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In This Issue

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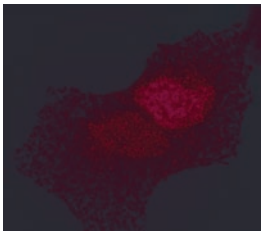
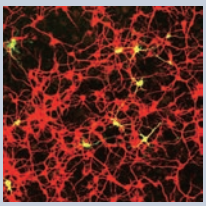


Although the tumor suppressor p53 is a potent inducer of tumor cell death, the development of p53-targeted approaches for the treatment of cancer is confounded by the fact that genetic mutations cause loss or inactivation of p53 in approximately 50% of human cancers. As the p53-related protein p73, which can also induce tumor cell death, is rarely mutated in human cancers, Bell and colleagues hypothesized that it might represent a more viable target than p53 for the development of broadly applicable anticancer therapeutics (pages 1008–1018). They generated a peptide of 37 amino acids in length from human p53 (termed 37AA) that induced both p53-sufficient and p53-deficient human tumor cell lines, but not primary untransformed human cells, to undergo apoptosis. 37AA mediated tumor cell death by binding to the negative regulator of p53 family proteins iASPP and preventing it from repressing the death-inducing function of p73. Systemic administration of 37AA to mice with established tumors of human origin (both p53-sufficient and p53-deficient tumors) induced p73-dependent tumor regression, leading the authors to suggest that targeting the p73-mediated pathway of tumor cell death might provide a new avenue of research for the development of anticancer therapeutics.

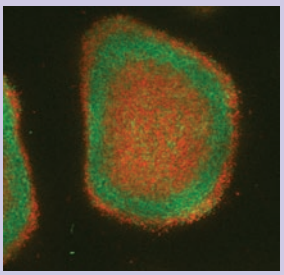
CADPS2 implicated in autism



There is a substantial body of evidence to suggest that whether or not an individual develops autism, a common neurodevelopmental disorder characterized by severely impaired social, communicative, and behavioral functions, is determined largely by genetic makeup. One of the susceptibility loci identified is found on chromosome 7, but none of the genes in this locus have been directly implicated in the disorder. In this issue (pages 931–943), Sadakata and colleagues assessed the function of one of the genes in this autism susceptibility locus, *CADPS2*, by generating mice lacking CADPS2. CADPS2-deficient mice showed impaired social interactions (when pairs of CADPS2-deficient mice that had never met were placed together, they interacted substantially less frequently than did pairs of wild-type mice that had never met), hyperactivity, decreased exploration of a new environment, and an abnormal circadian rhythm, all of which are characteristics of individuals with autism. The brains of CADPS2-deficient mice also showed cellular abnormalities and impaired release of neurotrophin. Importantly, an aberrant alternatively spliced form of *CADPS2* mRNA was detected in some individuals with autism and was never detected in their healthy immediate relatives. When expressed in primary neuronal cultures generated from the CADPS2-deficient mice, this CADPS2 variant showed improper subcellular localization. These data led the authors to suggest that defects in CADPS2 function might predispose individuals to develop autism.

Gallium: a new antibacterial agent?

New antibacterial strategies are needed because an increasing proportion of bacterial infections are caused by antibiotic-resistant bacteria and because antibiotics are not effective at eradicating chronic bacterial infections. The approach taken by Kaneko and colleagues was to combat bacteria by imposing on them an environment in which they cannot survive, an environment in which their access to Fe, which is critical for growth, is limited (pages 877–888). The presence of Ga, which is chemically similar to Fe, in culture medium inhibited the growth of *Pseudomonas aeruginosa*, even multidrug-resistant strains of *P. aeruginosa* isolated from individuals with cystic fibrosis. Ga also prevented *P. aeruginosa* from forming biofilms, the multicellular bacterial communities responsible for chronic bacterial infections, and killed both free-living bacteria and bacteria in biofilms. Furthermore, inhalation of Ga protected mice from both acute and chronic *P. aeruginosa* lung infections. As Ga is already FDA approved for the treatment of hypercalcemia of malignancy, these data suggest that Ga might be a promising new therapeutic for the treatment of infection with *P. aeruginosa*.



Deleterious effects of prenatal exposure to glucocorticoids

Although studies in rodents and other nonprimates indicate that prenatal exposure to glucocorticoids (through either administration of dexamethasone or severe maternal stress) have long-lasting deleterious effects on cardiovascular, metabolic, and neuroendocrine function, glucocorticoids are still widely used in obstetric practice. In an attempt to determine the relevance of the rodent and nonprimate data to human pregnancy, de Vries and colleagues studied pregnant nonhuman primate African vervet monkeys (*Chlorocebus aethiops*) treated with different doses of dexamethasone from midgestation onward (pages 1058–1067). The birth weight of offspring born to dexamethasone-treated mothers did not differ from that of offspring born to untreated mothers. However, high levels of prenatal dexamethasone impaired postnatal growth, impaired glucose-insulin homeostasis, increased blood pressure 12 months after birth, and increased cortisol production in response to mild stress. These data are consistent with earlier results in rodents and nonprimates and suggest that both repeated glucocorticoid therapy and severe maternal stress late in gestation are likely to have long-term deleterious effects on developing human fetuses.