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The contribution of Langerhans cells to cutaneous malignancy

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Abstract

The skin is at the forefront of environmental exposures, such as ultraviolet radiation and a myriad of chemicals, and is at risk for malignant transformation. The skin is a highly responsive immunological organ that contains a unique population of immature intraepidermal dendritic cells (DCs) called Langerhans cells (LCs). Although LCs show morphological and migratory changes in response to epidermal perturbation, and can function as antigen-presenting cells to activate T cells, their role in carcinogenesis is unknown. Here we review recent studies that have provided clues to the potential roles that LCs might play in the pathogenesis of skin cancer, beyond their stimulation or regulation of adaptive immunity. Understanding this role of LCs might provide new perspectives on the relevance of DC populations that are resident within other epithelial tissues for cancer.

Epidermal Langerhans cells (LCs) and the response to environmental stimuli

Epithelial linings are physical barriers as well as dynamically responsive tissues, and are found at the interface between the body and the environment. Within the epidermis, keratinocytes proliferate from the basement membrane to produce self-renewing as well as differentiated cells. This continuous regeneration facilitates the elimination of damaging agents and the shedding of damaged keratinocytes. A similar proliferation and specialized barrier function is common among the different epithelia, including in gastrointestinal, pulmonary and genitourinary tissues [1]. The extent and diversity of exposure to potentially damaging agents, such as microbes, toxins and mutagens, poses a substantial risk to the regenerative epithelial cells. Such exposures can cause direct genomic alterations or epigenetic dysregulation, or can alter the local environment to make it conducive to genetic modifications. Accumulation of genetic changes, in combination with immunological and stromal influences, largely drive progression of individually altered cells to clonal expansion, to tumor development and growth, to malignant progression, invasion, and metastasis. Thus, it is perhaps not surprising that epithelium-derived malignancies [e.g. cutaneous squamous cell carcinoma (SCC), head and neck SCC, and lung, esophageal, gastric, colon, bladder and cervical cancer] are among the most common and lethal [2], and are clearly associated with environmental factors (Table 1). Among the various epithelia, only the skin must contend with ultraviolet radiation (UVR), which has a major role in the pathogenesis of human cutaneous malignant transformation. UVR, including the differential effects of both UVA and UVB major wavelengths, can cause direct DNA damage, free radical activity, and profound immunological changes in the skin.

To understand how skin cancer develops, the various cutaneous cell types and how they influence each other, particularly under conditions of epidermal perturbation, must be considered. In close juxtaposition with keratinocytes are resident immature dendritic cells (DCs) that are known as epidermal LCs. In mouse (as well as in most mammals but not human) skin, there is also another immune cell population of T cells, which bear $\gamma\delta$ T cell receptors, the so-called dendritic epidermal T cells (DETCs). In mice, LCs and $\gamma\delta$ DETCs form spatially complementary, intraepidermal DC networks. Although LCs might be situated more superficially than $\gamma\delta$ DETCs in mouse skin, dendrites of both immune cells extend to contact each other and the majority of basal keratinocytes [3]. When considering how local immune cells might influence keratinocyte transformation, it is therefore relevant that LCs and $\gamma\delta$ DETCs are both in contact with the renewing basal keratinocytes, which are the key targets of epidermal neoplastic transformation. Furthermore, LCs and $\gamma\delta$ DETCs have both been shown to: (i) respond coordinately and rapidly to epidermal stress [3]; (ii) to influence the nature of downstream inflammatory and immunological responses [4]; and (iii) have profound effects on chemically induced carcinogenesis [3,5–8]. Thus, the skin of mice serves as a model epithelium to study epithelial/immune cell interactions and their relevance to cancer, as all epithelial tissues are variably populated by local DCs and resident T cells [9,10].

LCs have traditionally been thought of as potent antigen-presenting cell (APCs) that stimulate adaptive immunity. Recent studies have confirmed the capacity of LCs to process and present antigens to activate the CD4 helper T cell and CD8 cytotoxic T cell compartments, including potent antitumor effector cells, and strategies have been employed to leverage the epicutaneous accessibility and immunostimulatory potential of LCs in the therapy of cancer [11]. However, emerging data have also revealed that LCs might play a more physiological role in suppressing T cell function, and suggest that LCs might contribute to cutaneous responses that facilitate keratinocyte transformation and tumor growth. In this review, we discuss the role of LCs in responses of the skin to environmental stimuli, and in this context, explore the potential contributions of LCs to cutaneous carcinogenesis.

Chemical carcinogenesis and the potential tumor-promoting role of LCs

In mice, LC motility and dendrite extension and contraction patterns have been visualized by intravital confocal microscopy [12]. This provides evidence that LCs are dynamic intraepidermal cells with the potential to patrol and survey the epidermis rapidly. Within mouse and human skin, LCs can be visualized suprabasally with dendrites that reach in all directions. In fact, after epidermal physical perturbation or cytokine activation, tips of LC dendrites have been identified at the level of the stratum corneum, extending through keratinocyte tight junctions that contain claudin-1 [13] (Figure 1). The potential for endocytosis at these “periscopic tips” suggests that LCs readily have access to chemical percutaneous exposures, and perhaps to airborne microparticulates that contain mutagens.

The major function of LCs has been considered by many to serve as the APCs of the skin. LCs have the capacity to internalize compounds, apoptotic cells and microbes, migrate to the draining lymph nodes, and to present processed antigens to T cells [12]. It has been proposed that LCs play a role in the induction of contact hypersensitivity, but this notion is challenged by studies that have used the *CD207* (Langerin)-driven diphtheria toxin A transgenic (huLangerin-DTA) mouse [4,14]. Unlike other models of LC deficiency [15,16], huLangerin-DTA mice are selectively deficient in LCs (with normal numbers of other Langerin⁺ DC populations, including those in the dermis, lymph nodes, and spleen). These mice show augmented contact hypersensitivity responses (see Kaplan, in this issue).

T cells and other immune cells might infiltrate damaged and/or inflamed skin to become readily available to interact with keratinocytes and local immune populations such as LCs. Interactions between such cells are fundamental to the pathophysiology of cutaneous disease and malignancy. To help elucidate these interactions, the two-stage cutaneous chemical carcinogenesis model has been used. In this model, carcinogenesis is induced by 7,12-dimethylbenz[*a*]-anthracene (DMBA), coupled with repeated applications of a proinflammatory tumor promoter, 12-*O*-tetradecanoyl-phorbol-13-acetate [17].

DMBA is a prototypic polycyclic aromatic hydrocarbon (PAH); a class of molecules that include ubiquitous exogenous mutagens and endogenous compounds that bind the intracellular aryl hydrocarbon receptor (AhR). PAHs are present in automobile emissions, tobacco smoke, broiled meat, shellfish, industrial soot, and groundwater [18]. The handling and response of human skin and DCs to PAHs is important in a spectrum of epithelial cell processes, for example, the cellular stress response, proliferation, differentiation, UV-induced carcinogenesis and tanning [19–21], as well as in the activation of human monocytes and LCs [22].

Hence, this model possesses intrinsic and generalizable merits as a model for environmentally-induced cutaneous dysregulation and carcinogenesis. Understanding how immune cells such as LCs might influence susceptibility to two-stage chemical carcinogenesis offers insight into regulation of basic cutaneous pathophysiology, handling of environmental toxins by the skin, as well as the pathogenesis of skin cancer. Using this system, distinct roles for specific immune cell subsets for enhancing and reducing malignancy have been reported [3,5–8,23,24].

Despite the implicated role of LCs in immune surveillance and stimulation of antitumor immunity, mice deficient in LCs are almost completely resistant to tumor formation by this two-stage carcinogenesis regimen [3]. This is remarkable given that this tumor-induction protocol, and its application in FVB mice, were each used because in combination they evoke high tumor incidence [25]. Although these observations were made in a transgenic mouse (huLangerin-DTA) that is constitutively devoid of LCs, and therefore, consideration must be given to raising the possibility of an altered epidermal or local immune development, it is noteworthy that: (i) no other epidermal abnormalities were noted (e.g. the $\gamma\delta^+$ DETC population was intact); and (ii) the tumor-resistant phenotype in LC-deficient mice was the same even if mice were also deficient in all $\alpha\beta$ or $\gamma\delta$ T cells [3]. These data suggest that LCs can promote cutaneous malignancy.

How might LCs promote tumor formation, at least in the model described? Although most models for dissecting skin biology study LC function in the context of the adaptive immune response, LCs might have the capacity to internalize and metabolize and increase mutagenicity of PAHs [26]. Moreover, the proximity of LCs to basal keratinocytes raises speculation for other influences of LCs on facilitating survival and/or providing a growth advantage to genetically altered keratinocytes. We hypothesize that LCs might also influence the outgrowth of neighboring mutated epidermal cells, for example, via the local production of growth factors or anti-apoptotic factors, which raises consideration for potential effects in the setting of mutagenic UVR exposure. This model (Figure 2) might also portend an analogous role for local DC populations in cancers that arise in other epithelial tissues, for example, pulmonary tissue, the genitourinary tract, and the gastrointestinal tract. These tissues are, to varying degrees, all populated with resident DC populations and/or have the capacity to recruit myeloid DCs.

When considering the possible tumor-promoting influence of local DC populations during carcinogenesis, the association between chronic inflammation and cancer within epithelial

tissues is noteworthy [27]. The relevance of this phenomenon to keratinocyte-derived malignancies is suggested by reports that SCC development in several cutaneous inflammatory disorders is associated with epidermal hypertrophy, for example, lupus vulgaris [28,29], discoid lupus erythematosus [30–32], and lichen planus [33–37]. The complexity of the inflammatory infiltrates in human SCC [38–41], and the crucial role of UV-induced inflammatory mediators in human keratinocyte transformation [4,42], further implicate chronic inflammation in promoting cutaneous SCC. Although the term inflammation represents a spectrum of processes or disease states, experimental models have provided opportunities to pinpoint the contributions of specific proinflammatory cells or immune effectors. The pro-tumorigenic effects of tumor-associated macrophages (TAMs) that enhance tumor proliferation, invasion, and metastasis, raises speculation for similar activities of LCs in cutaneous malignancy [43].

As well as having a major influence on tumor initiation, LCs might also influence other aspects of tumorigenesis via interactions with other immune cell populations (e.g. tissue-resident $\gamma\delta$ T cells, and tumor-promoting $\alpha\beta$ T cells). For example, it has recently been demonstrated that intraepithelial $\gamma\delta$ T cells and LCs show a coordinated response to NKG2D-ligand upregulation by keratinocytes, in a system that models the response to environmental stress and keratinocyte damage. This results in the rapid influx of intraepidermal natural killer T (NKT) cells [3], an immune population with regulatory function that might be activated by LCs [44]. Second, LCs have recently been reported [45] to be capable of cross-presentation of epidermal antigens, which raises the possibility that internalized damaged and/or transformed keratinocytes might provide MHC-I-presented self- or neo-antigens that permit the direct activation by LCs of infiltrating CD8⁺ $\alpha\beta$ T cells, or CD8⁺ $\alpha\beta$ T cells within regional lymph nodes. Recently, a novel population of tumor-promoting CD8⁺ T cells has been identified [23] and characterized [46], which raises consideration that LCs might interact with these T cells to enhance malignant progression (Figure 2).

PAHs and their relevance to cutaneous malignancy and LC biology

Epidemiological and experimental evidence associates PAH with increased cancer risk across a variety of carcinomas including skin, oral mucosal, pulmonary, gastrointestinal, and genitourinary malignancies [47]; H-ras mutations are highly representative among these epithelial tumors [48]. Cutaneous exposure via airborne particles that are present in industrial climates, in which dermal contact incremental lifetime cancer risk for PAH exposure has orders of magnitude indicative of “high potential carcinogenic risk” [49]. Although probably a less significant factor than UVR exposure, airborne exposure to PAH-containing particulate matter might represent an under-appreciated environmental factor in human skin cancer.

In mice, extracts of airborne particles topically applied to the skin result in SCC development that is dependent on the AhR for PAHs [50]. At doses at which neither induce tumors alone, UVR combined with a topically applied PAH is highly carcinogenic [51]. In response to UVB, AhR converts endogenous tryptophan to a PAH (6-formyl-lindolo[3,2-b]carbazole), which binds AhR to trigger PAH-associated gene expression and activation of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) phosphorylation. Indeed, AhR-deficient mice show compromised UVB responses [52]. The AhR plays a key role in immune cell activities [19], including the differentiation and activation of LCs [22]. AhR-mediated cutaneous responses and H-ras activation, which are fundamental characteristics of two-stage chemical carcinogenesis, are therefore both highly relevant to human SCC development. Thus, through the complimentary study of carcinogenesis, via chemical and UV induction, a more complete understanding of the role

of LCs in cutaneous tumor initiation and promotion might be elucidated. As UVR is the primary inducer of human keratinocyte mutations, and because UVR-induced immune suppression might help transformed keratinocytes to escape immune detection and elimination, we consider the potential role that LCs might play in both these processes.

UV-induced carcinogenesis and potential influences of LCs

The majority of UV-associated keratinocyte mutations arise from errors in repairing cyclobutane pyrimidine dimers (CPDs) induced by DNA absorption of UVB, which are responsible for most of the mutations within the tumor-suppressor gene p53 that is prevalent in human SCC. After UVB exposure, keratinocytes also manifest a UVB stress response that is characterized by c-Src receptor clustering, MAPK/ERK phosphorylation, and cyclooxygenase-2 activation; these events are crucial for UV-induced inflammation and carcinogenesis. LCs are situated suprabasally, therefore, their proximity suggests they sense and/or influence UV damage directly, or indirectly through apoptotic vesicles and soluble mediators derived from surrounding keratinocytes. To date, however, few studies have been published to investigate the role of LCs during early events of UV-induced cutaneous neoplasia; most studies have focused on LCs in UV-induced immune suppression. Indeed, investigating the potential role of LCs in UV-induced keratinocyte mutagenesis, apoptosis, oxidative stress, and proliferation is complicated by the (somewhat conflicting) studies in animal and human skin that have shown an apparent LC depletion from the epidermis in response to UV exposure. This might involve one or more of the following: LC apoptosis (albeit over a longer time period than observed for keratinocytes); LC migration to the dermis and/or draining lymph nodes [53–55]; and changes in LC surface marker expression [56]. Nevertheless, this would not preclude the possibility that naïve LCs influence neighboring keratinocytes during the stress response following acute UV exposure. Furthermore, the identification of replacement populations of epidermal Langerin⁺ DCs from peripheral blood monocytes [57–59], for example, after UVR exposure, suggests that not all intraepidermal Langerin⁺ DCs function similarly, which might include their role in carcinogenesis. In any event, the observation of Langerin⁺ DCs in close proximity to acutely UVR-damaged keratinocytes [60] raises consideration for the influence of LCs on these processes that are fundamental to carcinogenesis.

UVR-induced immune suppression and LCs in tumorigenesis

The increased rate of cutaneous SCC in organ transplant recipients that are iatrogenically immune-suppressed to prevent rejection, shows the importance of the immune system in controlling malignancy. Thus, it is relevant that UVR not only induces direct DNA damage and oxidative free radicals, but also suppresses potential antitumor immunity in the skin. UVR was first linked to immune suppression by investigating UV-induced skin cancers in mice. UV-induced tumors are highly antigenic and most often are rejected when transplanted into normal syngeneic recipients. However, if recipients are first exposed to UVR, the capacity for tumor rejection is largely abrogated. This immune suppression is tumor-specific and can be passively transferred with T cells from a UV-treated donor [61–63]. Consistent with the loss of tumor rejection capacity, UVR has also been shown to suppress contact hypersensitivity (CHS) responses. It has been found that hapten applied to skin that has previously been exposed to low doses of UVB fails to induce CHS [64]. This correlates with a change in morphology and decreased numbers of LCs. When attempts are made to sensitize these mice to the same hapten at a later time point, through non-irradiated skin (i.e. containing a full complement of LCs), it has been found that antigen-specific tolerance is induced. When much higher doses of UVR are used, induction of peripheral tolerance is observed, even when the hapten is applied to non-irradiated skin [65]. Subsequently, it has been shown that T cells can passively transfer this specific

unresponsiveness [66,67]. In this manner, LCs might facilitate UVR-induced tolerance and inhibit adaptive immunity to damaged keratinocytes, thereby indirectly promoting tumor outgrowth.

Although T cells have been shown to transfer UV-induced suppression of tumor rejection and CHS, it is not clear if the same subset functions in both systems. In one study, it has been reported that CD3⁺ CD4⁺ DX5⁺ interleukin (IL)-4-secreting NKT cells are responsible for suppression of tumor rejection [68], whereas in another study, CD4⁺ CD25⁺ CTLA-4⁺ IL-10-secreting regulatory T cells mediate CHS suppression [69]. To complicate matters, the range of APC types in the skin, which might be involved in generating these regulatory T cells, expands with the identification of dermal Langerin⁺ and Langerin⁻ DC subsets in addition to LCs [59,70,71]. Two groups have attempted to clarify the role of epidermal LCs versus dermal Langerin⁺ DCs in the induction of UV-induced immune suppression using the *CD207* (Langerin)-diphtheria toxin receptor (DTR) knock-in (muLangerin-DTR) mice [16]. Injection of diphtheria toxin in these mice results in depletion of all Langerin⁺ cells. In one study, bone marrow chimeras were prepared in which epidermal LCs (radioresistant) could be maintained while dermal Langerin⁺ DCs (bone marrow donor derived) could be depleted by diphtheria toxin injection, or vice versa [72]. By measuring the effect of UVR on an ovalbumin-specific CD8 T cell response in this setting, it was found that UV exposure induced suppression even in the absence of epidermal LC. In another study [73], the differential repopulation kinetics of epidermal LCs and dermal Langerin⁺ DCs in muLangerin-DTR mice was used to examine the effect of UV exposure on CHS to dinitrofluorobenzene. At a time after UV exposure, when dermal Langerin⁺ DCs had substantially repopulated, but epidermal LC were still absent, suppression of CHS and induction of regulatory T cells did not develop, which suggests that epidermal LCs are required for UV-induced immune suppression. Perhaps these seemingly contradictory results are due to variations in the assay systems or UV doses employed. In any event, they highlight the complexity of mechanisms of UV-induced immune suppression, and the role of LCs in this important but incompletely understood phenomenon.

Insight into UV-induced immune suppression might come to some degree via the study of the molecular events induced by UVR exposure. At least three major photoreceptors are important for UV-induced cutaneous carcinogenesis and immune suppression: (i) DNA, where UV-induced lesions lead to CPD formation [74,75]; (ii) *trans*-urocanic acid (UCA), which undergoes isomerization to the immunosuppressive *cis* conformation [76,77] and binds the serotonin receptor 5-HT_{2A}; and (iii) membrane phospholipids, whose peroxidation following reactive oxygen species formation leads to transcriptional activation and release of immunosuppressive cytokines [78,79], including platelet activating factor (PAF) [80], IL-10 and prostaglandin E2. Repair of CPDs, by enhancing nucleotide excision repair (NER), has been shown to reduce immune suppression [81]. Blockade of 5-HT_{2A} receptor binding [82], PAF receptor binding [83], or neutralizing the activity of *cis*-UCA [84], has also been shown to reduce UV-induced immune suppression, and in the case of *cis*-UCA, to block UV-induced carcinogenesis [85]. These pathways might converge at a common point, which has been suggested by the recent observation that PAF and 5-HT_{2A} receptor antagonists accelerate NER following UVR [86]. In addition, IL-12 [87,88] and IL-18 [89] prevent UV-induced immune suppression by induction of NER. IL-12 also prevents the loss of LCs from the epidermis following UV exposure in normal, but not NER-deficient mice [90], which suggests that DNA damage is one factor that leads to LC emigration from the skin. MHC-II⁺ cells with CPDs have been detected in the draining lymph nodes following UV exposure [75,90], although it is not clear if these represent LCs or dermal DCs. In either case, it has been suggested that these damaged skin-derived DCs are required for the induction of the regulatory T cells that mediate UV-induced immune suppression of CHS [91].

Concluding remarks

Cutaneous carcinogenesis is largely driven by mutation accumulation within keratinocytes, but the process is complex and involves various cells of the skin and their responses to mutagenic exposure and damaged keratinocytes. The fact that skin devoid of LCs is almost completely resistant to chemical carcinogenesis exemplifies the powerful influence that non-keratinocytes might have on the development and/or growth of tumors. Not only does UVR exposure induce direct DNA damage within keratinocytes, but also has other effects (e.g. oxidative stress, apoptosis, and immune alteration) that can profoundly affect mutated keratinocyte growth and survival. Although much needs to be elucidated with regard to the role of LCs in cutaneous carcinogenesis, LC proximity to basal keratinocytes, behavior in response to chemical and UVR damage, and known immunological influences, justify further investigation in this area. If, for example, LCs can influence the survival and/or outgrowth of mutated keratinocytes, then their influence on tumor development might be independent of mutagenic events. LC induction of immune stimulation or immune regulation, which is not focused upon in this review, might also influence tumor development. In any event, understanding the role of LCs in cutaneous carcinogenesis will probably have implications for the local DC influences on epithelial tumor development more generally, and could provide novel targets for cancer prevention and treatment.

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Figure 1. LC dendritic processes might extend superficially to the sub-stratum corneum
 Suprabasal LCs might extend their dendritic processes superficially, through claudin-1-containing tight junctions, to just below the stratum corneum [13]. This occurs most notably after epidermal perturbation or cytokine activation. These LC dendritic tips appear to have endocytic capabilities, and might represent a potential entry for chemical mutagens into the basal skin and draining lymph nodes.

Figure 2. Hypothetical model of the spectrum of potential pro-tumor influences of LCs on cutaneous chemical carcinogenesis

LCs could contribute to initiation of mutagenesis by internalizing and metabolizing PAHs to increase mutagenicity, or by serving as a depot or relay station for mutagens [20]. The proximity of LCs to basal keratinocytes raises speculation for other pro-tumor influences of LCs, for example, facilitating survival and/or providing a growth advantage to any genetically altered keratinocytes, or by preventing antitumor immunity, through production of growth factors or cytokines. KC: keratinocyte.

Table 1

Epithelia-derived carcinomas and their implicated environmental factors.

Carcinoma	Environmental / local factors
Cutaneous SCC	Ultraviolet light, HPV, arsenic, chronic inflammation
HNSCC	PAHs in tobacco smoke and chewing tobacco, alcohol, chronic inflammation
Lung cancer	PAHs in tobacco smoke and air pollution, radon gas, chronic inflammation (e.g. chronic bronchitis)
Esophageal cancer	Alcohol, nitrates, chronic inflammation (e.g. Barrett's esophagitis)
Gastric cancer	PAHs in smoked foods, nitrates, aflatoxins, chronic inflammation (e.g. secondary to <i>H. pylori</i>)
Colon cancer	PAHs in charbroiled meats, chronic inflammation (e.g. inflammatory bowel disease)
Bladder cancer	PAHs in tobacco smoke, arsenic, aniline dyes, chronic inflammation (e.g. chronic cystitis, schistosomiasis)
Cervical cancer	HPV, chronic inflammation (e.g. chronic cervicitis secondary to other STDs)

SCC, squamous cell carcinoma; HPV, human papilloma virus; HNSCC; head and neck SCC; STD, sexually transmitted disease.