Research News

Triallelic inheritance

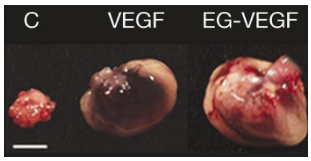
Bardet–Biedl syndrome (BBS) is a rare genetically heterogeneous disorder that displays a collection of phenotypes including pigmentary retinal dystrophy, obesity, polydactyly, renal dysplasia and learning disabilities, among others. Six gene loci have been implicated in the disorder (*BBS1* through *BBS6*), and two of these genes (*BBS2* and *BBS6*) have recently been cloned. In the 21 September issue of *Science*, Katsanis *et al*. describe their analysis of 163 BBS families with respect to mutations in *BBS2* and *BBS6*. They report that in BBS-afflicted individuals within four pedigrees, three mutant alleles of *BBS2* and *BBS6* appear to cosegregate. In two separate lineages, unaffected individuals bear mutations in both alleles of *BBS2*, but no mutations in *BBS6*, suggesting a triallelic model of inheritance of the disease. Familial segregation had previously informed the assumption that BBS is inherited in an autosomal recessive manner. These results appear to be the first documented requirement for three distinct alleles in the manifestation of a recessive mendelian disorder, and represent a key step in our understanding of the molecular mechanism of BBS.

FOXC fat regulator

Obesity, high serum lipids and insulin resistance are key factors in the development of Type 2 diabetes. In the September 7 issue of *Cell*, Enerbäck *et al*. demonstrate a key role for the winged helix/forkhead family transcription factor FOXC2 in these processes. *FOXC2* (previously known as *Mfh1* or *Fkhl14*) is normally expressed in a wide range of tissues, including fat. However, knock-out of *Foxc2* in mice is embryonically or perinatally lethal. Enerbäck and colleagues now show that specific overexpression of FOXC2 in adipose tissue increases the size of brown fat depots, while decreasing amounts of white fat. The transgenic mice are lean, with lower lipids, glucose and insulin in serum, and higher insulin sensitivity. Their white fat contains increased numbers of mitochondria and displays increased oxygen consumption. Wild-type mice have increased *Foxc2* expression on a high-fat diet, and experiments *in vitro* suggest that FOXC2 activity increases the sensitivity of protein kinase A signaling. As a possible 'anti-thrifty' gene that enables increased energy expenditure by altering metabolic efficiency, FOXC2 may therefore be a novel drug target for the treatment of obesity and diabetes.

Endocrine angiogenesis

Vascular endothelial growth factor (VEGF) is believed to be the most important of the pro-angiogenic factors. Although VEGF is produced by most organs, each organ places different demands on its vascular supply, and the endocrine glands in particular require leakier vessels to allow hormones produced by the testes and ovaries to reach the bloodstream. In the 30 August issue of *Nature*, LeCouter *et al*. identify an endocrine-specific angiogenic factor, endocrine-gland–derived VEGF (EG-VEGF). EG-VEGF functionally resembles and complements the actions of VEGF. EG-VEGF induces proliferation, migration and fenestration (formation of membrane discontinuities to make the vessel leaky) of endocrine endothelium, but has no effect on endothelia from other tissues. Whereas VEGF stimulates significant angiogenesis of ocular endothelial cells in a rat corneal pocket assay, EG-VEGF does not. However, both stimulate extensive angiogenesis and cyst formation when delivered via adenovirus to ovaries, as shown in the picture above. These findings provide insight into how organs develop specialized blood supplies and may have implications in fighting cancer and in tissue regeneration.

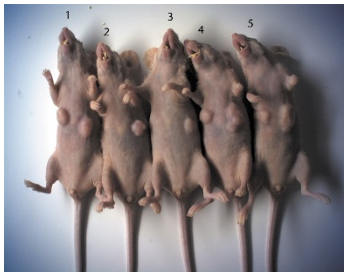


A live attenuated AIDS vaccine

Development of an HIV vaccine that elicits a potent and long-lasting cell-mediated immune response is of critical importance in controlling the AIDS epidemic. Live attenuated virus vaccines have proven efficacious in the virtual eradication of smallpox and poliovirus, and a similar route may prove successful in preventing HIV infection. In the 7 September issue of *Cell*, Rose *et al.* describe an attenuated vesicular stomatitis virus (VSV), modified to encode the genes for HIV envelope (*env*) and glycoprotein (*gag*), that confers sustained protection from HIV replication and disease progression in rhesus macaques. The authors report stable $CD4^+$ T-cell counts and HIV-specific cytotoxic T-cell responses against the Env and Gag epitopes following vaccination with the modified VSV and subsequent challenge with a pathogenic AIDS virus, SHIV89.6P. The vaccinated animals remain healthy 14 months after infection with SHIV89.6P, whereas most control monkeys display elevated viral loads coincident with low $CD4^+$ T-cell numbers and eventually develop AIDS. In these initial studies, the VSV recombinants appear safe, with no obvious vector-related side effects. VSV is eventually cleared from the host, but memory cells persist for at least six months. The authors are currently assessing whether intranasal administration is as effective as the combined intranasal and intramuscular approach described in this paper, as this would greatly facilitate the administration of the vaccine to a large population.

Hairpin help

The gene encoding tumor suppressor p53 is mutated in more than 50% of human cancers, and is believed to be a major determinant of tumor sensitivity to cytotoxic agents, and proliferative capacity. In the 30 August issue of *Nature*, Raj and colleagues specifically eradicate cancer cells using a single-stranded DNA virus called adeno-associated virus (AAV). AAV triggers a DNA damage response by virtue of its single-stranded hairpin loops. In cells expressing p53, uptake of AAV leads to the activation of a DNA damage checkpoint and cell-cycle arrest in the G2 phase, followed by recovery after a few days. In p53-deficient cells, this hairpin structure induces a transient G2 arrest followed by apoptosis and cell death. Importantly, this virus potently inhibits the growth of p53-deficient cancer cells *in vivo*. Injection of AAV into subcutaneous tumors in nude mice prevented both the development and progression of p53-deficient tumors. The picture below compares the growth progression of tumors in mice injected with AAV (right flank) or with phosphate-buffered saline (left flank). Mouse 1 is the untreated control. The inhibition of growth of p53-expressing tumors was not as effective, probably due to the eventual recovery from AAV-induced cell-cycle arrest. Thus, this virus provides a novel tool to selectively target and eliminate p53-deficient tumors, while preserving the integrity of normal cells.



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