IN BRIEF

IMMUNOGENETICS

Narcolepsy is strongly associated with the T-cell receptor alpha locus

Hallmayer, J. *et al. Nature Genet.* 3 May 2009 (doi:10.1038/ng.372)

Narcolepsy is a rare neurological disorder characterized by extreme daytime sleepiness and sudden muscle weakness. A genetic association between the MHC class II allele HLA-DQB*0602 and narcolepsy is well known. Now this study identifies a strong association with the T cell receptor-α (*TCRA*) locus, providing further support for a pathogenic role for autoimmune T cells in this disorder. The authors initially carried out genome-wide association studies in 807 cases and 1,074 controls of mixed European ancestry and identified three single nucleotide polymorphisms in the *TCRA* locus on chromosome 14. The findings were then replicated across three ethnic groups — Caucasians, Asians and African Americans — confirming that the highest association mapped to the TCRα joining segment. This is the first reported genetic involvement of the *TCRA* locus in any disease and should prove to be useful for understanding HLA–TCR interactions in other HLA-associated autoimmune diseases.

PARASITE IMMUNITY

IP-10-mediated T cell homing promotes cerebral inflammation over splenic immunity to malaria infection

Nie, C. Q. *et al. PLoS Pathog.* **5**, e1000369 (2009)

Cerebral malaria caused by infection with the parasite *Plasmodium falciparum* is responsible for 2.5 million deaths each year. Although the immune system is crucial for the control of parasitaemia, it also contributes to the detrimental brain inflammation that occurs in this neurological syndrome. This study shows that neutralization or genetic deletion of CXC-chemokine ligand 10 (CXCL10; also known as IP-10) reduces cerebral intravascular inflammation and protects mice infected with *Plasmodium berghei* ANKA (a mouse model of cerebral malaria) from dying. Blockade of CXCL10 was also associated with increased splenic antiparasite immune responses, owing to increased retention of parasite-specific T cells in the spleen, and this contributed to reduced peripheral parasitaemia. So, blockade of CXCL10-mediated trafficking to the brain seems to be crucial for reaching a balance between protective immunity and immunopathogenesis.

NEUROIMMUNOLOGY

Caveolae-mediated internalization of occludin and claudin-5 during CCL2-induced tight junction remodeling in brain endothelial cells

Stamatovic, S. M. *et al. J. Biol. Chem.* 7 May 2009 (doi:10.1074/jbc.M109.000521)

Pro-inflammatory mediators such as CC-chemokine ligand 2 (CCL2) are known to disrupt the tight junctions between brain endothelial cells, increasing paracellular permeability and allowing leukocyte entry into the brain. However, the molecular mechanisms behind this disruption are not fully known. Stamatovic ***et al.*** now show that the tight junction proteins occludin and claudin 5 expressed by brain endothelial cells are internalized following exposure to CCL2 through a caveolae-mediated pathway, resulting in alterations in blood–brain barrier permeability. The proteins are 'stored' in endosomes and are recycled to the cell surface; blocking recycling prevented the recovery of blood–brain barrier integrity. So, this study provides a molecular mechanism for blood–brain barrier disruption during brain inflammation.