Animal models of disseminated disease for the development of nanoparticle-directed delivery of cancer therapy

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Nanomedicine offers an unprecedented opportunity for targeted drug delivery. The ability of nanometric size particles to enter cells through receptor-mediated endocytosis opens the possibility of designing vehicles for the specific delivery of therapy to disease cells. This directed delivery will highly increase the therapeutic window, by reducing the toxicity on normal cells whereas achieving an enhanced therapeutic response. Even rational therapies (e.g. monoclonal antibodies (mAb)) have limiting toxicities because they are biodistributed to both normal and diseased cells (1). Thus, the combined effect of a specific delivery vector and a targeted drug, loaded into it, promises to improve current therapeutic approaches.

Most cancer patients have macroscopic or subclinical metastases at diagnosis. Moreover, therapy for metastatic cancer is faced with high level of recurrence, acquired resistance and systemic toxicity (2); thus, most patients nowadays still die because of metastases (3). Novel targeted therapies, including mAbs have not significantly improved outcome in this disease (4). Existing cancer therapies, including mAbs have been developed to block the primary tumor rather than the metastatic process. However, it is known that the same tumor displays a differential regulation of the cell cycle and cell death pathways (5) and a dramatically different response to the same drug (6) depending on the organ where it is growing. The fact that currently used preclinical drug development models (mainly subcutaneous xenografts) do not predict clinical response to antitumor drugs (7) could be in part due to these differences.

Animal models of disseminated disease can be used to assess the efficacy of targeted delivery systems as well as antimetastatic effect. We have developed orthotopic xenograft models of human colorectal and pancreatic tumors, as well as human lymphoma and leukemia, which closely reproduce the metastatic pattern observed in humans (8-11). We are characterizing tumor cells for their mutational spectrum, to define targets for therapy, as well as the over-expression of membrane receptors, to identify target receptors for the selective delivery of therapy. The design of targeted vectors able to undergo receptor-mediated endocytosis in tumor cells and their ability to selectively deliver targeted therapy, against the oncogenes driving the tumor, inside tumor cells is being tested in such models. This approach may have a significant impact on cancer therapy (12). Our capacity of using non-invasive radioactive, fluorescent or optical methods, to assess nanoparticle biodistribution and antimetastatic effect, will greatly facilitate our ability to evaluate the effectiveness of these novel therapies.

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