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Related Content

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Abatacept Targets T Follicular Helper and Regulatory T Cells, Disrupting Molecular Pathways That Regulate Their Proliferation and Maintenance

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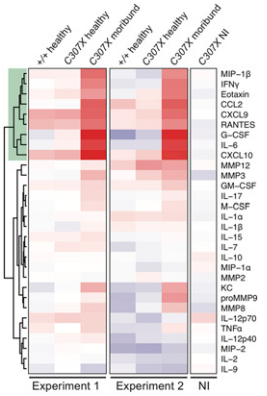
A *Rel*-evant Mutation

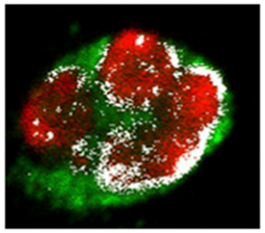


Herpes simplex virus type 1 (HSV-1) can cause acute encephalitis, and human genetic studies have suggested that mutations in TLR3/type I IFN–associated genes can predispose individuals to this complication. Here, Mancini et al. (p. 1479) use *N*-ethyl-*N*-nitrosourea (ENU) to carry out a forward mutagenesis screen in male mice for genes that promote resistance to herpes simplex encephalitis (HSE). They identified a mutation in the reticuloendotheliosis oncogene (*Rel*), Rel^{C307X} that caused increased susceptibility to HSE in homozygous mice. Lymphocytes, particularly $CD4^+$ $CD25^+Foxp3^+$ T regulatory cells, NK cells, and $CD4^+$ effector T cells, and CNS-resident cells contributed to HSE in Rel^{C307X} mice. This mutation was associated with poor control of viral replication, significant neuroinflammation, and increased cell death in CNS. Together, these results reveal a role for c-Rel in both lymphocytes and CNS-resident cells in protecting HSV-1–infected mice from HSE susceptibility.

LRP1 Regulates Macrophage TNF Release

A disintegrin and metalloproteinase 17 (ADAM17) is essential for regulating inflammation by releasing TNF from its precursor. Previous work demonstrated that the endogenous inhibitor of ADAM17, activity tissue inhibitor of metalloproteinases 3 (TIMP-3), was regulated posttranslationally by endocytosis via the scavenger receptor low-density lipoprotein receptor-related protein 1 (LRP1). In this issue, Schubert et al. (p. 1501) investigated whether LRP1 has an impact on the duration of ADAM17 activity and TNF release in human macrophages. Pharmacological blockade of LRP1 increased surface levels of TIMP-3 and inhibited ADAM17-mediated release of TNF in endotoxin-activated human macrophages. Following LPS stimulation, TIMP-3 levels on the surface of macrophages increased for 6 h before returning to baseline at 8 h. These observations were independent of changes in TIMP-3 mRNA levels, but correlated with shedding of LRP1 from the surface of LPS-stimulated macrophages. Finally, the authors showed that regulation of TIMP-3 by LRP1 was specific to myeloid cells, and not lymphoid lineages. Together, these results demonstrate that the endocytic receptor LRP1 contributes to resolution of inflammation by regulating TIMP-3 on the surface of activated macrophages, thereby modulating TNF release.

PAT1 as a Regulator of NADPH Oxidase



Production of reactive oxygen species (ROS) is an essential component of host defense against microbial pathogens. NADPH, the enzyme responsible for ROS production, is a multicomponent enzyme comprising several units, including p22phox. In this issue, Arabi-Derkawi et al. (p. 1549) sought to identify new proteins interacting with the cytosolic p22phox region by performing a yeast two-hybrid screen of a human spleen cDNA library using the cytosolic C-terminal region of p22phox as bait. The screen and confirmatory studies identified amyloid precursor protein tail 1 (PAT1), a kinesin L chain–related protein, as a binding partner of p22phox. PAT1 was found to be expressed by human neutrophils and monocytes and colocalized with p22phox within these cells. Additionally, overexpression of PAT1 in human monocytes and COS cells transfected with NADPH components increased superoxide anion production. Conversely, depletion of PAT1 via small interfering RNA in human monocytes resulted in inhibition of total superoxide anion production, but not the initial rate of superoxide production. Together, these results identify PAT1 as a new binding partner for p22phox and suggest that PAT1, rather than being involved in the initiation of NADPH oxidase activation, is required to sustain NADPH oxidase activation in human monocytes.

A Better View of Abatacept

Abatacept, a fusion protein composed of the CTLA4 extracellular domain and IgG Fc domain, blocks CD28-mediated costimulation and T cell activation. Abatacept has had some therapeutic success in treating autoimmune diseases, including rheumatoid arthritis, but has not been effective in treating other immunologic diseases such as relapsing-remitting multiple sclerosis (RRMS). To better understand this discrepancy, Glatigny et al. (p. 1373) studied T cell subsets in longitudinal samples from the Immune Tolerance Network ACCLAIM trial using abatacept to treat RRMS. Abatacept administration was associated with lower frequencies of T follicular helper (Tfh) cells and plasmablasts in the periphery, as well as fewer activated Tfh and regulatory T cells. Transcriptional analysis revealed that abatacept treatment led to decreased expression of genes associated with cell proliferation, but these changes were reversible upon withdrawal of the drug. Taken together, these data provide mechanistic insight into abatacept's function in patients with multiple sclerosis or other diseases with abnormal Tfh responses.