OncoImmunology 2:3, e23083; March 2013; © 2013 Landes Bioscience

TGFβ1 microenvironment determines dendritic cell development

Kristin Seré, Piritta Felker, Thomas Hieronymus and Martin Zenke*

Institute for Biomedical Engineering; Department of Cell Biology; RWTH Aachen University Medical School; Aachen, Germany; Helmholtz Institute for Biomedical Engineering; RWTH Aachen University; Aachen, Germany

Keywords: TGFβ1, Langerhans cells, dendritic cells, Id2, cell differentiation

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.

TGFβ1 Signaling in the Development of Langerhans Cells

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.[1] 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.[2] 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.[2,3] 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.[4] 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.[5]

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.[6] 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.,[2] 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.[6] 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.[7] 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.[3] So far it remains unclear whether in *Id2*$^{-/-}$ and *Runx3*$^{-/-}$ mice 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.

*Correspondence to: Martin Zenke; Email: martin.zenke@rwth-aachen.de
Submitted: 11/28/12; Accepted: 12/01/12
Citation: Seré K, Felker P, Hieronymus T, Zenke M. Microenvironmental TGFβ1 determines dendritic cell development. OncoImmunology 2013; 2:e23083; http://dx.doi.org/10.4161/onci.23083

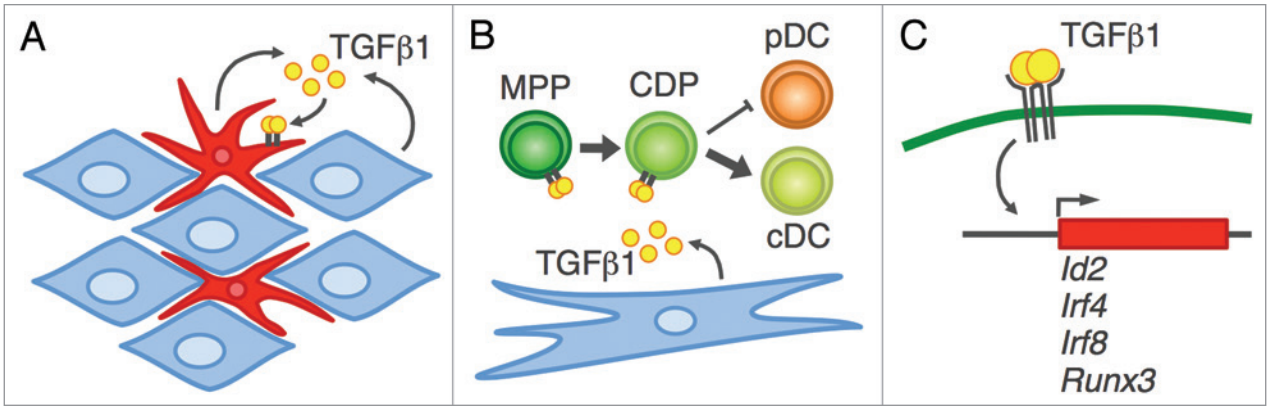

Figure 1. TGFβ1 impacts on dendritic cell differentiation. (**A**) Autocrine and paracrine transforming growth factor β1 (TGFβ1) production in the epidermis by Langerhans cells (LCs, red) and keratinocytes (blue). (**B**) TGFβ1 produced by stromal cells (blue) impacts on multipotent progenitor cells (MPPs) and committed dendritic cell precursors (CDPs) during dendritic cell (DC) commitment and differentiation into conventional and plasmacytoid DCs (cDCs and pDCs, respectively). (**C**) TGFβ1 induces the expression of *Id2*, *Irf4*, *Irf8* and *Runx3*, which are key transcription factors for DC development.

TGFβ1 Signaling in the Development of Lymphoid Tissue DCs

TGFβ1 signaling is not restricted to LCs.[8] 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 *Irf4*, were readily upregulated (**Fig. 1B and C**).[9] 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**).[10] 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 *Id2*$^{-/-}$ 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.

References

1. Borkowski TA, Letterio JJ, Farr AG, Udey MC. A role for endogenous transforming growth factor beta 1 in Langerhans cell biology: the skin of transforming growth factor beta 1 null mice is devoid of epidermal Langerhans cells. J Exp Med 1996; 184:2417-22; PMID:8976197; http://dx.doi.org/10.1084/jem.184.6.2417.
2. Bobr A, Igyarto BZ, Haley KM, Li MO, Flavell RA, Kaplan DH. Autocrine/paracrine TGF-β1 inhibits Langerhans cell migration. Proc Natl Acad Sci U S A 2012; 109:10492-7; PMID:22689996; http://dx.doi.org/10.1073/pnas.1119178109.
3. Kel JM, Girard-Madoux MJ, Reizis B, Clausen BE. TGF-beta is required to maintain the pool of immature Langerhans cells in the epidermis. J Immunol 2010; 185:3248-55; PMID:20713882; http://dx.doi.org/10.4049/jimmunol.1000981.
4. Hacker C, Kirsch RD, Ju XS, Hieronymus T, Gust TC, Kuhl C, et al. Transcriptional profiling identifies Id2 function in dendritic cell development. Nat Immunol 2003; 4:380-6; PMID:12598895; http://dx.doi.org/10.1038/ni903.
5. Merad M, Ginhoux F, Collin M. Origin, homeostasis and function of Langerhans cells and other langerin-expressing dendritic cells. Nat Rev Immunol 2008; 8:935-47; PMID:19029989; http://dx.doi.org/10.1038/nri2455.
6. Seré K, Baek JH, Ober-Blöbaum J, Müller-Newen G, Tacke F, Yokota Y, et al. Two Distinct Types of Langerhans Cells Populate the Skin during Steady State and Inflammation. Immunity 2012; 37:905-16; PMID:23159228; http://dx.doi.org/10.1016/j.immuni.2012.07.019.
7. Chorro L, Sarde A, Li M, Woollard KJ, Chambon P, Malissen B, et al. Langerhans cell (LC) proliferation mediates neonatal development, homeostasis, and inflammation-associated expansion of the epidermal LC network. J Exp Med 2009; 206:3089-100; PMID:19995948; http://dx.doi.org/10.1084/jem.20091586.
8. Strobl H, Knapp W. TGF-beta1 regulation of dendritic cells. Microbes Infect 1999; 1:1283-90; PMID:10611756; http://dx.doi.org/10.1016/S1286-4579(99)00256-7.
9. Seré KM, Lin Q, Felker P, Rehage N, Klisch T, Ortseifer I, et al. Dendritic cell lineage commitment is instructed by distinct cytokine signals. Eur J Cell Biol 2012; 91:515-23; PMID:22078373; http://dx.doi.org/10.1016/j.ejcb.2011.09.007.
10. Felker P, Seré K, Lin Q, Becker C, Hristov M, Hieronymus T, et al. TGF-beta1 accelerates dendritic cell differentiation from common dendritic cell progenitors and directs subset specification toward conventional dendritic cells. J Immunol 2010; 185:5326-35; PMID:20881193; http://dx.doi.org/10.4049/jimmunol.0903950.