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Magnetic cells for cancer therapy

Adopting magnets for cell-based cancer therapies

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Finding cells that genuinely traffic to tumors has not been straightforward. Many have been tried, including T cells,[1,2] macrophages,[3] stem cells[4] and even other tumor cells.[5] Most of these cell types have been found in tumors following adoptive transfer but, invariably, they also traffic to other tissues and organs and this both dilutes their own therapeutic effects on the tumor and poses potential for toxicity if they carry additional therapeutic payloads. A potential solution may now be at hand, as described in a recent paper by Muthana *et al*.,[6] who show that adoptively transferred cells can be loaded *ex vivo* with magnetic nanoparticles (MNPs) and subsequently be attracted by an exogenously applied magnetic field.

For many years, cancer researchers have been trying to identify cell type(s) that have the ability to: (1) be expanded easily *ex vivo*, (2) be adoptively transferred back into the patient and (3) traffic efficiently and, preferably, exclusively, back to the tumor. These adoptively transferred cells should then be manipulated to either have direct antitumor effector activity,[1,7] be the platform for delivery of therapeutics, such as viruses, radioisotopes or chemotherapeutic drugs,[8] or both.[9]

In early *in vitro* studies, Muthana *et al*.[6] show that MNP-loaded cells can be made to pass across a barrier of endothelial cells and into a spheroid of human tumor cells by application of a magnetic field. Impressively, the magnet is not only able to drag the cells into the spheroid but also ensures they become effectively distributed throughout the spheroid. This is of particular significance because the deeper areas of tumors are often hypoxic, and malignant cells can evade conventional chemo- or radiotherapeutic treatments. Cells could be coaxed through the endothelial cell layer by the magnet even in the presence of active flow, at rates mimicking those in the circulation. The results showed that 5 h following transfer *in vivo*, cells loaded with MNP reached established human tumor xenografts at significantly higher levels if a magnet was strapped over the tumor than in the absence of the magnet.[6] Whether these cells really stayed in the tumor, or continued to accumulate, is unclear.

Muthana *et al*.,[6] used monocytes as their cells of choice, based on previous observations that macrophages and monocytes have some intrinsic homing to, and retention in, tumors.[3] One of the attractions of magnetic loading, however, is that, at least in theory, it opens up the field to exploit multiple other cell types, which do not necessarily need to have any intrinsic tumor-trafficking capabilities. A high enough cell-loading efficiency with MNP combined with a strong enough magnetic field focused onto the tumor would, presumably, allow any circulating cells to be pulled out of the circulation and into the tumor mass. Candidates cell types for adoptive transfer will need to be tested for the efficiency with which they can be loaded with MNP, and the biological effects of this loading. The monocytes used in this study were not affected by loading, however, in cases where the primary purpose of the adoptive transfer is to exploit direct effector functions of the cells at the tumor site,[1,7] careful assessments of these functions in cells loaded with MNP will need to be carried out. Similarly, where the purpose is to carry therapeutic reagents to the tumor,[2,5] it will be important to show that MNP-loading does not affect critical parameters required for release, or expression, of these reagents.

Although the authors show attraction of MNP-loaded monocytes to established tumors *in vivo*, they stopped tantalizingly short of showing that this can be exploited as a *fatal* attraction for tumor therapy. No doubt such studies using monocytes manipulated to increase their therapeutic potency are well on their way. In addition, these studies were carried out in immune incompetent mice and any concerns that MNP may confer increased immunogenicity in the presence of other components of the immune system still need to be addressed.

The application of this approach for the treatment of highly localized, accessible disease will necessitate the focusing of powerful magnetic fields onto the tumors. A major theoretical attraction of adoptive cell therapy is that the transferred cells will find tumors that are not necessarily detectable, or accessible to other more conventional weapons (such as the surgeon's knife or the radiotherapist's beam). Therefore, maximal clinical potential may require the focusing of magnetic fields onto areas, tissues or organs where metastatic disease is likely to exist, but is not accessible to treatment in any other way. Initial magnetic localization of the adoptively transferred cells to these areas, maybe followed by release from magnetic tethering, may significantly enhance the chances of the cells finding tumor deposits within a spatially limited environment where the risk of disease is very high. In such a clinical situation, the need for the adoptively transferred cells to have some further locoregional tumor tropism would again become important.

Magnetic attraction between cells and tumors may provide a valuable method by which adoptively transferred cells are forced into tumors in significantly greater numbers than is possible by relying on natural cell trafficking; however, the level of therapeutic efficacy remains to be tested with MNP-loaded cells containing antitumor payloads or previously manipulated to carry out antitumor effector functions. ■

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