A chaperone for killers

A new approach has been devised that may lead to new types of immunotherapy for combating cancer and virus infections (*PNAS* **94**:13146–13151, 1997). Until now, manipulating cellular immune responses to destroy latent pathogens like HIV and many types of tumor has been notoriously difficult, requiring the use of sophisticated gene therapy techniques or inflammatory adjuvants. Now, a research team led by Richard Young has succeeded in elevating cytotoxic T cell responses against tumors in mice. They injected mice with a peptide marker unique to the tumor cells, fused to a heat-shock protein (hsp70) from *Mycobacterium tuberculosis*. Because this bacterial chaperone is known to induce a killer cell response through presentation on major histocompatibility complex (MHC) class I receptors, the researchers reasoned that it might be able to target other peptides to the same pathway. Young explains: "The new innovation is that class I dependent antigen presentation is being stimulated, and that's unusual, because soluble proteins. . .typically don't engender this response." The technology has been licensed to StressGen (Victoria, BC), and Young's group is now collaborating with Hidde Ploegh of Harvard University (Cambridge, MA) to develop experimental HIV vaccines.

Refractive sensor chip

A biological sensor has been developed that may have wide applications in medical diagnostics and environmental chemistry (*Science* **278**:840–842, 1997). Scientists at the University of California, San Diego and the Scripps Research Institute (La Jolla, CA) have etched closely spaced microscopic pits into silicon wafers, leaving a "forest" of rod-like projections that can be festooned with molecular probes. Changes in the refractive properties of the chip surface when molecules in a sample bind to these probes can be measured using a spectrometer: Complexes on the tiny rods cause a much stronger optical change than expected, yielding unprecedented sensitivity. The team describes chips with DNA oligonucleotide probes that detect femtogram quantities of their target molecules—several orders of magnitude more sensitive than current techniques. Similar sensors might be used for instantaneous medical tests, and Michael Sailor, who led the UCSD team, envisions chips that will detect such environmental toxins as ". . .nerve agents on the battlefield, carbon monoxide building up in an room, or benzene coming out of a gasoline pump." In earlier "proof of concept" experiments the researchers sculpted microscopic images into the chips (see above). Like a cultural icon, the biosensor chips might also soon be seen everywhere.

Reconstituting telomerase

Telomerase, the enzyme that replicates the ends of chromosomes, is thought to have a crucial role in aging and cancer. Two papers in *Nature Genetics*—one from a collaboration of scientists at Geron (Menlo Park, CA) and the University of Texas Southwestern (Dallas, TX) headed by Greg Morin (*Nat. Genet.* **17**:498–502, 1997), and the other from a Japanese group (*Nat. Genet.* **18**:65–68, 1998)—describe the results of transient transfection of human telomerase reverse transcriptase (hTRT) into normal fibroblasts. In normal somatic tissues, telomerase is undetectable, whereas in germ and cancer cells, it shows significant activity. In both papers, transient transfection of hTRT into normal fibroblasts is shown to restore telomerase activity to these cells. This indicates that, in normal somatic cells, hTRT is the limiting component of the enzyme. In addition, the US group reconstitute enzyme activity in vitro by producing only the human telomerase RNA component (hTR) and hTRT in a transcription/translation system. "With these results, we'll be able for the first time to confirm the hypothesis that telomerase is involved in cell senescence and aging," says Morin of Geron. He also believes that "the in vitro reconstitution of the enzyme will allow the development of screens for telomerase inhibitors," which may elucidate the role of telomerase in cancer.

Research News Briefs written by Alan Dove, Alexander Castellino, and Margret Einarson.

Taxol solution provided by enzymes

An approach combining enzyme catalysis and traditional organic synthesis has been used to produce a water-soluble form of paclitaxel, the anticancer compound originally isolated from the Pacific Yew tree. A team headed by Jonathan Dordick of the University of Iowa has used a two-step process involving the bacterial protease thermolysin and yeast lipase to carry out selective modification of the paclitaxel molecule (*J Am. Chem. Soc.* **19**:11554–11555, 1997). Dordick explains that, in contrast to multistep organic syntheses, "the enzymatic approach. . .is very mild and extremely selective. Thus, direct modification is possible. No blocking and deblocking is necessary and this really simplifies the approach." The resulting 1,600-fold increase in water solubility is expected to improve the absorption of paclitaxel into the body, which currently limits its clinical usefulness. According to Dordick, broader applications may be on the horizon: "Both enzymes and all substrates are commercially available. This is what makes this approach so attractive. . .the methodology [could] be considered as a paradigm for the generation of selective derivatives of a wide variety of complex natural products." The work was carried out at the University of Iowa, the University of California, Berkeley, and EnzyMed (Iowa City, IA).

Antiangiogenic therapy

Tantalizing results by Judah Folkman and his group at the Children's Hospital and Harvard Medical School, Boston, suggest that antiangiogenic therapy may circumvent tumor drug resistance acquired during chemotherapy. The work, reported in *Nature* (**390**:404–407, 1997), studies the intermittent treatment of three different experimental tumors with an inhibitor of angiogenesis, endostatin. In all cases, tumor regression occurred without any concomitant acquired resistance. In sharp contrast, animals treated with maximal doses of cyclophosphamide developed partial drug resistance as early as the second or third round of treatment. Surprisingly, all tumors remained dormant when endostatin therapy was discontinued after a few cycles. Histological examination of endostatin-treated tumors shows hypovascularization with little angiogenic activity and no lung metastasis compared with untreated animals. Folkman believes "the therapy will initially be important for lowering toxicity effects of other treatments and getting rid of drug resistance." "It could also be used as an adjunct to chemotherapy, radiotherapy, immunotherapy, gene therapy, and vaccine therapy,"he says. Ultimately, though, it may stand on its own as a first-line therapy. The group is now poised for trials in spontaneously occurring canine tumors, with human trials planned in a year or so by EntreMed (Rockville, MD) and The National Cancer Institute (Bethesda, MD).