Published February 2, 2015

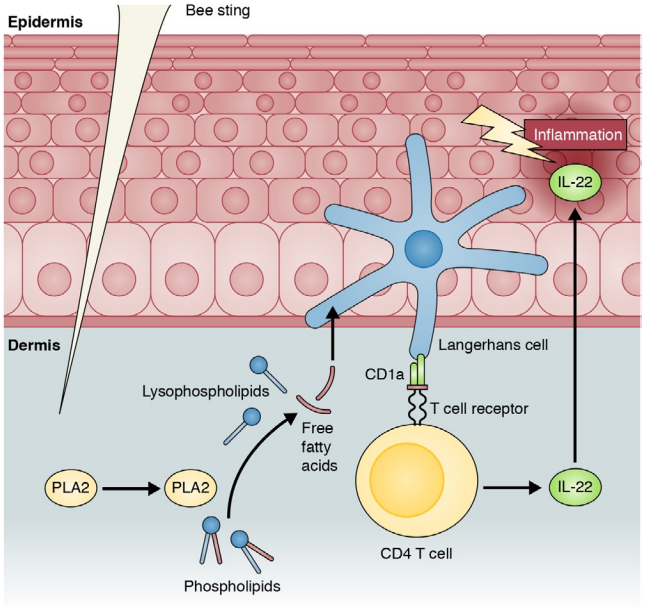
Bee venom stirs up buzz in antigen presentation

Insight from Luc Van Kaer

While most T cells recognize peptide antigens presented by major histocompatibility complex (MHC) class I and class II molecules, some T cells react with lipid antigens presented by MHC-related CD1 proteins. In this issue, Bourgeois et al. establish the concept that enzymes in bee venom can cleave host skin-derived phospholipids into lipid neoantigens that activate CD1a-restricted T cells to promote a local inflammatory response.

Humans have four CD1 proteins: CD1a, CD1b, CD1c, and CD1d. The CD1a molecule has long been known as a specific surface marker for human Langerhans cells, and recent studies have shown that CD1a-restricted T cells are recruited to the skin. Such T cells are intrinsically autoreactive, recognizing skin-specific oils produced by sebaceous glands.

In searching for potential contributions of CD1a-reactive T cells to inflammatory responses in the skin, Bourgeois et al. investigated human T cell responses to the venoms of bees and wasps. They found that such venoms induce a CD1a-mediated response in both individual T cell clones and primary human T cells. However, further analyses revealed that the antigenic substance unexpectedly partitioned within the lipid rather than the protein fractions, raising the possibility that enzymes in the venom generate lipid antigens by cleaving common phospholipids. The investigators were able to zoom in on phospholipase A2 (PLA2), an enzyme that is abundant in insect and snake venoms, which acts on phospholipids to release fatty acids and lysophospholipids.



Phospholipase A2 (PLA2) in bee venom is introduced into human skin and cleaves ubiquitous phospholipids into free fatty acids and lysophospholipids that function as neoantigens. These fatty acid neoantigens are now available for sampling by epidermal Langerhans cells, which load them onto CD1a proteins and present them at their surface to skin-resident CD1a-reactive T cells. These T cells produce cytokines such as IL-22 that contribute to the inflammatory response.

These intriguing findings support a model of T cell activation involving insect-mediated PLA2 introduction into the skin, inducing the release of fatty acid neoantigens from common skin phospholipids, subsequently sampled by Langerhans cells, loaded onto CD1a molecules, and presented to T cells. Activated CD1a-reactive T cells produce IL-22, a cytokine that plays a role in antimicrobial defenses, promotes keratinocyte proliferation, and contributes to the pathogenesis of a variety of skin inflammatory diseases. In this manner, CD1a-reactive T cells may contribute to the local inflammatory response to venoms. The findings also provide a potential molecular explanation for the generation of autoantigens in normal skin, which expresses secreted phospholipases. It has been proposed that such natural lipids are present at the surface of the skin and are thus inaccessible to CD1a-restricted T cells in the dermis. However, a breach in the skin barrier might make these natural oils available to Langerhans cells in the epidermis, resulting in their presentation to CD1a-reactive T cells and the subsequent induction of antimicrobial and inflammatory responses. Moreover, infections and inflammatory processes can modulate the expression patterns of phospholipases in the skin, which may represent a mechanism to control inflammation via CD1a-reactive T cells. Finally, certain skin pathogens secrete PLA2 enzymes, raising the possibility that such infections can induce CD1a-mediated T cell responses that contribute to host immunity and disease pathogenesis. These proposed scenarios, together with their potential therapeutic applications, will provide rich and fertile avenues for future investigation.

Bourgeois, E.A., et al. 2015. *J. Exp. Med.* http://dx.doi.org/10.1084/jem.20141505.

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The Journal of Experimental Medicine

Downloaded from jem.rupress.org on February 15, 2015

Published February 2, 2015

PI3-kinase, the key for bugs to get in?

Insight from Grégoire Lauvau

Using the intracellular bacterium *Listeria monocytogenes* as a model of pathogen crossing of host epithelial barriers, Gessain et al. provide a mechanistic explanation for the requirement of two internalins used by *L. monocytogenes* during infection at the placental barrier, showing that phosphoinositide 3-kinase (PI3-K) is a key factor regulating microbial pathogen permissiveness at epithelial barriers.

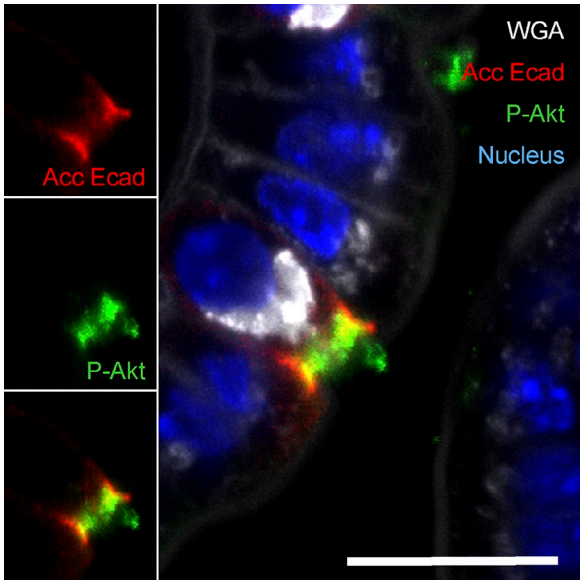
L. monocytogenes possesses two internalins (Inls), InlA and InlB, which bind to their respective receptors E-cadherin (Ecad) and c-Met. Both Inls–receptor interactions are species-specific with InlB–c-Met inducing membrane ruffling via PI3-K activation, a key step of *L. monocytogenes* invasion. *L. monocytogenes* is known to exhibit differential Inl requirements for crossing the intestinal and placental barriers. While both Inls are necessary for *L. monocytogenes* invasion at the placental barrier, only InlA is required for crossing the intestinal barrier. The mechanistic explanation for this difference was unknown.

In this study, Lecuit and colleagues used in vivo mouse models, human intestinal and placental cell lines and tissue samples, in vitro biochemical and microbial invasiveness assays, as well as state-of-the-art fluorescent microscopy analysis to test the hypothesis in vivo that PI3-K tissue levels affect *L. monocytogenes* invasion. They provide a thorough in situ correlation of the levels of PI3-K activity (as measured by Akt phosphorylation and Foxo1 cytosolic location) with *L. monocytogenes* invasiveness of the intestine and placenta. PI3-K activity, both in mouse and human intestinal tissues, was primarily detected in mucus-secreting goblet cells, extruding cells, and some enterocytes—which were all targeted by *L. monocytogenes*—yet it was barely detectable in placenta. Gain and loss of function experiments, knocking down or promoting overexpression of PI3-K activity in vitro, and comparative invasiveness assays with *L. monocytogenes* mutants for InlA, InlB, or both, together provide compelling support for a critical role of PI3-K in controlling host barrier permissiveness.

These results highlight how protective mechanisms may have been evolutionarily selected to restrict the invasiveness potential of mucosal pathogens. They also allow for an interesting reinterpretation of prior work that used an engineered *L. monocytogenes* with a murine version of InlA, which may not fully reflect the natural situation of intestinal infection in humans.

An important next step to follow up this study is to extend the proposed model to other organs and mucosal microbial infections, and to establish whether or not PI3-K, as proposed by the authors, is a general mechanism for other pathogens to breach epithelial barriers. In this regard, because many pathogens enter through epithelial barriers, the therapeutic potential of the reported finding may turn out to be very important.

Gessain, G., et al. 2015. *J. Exp. Med.* http://dx.doi.org/10.1084/jem.20141406.



Confocal microscopy image of intestinal villi from uninfected mice showing colocalization of luminally accessible E-cadherin (Acc Ecad, red), mucus stained by wheat germ agglutinin (WGA, white), the nucleus (blue), and phosphorylated Akt (P-Akt, green), an indicator of PI3-K activity.

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