Total synthesis of epothilone

Two groups have succeeded in chemically synthesizing epothilone A, a natural product from the myxobacterium *Sorangium cellulosum* with biological activities intriguingly similar to Taxol. Hot on the heels of a paper by Samuel Danishefsky and colleagues (*Angew. Chem. Int. Edn Engl.* 35:2801–2803, 1996), K.C. Nicolaou's team at Scripps Research Institute (*Angew. Chem. Int. Edn Engl.* 36:166–168, 1997) have now reported an alternative strategy for producing epothilone involving olefin metathesis. Nicolaou's method is marginally shorter and requires less protection of functional groups than Danishefsky's. According to Nicolaou, the work will allow construction of libraries of designed epothilones for biological screening. Other work has shown epithiolone A to be 2,000–5,000-fold more active than Taxol against multiple drug resistant cancer lines and 30-fold more soluble in water.

New technique for functional mapping

Traditional methods for creating deletion mutants in mice using whole-animal irradiation have proved extremely labor-intensive and costly. An alternative has been to use the Cre recombinase/*loxP* method for gene targeting in mouse embryonic stem (ES) cells. Now, a group of researchers headed by John Schimenti at Jackson Laboratories has designed a high-throughput approach for generating nested sets of deletions at defined regions of the genome by irradiation of ES cells. By targeting genes in F_1 hybrid ES cells using the herpes simplex virus thymidine kinase marker gene, selecting for mutants in which the marker had been deleted as a result of irradiation, and analyzing these mutants at several polymorphic microsatellite markers, the authors were able to generate defined mutant germline chimeras in mice at high rates. "In one experiment, we pulled out around 100 different deletion mutants, at least half of which were capable of making germline chimeras," says Schimenti, "This method can rapidly facilitate functional analysis of the genome." The results are reported in the March issue of *Nature Genetics* (16:285–288, 1997).

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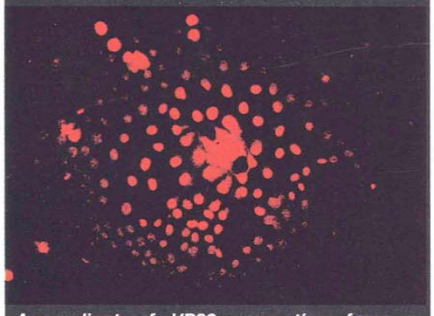
VP22: A new movement in protein transport

A novel pathway for protein trafficking has been described for the herpes virus structural protein VP22. Using immunofluorescence techniques, Gillian Elliot and Peter O'Hare at the Marie Curie Research Institute, UK have tracked the cellular localization of VP22 during transient expression in COS-1 cells. They found that VP22 first localizes in the cytoplasm of a transfected cell and then spreads to the nuclei of surrounding cells. The carboxy-terminal 34 amino acids are implicated in the trafficking, as VP22 lacking this sequence is unable to invade neighboring cells. Rather than involving classical endocytosis or the Golgi apparatus, the process appears to use the actin microfilament network. Heterologous peptides can be similarly targeted when fused to the VP22 protein. "The therapeutic applications of VP22 could range from gene and protein delivery to delivery of small molecules with low bioavailability," says O'Hare. The findings are reported in *Cell* (88:223–233, 1997).



A gradient of VP22 emanating from a transfected cell to its neighbors.

Ethylene implicated in control of nodule formation

Ethylene is known to control several aspects of plant development. Now, R. Varma Penmetsa and Douglas Cook report in *Science* (275:527–530, 1997) that it may be involved in a signaling pathway that governs rhizobial infection of root hair cells. They identified a mutant of the legume *Medicago trunculata*, designated *sickle*, that exhibits a level of infection more than an order of magnitude greater than the wild-type. These plants also show other defects like delayed petal and leaf senescence, which are also dependent on the production of ethylene. Unlike the wild-type, *sickle* plants are insensitive to 1-aminocyclopropane carboxylic acid, a precursor of ethylene production. Cook says that "all indicators point to *sickle* acting early in the ethylene perception pathway, encoding a function common to both plant development and control of rhizobial infection." Ethylene provides a signal for induction of infection arrest, he adds.

CHK breast cancer link

While attempting to identify novel genes important in the development of blood cells, scientists at the Deaconess and Beth Israel Hospitals in Boston led by Jerome Groopman and Hava Avraham have serendipitously uncovered a role for CHK (Csk-homologous kinase) in suppressing cell growth. By studying the function of CHK in tumor cells, they discovered that CHK was active in breast cancer cells, but not in normal breast tissue. Their findings, reported in the *J. Biol. Chem.* (272:1856–1863, 1997), may have implications in the detection and control of breast cancer, which is estimated to afflict 190,000 US women this year. The report indicates that CHK associates with a member of the heregulin receptor family in breast cancer cells following stimulation by heregulin. In subsequent unpublished work using a mouse model system, Avraham says that 12 out of 15 animals injected with both breast cancer cells and the CHK gene showed no signs of breast cancer, whereas control animals, which received breast cancer cells alone, all went on to develop tumors. "If the CHK gene is a defense mechanism trying to limit the growth of cancer, [one] might be able to treat breast cancer by manipulating the levels of the CHK gene in malignant breast cancer cells," says Groopman.

NGF sends mixed signals

Nerve growth factor (NGF), long linked with the survival and differentiation of immature neurons, has now also been shown to mediate apoptosis. Virginia Lee and colleagues at the University of Pennsylvania School of Medicine have demonstrated that NGF can cause massive death of medulloblastoma cell lines expressing the high-affinity trkA receptor for NGF (*J. Neurosci.* 17:530–542, 1997). In their experiments, Lee et al. found that only cells expressing the trkA NGF receptor undergo apoptosis, whereas those expressing the p75 NGF receptor alone do not. Moreover, this phenomenon was cell-type specific, occurred in dividing cells, and was not seen in other cells harboring both receptor populations. As medulloblastoma cells are derived from childhood tumors of the central nervous system, the activation of the trkA signaling pathway via NGF may regulate tumor growth by activating massive apoptosis. According to Lee, "If the cell culture experiments hold true, these observations may have bearing in the development of the cerebellum and be relevant to tumor therapy."