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In This Issue

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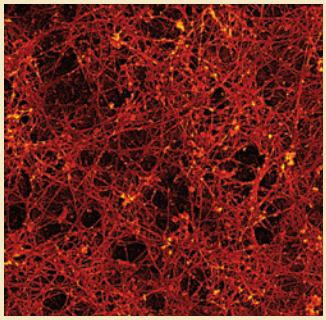
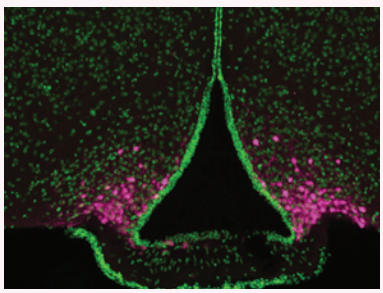
Heavy metal does mitochondrial damage in Wilson disease Wilson disease (WD) is a rare, fatal genetic disorder in which mutations in a copper transporter gene result in massive copper overload in the liver. It is not clear how the accumulation of copper in hepatocytes leads to liver failure, but it has been previously reported that the mitochondria in hepatocytes from WD patients are structurally abnormal. Zischka and colleagues therefore investigated the effect of copper accumulation on mitochondria in a rat model of WD (1508–1518). They found that high copper levels induced structural changes in mitochondria that preceded liver failure and that oxidative damage — previously thought to be one of the primary determinants of WD — was undetectable before animals displayed disease symptoms. Copper overload resulted in crosslinking of mitochondrial membranes. Importantly, this effect was reversible when rats were treated early in disease progression with copper-chelating agents. The researchers believe that these studies more clearly define the molecular pathology of WD. IL-2 could help overcome WASp defects Wiskott-Aldrich syndrome (WAS) is an immunodeficiency syndrome marked by susceptibility to infection, bleeding, and dermatitis. The causative gene encodes for WAS protein (WASp), which is expressed in hematopoietic cells and is known to be involved in controlling actin dynamics. WAS patients are susceptible to blood cancers and to infection with herpesviruses; both of […]

IL-2 could help overcome WASp defects



Wiskott-Aldrich syndrome (WAS) is an immunodeficiency syndrome marked by susceptibility to infection, bleeding, and dermatitis. The causative gene encodes for WAS protein (WASp), which is expressed in hematopoietic cells and is known to be involved in controlling actin dynamics. WAS patients are susceptible to blood cancers and to infection with herpesviruses; both of these features suggest that the NK cells of the immune system may be dysfunctional in this disease. However, it has previously been shown that when NK cells are isolated from WAS patients and put into culture, they regain their cytotoxicity. New insight into this phenomenon has now been provided by Orange, Roy-Ghanta, Pandey, and colleagues, who describe that a cytokine in the culture medium — IL-2 — is responsible for restoring the cytotoxicity of NK cells from WAS patients (1535–1548). They found that IL-2 induces the expression of a protein related to WASp called WAVE2, which can function in the absence of WASp to control cytoskeletal changes. In addition, the researchers found that administration of IL-2 improved NK cell function in a WAS patient, suggesting that this molecule might be a viable therapeutic for this disease.

Identifying the neurons that could make you DREADD your next meal



In the face of the growing obesity epidemic, much research has focused on the neuronal control of feeding behavior. Agouti-related protein (AgRP) neurons express three proteins that have been implicated in changes in energy balance, but the studies linking AgRP neurons to feeding behavior have produced mixed results. To directly analyze the role of AgRP neurons, Krashes, Koda, and colleagues used DREADD (designer receptors exclusively activated by designer drugs) technology to specifically control the activation and deactivation of these neurons in mice (1424–1428). They found that stimulation of AgRP neurons increased food intake and induced rapid weight gain. Similarly, inhibition of this neuronal population inhibited food intake. Furthermore, stimulation of AgRP neurons induced an intense, unrelenting food-seeking behavior. The researchers believe that this study demonstrates that AgRP neurons are critical regulators of a behavioral program that drives individuals to find and consume food.

Tuberculosis bacteria uses membrane vesicles to modulate immune responses

The World Health Organization estimates that one-third of the world population is infected with the bacteria that cause TB, *Mycobacterium tuberculosis*, though only a small percentage of those actually become ill. The immune response to *M. tuberculosis* in the host is mediated by signaling through TLRs; the bacteria secrete lipoproteins and glycolipids that bind to the TLRs, activating immune cells to kill the invading bacteria. However, activation of TLR2 within macrophages has also been implicated in allowing *M. tuberculosis* to inhibit the innate immune response. In addition, how these bacteria release the TLR ligands is unknown. Some pathogenic bacteria deliver ligands to host cells using membrane vesicles (MVs), which can also contain toxins and other molecules important for pathogenesis. In this issue of the *JCI*, Prados-Rosales, Baena, and colleagues found that *M. tuberculosis* and other related mycobacterium species also release MVs (1471–1483). Analysis of the proteins within these vesicles revealed that only the MVs from virulent bacteria contain TLR2 agonists, and the researchers found that MVs triggered immune responses in mice in a TLR2-dependent manner. The researchers hope that their findings may reveal new pathways to target in the development of tuberculosis therapeutics and vaccines.

Heavy metal does mitochondrial damage in Wilson disease

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