Time heals all wounds—but 12-HHT is faster

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Chronic nonhealing wounds such as diabetic ulcers are a major problem associated with human disease. In this issue, Liu et al. offer new hope for tackling nonhealing wounds by defining a novel role for the leukotriene B_4 receptor type 2 (BLT2) and its ligand 12-hydroxyheptadecatrienoic acid (12-HHT) in wound healing. They also show that high-dose aspirin delays wound healing by reducing the levels of 12-HHT.

Insight from Yael Gus-Brautbar (left) and Dipak Panigrahy
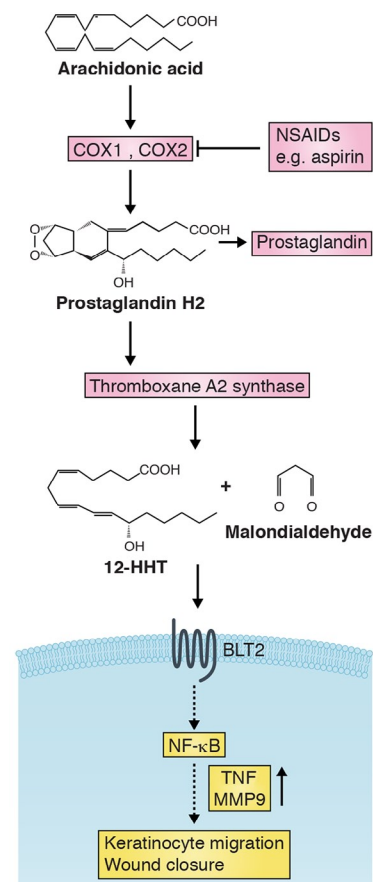
Endogenously produced lipid autacoids are locally acting, small molecule mediators that regulate diverse processes such as inflammation, asthma, colitis, tissue regeneration, and cancer. Unlike prostaglandins and leukotrienes, the biological roles of 12-HHT and its receptor BLT2 have been poorly characterized. 12-HHT, a downstream lipid metabolite of cyclooxygenase 1 (COX1) and COX2, was previously assumed to be an inert by-product of arachidonic acid metabolism until its recent identification as an endogenous high-affinity ligand for BLT2 by this group. It is known that high-dose aspirin, the most commonly used nonsteroidal anti-inflammatory drug (NSAID) targeting the COX pathway, delays wound healing but the mechanism by which this delay occurs has been poorly characterized. Most of aspirin's pharmacological effect has been attributed to its blockage of thromboxanes and prostaglandin production. However, low-dose aspirin has been found to trigger production of beneficial, anti-inflammatory, and pro-resolution mediators by COX2, the aspirin-triggered resolvins, and lipoxins, thus alleviating inflammation via stimulating endogenous resolution mechanisms. It is possible that high-dose aspirin inhibits a range of anti-inflammatory lipid metabolites, some yet unidentified, which may account for some of its side effects.

Now, in a series of elegant experiments using genetic and pharmacological manipulation of endogenous 12-HHT levels, Liu et al. demonstrate for the first time that 12-HHT promotes wound healing by accelerating keratinocyte migration via the BLT2 receptor, resulting in enhanced re-epithelialization in the skin. The 12-HHT/BLT2 axis induces keratinocyte migration and wound closure through NF-κB dependent up-regulation of TNF and matrix metalloproteinase 9 (MMP9). Remarkably, a synthetic BLT2 agonist accelerated wound closure in a mouse diabetes model. These pioneering studies by Liu et al. provide the first mechanistic insight into the deleterious effect of high-dose aspirin on wound healing.

These results suggest a direct anti-inflammatory role of BLT2 that is distinct from the proinflammatory roles of BLT1. Liu et al. offer a mechanistic rationale for evaluating BLT agonists as novel therapeutics to accelerate wound healing. Based on these exciting results, the largely unexplored lipid autacoid 12-HHT/BLT2 axis should now be evaluated as potential therapeutic targets in other inflammation-associated diseases such as cancer, atherosclerosis, and sepsis.

Liu, M., et al. 2014. *J. Exp. Med.* http://dx.doi.org/10.1084/jem.20132063.

The 12-HHT/BLT2 axis promotes wound healing by accelerating keratinocyte migration through NF-κB–dependent up-regulation of TNF and MMP9.

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Engineering adjuvants for predictable immunity

Insight from Steven Reed

A designer approach to adjuvant development may be required to improve upon natural immunity, to reliably induce protective immunity to pathogens against which we have no effective vaccines, and to develop effective therapeutic vaccines for cancer and other types of disease for which current therapies are inadequate.

The quest to design biological structures for adjuvant use began many years ago, exemplified by the work of Edgar Ribi to dissect the adjuvant activity from LPS while eliminating the toxic components. More recent work has defined the precise structure–function aspects of adjuvant binding to toll-like receptors (TLRs) using synthetic chemical entities. However, most adjuvants in current use, including those categorized loosely as "alum," are not homogeneous and their composition is not well characterized. The effects of chemical composition, charge, particle size, shape, and particle association (e.g., encapsulation

and internalization versus surface binding) all influence immunological responses, but precise, controlled studies with defined compositions and controlled variables, using innate responses ex vivo to predict adaptive responses in vivo, are relatively few.

The study by Williams et al. in this issue uses immune response readouts from cultured human and mouse dendritic cells to mathematically model the relationship between adjuvant materials and the immune responses they induce, adding a rational approach to the concept that "immunity can be determined purely by chemistry." The authors used physically and chemically defined structures that resemble alum (layered double hydroxides [LDH]; see figure). The modeling predicted that varying three key physicochemical properties of LDHs (the ionic radius, the c-parameter [the interlayer spacing within the LDH], and the zeta potential [the magnitude of the electrical charge of the layer around the LDH particle]; see figure) would influence innate and adaptive responses in a predictable manner. These predictions were tested and verified in mouse immunization studies and ex vivo studies on human macrophages.

While it may still be some way off, this novel mathematical approach to predicting the immune responses induced by candidate crystalline adjuvants offers the exciting possibility of rational design of superior adjuvants.

Williams, G.R., et al. 2014. *J. Exp. Med.* http://dx.doi.org/10.1084/jem.20131768.
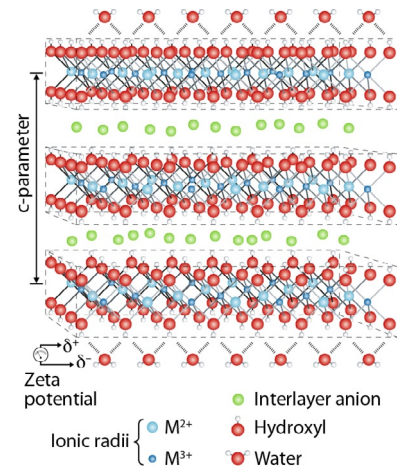
Schematic of a layered double hydroxide showing the positively charged cation layers (red/blue circles) and negatively charged anion layers (green circles) sandwiched between two layers of water molecules.

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Microbial hijacking of mammalian iron shuttling

In this issue, Liu et al. provide compelling evidence for a novel mechanism by which pathogenic bacteria can acquire iron from mammalian cells.

Iron is an essential nutrient for almost all organisms due to its central role in many enzymatic processes, mitochondrial respiration, and DNA synthesis. Most microbes are highly dependent on a sufficient supply of iron to secure their growth, and they can acquire this essential nutrient by multiple pathways. One of these acquisition strategies is via the release of bacterial siderophores, which capture iron in the environment and are then taken up by microbes.

Mammalian cells also produce a siderophore, which is presumably used for intracellular and transcellular iron shuttling. Liu et al. found that this mammalian siderophore, 2,5-dihydroxybenzoic acid (2,5-DHBA), can be taken up by bacteria and used as a source for iron. Synthesis of 2,5-DHBA was reduced upon bacterial infection, and knock out of this mammalian siderophore resulted in increased resistance of mice to infection with *E. coli*. Importantly, mammalian immune cells also produce the peptide lipocalin-2 in response to infection, which sequesters both bacterial and mammalian siderophores. Thus, combined down-regulation of 2,5-DHBA and up-regulation of lipocalin-2 restricts iron availability for microbes, resulting in a beneficial infection outcome.

Insight from Günter Weiss

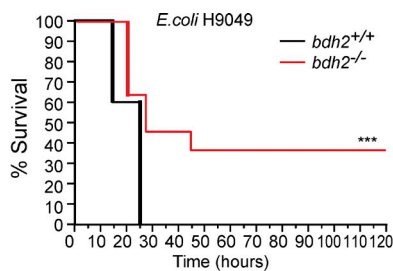**2,5–DHBA–deficient mice are resistant to *E. coli* infection.**

Given the importance of iron for microbial growth and for antimicrobial immune defenses, the struggle for control over iron availability is a central battlefield that may decide the fate of an infection. This study describes a novel pathway by which bacteria steal the nutrient iron from the mammalian host to secure their own growth and pathogenicity. Targeting both mammalian and microbial iron homeostasis is an attractive approach to tackle iron availability for microbes and to treat infections, a strategy first studied in malaria and hepatitis C virus infection with varying outcomes, but not yet in bacterial infections in humans. However, it has to be kept in mind that restricting iron availability for extracellular microbes may favor the growth of pathogens residing within cells and vice versa. Moreover, we need to gain further insights into the role of the mammalian siderophores in orchestrating mammalian iron homeostasis under normal and inflammatory or infectious conditions, and how the pharmacological inhibition of 2,5–DHBA synthesis will impact host immune function, erythropoiesis, and iron–dependent cellular processes.

Liu, Z., et al. 2014. *J. Exp. Med.* http://dx.doi.org/10.1084/jem.20132629.

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