Epidermale Langerhanszellen als Initiatorzellen für antimikrobielle Immunantworten

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7. Summary

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Introduction: Resident Langerhans cells form a reservoir of immature dendritic cells. Langerhans cells are bone marrow-derived and have many properties of white blood cells such as binding of immune complexes, expression of major histocompatibility complex class II products, and presentation of antigens to T cells. The functions of dendritic cells, in skin and in other tissues, fall into three broad categories of signals: *signal one:* antigen uptake, processing and association with MHC products; *signal two*: migration upon antigenic and/or cytokine stimuli to enable the antigen-presenting cell the interaction with T-cells in defined anatomic compartments; *signal three*: adjuvans functions include adhesion moleules, that mediate the binding of antigen-presenting cells to T cells, costimulator molecules, that help signal the T cells to make lymphokines or cytolytic molecules, and soluble products and cytokines. The migratory capacity, therefore, constitutes an essential accessory function of dendritic cells, but it is not yet fully understood which cytokine or which combination of cytokines triggers the emigration of Langerhans cells out of the epidermis.

In the present study I intended to investigate the effects of cytokines, namly tumor necrose factor-α (TNF–α) and interleukine-1ß (IL-1ß), on migration processes of cutaneous dendritic cells.

Methods: In this experimental system (a murine ear-skin culture model) cutaneous dendritic cells emigrate into the culture medium, where they can easily be enumerated. Alternatively, intraperitoneal injection in combination with the organ-culture model was used. The numbers of Langerhans cells remaining in the epidermis were detectable by immunohistochemistry. In contrast to hypersensitivity models, there is a substantial rate of spontaneous dendritic cells emigration that is not dependent on exogenous cytokines. This requires modifications to the culture system.

Results: 1) The spontaneous emigration of dendritic cells is reduced in a modified culture system: the modification consisted in resting the explanted skin at 4°C for 26 hours before starting the organ-culture

2) The addition of TNF–α to the skin culture affected the emigration of cutaneous dendritic cells from the skin into the medium in a dose-dependent way: low doses of TNF–α (50 U/ml and 100 U/ml) enhanced emigration, high dose of TNF–α (1000 U/ml) suppressed the emigration considerably.

3) Intraperitoneal injection of TNF–α (100 U/ml) before the onset of the skin organ culture induces an even higher rate of emigration of cutaneous dendritic cells from the epidermis.

4) Intraperitoneal administration or addition to the skin culture of neutralizing anti-TNF–α mouse antibodies (anti-TNF–α mAb) inhibits the emigration of cutaneous dendritic cells.

5) Similar to the effects of TNF–α , the addition of IL-1ß (500 U/ml) to the explant cultures leads to enhanced emigration of cutaneous dendritic cells but, in contrast to TNF–α, intraperitoneal injection of IL-1ß before the onset of the skin organ culture induces no emigration.

6) The addition of reciprocal combinations of TNF–α, IL-1ß and their neutralizing anti-cytokine antibodies to the skin organ culture show that TNF–α may induce IL-1ß and together enhances the emigration, in contrast TNF–α only does not stimulate the migration, IL-1ß only enhances the emigration.

Conclusion: In the modified murine skin organ culture system I could reproducibly see effects of cytokines as well as of anti-cytokines. TNF–α and IL-1ß enhance the emigration of cutaneous dendritic cells from the skin. TNF–α influences the migratory capacity of cutaneous dendritic cells in a dose-dependent manner. Whether the negative effect of high dose TNF–α is due to cytotoxicity of the cytokine or to other suppressive mechanisms is not known. Intraperitoneally administreted neutralizing anti-TNF–α mAb substantially reduced the rate of dendritic cells emigration from the skin. Finally, I propose that the regulation of migration by cytokines may happen in the form of a cascade: TNF–α could act as an inducer for IL-1ß production. IL-1 itself might trigger the migration of cutaneous dendritic cells, perhaps by down-regulating adhesion molecules such as E-cadherin that normally hold Langerhans cells anchored in their epidermal environment. For this cascade I present some evidence in skin organ culture model by employing combinations of cytokines and neutralizing anti-cytokine antibodies.