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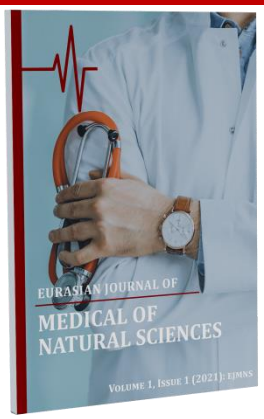

THE FUNCTIONS OF SKIN LANGERHANS CELLS IN IMMUNE TOLERANCE AND CANCER IMMUNITY

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ABSTRACT

Langerhans cells (LC) are a distinct population of tissue-resident macrophages with dendritic cell (DC) functionality, forming a dense network across the epidermis. Positioned at the skin barrier, LC serve as critical immune sentinels at the interface between the body and the environment. Historically classified as DCs, extensive research has focused on their ability to prime T cell immunity. However, LC possess unique macrophage-like properties, and recent studies reveal their immunoregulatory roles both in steady-state conditions and during specific inflammatory responses. This highlights the influence of the cutaneous microenvironment in shaping LC functionality. This mini-review explores emerging insights into the role of LC in immune tolerance under normal and pathological conditions, including malignant transformation and progression. Additionally, we examine LC functional plasticity in response to microenvironmental cues and the potential relationship between LC heterogeneity and functional diversity. Understanding the molecular mechanisms that enable LC to integrate environmental signals and modulate immune responses is crucial for advancing tumor immunology, vaccine development, and therapies for inflammatory skin disorders.

1.Introduction

Langerhans cells (LC) are a specialized population of mononuclear phagocytes located in the epidermis of the skin. These cells originate from embryonic macrophage precursors and are highly conserved across vertebrate species. Although LC were initially classified as a subset of dendritic cells (DC) due to their ability to migrate to skin-draining lymph nodes, recent studies on their lineage and development have revealed that LC are a distinct type of tissue-resident macrophages (TRM) that acquire DC-like characteristics and functions upon differentiation in the skin. Their strategic localization in the epidermis, the body's outermost

barrier, underscores their role as immune sentinels and a critical component of the first line of defense.

Over the years, research has largely focused on the DC-like properties of LC, particularly their ability to prime T cell immunity. However, emerging evidence suggests that LC, as macrophages, play a significant immunoregulatory role under steady-state conditions and in certain inflammatory contexts. This review summarizes recent findings on the role of LC in maintaining immune tolerance during homeostasis and disease, with a focus on their involvement in skin cancer development and progression. Additionally, it explores the influence of microenvironmental factors on LC functional plasticity and the relationship between LC population heterogeneity and functional diversity.

2.Langerhans Cells in Ultraviolet Radiation-Induced Immune Suppression

Ultraviolet (UV) radiation, particularly UVB, is a major risk factor for skin cancer and a key contributor to skin inflammation and immunosuppression. Experimental exposure to UV light has been widely used to study the activation and migration of LC.

UV radiation causes extensive DNA damage in keratinocytes (KC), leading to outcomes such as DNA repair, apoptotic elimination, or the acquisition of mutations that enable resistance to apoptosis and clonal expansion. Following UV exposure, LC migrate to lymph nodes and promote the induction of antigen-specific regulatory T cells (Treg), a central mechanism in UV-induced immunosuppression. However, studies have shown that in some cases, dermal langerin+ cells, rather than LC, play a dominant role in suppressing T cell expansion during specific immune responses. These discrepancies are likely influenced by differences in experimental models, methodologies, and disease phases under investigation.

LC also contribute to the resolution of UV-induced cutaneous inflammation by phagocytosing apoptotic KC. This process is associated with the release of anti-inflammatory factors, such as transforming growth factor beta (TGF-β), prostaglandin E2 (PGE2), and platelet-activating factor (PAF). Interactions between receptor activator of nuclear factor κ B (RANK) on LC and RANK ligand (RANKL) on inflamed KC further enhance LC's ability to drive IL-10-mediated Treg responses. Such mechanisms highlight the role of LC in modulating local immune responses within the skin.

Interestingly, LC's regulatory role can vary depending on the context. In some instances, interactions between apoptotic KC and specific LC subsets can limit Treg numbers, which may be beneficial in certain immune responses, such as controlling gut infections, but potentially detrimental in skin inflammation. This variability underscores the context-dependent nature of LC-mediated immune regulation and their role in maintaining immune balance in epithelial tissues.

In addition to their involvement in immune suppression, LC have been implicated in UVB-induced carcinogenesis. For example, LC-intact skin is more prone to developing UVB-induced tumors than LC-deficient skin, as LC facilitate the clonal expansion of p53-mutant KC independently of T cells. LC also contribute to shifts in innate lymphoid cell populations, such as RORγt+ IL-22+ IL-17+ cells, which promote the expansion of UV-induced p53-mutant KC. These findings emphasize LC's dual role in regulating immunity and promoting tumorigenesis under UV exposure.

A summary of LC-related mechanisms in UV-mediated immune suppression is provided in Table 1.

Table 1. Langerhans cells in UV-mediated immune suppression.

Model Type	Observed LC Function	LC Location	Reference
UVR, Mu-Langerin-DTR	migration and induction of antigen-specific Treg post UVR	LN	[8] Schwarz A et al.
UVR, Mu-Langerin-DTR, Ag-specific CD8T transfer	Dermal Langerin^{+} DC but not LC reduce CD8 T expansion post UVR	LN	[9] Wang L, et al.
UVR, Mu-Langerin-DTR	phagocyte apoptotic KC, anti-inflammation post UVB	Skin	[11] Hatakeyama M et al.
UVR, K14-RANKL^{Tg}	RANK (LC)-RANKL (KC) interaction enhance Tregfunction	LN, Skin	[15] Loser K et al. [16] Yoshiki R et al.
UVR, Mu-Langerin-DTR	OX40L (LC)- OX40 (T) interaction induce T reg	LN, Skin	[16] Yoshiki R et al.
CD300a$^{-/-}$ mice	CD300a (LC)-PC (apoptotic KC) interaction inhibit Treg.	Skin	[17] Nakahashi-Oda C et al.
UVR, hu-Langerin DTA	promote p53 mutant KC clonal islands expansion	Skin	[18] Lewis JM et al.
UVR, hu-Langerin DTA	facilitate ILC3 shift enhance mutant KC growth upon UV	Skin	[19] Lewis JM et al.

3. Langerhans Cells in Steady-State Skin Immune Homeostasis

Tissue-resident macrophages (TRM) play a critical role in maintaining immune homeostasis within tissues, largely through their ability to rapidly clear debris from dying cells under both normal and pathogenic conditions. Similarly, Langerhans cells (LC), as a specialized subset of TRM, utilize innate mechanisms to regulate local immune tolerance in the skin. The phagocytosis of apoptotic cells by macrophages and dendritic cells suppresses inflammatory immune responses, a process central to maintaining tissue equilibrium.

Transforming growth factor-β1 (TGF-β1) is a key regulatory molecule involved in the development, maintenance, and function of LC. This cytokine regulates LC through context-specific signaling pathways. For example, during LC differentiation, TGF-β1 induces the upregulation of Axl, a receptor tyrosine kinase from the TAM (Tyro3, Axl, Mer) family. Axl enhances LC phagocytosis of apoptotic keratinocytes (KC) expressing its ligand, growth arrest-specific 6 (GAS6), and suppresses inflammatory cytokine production. Additionally, Axl expression can be upregulated independently of TGF-β1 during inflammation, providing a feedback mechanism to control excessive cytokine production.

In resting conditions, LC interact selectively with skin-resident memory T cells, particularly regulatory T cells (Treg). While resting LC promote the activation and proliferation of Treg to maintain immune tolerance, they shift their function upon

encountering pathogens. Activated LC stimulate the proliferation of effector memory T cells while limiting Treg activation, enabling an effective protective immune response.

LC also play a continuous role in establishing immune tolerance by migrating to draining lymph nodes under homeostatic conditions to present self-antigens. Additionally, LC are in constant contact with the skin's bacterial flora, which suggests their involvement in preventing the reactivation of bacteria-specific memory T cells. Although LC have a limited capacity to internalize and process bacteria, skin commensal bacteria-primed LC drive the development of Foxp3+ Treg, promoting immune tolerance to commensal organisms.

Long-term absence of LC in the epidermis leads to significant changes in gene expression within local keratinocytes and resident epidermal T cells, further demonstrating LC's active role in maintaining epidermal homeostasis. These findings highlight LC's dual function in preserving immune tolerance during steady-state conditions and activating appropriate immune responses when challenged by pathogens.

A summary of LC's roles in steady-state skin homeostasis is depicted in Figure 1.

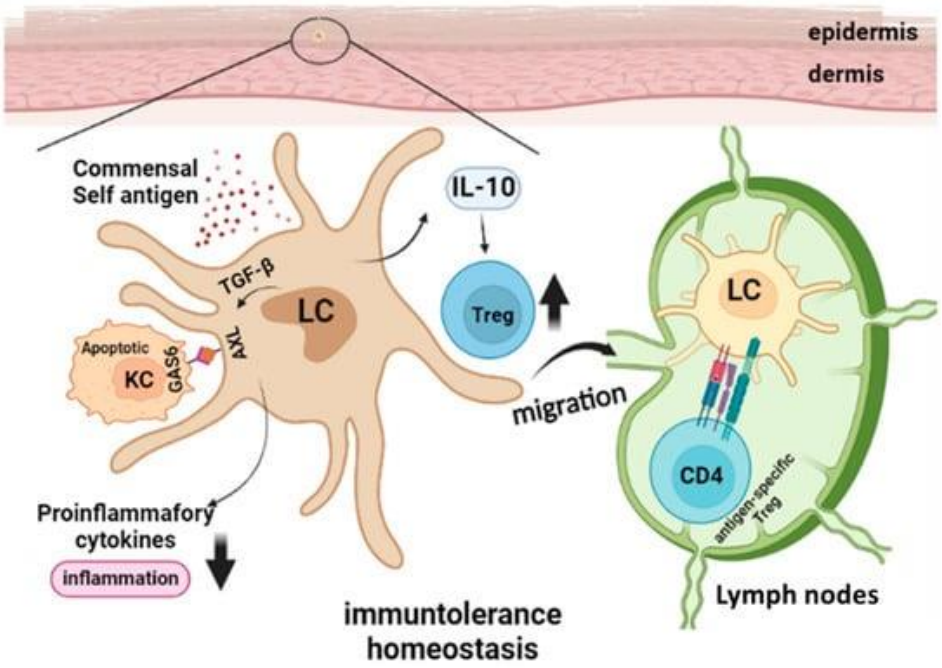

Figure 1. Langerhans Cells in Steady-State Skin Immune Homeostasis. Under homeostatic conditions, LC continuously migrate to draining lymph nodes, where they present self or commensal antigens to promote the development of regulatory T cells (Treg). Additionally, the amplification of local skin Treg can be stimulated by IL-10 produced by LC. The differentiation of LC, driven by transforming growth factor-β1 (TGF-β1), is associated with the upregulation of Axl. This enhances the phagocytosis of apoptotic keratinocytes (KC) expressing the Axl ligand GAS6 and suppresses the production of inflammatory cytokines.

4. Langerhans Cells in Skin Treg Differentiation and Inflammatory Disease Models

Tissue-resident macrophages (TRM), including Langerhans cells (LC), play a pivotal role in suppressing local adaptive immunity through direct and indirect interactions with regulatory T cells (Treg). TRM from various tissues, such as the intestine, lungs, liver, and brain, promote Treg differentiation by producing cytokines like IL-10, TGF-β, and retinoic acid (RA). Similarly, antigen-presenting dendritic cells (DC) also facilitate Treg differentiation

through the secretion of these mediators. In steady-state conditions, LC encountering self-antigens induce Treg differentiation, while exposure to foreign antigens triggers an inflammatory cascade.

Beyond cytokine-mediated Treg promotion, TRM, including LC, directly interact with Treg in situ. For example, studies in experimental autoimmune encephalomyelitis have shown that TRM expressing sialoadhesin (Sn) interact with Treg via Sn-accessible sialic acid residues, influencing local immune suppression and disease progression. These findings highlight a shared strategy among TRM and DC, including LC, in promoting immune tolerance and maintaining tissue homeostasis.

LC have been implicated in various Treg-dependent models of skin immune suppression. In contact hypersensitivity (CHS), an experimental model of allergic contact dermatitis, LC are essential for establishing tolerance to mild allergens by activating and expanding Treg and inducing allergen-specific CD8+ T cell tolerance. Additionally, transgenic overexpression of RANKL in keratinocytes enhances LC's ability to expand Treg and suppress CHS responses. However, conflicting reports suggest that LC deletion in certain mouse models mitigates CHS responses, potentially due to functional redundancy between LC and dermal DC or experimental differences in hapten dose, route, and skin penetration.

LC also play a regulatory role in other inflammatory skin diseases. In an autoimmune dermatitis model involving Desmoglein-3 autoantigen, LC present antigens to induce Treg expansion, mediated by IL-2 signaling. LC's functional flexibility is further demonstrated in neoantigen presentation models, where steady-state LC induce Treg and cytotoxic T lymphocyte (CTL) tolerance, while activated LC elicit memory CTL responses.

In atopic dermatitis (AD), LC exhibit anti-inflammatory functions mediated by the aryl hydrocarbon receptor (AhR), which reduces allergen-induced inflammation. However, defective TLR2-mediated sensing of *Staphylococcus aureus* signals by LC may contribute to immune deviations and poor bacterial clearance in AD patients.

The role of LC in psoriasis remains controversial, with studies reporting varied LC levels in psoriatic lesions. In psoriasis models, LC can contribute to inflammation by interacting with keratinocytes, T cells, and cytokines like IL-17 and IL-23, driving a positive feedback loop. However, LC also play a regulatory role in the late stages of inflammation, as their depletion leads to increased neutrophil infiltration. This regulatory function involves the PD-1/PD-L1 axis, which helps maintain immune balance during chronic inflammation.

The functional plasticity of LC in inflammatory skin diseases is illustrated in Figure 2, which highlights their dynamic roles in inflammation initiation, maintenance, and resolution. Understanding the molecular mechanisms that enable this functional flexibility remains a key area for future research.

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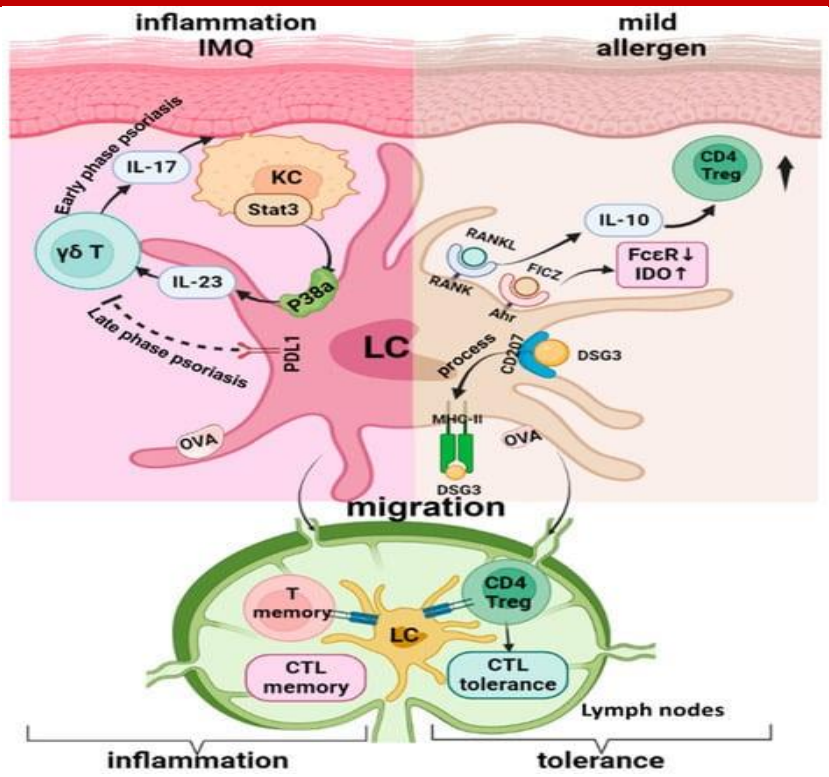

Figure 2. Langerhans Cells in Inflammatory Skin Diseases. The right panel illustrates the tolerance-inducing functions of Langerhans cells (LC) in mild allergen-induced contact hypersensitivity (CHS). Keratinocyte (KC)-expressed RANKL suppresses CHS responses by enhancing LC's capacity to expand regulatory T cells (Treg). In human LC, activation of the aryl hydrocarbon receptor (AhR) by the agonist FICZ reduces FcεRI expression, upregulates indoleamine 2,3-dioxygenase (IDO), and mitigates inflammation. LC can also uptake Desmoglein-3 (DSG3), a keratinocyte-associated autoantigen, via Langerin (CD207) and present it through MHC-II to promote Treg proliferation.

The left panel highlights the pro-inflammatory role of activated LC in an inflammatory environment. In the imiquimod (IMQ)-induced psoriasis dermatitis model, STAT3 activation in KC stimulates LC to produce IL-23 via the p38α signaling pathway. This IL-23 activates skin γδT cells and other T cells, leading to IL-17 production and exacerbation of KC-driven inflammation. However, during the late phase of the IMQ model, LC-specific PD-L1 expression can alleviate skin inflammation through the PD-1/PD-L1 axis.

Additionally, in a mouse model with LC-specific inducible ovalbumin (OVA) expression, the presentation of endogenous OVA by activated LC induces a recallable cytotoxic T lymphocyte (CTL) memory response. In contrast, OVA presentation by steady-state LC leads to Treg accumulation and CTL tolerance, demonstrating the context-dependent functional flexibility of LC.

5. Langerhans Cells in Skin Cancer Development and Progression

In the mouse epidermis, Langerhans cells (LC) and dendritic epidermal T cells (DETC) form a complementary network, with their dendrites extending to contact each other and most basal keratinocytes (KC), where epidermal malignant transformation typically begins. LC play a key role in continuously surveying and responding to epidermal stress, triggering

downstream inflammatory and immunogenic responses. This dynamic interaction between epithelial and immune cells makes mouse skin a valuable model for studying mechanisms of skin cancer and their relevance to epithelial tissues, which universally contain local dendritic cells (DC) and resident T cells.

The critical role of immune surveillance in preventing skin cancer is evident in patients with solid organ transplants, who face an elevated risk of developing skin cancer, particularly squamous cell carcinoma (SCC), due to prolonged immunosuppression. Supporting this, studies show that while somatic driver mutations are present in both cancerous and adjacent normal skin, malignant transformation is kept in check by immune surveillance in the normal tissue.

Traditionally, LC have been recognized as antigen-presenting cells (APCs) that activate adaptive immune responses. Recent studies confirm their ability to process and present antigens to CD4+ helper T cells and CD8+ cytotoxic T cells, including potent antitumor effector cells. This unique accessibility and immunostimulatory potential make LC attractive for developing therapeutic cancer strategies.

Role of MIF in LC-Mediated Tumor Dynamics. Migration inhibitory factor (MIF), produced by KC, recruits and maintains APCs in the epidermis and dermis. The absence of MIF reduces skin APCs, leading to accelerated and increased formation of nonmelanoma skin tumors during chemical carcinogenesis. However, MIF-deficient mice exhibit reduced acute inflammatory responses to UVB exposure, delayed tumor progression, and lower angiogenesis, indicating a complex, model-dependent role for MIF in tumorigenesis.

LC in Chemical Carcinogenesis Models. In a two-stage chemical carcinogenesis model using DMBA (a carcinogenic polyaromatic hydrocarbon) and TPA (a tumor promoter), LC are critical to tumor formation. Despite their role in immune surveillance, LC-deficient mice show resistance to tumor formation, as LC metabolize PAHs into oncogenic intermediates, enhancing DNA damage and mutagenesis in KC. The p450 enzyme CYP1B1, produced by LC, further contributes to DNA damage in KC, facilitating neoplastic transformation and tumor progression. LC's physical proximity to basal KC suggests their potential role in supporting the survival of transformed KC by producing growth or anti-apoptotic factors.

Human LC in Skin Cancer. In human skin, LC reside in the basal and supra-basal layers, forming a dense network to defend against pathogens. Studies reveal significantly reduced LC frequencies in SCC lesions and adjacent epidermis compared to normal skin, with a more pronounced reduction in SCC than basal cell carcinoma (BCC) lesions. Despite this reduction, LC in SCC and peritumoral skin can induce robust T-cell proliferation and IFN-γ production, even in the presence of immune-suppressive cytokines.

LC's superior immunogenic capacity is attributed to their preferential production of IL-15, which enhances CD8+ T cell proliferation and memory development. Clinical trials using DC-based vaccines for melanoma have shown that LC-like DC are more efficient at priming antigen-specific CD8+ T cells than their monocyte-derived counterparts. Furthermore, LC demonstrate advanced capabilities in priming naïve CD4+ T cells compared to other skin DC subsets, making them a promising target for immunotherapy development in SCC and other cancers.

Studies on LC in murine skin tumor models and human skin cancers are summarized in Table 2.

Table 2: Langerhans Cells in Murine Skin Tumor Models and Human Skin Cancers

Model Type	Tumor Model	Skin Tumor Development	LC or DC Phenotype	Reference
Mouse MIF KO	Chemical (DMBA-TPA)	Decreased tumor	Decreased skin LC and other immune cells	[84] 2017
Mouse MIF KO (BALB/C)	UV-induced	Increased tumor	N/A	[85] 2009
Mouse MIF Tg	UV-induced	Decreased tumor	N/A	[86] 2009
Mouse LC Deletion	Chemical (DMBA-TPA)	Decreased tumor	N/A	[91] 2008
Mouse LC Deletion	Chemical (DMBA-TPA)	Decreased tumor	LC metabolize DMBA, inducing Hras mutation	[92] 2012
Mouse LC Deletion	Chemical (DMBA-TPA)	Decreased tumor	LC-derived CYP1B1 required for keratinocyte (KC) DNA damage	[93] 2015
Human	BCC, SCC	N/A	Decreased LC in BCC/SCC compared to HC; more LC in BCC than SCC	[95] 2020
Human	Summary of 30 studies	N/A	Increased LC in BCC compared to SCC	[96] 2020
Human	SCC	N/A	LC in SCC are superior at inducing CD4/CD8 T activation compared to peritumoral LC	[98] 2012
Human	In vitro monocyte differentiation	N/A	IL-15 skews monocytes into LC	[100] 2001
Human	In vitro monocyte differentiation	N/A	LC-like IL-15-DC better at inducing tumor-specific CTL than IL-4-DC	[101] 2007
Human	Non-tumor skin	N/A	LC-derived IL-15 induces CD8 T effector function	[99] 2012
Human	In vitro T cell differentiation	N/A	LC are superior to CD1c+ dermal DC (DDC) in inducing CD4 T activation	[103] 2010
Human	In vitro T cell differentiation	N/A	LC outperform DDC in inducing CD4 T cell production of IL-21 and IL-22	[102] 2012

The seemingly contradictory roles of Langerhans cells (LC) in murine PAH-induced skin cancer and human skin cancer may be attributed to several factors.

First, significant differences exist between murine and human study models as well as the timelines of disease development. Murine models with genetic LC deletion primarily focus on early events in malignant transformation driven by chemical-induced mutagenesis or UV-induced immune suppression. In contrast, clinical studies on human skin cancer involve fully developed tumors influenced by a wide range of factors, including ultraviolet-induced mutagenesis and immunosuppression, which are not entirely represented in murine models.

Second, the constitutive LC deletion used in murine PAH-induced skin cancer models may disrupt the normal skin environment and homeostasis. Using mouse models with inducible LC targeting would provide a more refined approach to studying the role of LC in immune responses to malignant transformation or other insults.

Third, the migration and replenishment capabilities of LC must be considered. When LC are lost due to severe inflammation, they are replaced by bone marrow-derived monocytic precursors, whereas milder stimuli can lead to LC replenishment through local proliferation. Consequently, the composition and functionality of the LC population, as well as their contribution to antitumor immune responses, may vary depending on the experimental model and stage of tumor development being studied.

Finally, despite many similarities in LC biology between mice and humans, significant anatomical and immunological differences exist. For instance, human LC are more efficient at activating naïve CD8+ T cells than dermal DCs, a feature with important implications for antitumor responses. Such differences highlight the challenges of extrapolating murine data to human biology. Variations in the role of LC in regulating cutaneous immune responses may be due to differences in immune cell composition, such as T cell types within the epidermis, between humans and mice. Understanding these distinctions is crucial for interpreting LC function in human skin cancer.

6. Potential Mechanisms of Langerhans Cells in Priming Treg Versus Effector T Cell Responses

Langerhans cells (LC) play a dual role in the immune system. On the one hand, LC-induced regulatory T cell (Treg) priming and immune tolerance are critical for maintaining cutaneous immune homeostasis. On the other hand, LC are adept at priming naïve conventional T cells in draining lymph nodes, promoting their differentiation into effector or memory T cells during pathogen invasion or inflammation. Additionally, LC have been shown to license effector functions of CD8+ T cells directly within the epidermis. However, the signaling pathways and transcriptional programs that regulate the balance between LC-driven tolerance and immunity remain unclear. Questions persist about whether transcriptional programs during homeostasis are overridden by pathogen-triggered signals or whether distinct LC subpopulations with tolerogenic or immunogenic potentials coexist in the epidermis.

The role of **TGF-β** in inducing tolerogenic dendritic cells (DC) and Tregs has been extensively studied across tissues and tumors. TGF-β is crucial for preventing tumor immune suppression, autoimmunity, and resolving inflammation. In LC, TGF-β is required for development, epidermal residency, and steady-state maintenance, as well as inflammation-

induced repopulation through distinct downstream signaling pathways. Keratinocyte-expressed integrins αvβ6 and αvβ8 are essential for TGF-β activation, mediating LC retention in the epidermis and fostering tolerogenic potential.

Recent genomic and epigenomic studies propose that LC tolerogenic and immunogenic states are controlled by opposing gene regulatory networks tied to a shared core maturation module. TGF-β promotes LC–keratinocyte interactions, retaining LC in an immature, tolerogenic state. Disruption of TGF-β signaling, or loss of epithelial cell adhesion molecule (EpCAM), promotes LC migration, maturation, and tolerogenic programming through β-catenin signaling and interferon regulatory factor 4 (IRF4) induction. IRF4 is antagonistic to E-cadherin-mediated LC–keratinocyte adhesion and is positively regulated post-translationally by ROCK2 kinase, suggesting a complex regulatory interplay.

The tolerogenic transcriptional program in LC includes genes such as **IDO1**, **LGALS1** (Galectin-1), and **IL-4I1**, regulated by IRF4 and aryl hydrocarbon receptor (AhR) signaling. AhR, activated by kynurenine metabolites from IDO-mediated tryptophan catabolism, creates a positive feedback loop to sustain tolerogenic LC function. These mechanisms orchestrate a self-reinforcing circuit of LC maturation, migration, and tolerance induction.

During infection or inflammation, **toll-like receptor (TLR)** and proinflammatory cytokine signaling override TGF-β pathways. Pathogen-associated signals and activated keratinocytes induce an immunogenic LC transcriptional program mediated by IRF1 and NF-κB. IRF1 and IRF4 counter-regulate each other, modulating LC function. TNF-α signaling, for instance, upregulates IRF1, driving LC-mediated cytotoxic T cell responses. Recent single-cell RNA sequencing studies confirm that IRF1 is a key regulator of the LC immunogenic program, particularly during TNF-α-enhanced immunogenic activity.

Emerging evidence highlights heterogeneity within LC populations, marked by distinct transcription factor profiles. This heterogeneity translates into varied susceptibility to inflammatory versus tolerogenic signaling, creating an LC immunocompetence spectrum. Studies in murine models reveal LC subtypes with diverse transcriptomes originating from the embryonic stage, suggesting the existence of functionally distinct LC subsets. These subsets likely respond differently to environmental cues, reciprocally regulate each other, and maintain skin homeostasis while preserving the capacity for robust immunogenic responses to pathogens or malignant transformations.

The interplay between tolerogenic and immunogenic LC responses, their transcriptional programs, and the mechanisms governing their functional plasticity are illustrated in **Figure 3**. Further research is needed to elucidate the molecular pathways and signaling networks underlying the development, maintenance, and function of LC subtypes.

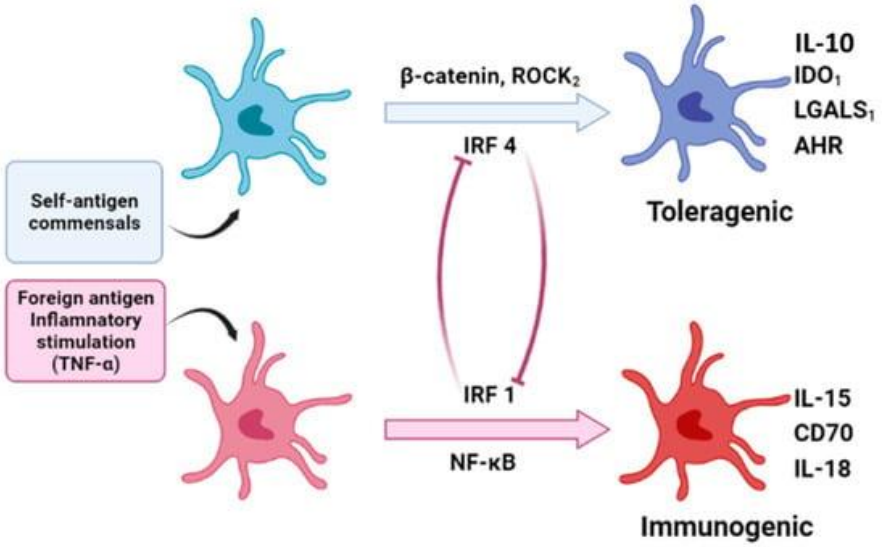

Figure 3. Schematic Representation of Proposed Functional Plasticity. The **left panel** illustrates the heterogeneity of Langerhans cells (LC) and their development into tolerogenic or immunogenic subsets, influenced by various environmental factors. The **middle panel** highlights the distinct signaling pathways that drive LC activation and regulate the counter-balancing roles of different LC types. The **right panel** depicts the molecular mechanisms employed by LC to mediate either tolerogenic or immunogenic immune responses.

7. Conclusions

Langerhans cells (LC) represent a unique subset of tissue-resident macrophages (TRM), distinguished by their dual characteristics of macrophages and dendritic cells (DC). Beyond their well-established role in immune activation, recent studies highlight the immunosuppressive functions of LC under steady-state conditions and during specific inflammatory responses.

Despite advances in understanding LC's critical role in cutaneous immunity, the precise immunological factors within the skin that determine whether LC activate or suppress proinflammatory adaptive immune responses remain unclear. Further research is essential to uncover how LC integrate diverse microenvironmental signals to adapt their immune functions. Additionally, detailed studies on the molecular mechanisms and signaling pathways that govern LC functional plasticity are needed to clarify their roles in inflammatory skin diseases, enhance knowledge of skin tumor immunology, and advance vaccine development.

Future investigations will provide valuable insights into the functional versatility of LC and facilitate the translation of LC biology into clinical applications, paving the way for novel therapeutic approaches targeting skin immunity and beyond.

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