TGFβ1 microenvironment determines dendritic cell development

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We have recently described two types of Langerhans cells (LCs), which develop via separate pathways in steady-state conditions and during inflammation. Here, we propose that these two types of LCs differ in their requirement for transforming growth factor β1 (TGFβ1), and we discuss how TGFβ1 impacts on the development of other dendritic cell subtypes.

Hematopoiesis is guided by growth factors and cytokines produced by the local microenvironment. A first clue on the environmental requirements for Langerhans cell (LC) development came from transforming growth factor β1 (TGFβ1)-deficient mice, which lack LCs. The normal skin is particularly rich in TGFβ1, which is produced by LCs themselves and by keratinocytes (Fig. 1A). It has been shown that both autocrine and paracrine TGFβ1 impact on LC development. Recently, it has become clear how TGFβ1 affects LC homeostasis in steady-state conditions. Studies on conditional gene knockout mice showed that TGFβ1 signaling maintains LCs in the epidermis by inhibiting their migration and maturation. Deletion of either TGFβ1 or its receptor in LCs caused them to acquire a migratory phenotype. In particular, adhesion appeared to be reduced through the downregulation of E-cadherin and EpCAM, while the expression of CCR7, MHC Class II and co-stimulatory molecules, like CD86, were upregulated.

The importance of TGFβ1 signaling in the biology of LCs is further demonstrated by the analysis of mice lacking TGFβ1 target genes. We have shown that TGFβ1 induces the expression of the transcription regulator Id2 (inhibitor of differentiation and DNA binding 2) in dendritic cells (DCs) and that the epidermis of Id2−/− mice is devoid of LCs. TGFβ1 also regulates the expression of Runx3 (Runt-related transcription factor 3) and Irf8 (interferon-regulatory factor 8). Runx3−/− mice completely lack LCs and Irf8−/− mice have reduced numbers of LCs.

In a recent study, we have used Id2−/+ mice as a model system to analyze the requirements for LC development and maintenance in more detail. We found that LC development is induced in Id2−/+ mice by UV light-triggered skin inflammation. This suggests that, in contrast to steady-state conditions, TGFβ1 signaling is not critical for the development of inflammatory LCs. Indeed, we observed that the expression of TGFβ1 target genes (Smad7, Langerin, Id2) in inflammatory LCs was clearly lower than in steady-state LCs. This is in line with the observation of Bobr et al., who reported that inflammation disrupts TGFβ1 signaling in steady-state LCs and causes them to migrate. Importantly, we have also observed that inflammatory LCs do not upregulate EpCAM to the same levels as steady-state LCs. Possibly as a result of an impaired TGFβ1 signaling, inflammatory LCs are not maintained in the epidermis and disappear when inflammation is resolved.

We have demonstrated that the transplantation of Id2−/− bone marrow cells into irradiated Id2−/− mice results in the generation of the LC network in Id2−/− mice. Thus, the restoration of the TGFβ1/Id2 axis in the hematopoietic compartment is sufficient to support LC development in adult Id2−/− mice. These results also indicate that the bone marrow contains LC precursors, although their identity remains unknown.

The precise mechanism whereby LCs develop is still under investigation. In wild type mice, LCs have been shown to develop from precursors that seed the skin during embryogenesis. In the first days after birth, these precursors proliferate and differentiate into LCs. A recent study reported that in neonates that lack TGFβ1 signaling specifically in the DC compartment, the initial seeding of LC precursors occurs normally. However, these cells do not acquire a steady-state LC phenotype, but mature and quickly disappear from the epidermis. So far it remains unclear whether in Id2−/− and Runx3−/− mouse precursor seeding and LC disappearance follow similar kinetics. Lineage tracing experiments should reveal at which point of the development of LCs these two factors are important.

TGFβ1 Signaling in the Development of Langerhans Cells

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TGFβ1 Signaling in the Development of Lymphoid Tissue DCs

TGFβ1 signaling is not restricted to LCs. We have shown that TGFβ1 signaling impacts on different stages of DC development from bone marrow cells. When multipotent progenitor cells (MPPs) were treated with TGFβ1, genes that are important for steady-state DC development, like Flt3, Irf8 and Irf6, were readily upregulated (Fig. 1B and C). This upregulation was sustained, indicating that TGFβ1 activates a DC program in MPPs and thus triggers DC commitment.

Furthermore, we have shown that in committed DC precursors (common dendritic cell progenitors, CDP), TGFβ1 accelerates DC differentiation (Fig. 1B). More precisely, TGFβ1 promotes conventional DC (cDC) development and blocks plasmacytoid DC (pDC) development. This occurs upon the specific induction of cDC-associated genes and concomitant repression of pDC-related genes. In line with this observation, specific DC subsets might be critically dependent on TGFβ1 signaling. For instance, CD8α+ DCs are severely reduced in Idf2−/− and Irf8−/− mice. We have also shown that, similar to the case of inflammatory LCs, the effects of TGFβ1 on inflammatory DC development are limited. This is surprising, given the fact that TGFβ1 is a pro-inflammatory cytokine. This apparent contradiction warrants further investigation.

Taken together, our data indicate that TGFβ1 impacts on the development of both lymphoid tissue DCs and non-lymphoid tissue DCs, like LCs. By affecting the expression of DC subset-specific genes, TGFβ1 plays an active role in the development and maintenance of these cells.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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