Seminars in Cell & Developmental Biology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

The clash of Langerhans cell homeostasis in skin: Should I stay or should I go?

Thomas Hieronymus[a,b,*], Martin Zenke[a,b], Jea-Hyun Baek[c,1], Kristin Seré[a,b,1]

[a] Institute for Biomedical Engineering, Department of Cell Biology, Medical Faculty, RWTH Aachen University, Aachen, Germany
[b] Helmholtz Institute for Biomedical Engineering, RWTH Aachen University, Aachen, Germany
[c] Division of Renal Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Langerhans cell
Dendritic cell
TGF-β-signalling
Receptor tyrosine kinase
Met-signalling
Epithelial-to-mesenchymal-transition

ABSTRACT

Langerhans cells (LC), the skin epidermal contingent of dendritic cells (DC), possess an exceptional life cycle and developmental origin. LC, like all mature blood cells, develop from haematopoietic stem cells (HSC) through successive steps of lineage commitment and differentiation. However, LC development is different to that of other DC subsets and not yet fully understood. Haematopoietic cell fate decisions are instructed by specific growth factors and cytokines produced in specialized microenvironments or niches. Upon ligand binding the cognate surface receptors on HSC and further restricted progenitor cells regulate the signalling pathways that eventually leads to the execution of lineage-determining genetic programs. In this review we focus on a specific set of surface receptor kinases that have been identified as critical regulators of LC development using genetically modified mice. Recent studies suggest for some of these kinases to impact on LC/LC progenitor interaction with the local niche by regulating adhesion and/or migration. During embryonic development, in wound healing and aberrantly in tumour invasion the same kinase receptors control a genetic program known as epithelial-to-mesenchymal-transition (EMT). We will discuss how EMT and its reverse program of mesenchymal-to-epithelial-transition (MET) can serve as universal concepts operating also in LC development.

Contents

Abbreviations: LC, Langerhans cell; DC, dendritic cell; BM, bone marroe; LN, lymph node; TGF-β, transforming growth factor beta; Csf1, colony stimulating factor 1; Flt3, fms-like tyrosine kinase 3; HGF, hepatocyte growth factor; EMT, epithelial-to-mesenchymal-transition; MET, mesenchymal-to-epithelial-transition.

* Corresponding author at: Institute for Biomedical Engineering, Department of Cell Biology, Medical Faculty, RWTH Aachen University, Pauwelsstrasse 30, 52074 Aachen, Germany. Tel.: +49 2418085249; fax: +49 2418082008.
E-mail address: thomas.hieronymus@rwth-aachen.de (T. Hieronymus).

[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.semcdb.2014.02.009

Please cite this article in press as: Hieronymus T, et al. The clash of Langerhans cell homeostasis in skin: Should I stay or should I go? Semin Cell Dev Biol (2014), http://dx.doi.org/10.1016/j.semcdb.2014.02.009

1. Introduction

Langerhans cells (LC) represent the dendritic cell (DC) subset in skin epidermis and other stratified epithelia. Due to their specialized location LC constitute the first immune barrier for invading pathogens but have also been implicated in tolerance induction [1–4]. Two further major DC subpopulations are plasmacytoid DC (pDC) and tissue/interstitial/dermal DCs (dDC) (frequently referred to as "conventional" or "classical" DC, cDC). All DC in peripheral organs act as sentinels of the immune surveillance system and are therefore particularly abundant in tissue that serves as an interface to the environment, such as skin, airways, and intestine. pDC and cDC represent also the two major lymphoid tissue-resident DC populations in steady state [5,6].

Notably, the functional and phenotypic diversity of DC subsets was not instrumental to delineate DC lineage specificity. For example, it was found that all cDC and pDC can originate from both early clonal common lymphoid progenitors (CLP) and myeloid committed progenitors (Fig. 1) [5,7]. Additionally, cDC and pDC share a common developmental origin that became apparent with the identification of common DC progenitors: a Flt3+ Csf1R+ CX3CR1+ common macrophage/DC progenitor (MDP) [8–11] and a Flt3+ c-kitint Csf1R+ common DC progenitor (CDP) [11–13]. MDP give rise to macrophages and DC but not granulocytes. MDP are the direct progenitors of CDP, which are DC-restricted and do not generate other cell types. However, these studies did not address the potential of MDP/CDP to differentiate into LC.

While much is known about LC activation and trafficking towards the skin-draining lymph nodes (LNs), only recent studies addressed questions on the developmental origin of LCs and the molecular mechanisms involved [2,4,6,14–16]. It becomes increasingly evident that LC are unique in their development and homeostasis compared to other DC subtypes. This will be the focus of this review.

2. Langerhans cell development

LC were discovered by Paul Langerhans in 1868 [17] and based on the histological staining considered as of neuronal origin. It took another century before it became evident that LC belong to the haematopoietic system and originate from bone marrow (BM) precursors [18,19]. Finally, the pioneering work by Schuler and Steinman acknowledged LC as a non-lymphoid tissue contingent of DC in skin [20]. LC have been regarded for long time as the archetype of a migratory DC that exhibit the classical text-book DC life cycle and thus frequently referred to as the Langerhans cell paradigm [3,21]. This view has been revisited as it became clear that distinct DC populations emerge from independent developmental branches and possesses non-overlapping immune functions [5,6,21].

2.1. LC ontogeny

LC are unique in their development compared to other DC subsets and are exceptionally long-lived cells [2]. LC are maintained locally in skin without the need of a BM-derived precursor due to self-renewal of LC or LC precursors in the epidermis [2,22,23]. Further studies suggest a local pool of proliferating haematopoietic precursor cells that populate the skin during embryonic development [24–26]. Therefore, it has been questioned whether or not under steady state conditions BM-resident LC precursors contribute to LC homeostasis throughout life [22]. Recent studies suggested the major contribution of a foetal liver-derived LC precursor with a myelo-monocytic phenotype similar to primitive yolk sac (YS) macrophages [27]. Lineage-tracing experiments revealed indeed contribution (~10%) of YS progenitors to the pool of the adult LC network [27,28]. The phenotype of these foetal LC precursors is partially overlapping with the one described for MDP in adult BM showing expression of the Csf1 receptor and the chemokine receptor CX3CR1. In contrast, MDP are further characterized by expression of Flt3 that is not required for LC development (see Section 3.2.2) and MDP have not formally proven to represent a BM-derived precursor of LC. However, BM transplantation and fate mapping experiments clearly demonstrated the presence of a steady-state LC precursor in adult BM [18,19,23,29,30]. In addition, we found the development of LC to be differentially regulated in steady state and under inflammatory conditions. Our data demonstrated the existence of two types of BM-derived LC, short-term and long-term LC, that develop through different pathways in inflammation and steady state, respectively [30]. These findings were recently corroborated by further studies [31,32]. Long-term LC are critically dependent on the transcription regulator Id2 (inhibitor of DNA binding 2) during ontogeny and in steady state. Id2 is a TGF-β1 target gene, pointing towards the critical role of TGF-β1-signalling for development and maintenance of steady-state LC (see Section 3.1) [33]. Since the identity of the steady-state LC precursor in adult BM have so far not been precisely determined the exact mechanisms that regulate LC development and homeostasis in the adult remain elusive.

3. Receptor kinases in LC development

LC, like all mature blood cells, originate from a population of multipotent haematopoietic stem cells (HSC), which due to their sustained self-renewal capacity maintain haematopoiesis throughout life (long-term HSC; Fig. 1). Lineage specification and development of mature blood cells involves the activation of lineage specific genes and the selective repression of genes for alternative lineages, thereby leading to the establishment of a lineage specific differentiation program. Numerous cytokines and growth factors are known as essential mediators of lineage decisions [34]. Accordingly, various cytokines and growth factors have been identified to be vital for DC and/or LC development, such as Flt3-ligand (Flt3L), GM-CSF, IL-34, and TGF-β1 [6,7].

All haematopoietic factors are produced in local niches, which provide a distinct cytokine/growth factor environment that concomitantly acts on all stem, progenitor and differentiated cell populations present. Some cytokines will act in concert, partially with overlapping functionalities, while other factors have a unique function that eventually will lead to a specific and/or unidirectional lineage commitment from the choice of several. Thus, it becomes apparent that for a given cytokine milieu the susceptibility of stem/progenitor and mature cells is to a large extent determined by their expression of a specific repertoire of cytokine/growth factor receptors. Given the importance of Flt3L for DC development the expression of its receptor Flt3 is prototypical: the differentiation potential towards DC is maintained in all progenitors expressing Flt3 (Fig. 1) and loss of Flt3 expression correlates with loss of DC differentiation potential [35]. However, contrary to other DC subsets LC develop independently of Flt3 and Flt3L (see Section 3.2.2) [36,37].

Protein phosphorylation by the cytokine/growth factor receptors upon ligand binding is one of the key events of the signal transduction cascades that finally regulate cell fate determining gene activities. Protein kinases (PKs) are among the largest families of mammalian genes. The human kinome (the entire set of protein kinases) consists of 518 genes and the mouse kinome has 540 genes of which 510 are orthologs of human protein kinases [38,39]. Kinases were classified into 9 groups comprising 134 families with 196 subfamilies (Fig. 2A) [38].

Please cite this article in press as: Hieronymus T, et al. The clash of Langerhans cell homeostasis in skin: Should I stay or should I go? Semin Cell Dev Biol (2014), http://dx.doi.org/10.1016/j.semcdb.2014.02.009