RESEARCH NEWS

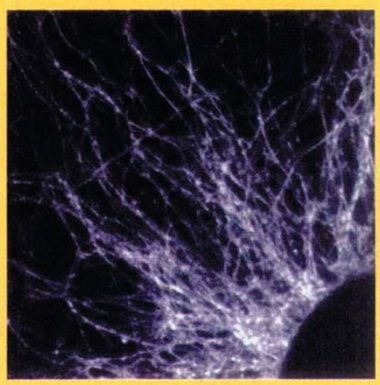
Bax implicated as tumor suppressor

Bax, the Bcl-2 related protein that promotes apoptosis in cell cultures, has been shown to suppress the growth of brain tumors. Terry Van Dyke and colleagues (*Nature* 385:637–640, 1997) at the University of North Carolina School of Medicine at Chapel Hill have studied wild-type and *bax*-deficient transgenic mice in which malignant growth of choroid plexus brain cells was induced through brain-specific expression of T_{121}—a truncated SV40 T antigen that inactivates retinoblastoma, but not p53, tumor suppressor proteins. They observed significantly increased tumor growth rates in $bax^{-/-}$ mice compared with $bax^{+/-}$ mice. The p53-dependent induction of *bax* in T_{121}-expressing choroid plexus cells suggests that Bax is a downstream effector of, and may be partly responsible for, p53-dependent apoptosis. However, according to Van Dyke, $p53^{+/-}$ mice have "considerably enhanced tumor growth rates compared with $bax^{+/-}$ animals, suggesting that the loss of a p53 allele has an additional effect on genetic stability." A paper published concurrently in *Science* (275:967–969, 1997) also links the progression of cancer with Bax inactivation: Manuel Perucho and colleagues at The Burnham Institute in La Jolla report that >50% of colon adenocarcinomas and primary tumors of the microsatellite mutator phenotype have frameshift mutations in a tract of eight deoxyguanosines within the *BAX* gene.

Human β-defensin-1 inactivation linked with CF

A novel cytotoxic peptide, human β-defensin-1 (hBD-1), has been identified that plays a crucial role in combating lung infection. By seeding bronchial xenographs from cystic fibrosis (CF) and non-CF patients in the lungs of *nu/nu* mice, researchers at Magainin Pharmaceuticals (Plymouth Meeting, PA) and the University of Pennsylvania (Philadelphia, PA), headed by James Wilson, have shown that antimicrobial activity of this peptide is severely impaired in CF. Their work in *Cell* (88:553–560, 1997) indicates that airway surface fluid (ASF) from xenografts of CF patients has a high salt concentration and fails to kill bacteria. They also found that dilution of the CF ASF restores the bactericidal effect seen in normal ASF. By expressing the CF transmembrane conductance regulator (CFTR) in mice with CF bronchial xenografts, they were able to correct the properties of CF epithelia. In addition, antisense DNA specific for the 5′ region of the hBD-1 gene ameliorated the antimicrobial effects of ASF in mice with non-CF xenographs. These results indicate that hBD-1 is an important mediator of innate immunity in the lung and is compromised in CF. "We believe CFTR gene transfer to the lung restores antimicrobial activity by correcting the high salt concentrations that inactivate hBD-1," says Wilson.

Small molecule regenerates nerve tissue



In the March 4 issue of *PNAS* (94:2019–2024, 1997), researchers at Guilford Pharmaceuticals (Baltimore, MD) report a novel small molecule, GPI-1046, that stimulates nerve regeneration in vitro and in vivo with picomolar potency. The drug mediates its action by binding to cellular immunophilins—a family of proteins involved both in regulating T-cell responses and in stimulating nerve growth. On the basis of work with Solomon Snyder at Johns Hopkins University School of Medicine (*Nature Med.* 3:421–428, 1997), Guilford researchers have developed a series of novel immunophilin ligands, including GPI-1046, that possess potent neurotrophic activity, but lack immunosuppressive activity. They found that GPI-1046 induces neurite outgrowth in neuronal cultures and protects >80% of nigral-striatal dopamine neurons in a MPTP mouse model of Parkinson's disease, producing regrowth of functional neurons up to one month after nerve lesioning—an "unprecedented" finding, according to Craig Smith, Guilford's president and CEO. Guilford has two other immunophilin ligands that are up to 50-fold more potent than GPI-1046. "All these drugs are orally bioavailable, cross the blood-brain barrier, cause no aberrant sprouting in normal neurons (a problem with NGF), and are at least as potent, if not more potent, than NGF," he adds.

Human hemoglobin from transgenic plants

Scientists at the French research institute INSERM (Le Kremlin-Bicêtre) and at Biocem (University of Cézeaux, Aubière, France) have come up with a useful alternative production system for human hemoglobin-based blood substitutes. In a scientific correspondence to *Nature* (386:29–30, 1997), Michael Marden and colleagues report the successful overexpression of the α- and β-subunits of human hemoglobin, HbA, in transgenic tobacco plants, obtaining a fully functional complex hemoglobin molecule, as measured by flash photolysis. Hemoglobin is currently derived from outdated human blood, but supplies are limited and blood-type matching to recipients is required. Marden believes HbA expression in plants has several advantages over recombinant expression in yeast or bacteria: "You can get higher yields in plants, there is less contamination of the product, and it is easier to scale up the process," he argues. Ongoing research will test HbA expression in plants other than tobacco to see if higher yields are possible, with simpler purification and sterilization steps.

Chimeric protein cytotoxic against KS tumors

A chimeric protein composed of interleukin (IL)-13 and a truncated form of *Pseudomonas* exotoxin A has been shown to be highly toxic to five AIDS-associated Kaposi's sarcoma (AIDS-KS) derived cell lines. Raj Puri and colleagues report these findings in a recent issue of *Clinical Cancer Research* (3:151–156, 1997). The chimeric protein, IL13-PE38QQR, was toxic at very low concentrations to all AIDS-KS derived cell cultures tested, but showed no cytotoxicity to other cell lines of lymphoid or bone-marrow origin expressing low levels of IL-13 receptor. Moreover, IL13-PE38QQR inhibited tumor growth in a human adenocarcinoma xenograft model in mice. Puri hopes the chimeric protein "will be more effective in treating Kaposi's sarcoma (and maybe cancer in general) than interferon-α, which has seen only limited success as it requires a relatively intact immune system."

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