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THE JOURNAL OF IMMUNOLOGY

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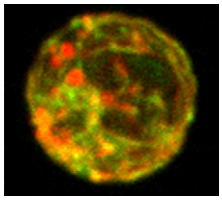
Intracellular Toll Road



TLR9 is expressed in the endosomal compartment of APCs, where it recognizes dsDNA. If TLR9 cannot make it from the endoplasmic reticulum to the endosome, autoimmunity and blunted innate immune responses can ensue. Avalos et al. (p. 695) illuminated the ER-to-endosome passage of APCs with the production of a TLR9–GFP fusion. The authors demonstrated that TLR9–GFP underwent proteolytic processing to function and target normally in APCs. Inhibition of proteolytic processing with z-FA-FMK, a thiol protease inhibitor, diminished TLR9 responses in APCs. Proteolytic processing of TLR9–GFP varied in different APCs: 1) the process was faster in B cells and almost all of the molecule resided in the endolysosomes when compared with bone marrow-derived macrophages, 2) cathepsins L and S were required for processing in macrophages, and 3) cathepsin L was necessary to cleave TLR9–GFP in B cells. In addition, TLR9 cleavage and trafficking was dependent on UNC93B1, an ER membrane-resident protein. APCs from mice deficient in UNC93B1 could not cleave TLR9–GFP, and UNC93B1 expression was correlated with correct TLR9–GFP processing. The data show that TLR9 must be cleaved for presentation and function. However, differences in trafficking between APCs indicate why TLR9-dependent responses may vary among cell types.

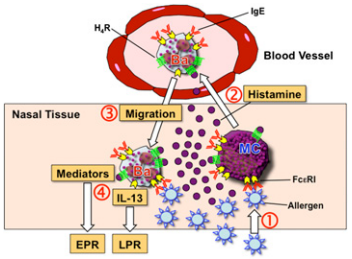
Macrophage Signal System

During innate immune responses, macrophages must be able to downregulate excessive inflammation and regulate the immune environment through production of cytokines such as IL-10. Although it has been known that PGE_2 and LPS have a synergistic effect on macrophage IL-10 production, the signaling pathway involved has yet to be completely elucidated. MacKenzie et al. (p. 565) demonstrated that PGE_2 and LPS act on macrophages to produce IL-10 and upregulate LIGHT (TNF superfamily 14), arginase 1 (arg1), and sphingosine kinase 1 (SPHK1) through the protein kinase A (PKA) pathway by using inhibitors and IL-10 knockouts. In contrast, induction of Arg1 was dependent on the PKA pathway but independent of IL-10. PGE_2 and TLR agonists caused the phosphorylation of Ser133 of CREB and the authors determined that mutating Ser133 to an alanine did not block PGE_2-driven IL-10 transcription. PGE_2 caused PKA to regulate the phosphorylation of the Ser343 residue of salt-inducible kinase 2 (SIK2), which inhibited the phosphorylation of CREB-regulated transcription coactivator 3 (CRTC3) and led to induction of IL-10 transcription. In addition, the inhibition of SIKs had the same effect as PGE_2 on IL-10 production, giving evidence that PGE_2 regulates macrophages and IL-10 production through a PKA–SIK–CRTC3 pathway.

Broad Interference

Antiviral responses in *Drosophila melanogaster* are not well understood. Previous research has suggested the involvement of the small-interfering RNA (siRNA) pathway and inducible expression of effector molecules. Kemp et al. (p. 650) clarified their roles by testing antiviral responses in both wild-type (WT) and mutant flies with deficiencies in either Dicer-2 (Dcr-2), an enzyme required for siRNA generation, or the JAK kinase Hopscotch (Hop), a component of the JAK–STAT pathway that contributes to inducible gene expression. Flies were infected with one of seven RNA or DNA viruses that were representative of different virus families. *Dcr-2*$^{-/-}$ flies were more susceptible to infection with different RNA viruses relative to WT flies, and were also more susceptible to infection with a DNA virus. In contrast, flies with loss-of-function mutations in Hop only showed increased susceptibility to viruses from the *Dicistroviridae* family relative to WT flies. Microarray analysis showed virus-specific gene expression patterns in response to infection with a DNA virus or two different RNA viruses. These data show that siRNA-mediated RNA interference is a broadly effective antiviral mechanism, whereas inducible gene expression via JAK–STAT signaling provides more limited antiviral protection.

Development of Allergic Rhinitis



Allergic rhinitis (AR) may not be fatal, but causes misery for millions and is a substantial socioeconomic burden. Shiraishi et al. (p. 539) completed a detailed study into how two cell types, mast cells and basophils, and the associated high-affinity IgE receptor (FcεRI) and histamine H4 receptor (H_4R) contribute to early (EPR) and late phase nasal response (LPR) AR. The authors used a combination of FcεRI and H_4R knockout mice and adoptive transfer to determine that AR responses developed by sequential receptor engagement on mast cells and then basophils. H_4R was required for development of both EPR and LPR, as H_4R-deficient mice did not develop AR to allergen sensitization and challenge. Further experiments revealed that AR was triggered from OVA inoculation in response to mast cell FcεRI ligation followed by histamine release, which in turn caused migration of basophils expressing H_4R to the nasal cavity. The final step was cross-linking of the FcεRI on the traveling basophils, which promoted release of mediators responsible for EPR and LPR-inducing IL-13. The authors have developed a comprehensive explanation for the sequence of events required for AR.

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