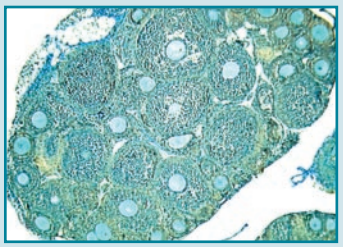
Pregnant women pass on the effects of smoking

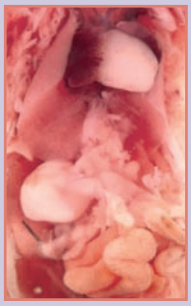
Smoking during pregnancy has many adverse effects on fetal development. In this issue (pages 3971–3978), the work of Jurisicova and colleagues suggests that smoking before pregnancy or while breastfeeding might substantially decrease the fertility of female offspring. Female mice exposed subcutaneously to polycyclic aromatic hydrocarbons (PAHs), environmental toxins found in cigarette smoke, prepregnancy or while lactating were found to have normal-sized litters. However, their female offspring had markedly reduced numbers of resting (primordial) and early growing (primary) follicles. Further analysis indicated that the effects of PAHs on the number of follicles in female offspring were mediated through the aryl hydrocarbon receptor (Ahr), which upregulated transcription of the gene encoding the proapoptotic molecule Harakiri. The potential importance of these findings for women of child-bearing age was demonstrated by the observation that PAHs triggered similar molecular pathways in human ovarian tissue transplanted into immunocompromised mice.



Recombinant adeno-associated virus vectors gag T cell responses

Clinical trials to test the utility of recombinant adeno-associated virus (rAAV) vectors engineered to encode HIV-1 proteins as HIV-1 vaccines have yielded disappointing results, despite promising preclinical studies. Lin and colleagues therefore set out to analyze the HIV-1–specific immune response induced in mice by immunization with rAAV vectors encoding the HIV-1 protein gag (pages 3958–3970). Although mice immunized with gag-encoding rAAV vectors based on various AAV serotypes mounted gag-specific $CD8^+$ T cell responses, these $CD8^+$ T cells did not proliferate when reexposed to gag — through immunizing the mice with different vector types carrying the same gag protein. Impaired proliferation in response to re-exposure to gag was a result of the gag-specific $CD8^+$ T cells being partially exhausted due to persistence of the gag-encoding rAAV vectors. In addition, the in vivo lytic function of gag-specific $CD8^+$ T cells induced by gag-encoding rAAV vectors was impaired when compared with the in vivo lytic function of gag-specific $CD8^+$ T cells induced by gag-encoding adenoviral vectors. Although further studies are needed to determine whether human T cells are similarly affected by priming with antigen-encoding rAAV vectors, these data indicate that the use of rAAV vectors encoding HIV-1 proteins as vaccines might actually dampen the immune response to natural infection with HIV-1 and speed up progression to AIDS.

Gene linked to body organ positioning



Primary ciliary diskinesia (PCD) can be caused by autosomal-recessive mutations in any one of a number of genes, including the gene encoding dynein, axonemal, heavy chain 5 (*DNAH5*). It is characterized by immotile or dysfunctional cilia, making individuals with PCD susceptible to chronic recurrent respiratory infections, and by situs inversus totalis, a condition distinguished by complete mirror-image reversal in the left-right positioning (situs) of organs of the body. Some individuals with PCD exhibit heterotaxy, a condition characterized by randomized left-right organ positioning. To determine whether genetic defects that lead to PCD are also responsible for heterotaxy, something that had not been previously established, Tan and colleagues analyzed a new strain of mice with a recessive mutation in *Dnahc5*, the mouse homolog of *DNAH5* (pages 3742–3752). A substantial proportion of fetuses homozygous for the *Dnahc5* mutation exhibited heterotaxy and, as observed in human heterotaxy syndromes, these embryos had variable combinations of complex structural heart defects. Further analysis confirmed that these mice are a robust model of PCD, indicating that a *Dnahc5* mutation causing PCD-like disease in mice also can cause heterotaxy. These data led the authors to suggest that individuals with PCD should be assessed for heterotaxy and associated congenital heart defects and, conversely, that patients with heterotaxy should be evaluated for undiagnosed PCD. Such combined diagnoses would dictate very different clinical strategies that may improve outcome.

CD200 stifles antitumor immunity

The prognosis for individuals with metastatic melanoma (MM) is not good. Therapeutic strategies to enhance the immune response have some clinical benefit; however, most patients eventually succumb to progressive disease, in part because their DCs fail to sustain an effective antitumor T cell response. In this issue (pages 3922–3929), Petermann and colleagues have identified one mechanism that represses DC function in MM. Expression of CD200 mRNA and protein was higher in human melanoma cell lines expressing high levels of phosphorylated ERK and in resected human melanomas than in normal human melanocytes, human melanoma cell lines expressing low levels of phosphorylated ERK, and other solid tumors. Consistent with this, expression of CD200 was regulated by the N-RAS/B-RAF/MEK/ERK/MAPK signaling pathway, which is aberrantly activated in approximately 80% of MMs. In vitro analysis indicated the potential functional significance of high levels of CD200 expression — it enabled melanoma cell lines to repress DC activation of antitumor T cell responses. The authors therefore suggested that targeting the interaction between CD200 and its receptor might provide a new strategy for the treatment of MM.