T-cells were isolated from cord blood, adenoids of infants and children or blood from adult volunteers. At time point „zero“ the pulsed monocytes were co-cultured with T-cells from the same volunteer and analyzed 3 days after beginning of the stimulation by flow cytometry.

RESULTS

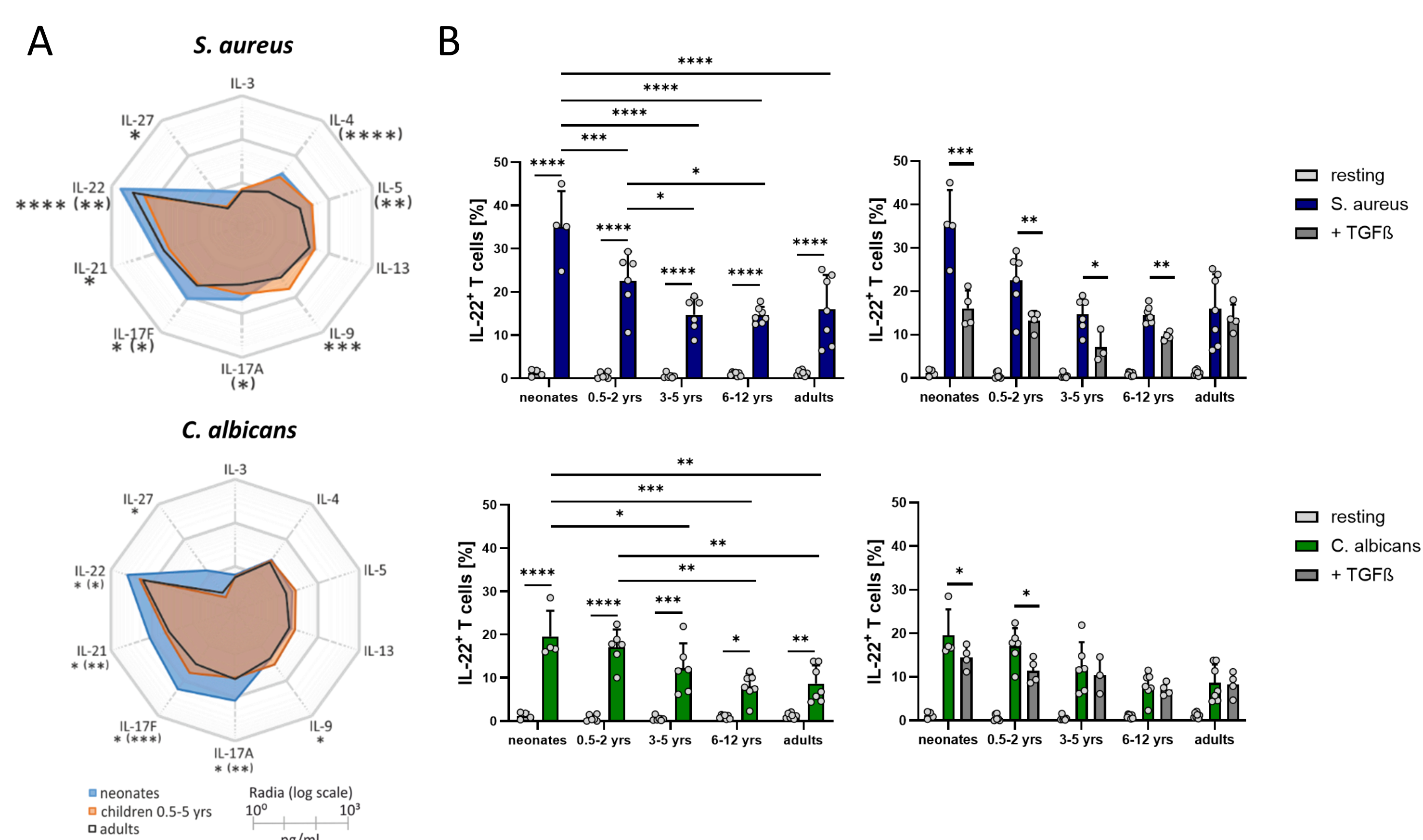


Fig. 2. Neonatal and infant T cells show a bias toward IL-22 production.

Neonatal, infant and adult naïve T-cells were co-cultured with monocytes and stimulated with *S. aureus* or *C. albicans*. (A) Cytokine production was measured in supernatants. The following radar plots illustrate the production of cytokines by neonates (blue), children up to the age of five (red), and adults (black line). (B) Bar graph showing age-dependent IL-22 expression of naïve T-cells in response to *S. aureus* or *C. albicans* (left). As illustrated in Figure B, right, the expression of IL-22 by T-cells is contingent on TGFβ. It has been demonstrated that there is a stronger dependence on TGFβ sensitivity in the early stages of life.

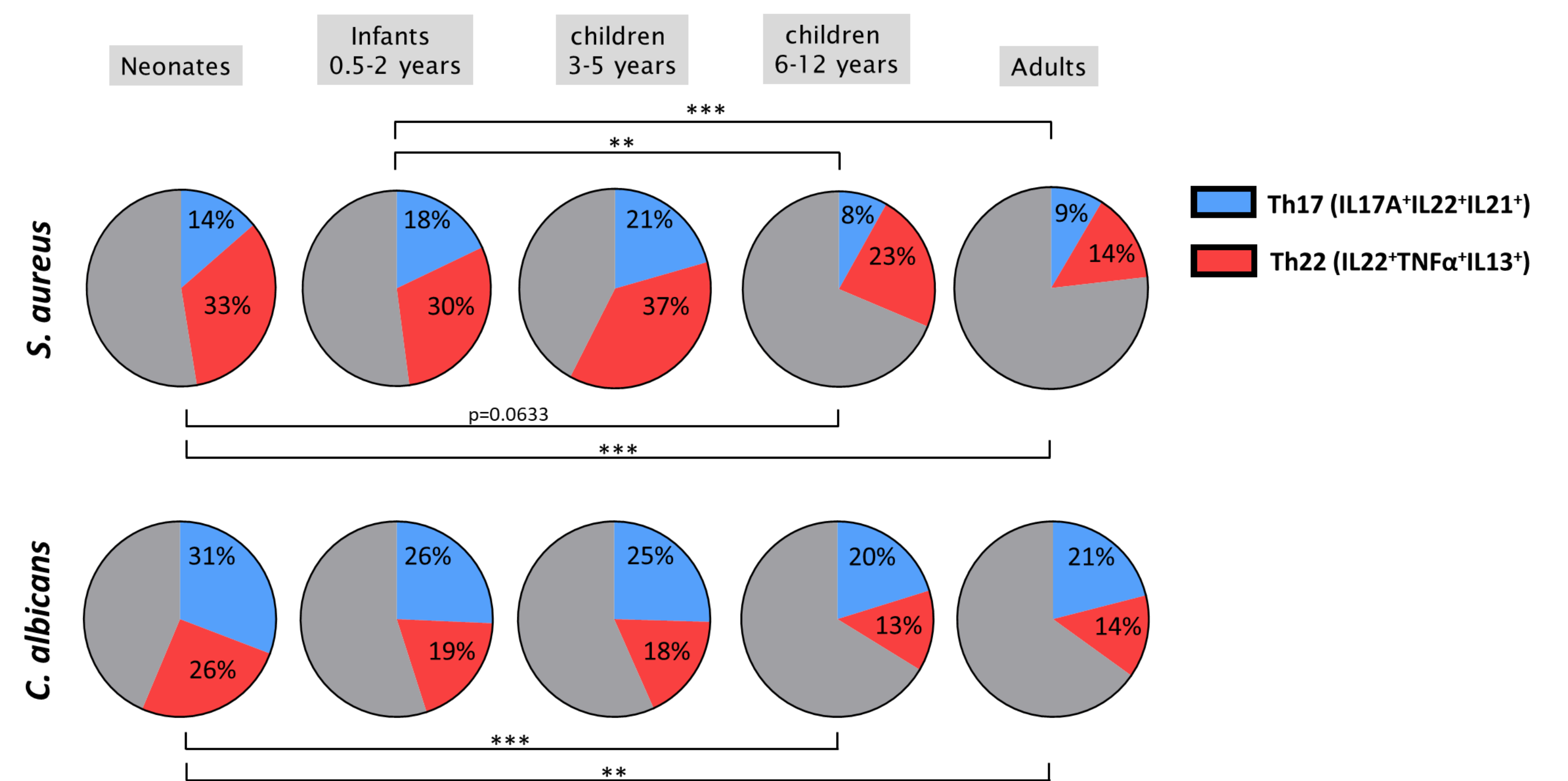


Fig. 3. Age-dependent formation of multi-functional Th22 cells.

Co-cultures of CD4⁺CD45RA⁺CD31⁺ T-cells with monocytes loaded with either *S. aureus* or *C. albicans* were analyzed for Th17 and Th22 cell responses. On day 3, intracellular cytokine expression was measured by flow cytometry and analyzed using Boolean gating. The results show that stimulation with *S. aureus* induces a predominantly Th22 response in an age-dependent manner. By contrast, stimulation with *C. albicans* triggers a mixed Th17 and Th22 response. This response shows a more pronounced Th17 component in all age groups.

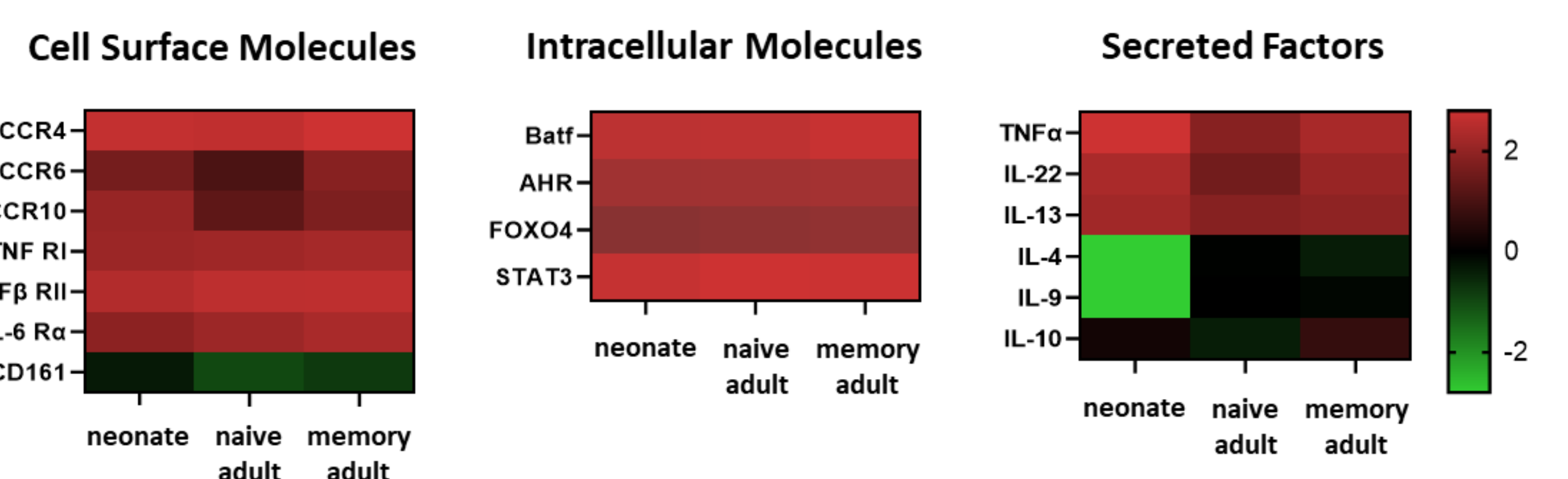
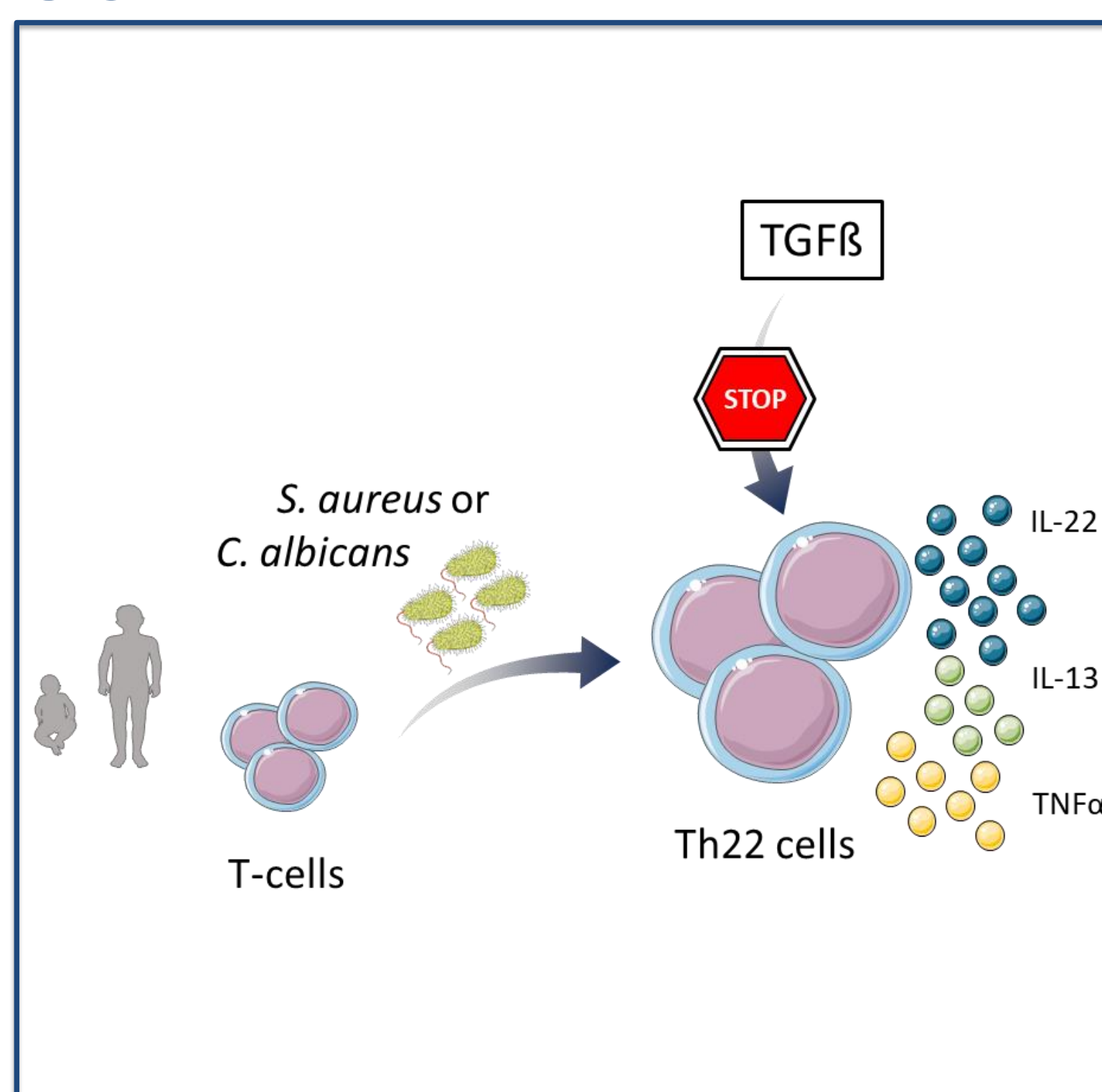


Fig. 4. Regulation of genes and molecules associated with Th22 cells.

In order to achieve a more profound comprehension of the Th22 cells specifically induced by *S. aureus*, RNA sequencing assays were performed. For this purpose, the T cells were enriched with MACSQuantTyto three days after the start of stimulation, the RNA was prepared, and RNASeq was performed. Following a comprehensive review of the extant literature, a list of 17 genes was compiled for molecules whose up- or downregulation is characteristic of Th22 cells.

SUMMARY



- Neonatal T-cells show a vigorous antigen-specific response of IL-22 against *S. aureus* and *C. albicans*.
- The IL-22 response of neonates and infants has been shown to be approximately double the level of cytokine secretion observed in older children and adults.
- Th22 cells are distinguished by the concurrent synthesis of IL-22, IL-13 and TNFα.
- In particular, neonatal and infant T cells demonstrate a significant response to TGFβ.

Conflict of interest

The authors declare that they have no conflict of interest.