

## This Week's Citation Classic®

Rowden G, Lewis M G & Sullivan A K. Ia antigen expression on human epidermal Langerhans cells. *Nature* 268:247-8, 1977.  
[McGill University Cancer Research Unit, Montreal, Quebec, Canada]

Epidermal Langerhans cells react positively by immunofluorescence with antisera raised in rabbits against human B lymphoblastoid cell line membrane glycoproteins, indicating the presence of Ia-like antigens on these dendritic cells. [The *SCI*® indicates that this paper has been cited in more than 470 publications.]

### Immune Defense Systems of the Skin

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In the early 1970s, the Langerhans cell of the skin was still a cell in search of a function. Almost a century after its description by Paul Langerhans,<sup>1</sup> the cell remained an enigma. Various workers, and Michel Prunieras in particular,<sup>2</sup> had speculated that it was a specialized epidermal macrophage, but no proof was forthcoming. Looking back from 1990, with the reagents now available, it all seems so obvious and easy to prove.

The events leading to the first description of the presence of major histocompatibility type II antigen on Langerhans cells illustrate for me the adage about being in the right place at the right time. Furthermore, that chance favors the prepared mind was also well illustrated by subsequent events. My interest had been in various aspects of epidermal biology, especially keratinization and melanin production. I was at the time with Martin Lewis investigating the role of immunity in malignant melanoma. In another laboratory in the McGill University Cancer Research Unit, Art Sullivan was working as a postdoctoral fellow with Martin Jerry. Their interests were the various B-lymphocyte surface glycoproteins known at the time as Ia-antigens. Fortunately, I had seen a paper suggesting that even

though Ia-antigens were associated with B cells, a small percentage of macrophages also might be positive. No direct visualization of this finding was available at that time.

After much discussion with Drs. Lewis and Sullivan about what Ia-antigen might represent, we decided to stain human skin with a polyclonal antiserum raised by the Jerry/Sullivan group. At the very first attempt, human skin biopsy frozen sections prepared by Terry Phillips showed remarkable staining of intraepidermal dendritic cells. These corresponded to the distribution of Langerhans cells as shown by ATPase staining. Within days we had completed the controls to prove that the epidermal cells stained by the anti-B lymphocyte antiserum were Langerhans cells.

In showing the results to Prunieras prior to the Pigment Cell Biology Meeting in Boston that year, I was delighted to note his excitement. He said, with some prophetic insight, that the slides I held in my hand were the basis for my future career. Twelve years after, I still find it difficult to get away from Langerhans cells. The paper was submitted to *Nature* and was published in an edition in which similar results were presented from Lars Klareskog's group<sup>3</sup> and the related demonstration of the expression of Fc and C3 receptors on Langerhans cells by Georg Stingl and his colleagues.<sup>4</sup>

This publication on human material was rapidly followed by confirming studies at the ultrastructural level<sup>5</sup> and in mice<sup>6</sup> in which Terry Delovitch in Toronto was instrumental in providing animals and antisera. Subsequent exploitation of the finding of MHC-Class II antigen in the skin has led to an enormous effort relating this molecule to various antigen-presenting functions of the Langerhans cell. From being mainly a curiosity of interest to anatomists, the cell was propelled into the forefront of immunological research. Studies continue at a bewildering pace, and it is clear that the complexity of immune regulation occurring in the periphery has not even now been fully resolved.

1. Langerhans P. Über die Nerven des menschlichen Haut (On the nerves of human skin). *Virchows Arch. Pathol. Anat. Physiol.* 44:325-36, 1868. (Cited 220 times since 1945.)
2. Prunieras M. Interactions between keratinocytes and dendritic cells. *J. Invest. Dermatol.* 52:1-17, 1969. (Cited 155 times.)
3. Klareskog L, Tjernlund U M, Forsum U & Peterson P A. Epidermal Langerhans cells express Ia antigens. *Nature* 268:248-50, 1977. (Cited 420 times.)
4. Stingl G, Wolff-Schreiner E C, Pichler W J, Gschnait F, Knapp W & Wolff K. Epidermal Langerhans cells bear Fc and C3 receptors. *Nature* 268:245-6, 1977. (Cited 395 times.)
5. Rowden G. Immuno-electronmicroscopic studies of surface receptors and antigens of human Langerhans cells. *Brit. J. Dermatol.* 97:593-608, 1977. (Cited 55 times.)
6. Rowden G, Phillips T M & Delovitch T L. Expression of Ia antigens by murine keratinizing epithelial Langerhans cells. *Immunogenetics* 7:465-76, 1978. (Cited 80 times.)

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