T CELLS

Skin oils trigger T cell responses

T cells that recognize the antigen-presenting molecule CD1a are common in the skin, but their CD1a-associated lipid auto-antigens were not known. Moody and colleagues now show that CD1a-restricted T cells are stimulated by lipids that lack polar head groups, that nest within the CD1a binding groove and that are present at high levels in the skin and sebum. The authors suggest that, when skin barriers are breached, the stimulatory headless lipids displace inhibitory lipids that have bulky or charged head groups (headed lipids), which triggers T cell immunity.

To overcome the problem that T cell responses to exogenous lipids are masked by background responses to endogenous antigens in antigen-presenting cells (APCs), the authors used an APC-free system to identify CD1a-binding antigens. The stripping of lipids (using acidic pH) from plate-bound, cell-derived, recombinant CD1a molecules reduced their ability to

activate CD1a-specific T cell lines. Initial analysis of the lipids eluted from the CD1a molecules revealed the presence of a broad range of lipids, with and without charged head groups. By comparing the T cell response to the eluted lipids with a panel of synthetic or purified lipids, triacylglyceride (TAG) was identified as a stimulatory CD1a-binding lipid, whereas many of the ubiquitous cell membrane lipids, such as glycolipids and phospholipids, were inhibitory. Surprisingly, unlike all other lipids that are known to interact with T cell receptors (TCRs), TAG lacks a polar head group.

Interestingly, different human tissues were shown to have differing antigenic potency: lipid extracts prepared from various human cell types and tissues, including the blood and thyroid gland, generally inhibited CD1a-specific T cell activation, whereas lipid extracts from the epidermis activated the T cells in a dose-dependent manner. Using a technique to separate lipids

on the basis of polarity, the authors confirmed that the epidermis has a greater proportion of small, apolar lipids, including TAG, fatty acids and wax esters, than other tissues, and these were all shown to stimulate CD1a-restricted T cells. Moreover, analysis of the lipid content of sebum, which is an oily substance secreted onto the surface of the skin by hair follicles and sweat glands, revealed an enrichment for TAG, wax esters and the apolar lipid squalene.

The finding that CD1a-restricted T cell lines could recognize a range of structurally related, apolar antigens of different sizes suggested that the mode of recognition is distinct from other known TCR-lipid-CD1 interactions, which involve binding of the TCR to charged elements of the lipid antigen. The authors' studies confirmed that apolar lipids bind in the groove of CD1a, as they could displace bound headed lipids and convert a T cell inhibitory complex into a stimulatory complex. So, the authors suggest that ubiquitous lipids with bulky head groups are normally loaded into CD1a molecules and interfere with TCR recognition of CD1a. By contrast, small apolar lipids nestle within the groove and do not block access of the TCR to CD1a. Exchange of the resident inhibitory lipids with stimulatory, apolar lipids could occur following an injury to the skin, which would allow surface skin oils to penetrate deeper epithelial layers that contain CD1a-expressing Langerhans cells that promote T cell activation and skin immunity.

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ORIGINAL RESEARCH PAPER de Jong, A. *et al.* CD1a-autoreactive T cells recognize natural skin oils that function as headless antigens. *Nature Immunol.* <http://dx.doi.org/10.1038/ni.2790> (2013)

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