Directed cancer drugs

How does an anticancer drug 'find' a tumor? The unfortunate answer, of course, is that most of the arsenal of anticancer drugs have absolutely no way of specifically locating the tumor for which they were designed. They must be flooded indiscriminately throughout the body where, as potent cellular toxins, they often wreak havoc with the normal tissues as they destroy the much faster growing tumor cells. It falls to the oncologist to judge carefully just how much drug a patient can tolerate, sometimes taking them to the brink of a lethal dose in order to deliver sufficient drug to destroy the cancer.

To circumvent this problem, therapeutics have been designed in which a potent cell toxin is coupled to an antibody specific for a particular tumor cell type. This approach is analogous to mailing a letter-bomb: the antibody recognizes the cellular address, becomes attached to the designated tumor cell, and then the toxin destroys the tumor cell while causing little damage to other body tissues. Although clever in design, the strategy has met with only limited practical success and has not yet found widespread use in chemotherapy. Erkki Ruoslahti and colleagues at The Burnham Institute (La Jolla, CA, USA) have devised a variation of this strategy. They use small peptides to deliver their antitumor letter-bombs to specific sites in the vasculature of a tumor. The peptides bind specifically to the endothelial cells lining the small blood vessels that are essential for the growth of a tumor and deliver a chemotherapeutic drug to destroy the vasculature of the tumor [Arap *et al.* (1998) *Science* 16, 377–380].

Vascular addresses

The key to this strategy is the idea that many tissues have what has been termed 'vascular addresses'. That is, vascular endothelial cells express certain proteins on their surface that are specific for a given tissue. In support of this notion, it is known that the endothelial cells lining the vasculature of some solid tumors contain a significant level of α_v-integrins, which are present in extremely small amounts on vascular endothelial cells of other tissues. Using phage peptide libraries, Ruoslahti and colleagues identified peptides with the RGD amino acid motif that bind specifically to the α_v-integrins. These peptides accumulated selectively in carcinoma, sarcoma and melanoma tumors. Another useful peptide had the NGR motif associated with adhesion proteins. They also found a variety of other interesting peptides. Some bound to tumors in a less-selective manner; others were selective for breast carcinoma, Kaposi's sarcoma and malignant melanoma.

Two of the peptides were chemically coupled to doxorubicin, which was selected in part because it is known to have anti-angiogenic activity. The conjugates were then used to treat mice with human MDA-MB-435 breast carcinoma tumors. Mice receiving a dose of the conjugate some 10–40-fold lower than the normal dose of systemic doxorubicin consistently outlived the control mice, all of which died. Histology indicated that the conjugates destroyed the vascular structure of the tumors and had much less hepatic toxicity than free doxorubicin. The investigators noted that the peptides selected for treatment of the mice also bind specifically to the vasculature of human tumors and should be suitable for targeting chemotherapeutic drugs in human patients. Moreover the strategy may be effective in overcoming the common problems associated with the development of resistance to chemotherapeutic agents. The target of the therapy, the vascular endothelium, is not composed of cancer cells and may be much less likely to form drug-resistant variants.

The potential for this strategy of chemotherapy seems bright. If successful, it may allow the use of considerably more-toxic drugs for the treatment of cancer than can normally be used in systemic therapy with far fewer side effects. The search must continue for additional peptides that will allow specific addresses within the body to be targeted. In the future, it may be possible to use such a strategy to deliver therapeutic agents for a variety of indications to the exact site in the body where they are designed to act.

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