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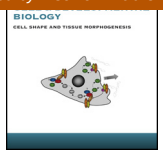

Review

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

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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.

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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].

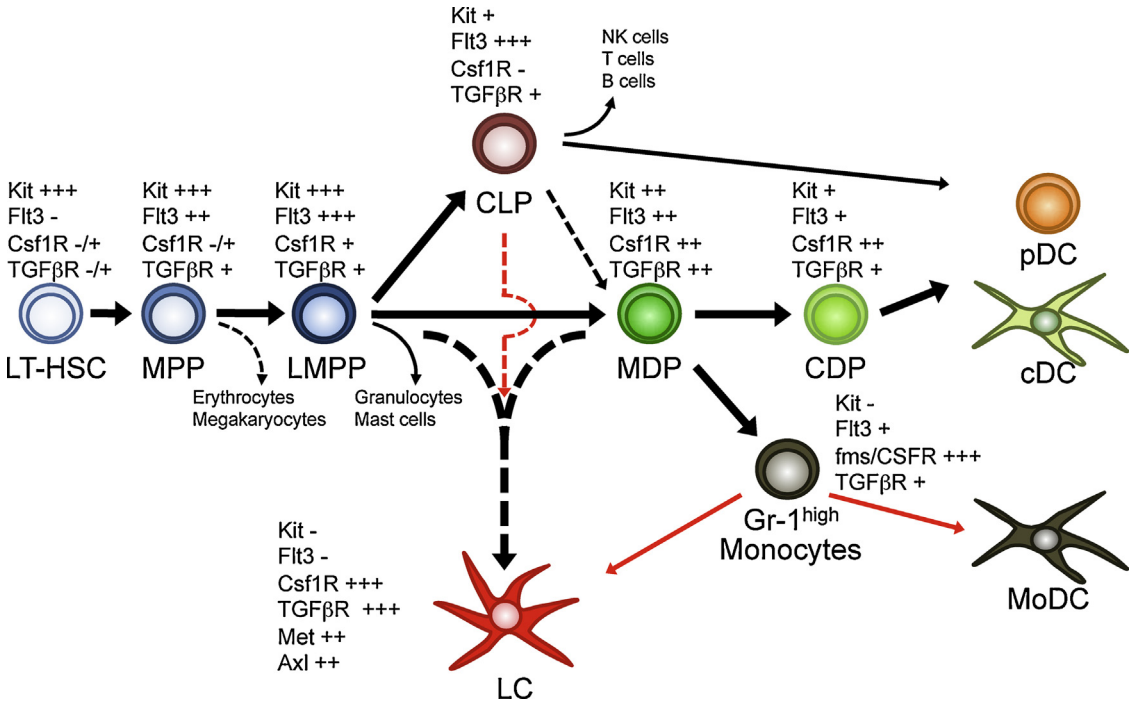

Fig. 1. DC and LC development from haematopoietic stem and progenitor cells. Receptor kinase expression is depicted on LC, HSC and progenitor cells with DC differentiation potential. Long-term reconstituting HSC (LT-HSC) maintain haematopoiesis throughout life due to their sustained self-renewal capacity and multilineage potential. LT-HSC give rise to multipotent progenitors (MPP) with diminished self-renewal potential that become increasingly restricted to specific lineage committed progenitors. Lymphoid-primed multipotent progenitor (LMPP) lost erythro-megakaryocytic potential but can give rise to all other lineages. Macrophage-DC progenitors (MDP) give rise to monocytes, macrophages, cDC, and pDC and are upstream of the DC-restricted common DC progenitors (CDP). MDP-derived Gr-1high/Ly-6C+ monocytes can further differentiate into inflammatory DCs (MoDC) and short-term LC. The DC-potential is also retained in Flt3 expressing CLP. Whether MDP, CDP or CLP have the potential for long-term LC development in steady state has so far not been addressed. Black arrows depict DC/LC development in steady state and red arrows under inflammatory conditions. Solid arrows, confirmed pathways; dashed arrows, putative pathways. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In the following sections we will focus on those cytokine/growth factor receptors that possess an intrinsic catalytic kinase domain and for which a particular role in LC development has been addressed in vivo using specific gene-knockout mouse models (Table 1). This includes the serine–threonine receptor kinases TGF-β receptor I and II and four RTKs (see Section 3.2). Fig. 2 shows the phylogenetic relationship of these receptor kinases and their domain organization.

3.1. TGF-β receptors

Members of the TGF-β receptor family are divided into two subfamilies, the type I and type II receptors [38]. In mammalian cells seven type I receptors have been identified and given a common nomenclature, i.e. activin-like kinase (ALK)1 to ALK7 (Fig. 2D). Five type II receptors are known that are constitutively activated through autophosphorylation of their cytoplasmic kinase domain [40]. Ligand binding causes interaction between type I and type II receptors, leading to phosphorylation of the type I receptors and further activation of Smad-signalling pathways [40].

TGF-β is the founding member of the TGF-β superfamily, which comprises more than 30 growth factors, including bone morphogenetic proteins (BMP) and activins [41]. TGF-β is a covalently linked homodimer and three isoforms exist, TGF-β1, TGF-β2 and TGF-β3. TGF-β exclusively binds TGF-β receptor II (TβRII), which then recruits and phosphorylates TGF-β-receptor I (TβRI, ALK5). ALK5 in turn phosphorylates Smad2 and Smad3. In some cell types, TGF-β has been shown to use ALK1-induced Smad1/5/8-signalling as an alternative pathway, which is normally considered as the BMP-induced pathway [40].

Table 1
Phenotype of receptor kinase-knockout mouse models on LC/DC development.

Mouse models lacking		Langerhans cell	cDC/pDC	Comment	References
Receptor	Ligand				
TβRI		absent	present		[52]
TβRII		absent			[51,53]
	TGF-β1	absent	present	MDP/CDP present	[50,51,53]
	BMP7	reduced			[55]
Flt3		present	reduced	MDP/CDP present	[9,36]
	Flt3L	present	reduced	MDP reduced NK cells reduced	[36,37]
Csf1R		absent	present		[36]
	M-CSF	present	reduced	Instructive on LT-HSC [59]	[64,65,69]
	IL-34	absent	present	Microglia reduced	[63,67]
Met		present	present		[85]
Axl		reduced			[73]

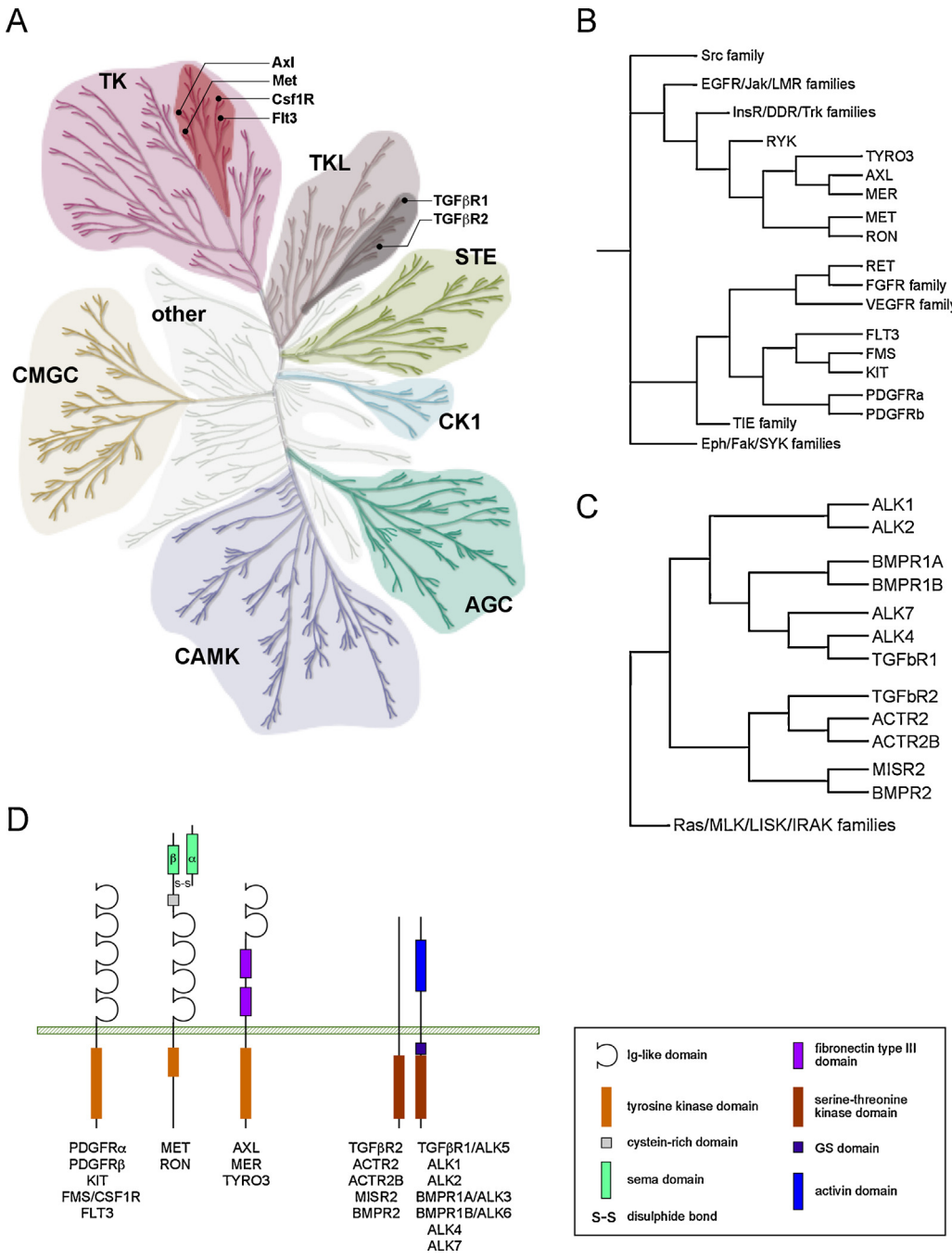

Fig. 2. Receptor kinases involved in LC development. (A) Phylogenetic tree of the complete superfamily of 478 human protein kinases containing a eukaryotic protein kinase (ePK) catalytic domain. The similarity between the protein sequences of these catalytic domains is inversely related to the distance between their positions on the tree diagram. Based on the sequence of their ePK domains, kinases are classified into seven major groups and other kinases, and are subdivided into families and colour-coded. The tyrosine kinases (TKs) Axl, Met, Csf1R, and Flt3 and the TGF-β receptors 1 and 2 that have a specific role in LC development are indicated. AGC, containing PKA, PKG, PKC families; CAMK Calcium/calmodulin-dependent protein kinase; CK1, Casein kinase 1; CMGC, containing CDK, MAPK, GSK3, CLK families; STE, homologs of yeast sterile kinases; TKL, tyrosine kinase-like. Modified from http://www.kinase.com/human/kinome/ according to [38]. (B) Dendrogram showing intrafamilial relationship of TKs involved in LC development. (C) Dendrogram showing intrafamilial relationship of serine–threonine receptor kinases (STRK) type I and type II including TGF-β receptors involved in LC development. Note that the distances to nodes in (B) and (C) are not in scale. (D) The domain structure of RTK and STRK families involved in LC development. The family members are listed beneath each receptor. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

TGF-β is a pleiotropic protein, which plays a role in many biological processes, including haematopoiesis and the immune system [42,43]. In general, TGF-β-signalling acts to maintain homeostasis by regulating processes like cell proliferation, differentiation and survival, however, the effect of TGF-β is cell type, status and location specific [41]. TGF-β preserves quiescence of HSC [44] and loss of TGF-β-signalling impairs their self-renewal capacity [45]. Furthermore, TGF-β differentially impacts on cell fate decisions and differentiation. It promotes for example proliferation and differentiation in myeloid-biased progenitors [46] but induces apoptosis in lymphoid progenitors [47]. Additionally, TGF-β1 induces DC commitment in multipotent progenitors [48] and biases DC differentiation towards cDC, by blocking pDC-specific gene expression [49].

TGF-β1-signalling is an absolute prerequisite for LC homeostasis in epidermis. TGF-β1-deficient mice lack LC [50] and TβRI/ALK5- and TβRII-deficient mice show substantially reduced numbers of LC [51–53]. TGF-β1-signalling is essential for retaining LC anchored in their epithelial environment in an immature and sessile state, while development and initial seeding of the epidermis occurs independently of TGF-β1-signalling. LC-specific elimination of TβRI/ALK5, TβRII or TGF-β1 results in downregulation of E-cadherin [52,53] that mediates homophilic interactions of LC and keratinocytes (reviewed in [54]).

Importantly, it was recently shown that another TGF-β family member, BMP7, modulates LC biology [55]. This BMP7/ALK3-signalling precedes TGF-β1/ALK5-signalling during LC ontogeny and BMP7/ALK3-signalling therefore appears to impact on LC differentiation instead of on LC maintenance. Accordingly, BMP7-deficient mice exhibit reduced numbers of LC [55].

3.2. Receptor tyrosine kinases

Based on their domain structure all 58 mammalian RTKs fall into 20 distinct families [56]. So far, there are only clues on 4 RTKs concerning their role for LC development or maintenance, including the Fms-like tyrosine kinase 3 receptor (Flt3, also known as Flk2 and CD135), the colony-stimulating factor 1 receptor (Csf1R, also named fms, M-CSFR or CD115), the hepatocyte growth factor (HGF) receptor Met, and Axl. Flt3 and Csf1R belong to the same family of class III RTKs that includes Kit (the receptor for stem cell factor, SCF) and the platelet-derived growth factor receptors (PDGFR) α and β, and thus referred to as the PDGF receptor family (Fig. 2A and D).

3.2.1. Csf1R

The receptor for Csf1/M-CSF is encoded by the fms proto-oncogene and its expression is restricted to the myeloid lineage, including progenitor cells, osteoclasts, and DC and to placental trophoblasts during foetal development [57]. The fms mRNA is detectable in the earliest yolk sac phagocytes formed during mouse development, prior to many other monocyte/macrophage markers, including the transcription factor PU.1 [58]. In line with this finding a recent report described that Csf1/M-CSF can directly induce PU.1 expression and instruct myeloid cell-fate conversion in mouse HSC [59].

Interleukin-34 (IL-34) represents the second functional ligand for Csf1R [60]. IL-34 shares no amino acid sequence homology to Csf1/M-CSF but exhibits a similar three-dimensional topology. Functionally, IL-34 can compete with Csf1/M-CSF for CSF1R binding, and can rescue the phenotype of Csf1/M-CSF-deficient (Csf1op/op) mice [61]. However, IL-34 and Csf1/M-CSF differentially bind to the extracellular domains of the receptor, which causes subtle differences in signal activation and biological activities [61,62]. Moreover, the two cytokines display differential spatiotemporal expression patterns, suggesting nonredundant roles in both developing and adult tissues [61–63].

The impact of Csf1R for DC development emerged just recently. Most striking was the discovery of complete absence of LC in adult Csf1R-deficient mice [64], while normal numbers of LC were present in adult Csf1op/op mice [64,65]. Noteworthy, newborn Csf1op/op mice showed also reduced numbers of LC [64,66]. Due to the fact that IL-34 had remained undiscovered as the second Csf1R-ligand for more than three decades the importance of the Csf1R has probably been underrated and the precise role of Csf1R in DC development still remains to be explored. Highest expression of murine IL-34 mRNA was found in brain and ear tissue (and very low expression in spleen) [61], while human IL-34 mRNA is most abundantly expressed in spleen [60]. In line with the expression profile in mouse, IL-34-deficient mice lack epidermal LC and have reduced number of microglia, the central nervous contingent of tissue macrophages [63,67]. In contrast, IL-34-deficient mice exhibit no defects in dermal DC and macrophages, monocytes, cDC and pDC.

Expression of the Csf1-receptor was found in all progenitors along the DC differentiation pathway, including MDP and CDP [8–13], and in multipotent progenitors including lymphoid-primed multipotent progenitors and HSC [59,68]. The Csf1-receptor is also expressed on lymphoid tissue pDC and cDC and in contrast to the IL-34-knockout phenotype Csf1op/op mice revealed an approximately two- and threefold reduction in splenic cDC and pDC, respectively [69]. In line with these results, both pDC and cDC can be generated in vitro from BM cultures with M-CSF only [49,70]. Furthermore, in vivo, pDC and cDC were increased in Flt3L-deficient mice treated with M-CSF, demonstrating that signalling via the fms/Csf1-R alone can induce DC generation independent of Flt3L [70].

3.2.2. Flt3

Flt3-ligand was identified as one of the key cytokines for DC development as both cDC and pDC are generated from all Flt3+ DC precursors (Fig. 1). Flt3 expression is found on short-term repopulating multipotent progenitors but not on long-term HSC [71]. Flt3 is also expressed on further downstream linage-restricted progenitors that retain DC-potential, including CLP and CMP [35,72], MDP [8–11], and CDP [11–13].

Flt3 expression is also maintained on pDC and cDC [35]. Accordingly, overexpression or injection of recombinant Flt3L in mice or humans leads to massive expansion of both pDC and cDC (reviewed in [6]). In line with its in vivo impact on DC, Flt3L is readily used to generate pDC and cDC from mouse BM or foetal liver cultures in vitro. Moreover, Flt3L is also frequently used in in vitro culture for generation of human LC derived from CD34+ HSC [33,55,73–76]. Based on the in vitro data it was unexpected that the LC compartment is virtually unaffected in mice lacking either Flt3 or Flt3L [36,37]. This is in stark contrast to the reduced numbers of pDC and cDC found in Flt3- or Flt3L-deficient mice [9,37]. Surprisingly, numbers of MDP and CDP were also found reduced in Flt3L-deficient mice [37] but not in Flt3-deficient mice [9,37]. Thus, Flt3 expression is apparently not required for the development of DC progenitors including MDP and CDP but rather for maintenance of DC homeostasis [9]. Such a concept would be in line with Flt3L amplifies Flt3-expressing DC precursors in vitro and in vivo, including LC progenitors but maintenance of DC/LC is dependent on different locally provided cytokines within the various lymphoid and nonlymphoid tissues.

3.2.3. Met

Met was originally identified as an oncogene and later found to represent the receptor for HGF, also known as scatter factor [77,78]. Met is a member of the HGF receptor subfamily of RTKs that includes the highly homologous kinase Ron (Fig. 2). Ron is the receptor for the macrophage stimulating protein (MSP), which is structurally related to HGF. Met and Ron share a distinct domain structure as disulphide-linked α/β heterodimers formed from a single-chain precursor by proteolytic cleavage. The transmembrane β-chain subunit contains the intracellular tyrosine kinase domain and extracellularly a so-called 'sema' domain that has structural analogies with the extracellular domains of semaphorins and plexins (Fig. 2). Met-signalling after HGF binding confers mitogenic, morphogenic, and motogenic activity to various cells and is essential during embryonic development, as shown by the lethal phenotype in utero of conventional Met- or HGF-null mutations [77,78].

Met expression in the haematopoietic compartment was found in stem and progenitor cells including long-term HSC [79,80], B cells [81,82], and monocytes [83]. Met expression was also found

in all DC subtypes so far analyzed including splenic cDC and pDC [84,85], dermal DC, LC and DC derived from BM cultures [85,86]. Met expression is further upregulated with maturation of DC [85]. Whether it is functionally expressed on DC-progenitors such as MDP or CDP has so far not been addressed.

Recently, it became evident that Met-signalling is critically involved in the emigration of LC and dDC from skin. Stimulation with HGF alone is sufficient to induce LC emigration from skin, while it did not serve as a chemoattractant for DC [85,86]. HGF stimulation enhances adhesion of DC to laminin, suggesting a functional interplay with integrins like in other cellular systems [86,87]. Interestingly, the α6 integrin, part of the laminin receptor α6β4 integrin, was found to be required for LC emigration from epidermis [88]. By using a conditional Met-deficient mouse model (Metflox/flox), we further demonstrated that Met-signalling in skin-resident LC and dDC is essential for their detachment and emigration from surrounding tissue upon inflammation. As a consequence, Met-deficient LC and dDC failed to reach draining LNs and thus lacked the capacity to mount an immune response in contact hypersensitivity reactions [85]. Additionally, Met-signalling in DC regulates matrix metalloproteinase (MMP)-2 and MMP-9 activity required for LC transmigration through extracellular matrix [85,89,90]. In contrast, Met-signalling was not required for stem cell homing into the BM and subsequent development and integration of LC into epidermis [85].

3.2.4. Axl

The RTK Axl (also known as Ark, Ufo, and Tyro7) is the founding member of the TAM family of RTKs, which also includes Tyro3 and Mer (Fig. 2) [91,92]. TAM receptors have identical structures and are activated by dimerization. The predominant ligand for Axl is the protein encoded by growth-arrest-specific gene 6 (GAS6), which is shared by its family members Tyro3 and Mer. Tyro3 is additionally activated by protein S, a factor with an additional function as an anticoagulant in blood. In cells co-expressing Mer and Tyro3, protein S is also a potent Mer agonist [91]. Hence, it is suggested that TAM receptors can form heterodimers among each other, but the mechanism and functional consequences of hetero- versus homodimerization remain still elusive [91].

Axl, Mer and Tyro3 are most closely related to Met and Ron (Fig. 2B) [38,91]. A crosstalk of Axl with Met-signalling is suggested to play a role in cellular migration and survival [93,94]. In line with this, expression of Axl in tumours correlates with invasion and metastatic cell migration [92].

In the haematopoietic compartment, Axl is expressed in DC and macrophages but not in monocytes, granulocytes, or lymphocytes and was found to be important for the homeostasis of the immune system. Axl is strongly induced in DC and macrophages by type I interferons upon Toll-like receptor (TLR) stimulation during inflammation [95,96]. TAM-signalling promotes uptake of apoptotic cells by phagocytes and negatively regulate innate immune responses by limiting pro-inflammatory TLR activation during inflammation [95–97]. Loss of Axl together with its family members has severe immunological consequences. TAM-triple knockout mice display constitutively activated DC, macrophages, T and B cells and develop a broad-spectrum of autoimmune disorders [91].

In steady state Axl plays a role in the homeostasis of skin immunity by maintaining the LC network in the epidermis [73]. Axl expression is rapidly induced during early LC differentiation and remains as a key downstream effector of TGF-β1-signalling. LC in skin are constantly exposed to GAS6 that is abundantly expressed in keratinocytes. As a result, uptake of apoptotic material is enhanced and TLR-mediated LC maturation is impeded. Consequently, down regulation of endogenous Axl-signalling is an essential step for LC maturation and emigration from skin [73].

4. EMT and MET in the LC life cycle

LC development and immunological function are closely interrelated to mobility. LC precursors leave their cradle (whether yolk sac, foetal liver, or bone marrow) to immigrate into the epidermis. LC become sessile and embedded within the tissue via adherens and tight junctions, and maintain homeostasis in situ by self-renewal. This stationary phenotype is abandoned only when LC become activated and start to emigrate from the epidermis to skin draining LNs.

A similar spatial and temporal sequence of cellular activities is referred to as 'invasive growth' and includes disruption of cell-to-cell contacts, mobilization from the primary tissue of residence, prevention of apoptosis, interstitial migration, crossing tissue boundaries, homing to secondary target tissue and proliferation [87,98]. The aberrant execution of this sequence is well known in tumour progression towards metastasis. Moreover, this sequence of events has a physiological relevance during embryonic development. In the adult it is reactivated in wound healing and tissue regeneration. The conversion of an immobile epithelial (or in some cases endothelial) cell to a motile and migratory phenotype is called epithelial-to-mesenchymal transition (EMT). This genetically driven program is transient and migratory cells at their secondary site of residence reconvert by mesenchymal-to-epithelial transition (MET) back into a stationary phenotype [99–101].

One of the molecular hallmarks of EMT is the loss of E-cadherin expression. EMT is characterized by downregulation of further components that build up adherens and tight junction complexes, including EpCAM, occludins, claudins, zonula occludens (ZO) proteins, and cytokeratins and thereby decomposes cell-to-cell contacts. Simultaneously, cells acquire mesenchymal features, such as expression of N-cadherin, vimentin, integrins, and matrix-metalloproteinases (MMP) and reorganization of the cytoskeleton, which altogether facilitate cell migration. The EMT and MET programs are controlled by an intricate network of transcriptional regulators belonging to three families: the zinc finger factors Snail and Slug, the zinc finger and E-box binding proteins (ZEB) 1 and 2, and basic helix-loop-helix factors (e.g. Twist1) (reviewed in [98,99,101]).

Both signalling by TGF-β receptor and Met have long been known to play important roles in invasive events during embryonic development, tissue regeneration, and cancer progression. Yet, there are open questions. TGF-β-signalling is involved in controlling both EMT and MET transitions. TGF-β is often found as a potent EMT inducer, while several BMPs, including BMP7, can promote MET [100,101]. It is nowadays reasoned that changes in components of the TGF-β signal-transduction machinery account for divergent cellular responses [41]. One example is the differential activation of ALK1 and ALK5 in endothelial cells. TGF-β-induced ALK1-signalling leads to Smad1 and Smad5 phosphorylation resulting in cell proliferation and migration, while ALK5-signalling activates Smad2 and Smad3 leading to inhibition of both proliferation and migration [102].

In LC development, TGF-β-signalling is essential to maintain the stationary, more epithelial-like phenotype rather than inducing EMT (Fig. 3). LC in skin express E-cadherin and various other epithelial-like junctional proteins, including claudin-1, EpCAM/TROP1, TROP2, ZO-1, occludin, JAM1, and cytokeratins, which allows them to functionally integrate into the keratinocyte layer [50,74,76,103,104]. By employing conditional gene-knockout mice recent studies showed that TGF-β-signalling retains LC in the epidermis by inhibiting their migration and maintaining their epithelial phenotype. Deletion of either TGF-β1 or its receptors TβRII and TβRI/ALK5 in LC causes them to acquire a migratory phenotype. In particular, adhesion appears to be reduced through

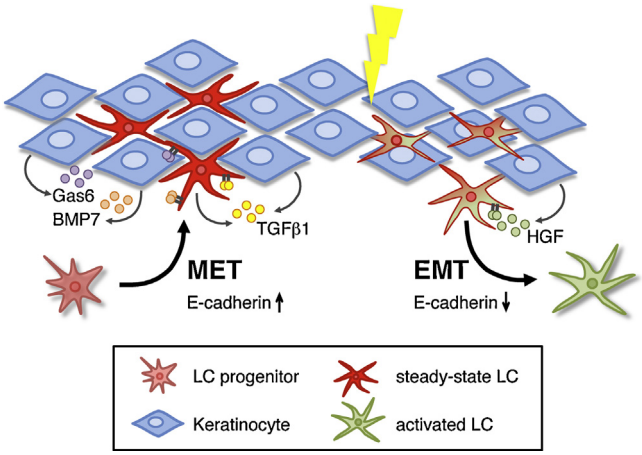

Fig. 3. EMT and MET in the LC life cycle. LC/LC precursors undergo MET in epidermis. TGF-β/BMP-signalling is essential to keep the stationary, epithelial-like phenotype. Met-signalling is an inducer of EMT critically involved in LC emigration upon activation.

the downregulation of E-cadherin and EpCAM, while the expression of maturation markers was upregulated [52,53]. Interestingly, Bobr et al. [53] showed that inflammatory activation of steady-state LC, which induced their emigration from epidermis, disrupts TGF-β1-mediated pSmad2/3-signalling.

Recent studies by the Strobl lab further corroborated the role of TGF-β- and BMP7-signalling in controlling EM- and ME-transitions in LC development [55,75,76]. They found that BMP7 is highly expressed in the basal and suprabasal layers of the epidermis where LC reside in steady state. BMP7 was able to induce LC differentiation in a human culture model via ALK3 in the absence of canonical TGF-β-ALK5-signalling, while TGF-β1 activated both ALK3 and ALK5 pathways. In BMP7-deficient mice LC numbers were significantly diminished [55] in line with the role of BMP7 in MET. Furthermore, TGF-β-signalling induced a number of epithelial adhesion molecules in LC during differentiation including E-cadherin [76]. Activation of LC was found to induce expression of the EMT regulators ZEB1 and ZEB2 and downregulation of E-cadherin accompanied by upregulated expression of N-cadherin, a marker of a mesenchymal phenotype [75]. In contrast, mesenchymal cytoskeletal markers such as vimentin and smooth-muscle-actin were not found to be regulated [75], which is in line with previous observed expression of vimentin in LC of mouse epidermis [105].

Taken together, the concept emerges that in long-term LC development cells execute a MET-like program, while short-term LC are unable to accomplish the full transition from their mesenchymal to an epithelial phenotype. MET during LC development appears to be tightly regulated by expression of and signalling via a specific combination of TGF-β receptors. Consequently, alteration or lack of one of these pathways will result in incomplete MET. Indeed, the expression of TGF-β1 target genes in short-term LC was found to be lower than in long-term LC [30]. It is tempting to speculate that ALK5-associated Smad 2/3-signalling pathways are inefficiently activated in short-term LC. Yet, whether genetically driven EMT and MET programs are in fact differentially executed in long-term versus short-term LC remains to be addressed.

Signalling by Met is a potent inducer of EMT. Met-signalling in LC appears to recapitulate properties of EMT (Fig. 3). Met-signalling regulates MMP activities in DC [85], which is a characteristic feature of a mesenchymal and migratory phenotype upon EMT induction. This is similar in tumour cells where Met-signalling can stimulate the proteolytic activity of MMPs, thus facilitating their dissociation and invasive scattering. Strikingly, the importance of MMPs, particularly MMP-2 and MMP-9, in LC migration has been well established [89,90].

However, it remains unclear how Met-signalling in LC induces EMT by exploiting downstream signalling pathways that are commonly shared by other RTKs. Where does the specificity for inducing LC emigration from the epidermis come from? Cooperation with other cell surface receptors important in regulating cellular migration, such as α6β4 integrin, plexin-B1, CD44, Axl, and Mif receptor have been considered to act in concert in a context and tissue environment-dependent fashion [82,87,94,98]. For some of these factors expression in LC has been already demonstrated. However, whether or not interaction with Met takes place in LC and the precise mechanisms of downstream signalling pathways remain to be addressed.

5. Conclusions

Cytokine/growth factor receptor kinases, including TGF-β-receptors and Csf1R, Met, and Axl RTKs are critically involved in LC homeostasis. Receptor kinase-signalling has a significant impact on the activation of lineage specific genes and the selective repression of genes for alternative lineages, thereby leading to the establishment of a LC specific differentiation program. Apparently, the entire set of cell surface receptors allows congregating all extrinsic cues from the local niches that impact on LC fate. Compared to the dimension of the mammalian kinome there is yet rather limited data about the signal transduction pathways critically involved in LC and DC development. This needs clearly more profound investigations.

The recent findings reviewed here emphasises the role of adhesion and migration for LC homeostasis and the control of these mechanisms by TGF-β- and Met-signalling pathways (Fig. 3). These pathways drive specific cell fate transition programs known as EMT and MET. However, mechanisms controlling cell motility might be different in mesenchymal cells and DC. Thus, further studies are needed (i) to corroborate the concept that EMT and MET programs are involved in LC development and (ii) whether or not this concept is also operating in other DC subsets, such as interstitial DC in gut, lung or other peripheral tissues.

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