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Langerhans Cell Migration: Not Necessarily Always at the Center of the Skin Sensitization Universe

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Since their discovery in 1868, the role of Langerhans cells (LCs) in skin immunity has been researched extensively. Recent data deriving from transgenic animals that are deficient in LCs have begun to challenge the dogma that there is a universal requirement for these cells in the development of skin sensitization. This Commentary addresses relationships between LC mobilization, draining lymph node activation, and skin sensitization using immunomodulators agonistic for a family of sphingosine-1-phosphate (S1P) receptors.

Journal of Investigative Dermatology (2009) **129,** 1852–1853. doi:10.1038/jid.2009.54

With very few exceptions, topical administration of contact allergens—at concentrations sufficient for the acquisition of skin sensitization—is associated with the rapid mobilization of a fraction of epidermal Langerhans cells (LCs) at the site of exposure, as well as their migration away from the skin. This is true for humans and mice, and with respect to LC function, these species display striking commonality regarding cell frequency within the epidermis, the cytokine signals required for mobilization, and the tempo of migration (Kimber *et al*., 2000; Griffiths *et al*., 2005).

The classic paradigm has been that LCs form an epidermal net to trap antigens—including chemical allergens—encountered at skin surfaces, and that these cells are responsible for the processing, transport, and presentation of allergens—or allergen-modified peptides—to responsive T lymphocytes. The legitimacy of this interpretation has been challenged recently by the availability of mice lacking LCs and by the use of complementary experimental strategies. The picture is complicated, but a case can be made that there are circumstances in which the presentation of topically applied chemical allergens—and the development of skin sensitization—can proceed without LCs (Kaplan *et al*., 2005; Romani *et al*., 2006; Kissenpfennig and Malissen, 2006; Bennett *et al*., 2007; Wang *et al*., 2008; Fukunaga *et al*., 2008).

One interpretation—the one we currently favor—is that in intact skin containing the normal complement of LC and dermal dendritic cell (DC) populations, LCs, possibly in tandem with other DCs, play pivotal roles in antigen delivery, processing, and presentation, and the effective translation of antigen encounters into an adaptive immune response. If, however, LCs are absent or functionally incapacitated, then dermal DCs can and will act in their place. This is not a novel interpretation. Two decades ago, using a palette of experimental approaches, the late and greatly lamented Wayne Streilein came to exactly the same conclusion (Streilein, 1989). To paraphrase the title of his elegant paper, Streilein concluded that "Langerhans cells are sufficient, but not required," for the induction of skin sensitization in mice. What is new, however, is that more recent investigations inform us that, in addition to antigen delivery and presentation, epidermal LCs may have immunoregulatory properties that serve to contain and constrain adaptive immune responses in the skin.

Of course, a more complex functional profile, if anything, makes LCs and their roles in skin sensitization even more interesting subjects for investigation. Reines and colleagues (2009, this issue) report on the relationship among LC mobilization, the activation of draining lymph nodes, and the acquisition of skin sensitization. For this purpose, the authors have made use of sphingosine-1-phosphate (S1P) and a novel immunomodulator, Fingolimod (FTY720), to dissect the induction phase of skin sensitization in mice. When administered orally to mice, S1P and FTY720 were previously shown to cause altered lymphocyte trafficking and marked lymphopenia, effects secondary to agonism of a family of S1P receptors (S1PRs; Mandala *et al*., 2002).

> LCs may contain and constrain adaptive immunity.

The approach taken by Reines *et al*. has been to explore the impact of topical administration of S1P and FTY720 on the induction and elicitation in mice of contact hypersensitivity to toluene diisocyanate (TDI), a known chemical allergen. Topical treatment with the S1PR agonists resulted in significant reductions in the weight and cellularity of regional lymph nodes draining the site of exposure to TDI, and a case is made that this is caused by an associated reduction in the ability of local LCs to become mobilized in response to TDI in mice treated with the agonists. Whether such a case is sustainable is uncertain, mainly because even local treatment with S1PR agonists caused systemic leukopenia and lymphopenia. It is therefore difficult to prove conclusively that the compromised immune

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activation of draining lymph nodes was attributable exclusively to induced inhibition of LC mobilization, rather than a consequence (at least in part) of systemic effects on lymphocyte trafficking and homing. Nevertheless, even if some uncertainty exists about a direct causal relationship among S1PR agonists, impaired LC mobilization, and the acquisition of skin sensitization, these investigations draw attention to an association between LC migration and contact allergen–induced changes in regional lymph nodes that signal the early stages of sensitization.

The coming months and years will undoubtedly witness a much clearer definition of the cellular and molecular mechanisms required for the effective induction of skin sensitization, in particular the roles that LCs play in orchestrating the process.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Protein Kinase Cε Reveals Importance of Extrinsic Apoptosis in Preventing UV Carcinogenesis

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UV-induced apoptosis, giving rise to "sunburn cells," has been thought to be primarily cell autonomous (or intrinsic) in nature, triggered by DNA damage and mediated through p53. However, *in vivo* the microenvironment appears to contribute to UV-induced apoptosis by activating the extrinsic route through death receptors. Protein kinase Cε lowers UV-induced expression of Fas and its downstream proteins in this extrinsic route, suppressing apoptosis and enhancing UV carcinogenesis.

Journal of Investigative Dermatology (2009) **129,** 1853–1856. doi:10.1038/jid.2009.170

Protein kinase C and cell fate

Protein kinase C (PKC) is the target of the skin tumor promoter 12-*O*-tetradecanoylphorbol 13-acetate (TPA), and it can be activated through growth factor receptors such as EGFR. PKC occurs as a family of 10 isotypes: 4 classical isotypes (α, βI, βII, and γ) that depend on phospholipids and calcium for their activation; 4 novel isotypes (δ, ε, η, and θ) that are not dependent on calcium; and 2 atypical isotypes (ζ and ι/λ) that are not dependent on either phospholipids or calcium. The PKCs play roles in many cellular processes, including proliferation, motility, differentiation, and apoptosis—all of which are of direct importance to carcinogenesis, including skin carcinogenesis (Breitkreutz *et al.*, 2007). As determined by the expression of adhesion molecules, cPKCβ and nPKCε induce the phenotype of basal cells in keratinocytes, whereas cPKCα and nPKCδ induce molecules that typify differentiated cells (Szegedi *et al.*, 2009). PKC isotypes are differentially expressed in the basal proliferative and overlying differentiated layers (Verma *et al.*, 2006). Although they are archetypal tumor promoters, phorbol esters, like TPA, can have different effects, depending on the cell type; e.g., instead of growth, androgen-dependent prostate cancer cells undergo apoptosis through excretion of death factors, whereas lung cancer cells undergo senescence (Xiao *et al.*, 2008). The outcome may depend on the balance of effects among PKC isotypes. PKCδ has been reported to promote apoptosis, whereas most of the others appear to exert the opposite effect, promoting survival and proliferation. PKCε, in particular, qualifies as a genuine oncogene—it activates RhoA/C, Stat3, and Akt, and it increases cell survival, proliferation, motility, and invasion. It is overexpressed in tumors from various organs, and it may serve as a tumor biomarker (Gorin and Pan, 2009).

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