Research News

Gangrene genes

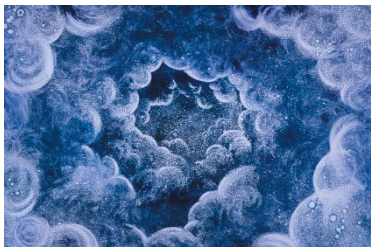
Genome analysis of the anaerobic bacteria that causes gangrene has revealed important clues about its activities during early stages of infection. *Clostridium perfringens* usually infects human tissue during traumatic injury or through surgical wounds. A long-time foe to wounded soldiers on the battlefield, the type A strain of *C. perfringens* causes gas gangrene (clostridial myonecrosis), leading to rapid tissue destruction, septicemia and death. It also causes necrotic enteritis and diarrhea. The completed genome sequence, reported by Shimizu *et al.* in the 22 January issue of *PNAS*, reveals several keys to the pathogenicity of the bacteria. *C. perfringens* lacks many enzymes for amino-acid biosynthesis, although it contains multiple genes encoding enzymes that are involved in importing amino acids and sugars. The bacteria is known to produce toxins during its early growth stage, making it likely that the pathogenicity of *C. perfringens* is linked to nutritional requirements—rapid and early tissue destruction provides essential growth media. Therapeutics designed to interfere with the mechanisms by which the bacteria fulfill their nutritional requirements may be a way to halt their growth during early stages of infection.

Betting on T-bet

T-bet, a 'master switch' for T-cell development, also seems to be involved in preventing asthma. T-bet is a transcription factor that activates expression of interferon-γ (IFN-γ) in T-helper 1 (T_H1) cells. It also has the unique ability to redirect T_H2 cells (which are associated with asthma induction) into T_H1 cells. In the 11 January issue of *Science*, two studies report the effects of T-bet deficiency. Szabo *et al.* show that helper $CD4^+$ T cells from T-bet-null mice express lower levels of the T_H1 cytokine IFN-γ and undergo a shift in their cytokine profile to a T_H2 phenotype. In the second study, Finotto *et al.* observed that T-bet-deficient mice develop spontaneous airway inflammation resembling acute and chronic forms of human asthma. The researchers also report that lung tissue from asthma patients contains below normal amounts of T-bet. The gene encoding T-bet is located on chromosome 11 in a region that has been genetically linked to airway hyper-responsiveness in mice and asthma in humans. Reactivation of T-bet-mediated signaling pathways might be a new approach to treating asthma.

DREAMing of pain relief

Mice lacking a transcriptional repressor called DREAM (downstream regulatory element antagonistic modulator) shed new light on mechanisms of pain processing. Effective pain-management strategies for patients suffering from diseases such as cancer remain elusive. Traditional analgesics, such as morphine, often provide insufficient relief and cause unwanted side effects. In the 10 January issue of *Cell*, Cheng *et al.* report that DREAM-deficient mice are less responsive than normal mice to painful stimuli such as heat, paw pressure and injection of noxious substances. These mice also exhibit reduced pain behaviors in models of chronic neuropathic and inflammatory pain. DREAM-deficient mice are normal in all other respects—including motor behavior, learning and memory—suggesting that DREAM functions specifically in pain perception pathways. The authors show that DREAM is essential for transcriptional repression of the *prodynorphin* gene, which encodes a ligand for the κ-opiate receptor. These receptors are expressed in spinal cord neurons, where they regulate pain perception. Activation of this receptor was enhanced in DREAM-deficient mice, leading to reduced pain-associated behaviors. Although further research is required to identify other transcription targets of DREAM and the factors that regulate its activity, agents designed to target this pathway might someday be developed for pain reduction.



Prostate cancer clue

Despite the fact that prostate cancer is one of the most common cancers, little is known about factors that influence genetic predisposition to the disease. In the February issue of *Nature Genetics*, Carpten *et al.* report the results of a genetic linkage study of hereditary prostate cancer. They examined several prostate susceptibility loci, including one on the long arm of chromosome 1, known as *HPC1*. Mapping and analysis of the region led the authors to *RNASEL*—a gene encoding the endoribonuclease RNase L. They found that hereditary prostate cancer patients possessed germline mutations in *RNASEL*, and that tumor cells from these patients expressed below normal levels of the gene product. RNase L activity was also reduced in lymphoblasts from heterozygous individuals compared with family members with the wild-type allele. Previous studies have suggested that this enzyme functions as a tumor suppressor—RNase L activity is completely lost in hepatoma cell lines. Mice deficient in this protein have defects in interferon-induced apoptosis and antiviral responses, indicating its role in controlling cell proliferation and survival. Although further studies are required to determine the role of RNase L in prostate cancer progression, the authors suggest that this gene could be valuable for prostate cancer diagnosis.

Blood cell gene therapy

Researchers have achieved lineage-specific gene expression in immune cells derived from hematopoietic stem cells (HSCs)—an important advance that may improve treatment for a variety of blood disorders. HSC-mediated gene therapy depends on efficient gene delivery into long-term repopulating progenitors and transgene expression in specific HSC progeny. This lineage-specific and high-level expression of transgenes in HSCs has been difficult to achieve, and has been a major goal of gene therapy for over a decade. In the 15 January issue of *Blood*, Cui *et al.* report using a modified lentivirus vector to express green fluorescent protein under the HLA-DR promoter—which is only active in antigen-presenting cells—in human adult and cord-blood stem cells. They report that their vectors efficiently transduce human pluripotent $CD34^+$ cells, and these cells can engraft into SCID mice. Furthermore, this vector directed transgene expression specifically in $HLA\text{-}DR^+$ cells and highly in differentiated dendritic cells. The dendritic cells derived from transduced and engrafted cells were able to stimulate allogeneic T-cell proliferation, indicating normal antigen-presenting function.

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