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Re-Examining Cutaneous Immunity

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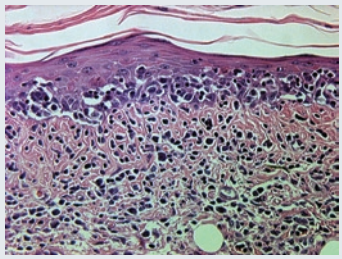

To better understand T-cell immunity, investigators at the National Institutes of Health used a variety of murine models to study the relative contributions of the antigen-presenting cells (APCs) of the skin. Specifically, Kim and co-workers in the laboratory of Steve Katz attempted to characterize the ability of Langerhans cells (LCs) and dermal dendritic cells (dDCs) to present antigen (Ag) in a modified mouse model of graft-versus-host disease (GVHD) (2009, this issue). After eliminating LCs via targeted diphtheria toxin in genetically susceptible mice and altering the antigen-presenting capability of dermal dendritic cells by bone marrow transplantation with β2-microglobulin-deficient cells, the investigators observed an unexpected phenomenon. When both LCs and dDCs were impaired, a GVHD reaction still occurred, presumably through keratinocyte-mediated antigen presentation. Keratinocytes were also found to be able to prime naive skin-reactive T cells.

These observations are part of an evolving understanding of skin immunity. Although it has been appreciated for some time that LCs and dDCs take up antigen in the periphery and migrate to regional lymph nodes, their ability to induce and maintain tolerance is a more recent observation, and much remains uncertain. For example, in studies of LCs in contact hypersensitivity reactions (CHS), three disparate outcomes have been observed: (i) no effect, (ii) attenuation, or (iii) enhancement of CHS responses (Bennett *et al*., 2005; Kaplan *et al*., 2005; Kissenpfennig *et al*., 2005). At the very least, the experiments in which LCs either had no effect or caused attenuation of CHS suggest that dDCs are likely to be important in mediating CHS. Additionally, the absence of LCs, which were long thought to be critical in skin graft rejection, was recently reported to enhance graft rejection in mice mismatched for minor histocompatibility antigens (Obhrai *et al*., 2008).

In the context of our changing understanding of the skin immune system, Kim and colleagues sought to add clarity using a novel methodology. Through the following questions, we will examine this paper and skin immunity in greater detail. For discussion and brief answers, please refer to the supplementary information linked to the online version of the paper at http://www.nature.com/jid.

REFERENCES

Bennett CL, van Rijn E, Jung S, Inaba K, Steinman RM, Kapsenberg ML *et al*. (2005) Inducible ablation of mouse Langerhans cells diminishes but fails to abrogate contact hypersensitivity. *J Cell Biol* 169:569–76

Kaplan DH, Jenison MC, Saeland S, Shlomchik WD, Shlomchik MJ (2005) Epidermal Langerhans cell–deficient mice develop enhanced contact hypersensitivity. *Immunity* 23:611–20

Kim BS, Miyagawa F, Cho Y-H, Bennett CL, Clausen BE, Katz SI (2009) Keratinocytes function as accessory cells for presentation of endogenous antigen expressed in the epidermis. *J Invest Dermatol* 129:2805–17

Kissenpfennig A, Henri S, Dubois B, Laplace-Builhe C, Perrin P, Romani N *et al*. (2005) Dynamics and function of Langerhans cells in vivo: dermal dendritic cells colonize lymph node areas distinct from slower migrating Langerhans cells. *Immunity* 22:643–54

Obhrai JS, Oberbarnscheidt M, Zhang N, Mueller DL, Shlomchik WD, Lakkis FG *et al*. (2008) Langerhans cells are not required for efficient skin graft rejection. *J Invest Dermatol* 128:1950–5

QUESTIONS

1. How is antigen thought to be presented?
2. How and why were the murine models used in the study developed?
3. How were the relative contributions of the different cell types to the graft-versus-host disease model determined?
4. What were the results of the study?
5. What were limitations of the study?
6. What were the conclusions of the study?

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