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Pathogen-specific differentiation trajectories of neonatal naïve CD4⁺ T cells towards IL-22-dominated effector states

K. Vogel[1], L. Vasconcelos Machado[1], I. Han[1], T. Vosikova[2], D. Bretschneider[3], D. Bruder[4,5], D. Schanze[6], M. Zenker[6], M. Durisin[2], M. Brunner-Weinzierl[1]

CONTACT Dr. Katrin Vogel
Department of Experimental Paediatrics, Otto-von-Guericke University, Magdeburg, Germany
katrin.vogel@med.ovgu.de

QUESTION & APPROACH

BACKGROUND
IL-22 acts directly on epithelial cells to promote antimicrobial defence, tissue repair and barrier integrity. Although IL-22 is associated with differentiated Th22- and Th17-like states in adults, the developmental origin and antigen specificity of human early-life IL-22 responses remain poorly defined.

QUESTION
Do neonatal IL-22 responses reflect a general developmental bias or a pathogen-instructed effector trajectory?

AIM
We investigated how pathogen identity and postnatal maturation shape IL-22-producing CD4⁺ T-cell states and whether the neonatal response supports epithelial barrier function.

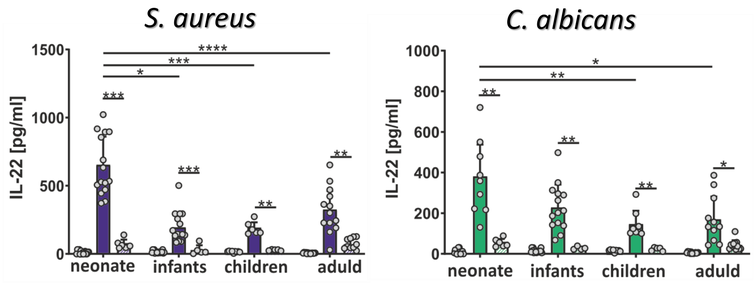
APPROACH
Naïve CD4⁺ T cells from neonates, infants, children and adults were stimulated with autologous monocytes loaded with heat-inactivated *S. aureus* or *C. albicans*.

Readouts: cytokine profiling · high-dimensional flow cytometry · Boolean analysis · RNA-seq/GSEA · epithelial barrier assays

AGE × PATHOGEN → EFFECTOR STATE → EPITHELIAL FUNCTION

1 · Pathogen-specific IL-22 trajectories across age

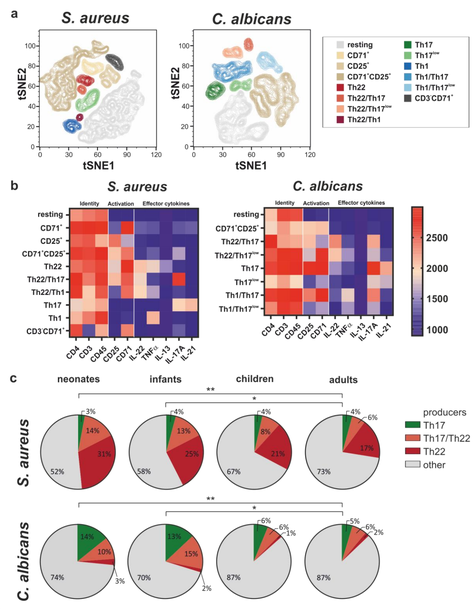
Naïve CD4⁺ T cells from neonates, infants, children and adults were stimulated with *S. aureus* or *C. albicans*, and IL-22 secretion was quantified on day 3.



Both pathogens induced a pronounced neonatal IL-22 response, whereas secretion was substantially lower in later age groups.

2 · Th22-like multifunctionality declines with age

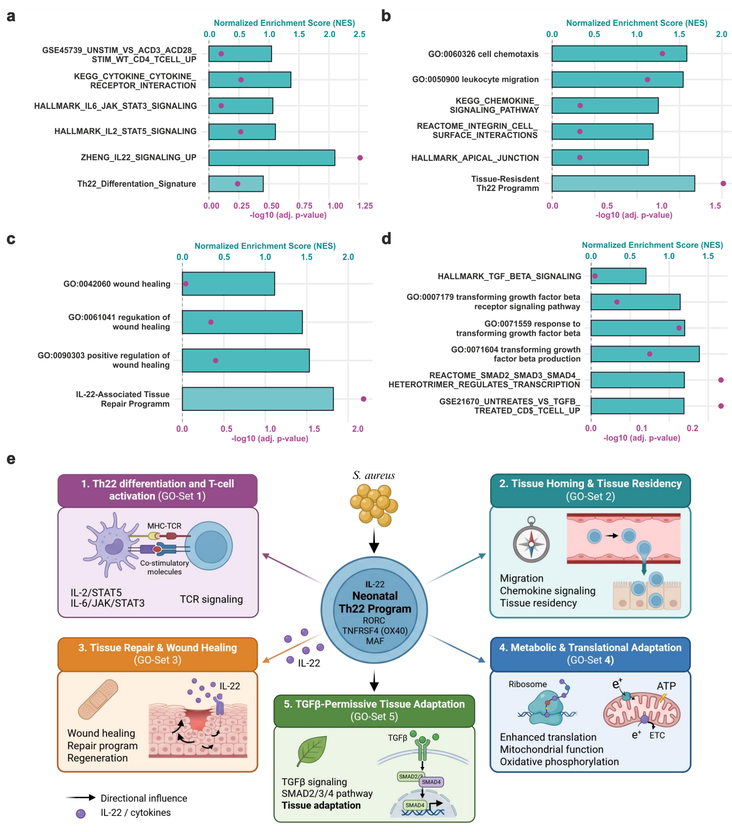
Boolean cytokine analysis and tSNE mapping resolved pathogen-specific effector populations across age groups.



Multifunctional IL-22⁺TNFα⁺IL-13⁺ Th22-like populations were most abundant in neonates and declined with age, particularly after S. aureus stimulation.

3 · TISSUE-ADAPTIVE TRANSCRIPTOME

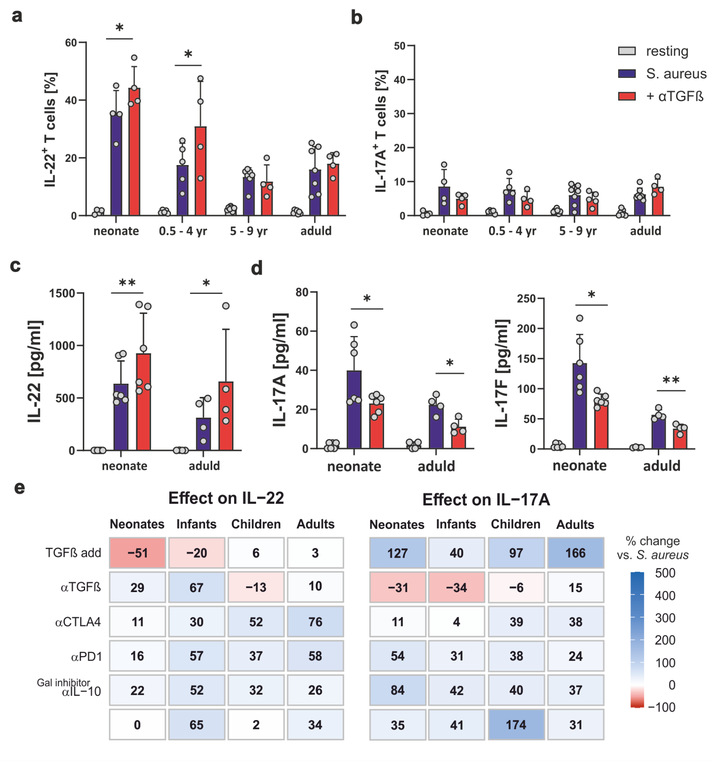
RNA-seq/GSEA comparing S. aureus-stimulated neonatal and adult naïve CD4⁺ T cells; positive NES indicates enrichment in neonates.



Transcriptomic profiling linked the neonatal IL-22 response to Th22 differentiation, tissue residency and repair, while TGFβ-related signatures suggested a permissive tissue-adaptation axis. A multivariable model identified MAF, TNFRSF4 and RORC as transcriptional predictors of IL-22 induction.

4 · TGFβ RESTRAINS EARLY-LIFE IL-22

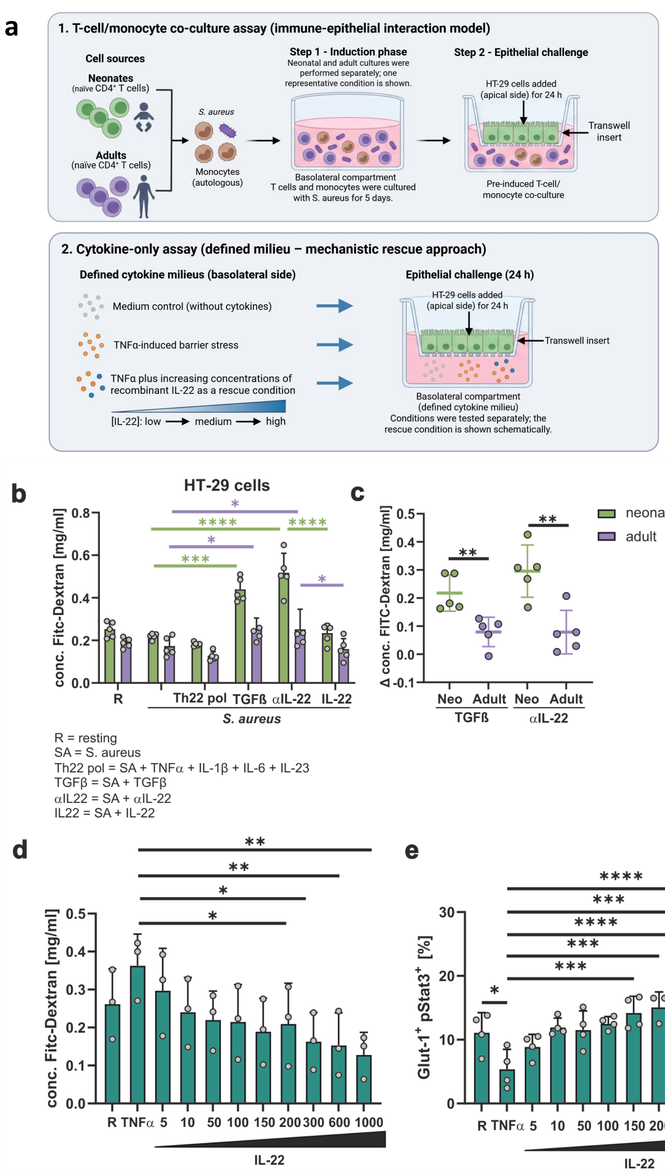
TGFβ perturbation reveals an age-dependent checkpoint controlling pathogen-induced IL-22 responses.



TGFβ preferentially restrains IL-22 in early life, whereas its blockade enhances IL-22 secretion while reducing IL-17A/F responses.

5 · NEONATAL IL-22 PROMOTES BARRIER FUNCTION

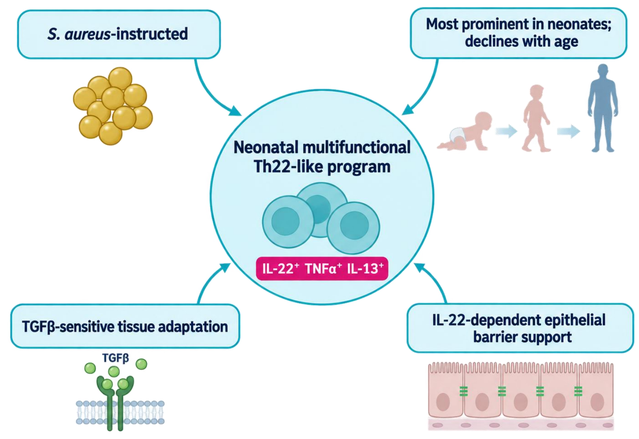
HT-29 cells were exposed to S. aureus-conditioned neonatal or adult T-cell/monocyte cultures or to TNFα with increasing concentrations of recombinant IL-22.



Barrier integrity in neonatal co-cultures was particularly sensitive to TGFβ and IL-22 blockade, while recombinant IL-22 dose-dependently restored barrier function under inflammatory stress.

CONCLUSION

Together, our data identify an S. aureus-instructed, age-restricted Th22-like trajectory in human naïve CD4⁺ T cells that couples multifunctional IL-22 production to tissue-adaptive transcriptional programs and epithelial barrier support.



TAKE-HOME MESSAGE

Early in life, S. aureus instructs a multifunctional, tissue-adaptive IL-22 program that declines with age and supports epithelial barrier function.

In relation to this presentation, I declare that there are no conflicts of interest.

[1] Experimental Paediatrics · [2] Otorhinolaryngology · [3] Hospital St. Marienstift · [4] Infection Immunology, OVGU · [5] HZI · [6] Human Genetics, OVGU