News
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****UT Southwestern researchers assess progress of cancer immunotoxins

DALLAS -- The idea of using the body's own immune system to deliver lethal blows to cancer cells has tantalized scientists for more than a decade. When the technology for linking poisons to antibodies was mastered, the resulting immunotoxins were dubbed "Magic Bullets." But 10 years later, scientists are still improving their ammunition and their aim.

In an article entitled "Redesigning Nature's Poisons to Create Anti-Tumor Reagents" in the Nov. 20 issue of Science, researchers at The University of Texas Southwestern Medical Center at Dallas who have been active in immunotoxin research for seven years review the progress of this field. Dr. Ellen Vitetta, director of the Cancer Immunology Program and principal author, concludes that there is still much to be done but that immunotoxins "offer hope for successfully treating the cancer patient."

The basis for immunotoxins was the development of monoclonal antibodies. In 1975 Cesar Milstein and George Kohler of the Medical Research Council in Cambridge, England succeeded in fusing an antibody with a rapidly reproducing cancer cell. The resulting hybrid cell contained genetic machinery for making an antibody plus cancer genes that made the cell immortal. It had the ability to divide forever, making clones of itself that would produce a single pure type of antibody.

Because the body produces an antibody to any antigen (a substance that it perceives as foreign) the advent of monoclonal antibodies made it possible to immortalize specific antibodies to react to bacteria, viruses, parasites or cancer cells.

It was then found possible to use the antibodies as carriers of toxins, natural poisons produced by plants or bacteria. When these toxins are combined with antibodies, they produce immunotoxins (ITs). ITs have the ability to seek out a specific type of cell, invade and kill it.

A number of toxins have been tested in producing ITs against cancer, but one that is commonly used is ricin, a deadly poison derived from the castor bean. It is, incidentally, a poison that made headlines in 1978, when a Bulgarian defector named Georgi Markov was killed in London. His assassin stabbed him in the leg with an umbrella tipped with a pellet containing minute amounts of ricin, investigators said.

Research with ITs containing ricin has revealed the strengths and weaknesses typical of the whole concept. Such research, including Vitetta's own in conjunction with Dr. Jonathan Uhr, chairman of the Department of Microbiology at UT Southwestern, has been conducted in mice and, more recently, in humans.

In the first place, a ricin molecule is made up of two molecular chains--A and B--as are most plant-derived poisons. The A chain works by destroying the cell's ability to produce protein molecules and therefore to reproduce itself; the B chain provides the mechanism for binding the toxin to virtually all cells of the body. Thus, whole ricin acts swiftly to poison the entire body. The A chain of ricin as an element of an immunotoxin is a highly effective "targeted poison" since the specific antibody replaces the non-specific B chain and guides the A chain to its target cell.

One of the early problems encountered involved the bond between the ricin molecule and the antibody. If the bond should dissolve before entering the targeted cell, the freed ricin could be taken up by other cells and cause death. It was judged, therefore, that whole-ricin IT is too toxic to inject systemically at targeted tumor cells although it has been used effectively in certain situations outside the body, such as treating bone marrow before transplantion, and in the body injected directly into the tumor.

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However, using only the A chain of ricin has proved much safer. In an IT, it allows the antibody to guide it to its target cell. If its carbohydrates are removed so that it is not attracted to the liver, it is harmless should it break away from the antibody. Because it lacks its own mechanism for entering a cell, it is less efficient than whole-ricin IT, but new techniques have been developed to boost both its delivery and its toxicity.

There are many other problems to be mastered. A patient might develop an antibody response against either the A-chain or the monoclonal antibody of an IT, thereby neutralizing it. Researchers think that using different plant toxins over a course of treatment could circumvent the problem.

The half-life of an IT in the blood may be only a few minutes to a few hours. In that time it must reach its target and be taken in. A target within the easy reach of the bloodstream is vulnerable. Cells within a solid tumor are less likely to be reached than the surface cells. Scientists are working on ITs with a longer half-life by changing the stability of the links between the antibody and the A chain.

Particular problems in working with cancer include the fact that the cells that do not divide frequently constitute the bulk of the cells seen in a cancerous growth. The cell giving rise to these non-reproducing cells may be a less mature dividing cell (progenitor cell). To be effective, the ITs must target the dividing progenitor cells. Furthermore, tumors tend to mutate and lose the target molecule, so ITs must target several antigens on the reproducing cells.

In addition, tumors can shed their surface antigens into the bloodstream. If ITs combine with the free antigen, they will be cleared by the kidneys. This could cause kidney damage and also prevent the IT from reaching its target cell.

Many of the problems encountered in first and second generation ITs may be overcome by using recombinant DNA technology for third generation ITs. Genetic engineering may be able to create smaller, more efficient versions of A-chain immunotoxin that are less likely to cause immune responses and be able to penetrate tissues or tumors more easily. Recombinant DNA technology may also be used to prepare the large amounts of high-quality ITs necessary for use with patients.

Vitetta points out that it took more than two decades to develop conventional chemotherapy after its first use in 1945. ITs are more complicated, and there are relatively few scientists investigating their basic biology and biochemistry. She feels it will probably take another five to 10 years to determine the limitations and potential of immunotoxin treatment for cancer.

Co-authors of the Science article are Dr. Jonathan Uhr, chairman of the Department of Microbiology at UT Southwestern, and Drs. R. Jerrold Fulton, Richard D. May and Mark Till of the department's faculty.

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Note: The University of Texas Southwestern Medical Center at Dallas was formerly named The University of Texas Health Science Center at Dallas. Its components are Southwestern Medical School, Southwestern Graduate School of Biomedical Sciences and Southwestern Allied Health Sciences School.