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In this issue

Fatty acids — good for the brain, good for Alzheimer disease A number of studies suggest a protective action of the omega-3 fatty acid docosahexaenoic acid (DHA) in cognitive decline and in Alzheimer disease (AD); however, the molecular mechanism has not been understood. Now, Lukiw et al. identify a specific mechanism by which DHA is neuroprotective in AD (pages 2774–2783). The authors report that DHA can decrease levels of pathogenic amyloid-β, which are associated with AD pathology in human brain cells. Meanwhile, the synthesis of neuroprotectin D1 (NPD1), an endogenous DHA-derived messenger, is upregulated. NPD1 inhibits apoptosis triggered by amyloid-β peptides. In a human AD donor brain, the authors show that DHA and NPD1 are reduced in vulnerable brain regions. These data raise the possibility that NPD1 is a key regulator of cell survival and might be manipulated for the development of novel therapeutic strategies against neurodegenerative diseases.A balancing act to generate immunity or tolerance Human dendritic cells (DCs) express activating and inhibitory isoforms of a low-affinity IgG Fc γ receptor, called CD32a and CD32b, respectively. These 2 receptor isoforms work together to establish a threshold of DC activation and allow immune complexes to mediate opposing effects on DC maturation and function. Clinical reports show that polymorphisms of the CD32a isoform influence the response to monoclonal antibody therapies used to […]

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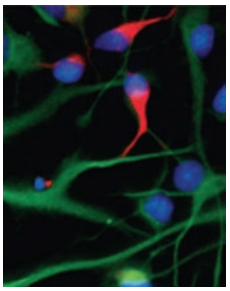

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A balancing act to generate immunity or tolerance

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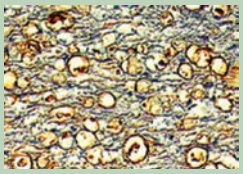
A cytokine not kind to an injury of the spine



Transverse myelitis (TM) is an autoimmune inflammatory disease of the central nervous system that is characterized by focal spinal cord demyelination and axonal injury. TM causes paralysis and other neurological disabilities, but treatment options are limited due to a lack of understanding of its underlying mechanisms. In this issue of the *JCI*, Kaplin et al. report on their finding that levels of the cytokine IL-6 are selectively increased in cerebrospinal fluid from TM patients (pages 2731–2741). The researchers show that elevated IL-6 levels are necessary and sufficient to mediate injury to both neuronal and glial cells in a manner that is dependent on nitric oxide. This is the first description of IL-6 as a mediator of neural injury. Further, high levels of IL-6 were directly correlated with tissue injury and clinical disability, suggesting that IL-6 may be an important biomarker of TM. This new data may aid in the development of effective therapies against TM and other inflammatory diseases of the central nervous system.

Skeletal disorders are in the genes

The spondyloepimetaphyseal dysplasias (SEMDs) are a group of skeletal disorders characterized by defective growth of the spine and long bones of the body. SEMDs can occur sporadically, but heritable forms of the disease with X-linked transmission have been reported. In this issue, Kennedy et al. show that a missense mutation causes a form of SEMD known as the Missouri type, characterized by features including pear-shaped vertebrae, shortened lower limbs, and bowlegs (pages 2832–2842). The authors pinpoint the chromosomal localization of the disease locus by a genome-wide search and analyze the candidate gene, *MMP13*. A mutation in the proregion domain of *MMP13*, an enzyme known to degrade components of the extracellular matrix and play a role in embryonic bone formation, leads to misfolding and intracellular degradation of the mutant enzyme such that only small, proteolytically inactive fragments of MMP13 were released. Functional studies in which wild-type and mutant MMP13 were expressed show that the loss of proper metalloprotease function is responsible for causing Missouri type SEMD. This disease is the first to be associated with an MMP13 mutation, and this research suggests that other skeletal dysplasias may also involve altered MMP function.