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〈シンポジウム I〉

『環境と皮膚免疫』

化学物質に対する皮膚免疫反応

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Skin Immune System and Simple Chemicals

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Abstract

The environment affects our immune system physically and chemically. The skin which forms the protective wrap over the body's surface is a kind of immune organ containing dendritic cells, skin resident T cells, and keratinocyte, a source of various cytokines and chemokines. The skin immune system is always under influence of physical and chemical insults of the environment. Allergic contact dermatitis (ACD) is a representative in which skin immune system responds to simple chemicals in the environment. These chemicals, called as sensitizers or haptens, share electrophilic properties and are able to react with various nucleophiles in immunocompetent cells, such as keratinocytes and dendritic cells, to form a covalent bond. These reactions are prerequisites for the sensitization of ACD. Namely, sensitizers bind to lysine, cysteine or histidine residue in the self-peptide complexed to MHC class I or II, which results in forming T cell epitopes. They stimulate dendritic cell or induce keratinocytes to release danger signals *via* the production of ROS. Recently, public and political concerns have been increasing regarding the use of animal testing for the hazard characterization of new chemicals, and consequently the development of *in vitro*, *in chemico* or *in silico* models for the replacement of animal testing is a high priority (EC, 2003; US National Research Council, 2007). As the alternatives to animal experiments, several *in vitro* sensitization tests have been developed. DPRA, h-CLAT, and MUUST are now evaluated within Colipa inter laboratory ring trial and accepted by ECVAM for pre-validation. Several authors recently have suggested that IL-8 production or mRNA expression by either monocyte-derived dendritic cells (MoDCs), U937 cells, or THP-1 cells can provides a promising *in vitro* tool for discrimination between allergens and irritants. So, we developed a high throughput method for detection of IL-8 mRNA induction by sensitizers, using a stable IL-8 reporter cell line. This assay named as IL-8 Luc assay can discriminate sensitizers from non-sensitizers with a high degree of accuracy.[1] On the other hand, several chemicals such as haptens induce keratinocytes to release danger signals *via* the production of ROS. ATP, which is a ubiquitous carrier of chemical energy and a building block of genetic material in all living organisms, is a representative danger signal. In response to various environmental stimuli, ATP can be released into the extracellular environment by non-lytic mechanisms *via* ion channels, connexin hemichannels, P2X7 receptor, or vesicular transport, and also, more frequently, as a consequence of cell damage or acute cell death. ATP activates purinergic P2 receptors which, based on their molecular structures and signal transduction pathways, are classified into the ionotropic P2X receptor family or the metabotropic P2Y receptor family. Thus, ATP also serves as an extracellular signaling molecule and influences various biological functions including immune response. Recently, Weber *et al.*[2] have reported the role of P2X7 signaling in sensitization of ACD. The authors demonstrated that P2X7 deficient mice could not develop allergic contact dermatitis to haptens, such as TNCB and oxazolone. The subcutaneous injections of hapten-modified dendritic cells into wild type or P2X7 deficient mice revealed that P2X7 receptor on dendritic cells are crucial for sensitization. Moreover, the role of P2X7 was compensated by the treatment with Alum, an inflammasome activator. Furthermore, the hydrolysis of extracellular ATP by apyrase significantly suppressed ACD. Finally, they also demonstrated the release of ATP in the skin after hapten painting by *in vivo* imaging. We also have reported that using DNA microarray and quantitative real-time PCR, IL-6, IL-20, CXCL 1 to 3, and ATF 3 mRNA are significantly augmented by ATP-treated keratinocytes.[3] In addition, ATP phosphorylated STAT3 in keratinocytes. These studies suggested the following. Namely, ATP released from keratinocytes under stress stimulates neighboring keratinocytes to secrete IL-8, Groa, IL-6 and IL-20, express ATF3, and phosphorylates STAT3. IL-8 and Groa are chemotactic to PMNs and play a role in wound healing. IL-6 and IL-20 and STAT3 activation induce keratinocyte proliferation and are responsible for wound healing. On the other hand, ATF3 may play a role in suppression of NF-κB

or AP-1 mediated inflammation and trigger apoptosis. In conclusion, the accumulating evidence has indicated that our skin immune system as well as cutaneous immune disorders, such as contact dermatitis, atopic dermatitis, and psoriasis, are affected or modulated by various environmental factors. So, for understanding the pathogenesis of skin inflammatory diseases and developing a new therapeutic modality, it is crucial to advance the understanding of these influences.

Key words: electrophiles, allergic contact dermatitis, dendritic cells, danger signals, ATP.