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INSIGHTS

Signals in space: TGF-β defines where and what gut macrophages become

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Macrophages are profoundly shaped by their tissue of residence. In this issue, Jayaraman et al. (https://doi.org/10.1084/jem.20240801) show that TGF-β signaling is crucial for maintaining the identity, function, and spatial organization of long-lived intestinal macrophages, highlighting an essential component of the gut niche.

Over the past two decades, extensive research has established that most resident tissue macrophages (RTMs) originate from embryonic progenitors and are maintained locally through self-renewal within their tissue niches under homeostatic conditions (Bleriot et al., 2020). Within this framework, intestinal macrophages were long considered an exception. Their high turnover, sustained by continuous recruitment of circulating monocytes, was thought to reflect the constant exposure of the intestinal mucosa to the microbiota (Bain et al., 2014). However, in 2018, two independent studies revealed that the term "intestinal macrophages" is an oversimplification, as the intestine contains multiple RTM subpopulations with distinct identities, dynamics, functions, and spatial localizations (Shaw et al., 2018; De Schepper et al., 2018). Importantly, these studies identified a population of long-lived macrophages associated with the submucosal region of the gut, less dependent on monocyte recruitment, that can be distinguished by the expression of markers such as CD4 or TIM4.

The study by Jayaraman et al. (2026) in this issue, from one of the two groups mentioned above, further advances our understanding of the biology of these long-lived gut macrophages. Challenging the traditional dichotomy between long-lived submucosal macrophages and short-lived mucosal macrophages, the authors propose that long-lived macrophages are also present in the mucosal lamina propria. However, these cells exhibit distinct identities and respond differently to environmental challenges compared with their submucosal counterparts. They notably identify CD163 as a marker distinguishing $CD163^{+}$ submucosal from $CD163^{-}$ $Tim4^{+}$ long-lived macrophages in the lamina propria. They further propose that Tim4 may serve as a marker of longevity, CD4 as a marker of maturation, and CD163 indicates subtissular localization (Jayaraman et al., 2026). Although this three-marker framework may appear reductive, given that single markers cannot fully capture cellular complexity, it nonetheless provides a practical guide for navigating the increasingly complex landscape of macrophage subpopulations revealed by high-throughput atlases (Hickey et al., 2023; Elmentaite et al., 2021).

However, the main contribution of this study likely lies elsewhere, namely in the identification of TGF-β as a key niche factor controlling the zonation of long-lived gut macrophages. TGF-β is a pleiotropic cytokine with well-established roles in immune regulation, epithelial homeostasis and tissue repair, and has long been recognized as a critical regulator of macrophage differentiation and function (Nelson et al., 1991). One of the clearest examples comes from the central nervous system, where TGF-β signaling is essential for establishing and maintaining the transcriptional identity of resident microglia, conferring a distinct profile compared with other brain myeloid cells (McKinsey et al., 2025; Butovsky et al., 2014).

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In the gastrointestinal tract, TGF-β signaling has long been recognized as a key regulator of homeostasis, particularly in controlling the differentiation of RTMs (Schridde et al., 2017). But the study discussed here adds an important dimension to this understanding by emphasizing a broader conceptual point: macrophage specialization is not solely determined by the presence of instructive signals but also by their spatial availability within tissues. In the intestine, where gradients of cytokines, metabolites, and microbial products are highly organized, the location of macrophages relative to sources and sites of TGF-β activation may be just as critical as the signaling pathway

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itself. Another important aspect is that, unlike many cytokines that are secreted in an active form, TGF-β is typically produced as a latent complex that must be locally activated before it can engage its receptors (Kanzaki et al., 1990). This activation can occur through various mechanisms, including proteolytic cleavage, integrin-mediated mechanical activation, or interactions with extracellular matrix components. Consequently, TGF-β signaling is often highly localized within tissues: although many cells may produce latent TGF-β, signaling occurs only where activation mechanisms are present. This property makes TGF-β particularly well suited to function as a spatially-restricted instructive signal. In the intestinal mucosa, multiple cell types, including epithelial cells, stromal cells, and immune cells, serve as sources of latent TGF-β. However, its activation is likely restricted to specific microenvironments where integrins or other activating mechanisms are present. As a result, RTMs located in different anatomical regions may be exposed to varying levels of TGF-β signaling. This spatial restriction is particularly relevant in the intestine, whose unique complex architecture generates steep gradients of environmental signals. The lamina propria lies directly beneath the epithelial layer, which interfaces with the microbiota, whereas deeper regions are associated with stromal cells, vasculature, and muscular layer. Consequently, RTMs distributed across these compartments are likely to encounter distinct levels and combinations of TGF-β signaling, depending on its local availability and activation.

These observations established an important conceptual framework: tissue macrophage identity is actively maintained by environmental cytokines rather than being irreversibly fixed by lineage. Similar principles have been described for other signals, including the local availability of colony-stimulating factor 1 (CSF-1), a key regulator of macrophage biology (Sehgal et al., 2021). Historically, macrophage specification has largely been interpreted through the lens of lineage-defining transcription factors (Mass et al., 2016). While understanding developmental origins remains essential, accumulating evidence indicates that tissue architecture and microenvironmental niches play equally critical roles in shaping immune cell identity and function (Chakarov et al., 2019; Lavin et al., 2014).

Lastly, Jayaraman et al. show that disruption of TGF-β signaling in resident macrophages using the *Timd4*^{cre}*Tgfbr2*$^{fl/fl}$ model leads to a phenotype that is intriguingly recapitulated in the *Cx3cr1*^{creER}*Tgfb1*$^{fl/fl}$ model. This finding, that both ligand and receptor deficiency have an impact, suggests that TGF-β signaling in RTMs may also operate through an autocrine mechanism, consistent with our recent observations in adipose tissue macrophages, where macrophage-derived TGF-β regulates adipocyte progenitor differentiation (Yu et al., 2025). However, as noted above, TGF-β production does not necessarily implies its activation, and future studies should investigate the additional signals required to enable the RTM-derived TGF-β signaling in the intestine.

In summary, the study by Jayaraman et al. identifies TGF-β as a key determinant of intestinal macrophage identity and provides important insights into the mechanisms underlying RTM specialization in tissues. Future work integrating spatial transcriptomics, imaging, and functional perturbation approaches will be essential to fully elucidate how localized TGF-β signaling interacts with other environmental cues to shape macrophage identity. Such efforts are likely to advance our understanding of tissue–immune interactions and may ultimately uncover new therapeutic opportunities to modulate macrophage function in inflammatory diseases.

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