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IMMUNE TOLERANCE

A window of opportunity

> "neonatal T_{Reg} cells were highly activated compared with T_{Reg} cells in adult skin"

Immune tolerance to commensal microbiota needs to be established at each barrier site. Reporting in *Immunity*, Rosenblum and colleagues show that immune tolerance to skin commensals requires early bacterial colonization and an influx of activated regulatory T (T_{Reg}) cells into neonatal skin.

The authors generated a mouse model in which the skin commensal *Staphylococcus epidermidis* was engineered to express the peptide antigen 2W (Epi-2W) linked to a fluorescent protein. The Epi-2W strain could stably colonize mouse skin without causing local inflammation, and colonized mice had increased numbers of activated 2W-specific $CD4^+$ T cells in both the skin-draining lymph nodes (SDLNs) and the spleen. Thus, commensal antigens were recognized both locally and systemically across an intact skin barrier.

S. Bradbrook/NPG

Next, 6-week-old adult mice were colonized with Epi-2W and, 3–4 weeks later, these mice were challenged with Epi-2W in combination with light scratching of the skin. This mimics the increased exposure to commensal antigens that occurs in response to incidental skin trauma — a situation in which immune tolerance needs to be active. Adult mice that were pre-colonized with Epi-2W and control mice that were not pre-colonized showed a similar increase in skin inflammation after challenge with Epi-2W. However, when mice were colonized on postnatal day 7 and challenged with Epi-2W in adult life, histological skin inflammation and neutrophilic infiltration were reduced compared with age-matched controls without prior Epi-2W exposure. Hence, microbial skin colonization in the neonatal period promotes tolerance to commensal bacteria.

The authors found that, between postnatal days 6 and 13, there was a marked increase of αβ T cells in the skin, of which T_{Reg} cells accounted for over 80% of $CD4^+$ T cells compared with around 50% in adult skin. By contrast, other T cell subsets did not accumulate during this period. Furthermore, the neonatal T_{Reg} cells were highly activated compared with T_{Reg} cells in adult skin. This early influx of T_{Reg} cells was not seen in the intestinal lamina propria or SDLNs and therefore seems to be unique to the skin.

Finally, the authors investigated whether the accumulation of T_{Reg} cells in neonatal skin is required to establish tolerance to skin commensals. Indeed, transiently blocking the migration of T_{Reg} cells into the skin in neonatal mice, before neonatal colonization with Epi-2W, led to increased skin inflammation after challenge with Epi-2W in adult mice. This inflammation was associated with increased numbers of antigen-specific effector $CD4^+$ T cells in the SDLNs and a reduction of antigen-specific T_{Reg} cells in the SDLNs and skin.

In summary, establishment of tolerance to commensal skin microorganisms depends on early bacterial colonization and an influx of T_{Reg} cells into neonatal skin.

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ORIGINAL ARTICLE Scharschmidt, T. C. *et al.* A wave of regulatory T cells into neonatal skin mediates tolerance to commensal microbes. *Immunity* **43**, 1011–1021 (2015)