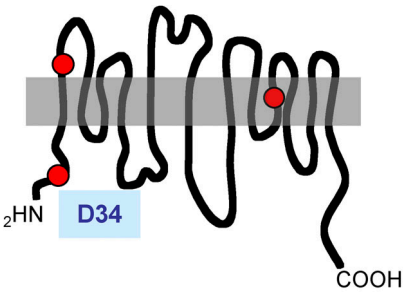


Amino acid 34 of Unc93B1 determines its specificity for TLR9 versus TLR7.

TLR choreography

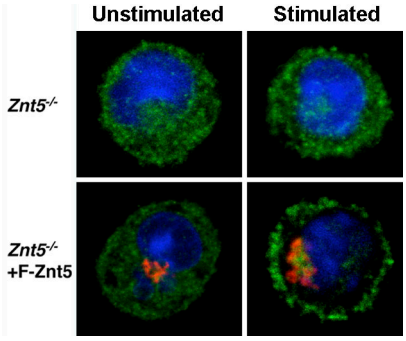
Pathogen-sensing Toll-like receptors (TLRs) must be deployed accurately. Here, Fukui et al. show how finely tuned these receptors are. Tweaking a single amino acid in a TLR-trafficking molecule determined whether the signal was green or red for nucleic acid–sensing TLRs (page 1339).

TLR7 and TLR9 recognize viral nucleic acids—RNA and DNA, respectively—in endolysosomes. By sequestering TLR7 and TLR9 within the ER, unstimulated dendritic cells and B cells avoid misfiring on bits of host DNA and RNA, which are normally degraded before reaching endolysosomes.

A second guard against TLR misfiring is provided by the membrane-spanning ER protein Unc93B1, which delivers TLR7 and TLR9 to endolysosomes only when the cell is properly activated. Without Unc93B1, nucleic acid–sensing TLRs stay in the ER and never send their signals.

Here, Fukui et al. show that Unc93B1 alternately dispatched TLR7 and TLR9 in dendritic cells, depending on whether the unabridged protein or a slightly altered one was expressed. And the TLR7/9 decision came down to a single amino acid. The usual aspartate at position 34 (D34) of Unc93B1 enhanced TLR9 trafficking and inhibited TLR7. Cutting off the N terminus of the protein or swapping the aspartate for alanine favored TLR7 trafficking over TLR9. The authors suspect that TLR7 inhibition requires an as-yet-unknown molecular middleman that binds to Unc93B1 via D34.

Because the more common version of Unc93B1 primarily traffics TLR9, the authors suggest that dendritic cells are biased toward DNA sensing. Both TLR7 and TLR9 lead to the production of type I interferons, known promoters of autoimmunity. By ensuring that only one of these TLRs leaves the ER at a time, Unc93B1 may be indirectly keeping type I interferon expression under control.



Translocation of PKC-β (green) to the plasma membrane of stimulated mast cells depends on Znt5 (red).

Galvanizing allergies

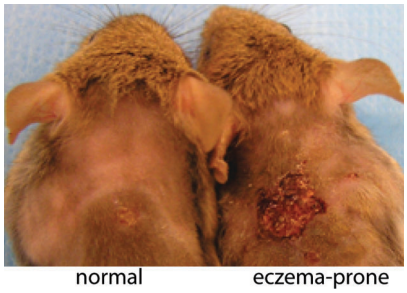
Zinc is a ubiquitous element welded into various metabolic, neurological, and immunological pathways. Here, Nishida et al. show how late-phase allergic responses rely on the zinc transporter Znt5, which shuttles zinc from the cytosol into the Golgi (page 1351).

Removing heavy metals, such as zinc, from mast cells disrupts their activation and blunts allergic responses. Now Nishida et al. show that Znt5 is dispensable for immediate allergic reactions, which are governed by degranulation, but is needed for late-phase allergic responses, which rely on cytokine production.

Without Znt5, protein kinase C (PKC) failed to translocate to the plasma membrane where it gets activated. And because PKC translocation drives NF-κB activation, NF-κB–dependent cytokine production was defective.

The zinc-finger motifs in PKC were required for PKC translocation. The authors suggest that the lack of Znt5 decreased the zinc that was available to bind to PKC in the Golgi.

Why the lack of Znt5 had no effect on degranulation is unclear, as this process also requires PKC translocation. The authors say that other independent pathways, perhaps triggered by a calcium flux, must have made up for the lack of zinc. Or, they suggest, the threshold of PKC activation required for degranulation might be lower than that for NF-κB activation.



IL-17 increases virus burden and lesion size in eczema-prone mice infected with vaccinia virus.

IL-17 propels infection

Vaccinia virus, a cowpox virus used to vaccinate against smallpox, can be lethal for people with the skin disease atopic dermatitis (AD). On page 1219, Kawakami and colleagues show that the cytokine IL-17A amplifies vaccinia virus infection by muffling natural killer (NK) cells.

When vaccinated, AD patients often develop eczema vaccinatum, a severe reaction characterized by erosive rashes. Although these patients are known to have increased levels of IL-17 in the skin and dysfunctional NK cells, it was unclear whether these observations were connected. Here, Kawakami et al. describe a new mouse model that mimics aspects of the human condition, allowing them to establish a link between IL-17 and NK cell defects. Excess IL-17A—but not IL-17F—suppressed NK cell activity, which increased virus titers and skin lesion size in mice with eczema.

The mice were protected when the authors neutralized IL-17A or injected activated NK cells. These treatments revived NK cell cytolytic activity and increased interferon-γ production. IL-17A may directly inhibit NK cells, as adding IL-17 to NK cell cultures in vitro inhibited the expression of interferon-γ, perforin, and granzyme B. IL-17 might also act indirectly through the type I interferons known to activate NK cells. What causes the initial boost in IL-17–secreting cells during the acute response to vaccination in mice with eczema remains unknown.

Text by Amy Maxmen
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Interleukins adapt to parasites

Thank parasites for making our interleukins into the inflammatory defenders they are today, according to a population genetics study by Fumagalli et al. on page 1395. However, you might also blame the bugs for sculpting some of those genes into risk factors for intestinal disorders.

Parasite-driven selection leaves a footprint on host genomes in the form of single-nucleotide polymorphisms (SNPs). Genetic variation (multiple SNPs) at a particular locus can be maintained within a population if a certain SNP helps the host fend off infections in one environment, but hinders the host in another environment with different parasitic pressures.

Here, Fumagalli et al. sift through 1,052 SNPs in human interleukin genes from roughly 1,000 people worldwide. Of 91 genes assessed, 44 bore signatures of selection, meaning that the genetic variation was due neither to chance nor to the migration of populations over time. And some of that variation correlated with parasitic diversity, indicating that parasites drove selection.

Parasitic worms appear to have applied a more powerful selective pressure on certain interleukin genes than did viruses, bacteria, or fungi (assuming that pathogen diversity has remained relatively stable over time). That isn't surprising, says senior author Manuela Sironi, because worms typically evolve slower than bacteria or viruses, giving their hosts time to adapt.

Worm-driven selection of SNPs in genes encoding IL-10 and IL-4 might have been predicted based on their known roles in promoting the Th2 responses needed to fight off worm infections. Without the IL-4 receptor, for example, mice cannot expel certain nematodes. SNPs in the gene encoding IL-19 correlated strongly with worm diversity as well. Because this cytokine promotes inflammation in the skin, the authors suggest that it might protect against skin-borne infections.

Surprisingly, six of the nine known risk alleles for Crohn's and celiac disease also appeared to be selected for by pathogen diversity. Like most of these disease-associated SNPs, those in the Crohn's risk gene *IL12B* correlated more closely with viral, bacterial, and fungal diversity than with worm diversity. In theory, these risky alleles have been maintained because they promote vigorous Th1 responses, which help fend off viruses and bacteria. But overly exuberant Th1 responses also contribute to inflammatory bowel diseases.

Other pathogen-selected SNPs were more puzzling. For example, SNPs in the gene encoding an IL receptor-associate protein, IL1RAPL1, correlated with worm diversity, yet the protein functions in brain development and has no reported role in the immune response.

CONSTANCE FINNEY

Intestinal worms helped shape human interleukin genes.

Modeling MS

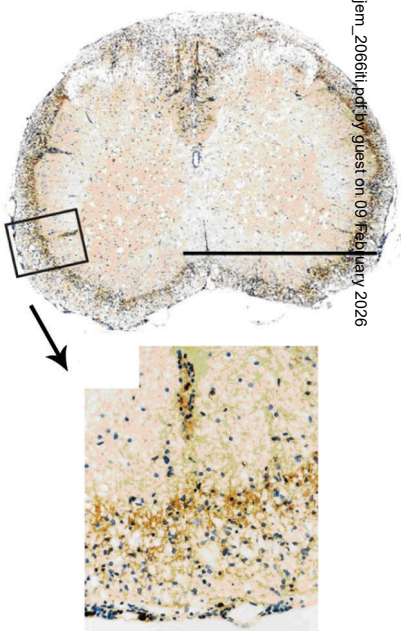
Multiple sclerosis (MS) is an enigmatic autoimmune disorder characterized by on-and-off neurological attacks with variable symptoms. On page 1303, Pöllinger et al. describe a new transgenic mouse model of MS that more closely mimics the human disease than many existing EAE models.

T cells in these transgenic mice (dubbed "RR" mice) recognize an epitope from the myelin protein MOG. The mice spontaneously developed EAE with relapsing-remitting attacks on different CNS tissues. Most existing EAE models, on the other hand, rely on immunization with CNS-derived antigens in adjuvant or injection of autoreactive T cells.

As occurs in MS, the RR mice developed variable symptoms. Motor problems and an unsteady gait might dominate the first attack, with paralysis dominating the next. CNS lesions in these mice contained autoantibody-producing B cells along with IL-17– and IFN-γ–producing T cells. And the expression of these cytokines correlated with phases of attack and remission. Whether or not these waves were a cause or consequence of inflammation remains unknown.

B cells were critical for disease development in the new model. A role for MOG-specific B cells has also been shown in other EAE models, but the RR mice are the first to activate autoreactive B cells from the endogenous repertoire (rather than a transgene). Once triggered, the B cells produced anti-MOG antibodies that, along with complement, destroyed MOG-expressing cells in vitro. The fact that transgenic RR mice with a healthy nervous system also developed anti-MOG autoantibodies suggests that antibody production precedes overt disease.

Transgenic T cells that access the CNS might create immunogenic conditions that recruit endogenous autoreactive B cells. Or, the authors propose, MOG-containing myelin debris could be transported by phagocytes from the brain to lymph nodes, where natural, MOG-specific B cells then get activated with help from transgenic T cells.



Endogenous MOG-specific B cells (blue) infiltrated the spinal cords of RR mice.