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In This Issue

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New genetic cause of a fatal immune disorder Familial hemophagocytic lymphohistiocytosis (FHL) is a fatal, autosomal recessive immune disorder characterized by uncontrolled activation of lymphocytes and macrophages infiltrating multiple organs. Disease-causing mutations have been identified in several genes encoding proteins involved in lymphocyte cytotoxicity, including syntaxin-11, which regulates membrane fusion. Now, Côte and colleagues have identified two distinct mutations in the gene encoding syntaxin-binding protein 2 (Munc18-2, also known as STXBP2) as causing disease in a subset of patients with FHL and have termed this form of the disease “FHL5” (3765–3773). The two distinct STXBP2 mutations led to substantially decreased STXBP2 protein in patient lymphoblasts and impaired cytotoxic granule exocytosis in patient NK cells. Further analysis indicated that the predominant protein to which STXBP2 binds in lymphocytes is syntaxin-11. The authors therefore conclude that STXBP2 binds syntaxin-11, thereby controlling a late step of the secretory pathway for the release of cytotoxic granules; in patients with FHL5, the STXBP2 protein deficiency means this process cannot occur efficiently. Disrupting male fertility via an orphan nuclear receptor The sexual function of male rodents can be impaired by in utero and/or neonatal exposure to molecules that disrupt endocrine homeostasis, such as the synthetic nonsteroidal estrogen diethylstilbestrol (DES), which was used as a treatment for various indications until the mid-1990s. In this issue ([…]

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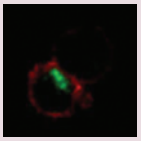
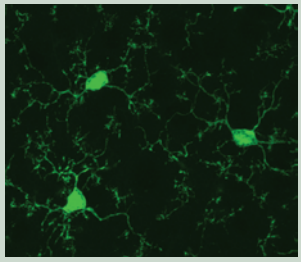


Familial hemophagocytic lymphohistiocytosis (FHL) is a fatal, autosomal recessive immune disorder characterized by uncontrolled activation of lymphocytes and macrophages infiltrating multiple organs. Disease-causing mutations have been identified in several genes encoding proteins involved in lymphocyte cytotoxicity, including syntaxin-11, which regulates membrane fusion. Now, Côte and colleagues have identified two distinct mutations in the gene encoding syntaxin-binding protein 2 (Munc18-2, also known as STXBP2) as causing disease in a subset of patients with FHL and have termed this form of the disease "FHL5" (3765–3773). The two distinct *STXBP2* mutations led to substantially decreased STXBP2 protein in patient lymphoblasts and impaired cytotoxic granule exocytosis in patient NK cells. Further analysis indicated that the predominant protein to which STXBP2 binds in lymphocytes is syntaxin-11. The authors therefore conclude that STXBP2 binds syntaxin-11, thereby controlling a late step of the secretory pathway for the release of cytotoxic granules; in patients with FHL5, the STXBP2 protein deficiency means this process cannot occur efficiently.

NSAIDs prevent early sign of Alzheimer disease



Emerging data indicate the induction of neuronal cell cycle events (CCEs) occurs early in the process of neurodegeneration in Alzheimer disease (AD). The properties of the AD brain that initiate neuronal CCEs, however, had not been clearly defined before now. In this issue (3692–3702), Varvel and colleagues report two lines of experimental evidence implicating neuroinflammation as a key factor in the initiation process, using the R1.40 mouse model of AD as their test system. First, administration of LPS, which elicits systemic inflammation, to R1.40 mice at an age before neuronal CCEs normally appear advanced the age of CCE appearance by nearly four months. Second, treatment of R1.40 mice with either of the NSAIDs ibuprofen or naproxen blocked both neuroinflammation and the induction of neuronal CCEs at their normal time. Importantly, although treatment of older R1.40 mice with an NSAID blocked the induction of new neuronal CCEs, existing CCEs persisted. These data provide a potential explanation for observations in humans: retrospective studies indicate long-term NSAID use is protective against AD, whereas prospective NSAID clinical trials have been unsuccessful in patients with mild to moderate AD. The authors therefore suggest that early NSAID treatment will be necessary if these drugs are to be useful in AD therapy.

MicroRNA mutation linked to osteoporosis

MicroRNAs (miRNAs), small, single-stranded, noncoding RNAs that negatively regulate the translation of specific mRNAs, play a key role in controlling many cellular processes. As their precise role in bone metabolism had not been determined previously, Li and colleagues used a small RNA cloning method to identify miRNAs in primary mouse osteoblasts (3666–3677). In addition to identifying many known miRNAs, the authors determined one to be new, and it has been named miR-2861; it was also found to be conserved in humans. In vitro analysis using a mouse stromal cell line indicated that miR-2861 promoted osteoblastogenesis and that it directly repressed expression of histone deacetylase 5 (HDAC5). In mice, in vivo silencing of miR-2861 inhibited bone formation and decreased bone mass. Of clinical importance, analysis of ten patients with primary osteoporosis revealed two related adolescents in whom disease was caused by a homozygous mutation in pre–miR-2861 that blocked expression of miR-2861. Consistent with the mouse data, bone samples from the two affected individuals exhibited increased HDAC5 levels. The authors therefore conclude that miR-2861 has an important role in controlling osteoblast differentiation and that defects in its processing can cause osteoporosis.

Disrupting male fertility via an orphan nuclear receptor

The sexual function of male rodents can be impaired by in utero and/or neonatal exposure to molecules that disrupt endocrine homeostasis, such as the synthetic nonsteroidal estrogen diethylstilbestrol (DES), which was used as a treatment for various indications until the mid-1990s. In this issue (3752–3764), Volle and colleagues report that some of the harmful effects of DES on the mouse testis are mediated through the orphan nuclear receptor small heterodimer partner (Nr0b2), a known target gene and transcriptional repressor of estrogen receptors. The pivotal studies demonstrated that neonatal exposure to DES led to a much more dramatic reduction in fertility in Nr0b2-sufficient male mice than it did in Nr0b2-deficient male mice because Nr0b2 deficiency protected male mice against the negative effects of DES on testis development and function. Nr0b2 deficiency also protected male mice from the detrimental effects of postnatal and adult exposure to DES. Mechanistically, Nr0b2 mediated the effects of DES in neonates by dysregulating specific estrogen-dependent and -independent pathways. In contrast, the effects of DES in adults were mediated by Nr0b2 inhibiting testicular testosterone production. Future work will determine whether similar pathways link human exposure to endocrine disruptors to the increased incidence of male reproductive disorders.