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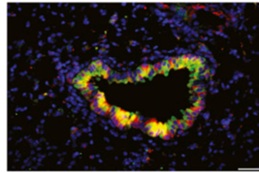
In This Issue

The Journal of Immunology

Bad CARMA in Allergic Asthma

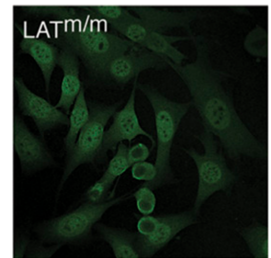


Airway epithelial cell (AEC) production of proinflammatory cytokines in response to stimulation with innate pattern recognition receptor ligands is integral to the initiation of adaptive immune responses in allergic asthma. Recent work has shown that AECs, when stimulated with the G protein–coupled receptor (GPCR) ligand lysophosphatidic acid, express a high level of caspase recruitment domain–containing membrane-associated guanylate kinase protein-3 (CARMA3), a protein involved in the activation of the transcription factor NF-κB (a critical player in allergic immune responses). To determine if CARMA3 influences the function of AECs during allergic airway inflammation, Causton et al. (p. 683) used GPCR ligands or allergens known to induce allergic airway responses to stimulate an AEC cell line that had been transduced with a lentiviral vector carrying CARMA3 short hairpin RNA. They found that knockdown of CARMA3 resulted in reduced production of AEC cytokines involved in the initiation of allergic adaptive immune responses, including thymic stromal lymphopoietin (TSLP), GM-CSF, IL-8, and CCL20/MIP-3α. In an allergic asthma model, mice specifically lacking CARMA3 in AECs exhibited attenuated airway inflammation and decreased production of Th2 cytokines in the lung tissue. The bronchoalveolar lavage fluid of these mice displayed reduced total cellularity and eosinophil numbers as well as reduced protein levels of GM-CSF, CCL20/MIP-3α, and TSLP. The authors also found evidence to suggest that dendritic cells, which are critical to the initiation of allergic asthma responses, had impaired maturation, Ag processing, and recruitment to the lungs in mice lacking AEC-specific CARMA3 expression. Together, these data implicate CARMA3 as a contributing factor to the ability of AECs to act as a bridge between innate and adaptive immunity in the development of allergic immune responses.

Purinergic Protection

Extracellular ATP (eATP) is produced following cell damage, such as that which occurs in ischemia/reperfusion (I/R) injury, and activates purinergic receptors (P2R). Dendritic cells (DC) express P2R, can be activated by eATP, and are implicated in I/R injury. In this issue, Chadet et al. (p. 651) sought to provide a mechanistic connection between these observations in human monocyte-derived DC. Use of a variety of P2R inhibitors revealed a role for P2Y11R in eATP-induced DC maturation. eATP also acted through P2Y11R to inhibit IL-12 production by DC that were activated by either LPS or a mixture of proinflammatory cytokines. These eATP-treated DC also strongly promoted Th2 polarization when cocultured with CD4^{+} T cells. When DC were subjected to 1 h or 5 h of hypoxia followed by reoxygenation, their maturation in response to eATP was reduced, with a greater effect on cells that had undergone 5 h versus 1 h of hypoxia. After 5 h of hypoxia, the eATP-induced reduction in IL-12 production was also eliminated; both of these results suggested that hypoxia impaired P2Y11R function. Indeed, P2Y11R expression in DC was downregulated following hypoxia, and expression could be restored via small interfering RNA–mediated knockdown of hypoxia-inducible factor-1α. Taken together, these data suggest that P2Y11R on DC acts to suppress inflammatory responses, and that prevention of its downregulation during episodes of I/R could help mitigate damaging inflammation associated with myocardial infarction and stroke.

T Cell IL-6 Drives Autoimmunity



The adaptor molecule linker for activation of T cells (LAT) plays important roles in T cell activation, proliferation, survival, and cytokine production following TCR stimulation. A point mutation in LAT, Y136F, eliminates the interaction between LAT and phospholipase C (PLC)γ1 and results in spontaneous T cell hyperproliferation and autoimmunity in LAT$^{m/m}$ mice bearing this mutation. To better understand how the LAT–PLCγ1 interaction modulates T cell activity, O'Brien et al. (p. 695) examined CD4^{+} T cells in LAT$^{m/m}$ mice. As previously demonstrated, IL-4 and other Th2 cytokines were upregulated in the CD4^{+} T cells of LAT$^{m/m}$ mice; in addition, IL-6 was strongly upregulated in these cells through a mechanism involving activation of p38, AKT, and NF-κB, but not MyD88. Interestingly, the CD4^{+} T cell hyperproliferation observed in LAT$^{m/m}$ mice was eliminated in IL-6$^{-/-}$LAT$^{m/m}$ mice, although the activated phenotype and Th2 skewing of LAT$^{m/m}$ CD4^{+} T cells were retained. The effect of IL-6 deficiency on CD4^{+} T cell numbers was not related to a change in thymocyte development, a defect in T cell proliferation, or restoration of the regulatory T cells that are missing in LAT$^{m/m}$ mice. Instead, CD4^{+} T cells from IL-6$^{-/-}$LAT$^{m/m}$ mice demonstrated reduced survival relative to those derived from LAT$^{m/m}$ mice, and IL-6 appeared to act indirectly to modulate T cell survival. In aged IL-6$^{-/-}$LAT$^{m/m}$ mice, CD4^{+} T cell hyperproliferation was restored, suggesting the existence of a compensatory mechanism; however, B cell class switching and autoantibody production were reduced relative to aged LAT$^{m/m}$ mice. The LAT–PLCγ1 interaction thus controls IL-6 production in CD4^{+} T cells, which is a key driver of the autoimmune syndrome that develops when this interaction is disrupted.

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