0022-202X/8/7501-0044$02.00/0
THE JOURNAL OF INVESTIGATIVE DERMATOLOGY, 75:44–45, 1980

Vol. 75, No. 1
Printed in U.S.A.

Antigen Presentation and Allogeneic Stimulation by Langerhans Cells

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Isolated Langerhans cells were studied for 2 immunologic functions, the ability to present antigen to sensitized T lymphocytes and the ability to act as stimulator cells for mixed lymphocyte reactions. Langerhans cells can perform both of these functions. This fact, with the previous finding that Langerhans cells possess surface Ia antigens and Fc and C3 receptors, strongly suggests that Langerhans cells act as epidermal macrophages.

The functional studies on Langerhans cells that I wish to describe were based on many previous studies on lymphocyte and macrophage function. Since the findings in Langerhans cells can be best understood in the context of these previous studies, I will briefly summarize them.

That lymphocytes from immunized animals proliferate *in vitro* in response to the same antigen was observed about 20 yr ago [1,2]. This *in vitro* reaction, best seen in animals that exhibit delayed sensitivity, is now a major correlate of delayed hypersensitivity. An enormous effort has been aimed at dissection of this phenomenon at the molecular level. Various manipulations of this *in vitro* system have been attempted in a search for the immunologic "Holy Grail" (at least of cellular immunologists), namely, the true molecular nature of the T cell receptor [3].

In the course of these many investigations it was unequivocally established that macrophages must be present if this antigen-induced proliferation is to take place [4–7]. The necessary macrophages can come from an unsensitized animal, but they must share surface histocompatibility antigens with the sensitized lymphocytes if a successful interaction leading to lymphocyte proliferation is to occur [8,9]. About 15 yr ago it was observed that when lymphoid cells from histoincompatible animals were mixed together, a proliferative response (called a mixed lymphocyte reaction [10,11]) occurred after 5 to 7 days. After strenuous efforts it was again shown that proliferation of T lymphocytes requires the presence of macrophages acting as principal stimulator cells [12]; no prior sensitization is necessary, and the macrophages must be histoincompatible with the responding T lymphocytes. The histocompatibility regions that are most important in both exogenous antigen-induced *in vitro* lymphocyte proliferation and in alloantigen-induced lymphocyte proliferation (the mixed lymphocyte reaction) are the I-region antigens [13]. These antigens are determined by genes on the 17th chromosome of the mouse and 6th chromosome of man [13]. The fact that both the foreign antigens taken up by the macrophage as well as the endogenous histocompatibility I-region antigen on the macrophage must be recognized by the T lymphocyte for proliferation to occur has led to a frantic search for theoretical explanations [14]. The importance of I-region antigens in these interactions was emphasized by a series of experiments in which it was observed that the presence of antibodies to the I-region surface antigens of macrophages specifically blocked both antigen-induced lymphocyte proliferation as well as the mixed lymphocyte reaction [15,16]. Thus, in the past 20 yr the macrophage has become recognized as a crucial partner in a variety of immunologically specific interactions.

When it was noted that the Langerhans cells of the epidermis consorted with lymphocytes [17], took up antigens and heavy metals [18], and possessed Fc and C3 receptors [19], it was natural to ask whether the Langerhans cell could function immunologically in the same way as a macrophage. The answer, in a nutshell, was yes. Considering the fact that cells of the epidermis are in the very first trenches with regard to host defense against infectious agents, it is somewhat surprising that it took so long for the function of this peculiar macrophage-like cell to be established. Identification on the Langerhans cells of Fc and C3 receptors led to both a high level of suspicion regarding the role of this cell and a convenient means to isolate Langerhans cells from other epidermal cells by means of rosette techniques. The stage was thus set for Langerhans cells to be put through the same immunologic paces as other, more common immunologic actors. To put it another way, all the technical advances and tricks learned after 20 yr of *in vitro* immunologic investigations of lymphocytes and macrophages became focused on the function of Langerhans cell.

It was very soon established that all Langerhans cells possess I-region surface antigens [20,21] (previously shown to be crucial for macrophage antigen-presenting functions [22]). Moreover, Langerhans cells from guinea pig epidermis act *in vitro* to present exogenous antigens to sensitized lymphocytes, and they act in the guinea pig as stimulator cells for mixed lymphocyte reactions [23]. Thus, the same laws of histocompatibility restriction first noted for lymphocyte-macrophage interactions also were shown to apply to lymphocyte-Langerhans cell interactions.

The belated recognition of Langerhans cells as epidermal macrophages has several important implications. The Langerhans cell as the only Ia-bearing epidermal cell may be crucial for the development and expression of contact sensitivity. Increased or decreased Langerhans cell function could be the basis of certain skin diseases. Finally, the Langerhans cell in allografts could be the chief sensitizing cell; selective and successful elimination of all the Langerhans cells from allografts of the epidermis might lead to permanent allograft survival [24].

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