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DNA transportation authority

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The pattern-recognition receptors of the innate immune system, such as Toll-like receptors, bind specific repetitive components of microbes, including lipoproteins, lipopolysaccharides and nucleic acids. The location of some of these receptors in distinct subcellular compartments facilitates detection of intracellular pathogens but presumably precludes activation by self molecules that are structural homologs of microbial ligands. For example, Toll-like receptor 9 (TLR9) is located within endosomes and recognizes double-stranded DNA released from bacteria and viruses, which often infect or traffic through endosomes and phagolysosomes.

In a recent study, Lande *et al.*¹ show how self DNA can move from an extracellular location directly to endosomes, resulting in activation of the innate immune system via TLR9. This activation may contribute to the pathogenesis of autoimmune disease but can also enhance host defense to infection.

Normally, the release of self DNA has no impact on the innate immune response, because the DNA cannot enter cells spontaneously to gain access to endosomes and TLR9. The breakthrough of Lande *et al.*¹ in understanding how self ligands gain access to and activate TLRs came from the study of psoriasis, a skin disease triggered by autoimmune T cells.

In planning their experiments, Lande *et al.*¹ followed clues from the clinic. In 1872, at the Silesian Society for National Culture, Heinrich Köbner presented the curious case of a patient. In this individual, several “traumatic” events, for instance, tattoos and animal bites, triggered new psoriatic skin lesions at exactly the same location and with the identical shape of the injured skin². Classically, psoriasis presents at the sites that are the most subjected to trauma: elbows and knees. Given such bedside observations, Lande *et al.*¹ reasoned that trauma would trigger keratinocyte cell death, releasing self DNA.

The next clue came from the observation that psoriasis lesions almost never get secondarily infected. Researchers tracing the cause found that psoriatic lesions contain elevated levels of the antimicrobial peptide cathelicidin (also known as LL-37)³, whose expression is increased in keratinocytes by specific stimuli⁴.

Lande *et al.*¹ reasoned that damaged keratinocytes could release cathelicidin and self DNA simultaneously. They further predicted that these two molecules could interact on the basis of charge interactions, because cathelicidin is a cationic α -helical protein, and DNA has a negatively charged phosphodiester backbone. Lande *et al.*¹ found that the combination of cathelicidin and self DNA created a surprisingly treacherous agglomeration. Aggregated complexes of DNA and cathelicidin were found to gain access to endosomes of plasmacytoid

dendritic cells, resulting in the activation of TLR9 and release of interferon- α , a trigger of autoimmune T cell responses.

These findings reveal that cathelicidin is a transporter for DNA, delivering it to TLR9 in endosomes. It remains to be determined whether a similar transport mechanism for RNA and its relevant TLRs contributes to host defense, disease pathology or both.

The nucleic acid transporter function of cathelicidin probably evolved for responding to wounding and microbial infection (Fig. 1). Cathelicidin is upregulated after tissue injury as part of the wound-healing response⁴. In this response, nucleic acids released from damaged cells complex with cathelicidin, leading to activation of intracellular TLRs and initiating an inflammatory response to augment the immune response to microbes. In human macrophages and epithelial cells, activation of cell surface TLR2 by microbial ligands triggers the vitamin D-dependent induction of cathelicidin and the destruction of bacteria and viruses⁴⁻⁶. DNA released by these damaged microbes would probably complex with cathelicidin and be transported to endosomes to activate intracellular TLRs—resulting in amplification of host defense pathways. The dual activation of TLRs triggers a synergy in host defense, as demonstrated by the cooperative roles of TLR2 and TLR9 in optimal resistance to mycobacterial infection⁷.

If the ability of cathelicidin to transport nucleic acids to TLR-bearing intracellular compartments is part of the physiological danger response to injury and infection, what has gone awry in autoimmune disease? Possible factors favoring autoimmunity include the persistent overproduction of cathelicidin and the trafficking of plasmacytoid dendritic cells to the disease site (in the normal wound healing response, cathelicidin production is transient, and plasmacytoid dendritic cells are not prominent). Although cathelicidin can mediate antimicrobial activity as part of innate immunity, its ability to allow self DNA to activate the innate immune system provides a possible mechanism to break tolerance to self antigens.

The work of Lande *et al.*¹ has broad implications for the pathogenesis of other human diseases. Other pathways may inappropriately trigger TLR9, such as immune complexes containing DNA-specific antibodies and DNA, which correlate with disease activity in individuals with systemic lupus erythematosus. Proteins other than cathelicidin with the capacity to bind self DNA may also facilitate transport across cell membranes into endosomes. What's more, the ability of microbial pathogens to mimic this transporter function may contribute to disease pathology. For example, the pigment hemazoin of *Plasmodium falciparum* targets parasite DNA to TLR9-containing compartments, providing a mechanism for the classic fever observed in malaria⁸.

The discovery that cathelicidin is the transportation authority for DNA provides new opportunities for therapeutic intervention. In the context of autoimmune disease, it should be possible to block the formation of nucleic acid-transporter protein complexes or limit the activity of accessory molecules which direct these complexes to endosomes.

The cathelicidin transport pathway could also potentially be harnessed to enhance wound healing and combat infection. For example, serum vitamin D concentrations correlate with the ability of the innate immune system to induce cathelicidin as part of an antimicrobial response. Already, clinical trials are underway to determine whether vitamin D supplementation of individuals at risk for infection will augment host defense mechanisms required to prevent infection or improve the response to therapy^{9,10}. Increasing cathelicidin levels may also facilitate the recognition of microbial nucleic acids by TLRs to further activate the host innate immune response. Bacterial DNA sequences are often used as vaccine adjuvants, and, therefore, modulation of trafficking pathways by adding cathelicidins or similar transport molecules could program optimal activation of the innate immune response.

The identification of a new nucleic acid transportation system provides the opportunity to intervene at the bedside. The challenge will be to harness the activity of this system to promote host defense without triggering autoimmunity.

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Figure 1.

Transportation authority for nucleic acids. As part of the danger response to injury, cathelicidin transports nucleic acids released from damaged cells to TLRs located in endosomes, activating appropriate pathways of inflammation. If the production of cathelicidin is dysregulated in the presence of plasmacytoid dendritic cells, autoimmune phenomenon may occur. As part of the innate immune response to microbial infection, the TLR-induced, vitamin D-dependent production of cathelicidin and the release of microbial nucleic acids may further activate TLRs located in endosomes, thereby amplifying host defense pathways. APC, antigen-presenting cell; pDC; plasmacytoid dendritic cell.