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SPOTLIGHT

Early architects: Eosinophils promote postnatal development of the small intestinal villus structure

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Smooth muscle cells in the intestinal villus form early postnatally and aid the uptake of dietary fats. In this issue, Petrova et al. (https://doi.org/10.1083/jcb.202505012) describe a second postnatal wave of smooth muscle cell formation from PDGFRβ⁺ perivascular cells induced by eosinophil-derived TGFβ.

The finger-like villi of the small intestine perform multiple functions, foremost the absorption of nutrients. Lined by a single epithelial layer and sustained by blood capillaries and lymphatic lacteals, each villus also contains an internal network of smooth muscle cells (SMCs) that contract rhythmically to push dietary nutrients into the lymphatic system (1). How this smooth muscle network develops during early life is still not fully understood.

In the first postnatal week, SMCs derive from PDGFRα⁺ fibroblasts in the villus. Guided by the lacteal lymphatic vessels, they arrange along the length of the villus, surrounding the lacteal ducts. Formation of this first wave of SMCs is dependent on DLL4-NOTCH3 signaling and largely completed by postnatal day 9 (P9) (2). When this SMC development is disrupted in mice, pups show reduced lipid absorption through the lymphatic vessels and are stunted in their growth (3). The SMC network thus plays a critical role for nutrient absorption. In the adult intestine, most villus SMCs are not directly associated with the lacteals (2, 3, 4). This nonlacteal SMC network continues to develop after P9 and is independent of PDGFRα⁺ fibroblasts, suggesting that it is driven by distinct pathways and derives from a different cell type. Which cell type gives rise to this second wave of SMCs, and how this transformation is promoted, however, remained unknown.

Eosinophils are increasingly recognized as tissue-resident immune cells, which carry out different and diverse functions in homeostasis and disease (5). In particular in the intestine, eosinophils have been shown to undergo major changes on the transcriptional, phenotypic, and functional level (6). Intestinal eosinophils promote immune homeostasis, extracellular matrix remodeling, intestinal barrier integrity, and antimicrobial defense. In their article, Petrova et al. (7) show in a detailed microscopy timeline how eosinophils populate the intestinal villi shortly after birth. At P4, eosinophils are mostly observed at the base of the villi, from which they travel toward the villus tip. By P10, eosinophils are distributed along the length of the villi, resembling the localization observed in adult mice.

This influx of eosinophils is temporally associated with a second wave of SMC formation (Fig. 1). Using lineage tracing, Petrova and colleagues find that these cells originate from PDGFRβ⁺ perivascular cells, with SMC development starting at the tip of the villi and extending downward. This second wave was independent of lacteals, as ablation by anti-VEGFR3 antibody treatment (8) early after birth did not interfere with the formation of spindle-shaped SMCs at P10. PDGFRβ⁺ perivascular cell–derived SMCs are therefore independent of the lymphatics. The authors convincingly link the second wave of SMC development to eosinophil migration into the intestinal villi. First, these two are spatiotemporally linked, with eosinophil migration being complete at P10 at which point the second wave of SMC formation is underway. Using 3D electron microscopy and high-resolution fluorescence microscopy, the authors demonstrate direct association between eosinophils and SMCs, as well as PDGFRβ⁺ lineage–traced star cells at P7. Second, eosinophil-deficient animals show a decrease in the non–lacteal-associated villus SMC network, which becomes apparent as early as P10.

In search for the mechanisms involved, Petrova and colleagues analyzed RNA-sequencing datasets of intestinal eosinophils and also generated new sequencing data on P9 fibroblasts from wild-type and eosinophil-deficient pups. They identified the TGFβ signaling pathway as a likely candidate. Intestine-adapted eosinophils expressed high levels of *Tgfb2*, while fibroblasts from eosinophil-deficient pups showed reduced expression of many SMC-associated genes like *Tagln*, *Mylk*, *Cnn1*, *Acta2*, *Actg2*, and *Myh11*. Importantly, these genes have previously been shown to be induced by TGFβ. The relevance of the TGFβ pathway was then directly tested in vivo. Anti-TGFβ treatment or genetic ablation of the TGFβ receptor on PDGFRβ⁺ cells reduced the SMC network in intestinal villi. Using an in vitro coculture system of intestinal eosinophils with neonatal PDGFRβ⁺ fibroblasts, the authors convincingly demonstrated that eosinophil-derived TGFβ induces conversion of fibroblasts to αSMA⁺ SMCs.

What is the functional relevance of this eosinophil-induced smooth muscle network? Earlier work has shown that

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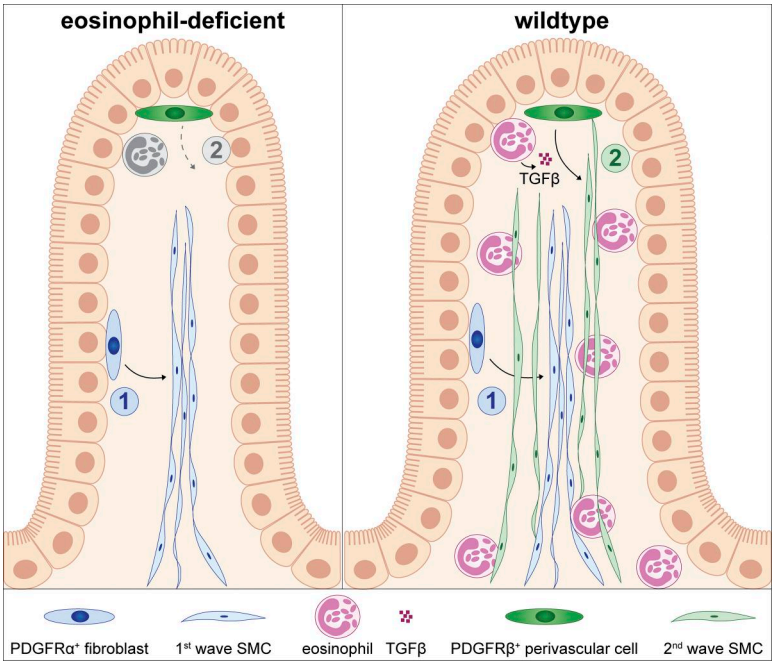

Figure 1. **Eosinophil-derived TGFβ promotes a second wave of SMC differentiation.** The first wave of SMC development is mostly completed by P9 and is independent of eosinophils. Here, PDGFRα⁺ subepithelial fibroblast–derived cells form the first SMC network associated with the lacteal duct. Eosinophil-deficient mice show reduced villus size due to the lack of the second wave of smooth muscle formation. Around P10, eosinophil-derived TGFβ promotes the outgrowth of PDGFRβ⁺ perivascular cells into SMCs via CNN1⁻ star cells. This second wave of SMCs is not associated with the lacteal duct.

eosinophil-deficient mice display reduced uptake of dietary lipids (9), which is linked to the function of the intestinal smooth muscle network, suggesting that eosinophils may indirectly be linked to efficient nutrient absorption. When pups were treated with TGFβ-blocking antibodies or by genetic ablation of the TGFβ receptor on PDGFRβ⁺ cells, however, no deficits in weight gain were observed. Of note, abrogation of lacteal growth through VEGFR3 blockade showed also no effect on pup weight, suggesting that this readout may be insufficient to measure reductions in lipid absorption, which was not assessed directly in these experiments. It is possible that in a context of nutrient abundance, the animal can compensate for a reduction in lipid uptake. This leaves the functional consequences of the eosinophil-dependent smooth muscle network to be explored further in the future.

Overall, the work by Petrova and colleagues identifies a novel function of eosinophils in the early postnatal development of the stromal structure of the intestine. They discovered the mechanism by which newly migrated eosinophils release TGFβ to induce the conversion of PDGFRβ⁺ perivascular cells into SMCs that expand from the tip to the base of the villi and form a second wave of the SMC network. While the functional implications of this network remain to be fully explored, their study links the immune system to the development of the intestinal structure in the early neonatal period.

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