Act locally, think globally

Locally growing malignant brain tumors provide a reasonable starting point for developing targeted strategies of anti-cancer therapy (pages 1354–1368).

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PRIMARY MALIGNANT BRAIN tumors comprise only a small proportion of the approximately 17,000 cancers that are diagnosed annually in the United States. Yet, two features of the most common and malignant brain tumor—glioblastoma—have made it the focus for studies into new anti-cancer therapies. First, glioblastoma is almost uniformly fatal, with a median life-expectancy of about one year. Second, death from glioblastoma is due to local growth of the tumor in the brain; involvement of other organs is rare. Therefore, a useful therapy need only be active locally, and this has led to the development of novel anti-tumor agents, two of which are described in this issue[1,2].

Ram and colleagues[1] implanted retroviral vector-producer cells into brain tumors to allow transfer of the herpes simplex virus (HSV) thymidine kinase gene, which can sensitize tumor cells to systemically administered ganciclovir. This concept was first explored in brain tumors in animal models[3,4], and the gene strategy used here was proposed by Moolten[5].

Tumor targeting uses the fact that integration by retroviruses requires cell division—tumor cells are mitotically active whereas normal brain cells are not. The authors show that stereotactically implanting producer cells into a tumor in the human brain is feasible, and it is tolerated with few complications. But the strategy fails due to physical constraints of the system: first, the producer cells are relatively large and non-motile; and, second, the vector used cannot replicate, so gene transfer occurs within only a few cell-distances of the producer cells. This means that only very small tumors can be treated, and many inoculation tracts must be used. Although transfer of phosphorylated ganciclovir to adjacent cells may extend the range of treatment, even this effect occurs over just a few cells. Ram *et al.*[1] note that only those tumors that were very small and had a high density of tracts responded. Thus, although gene delivery can be demonstrated it is very inefficient, consistent with prior animal studies[3].

Laske *et al.*[2] used a different intratumoral inoculation strategy to overcome this distribution problem—continuous direct infusion of transferrin-CRM107, which is a conjugate of human transferrin and a genetic mutant of diphtheria toxin. This allows a relatively large volume to be delivered to tumor cells at a distance. Larger tumors can be treated, and the authors noted a 50 percent reduction in more than half of the patients and a complete response in two. Although this needs to be confirmed, it is a very impressive initial result for recurrent glioblastoma, and may be better than simple diffusion delivery of chemotherapeutic compounds. However, the targeted molecule is only relatively tumor specific and, at higher doses, toxicity was seen in normal brain tissue.

Despite shortcomings in efficiency of delivery with the retroviral vectors, or toxicity at higher doses with the toxin-convection strategy, these reports set the stage for further improvements. For example, the vector strategy might be used with improved vector-gene systems, and the convection strategy with more specifically targeted compounds.

An alternative extension of these strategies is to develop a conditionally-replicating viral vector[6,7]. Wild-type HSV-1 can replicate in the brain[8], and the genes associated with this ability have been identified. Vectors that are deficient in such genes retain the ability to grow in human glioblastoma cells, but they cannot grow in normal brain or cause encephalitis. These are near the stage of clinical trials, and they should allow for conditional growth and spread within the tumor, theoretically providing better physical distribution than is possible with replication-defective vector systems. Moreover, although they were designed for growth in brain cancer but not in normal tissue of the nervous system, these HSV-1 vectors also grow efficiently in some cancers outside the nervous system.

Another approach to the problem of distribution and specificity is to develop a viral vector whose replication is even further restricted to cell type. For example, adenovirus mutants have been developed that target replication to p53-deficient cells[9]. And cell-specific promoters have been used to target replication of both HSV (ref. 10) and adenovirus[11]. Such improvements in vector specificity may ultimately allow intravascular delivery to be efficiently and safely performed, permitting systemic delivery of these agents.

Treatments such as those described by Ram *et al.*[1], Laske *et al.*[2] and others could come full circle—techniques initially conceived for treating widely spread tumors could be used against a local tumor such as glioblastoma. And as these techniques develop, they will likely use strategies that no longer act only locally, but can also be applied globally to treat some of the more common cancers such as lung, breast or prostate cancer.

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