The Skin as an Environmentally Responsive Immunological Barrier

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Although the skin provides a vitally protective physical barrier, it provides an equally important immunological barrier to environmental pathogens. Antigen presenting cells that are resident in the skin can initiate and direct the organism's immune response. These antigen presenting cells are derived from the blood. They migrate into the skin, where they remain for extended periods in an immature state. Foreign antigens provide one of the signals that promote the maturation of these cells and their cells migration to lymph nodes. Despite the central role of exogenous antigens and adjuvants in this cascade, local signaling that occurs among cells within the skin play important regulatory roles that are just beginning to be elucidated. Here, we will focus on emerging evidence that signals derived from local nerves modulate the maturation and function of immune cells. We will also describe recent evidence that the nucleotide ATP acts as an endogenous adjuvant that signals the existence of tissue damage to the immune system. Cutaneous nerves are in intimate contact with Langerhans cells (one of the antigen presenting cells in the skin); and Langerhans cells express receptors for both a classic neurotransmitter (norepinephrine) and for at least three neuropeptides (CGRP, VIP, and PACAP). These neurotransmitters inhibit the ability of Langerhans cells to present antigen *in vivo* and *in vitro*. These effects occurred, at least in part, by modifying cytokine and chemokine production. At an intracellular level, many of the effects of neurotransmitters are mediated by an inhibition of the phosphorylation of IkappaB kinase, which prevents IkappaBalpha degradation and the subsequent activation of the transcription factor NF-kappaB. Thus, cutaneous immune responsiveness is modulated by neural activity. While neurotransmitters are presumably derived from cutaneous nerves, ATP can be secreted by nerves, but ATP can also be released subsequent to tissue damage. Langerhans cells express several cell surface receptors for ATP. In contrast to neurotransmitter receptors, occupation of these receptors with either ATP or other purinergic agonists augments cutaneous immune responses, in part, by modulating the production of cytokines and co-stimulatory molecules. Activation of purinergic receptors results in activation of IkappaB kinase, increased IkappaBalpha degradation and activation NF-kappaB. Thus, the presence of ATP can be interpreted as a local indicator of tissue damage that is used to enhance immune responsiveness. To a first approximation, ATP acts in opposition to neurotransmitters in both a formal and a mechanistic sense, but there are many implications of this model that remain to be explored. It is clear that local signaling systems within the skin modulate immune responsiveness, and these signaling systems provide therapeutic targets that may be exploited to modulate cutaneous immunity.