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Cell-Based Targeting of Anti-Cancer Nanotherapy to Tumors

Deryl Troyer*

Department of Anatomy and Physiology, Kansas State University, Manhattan, KS66506, USA

There is emerging and convincing data that certain cells, administered systemically, have a natural propensity to migrate to cancerous tissues in preclinical models. Examples of such cells include neural stem cells [1], bone marrow mesenchymal stem cells [2], umbilical cord Wharton's jelly stem cells [3], and defensive cells [4].This homing ability can be exploited by using cells as stealth vehicles to ferry therapeutic nanomaterials to tumors to facilitate penetration, reduce potential toxicity, reduce potential unwanted immune consequences, and reduce removal by the reticuloendothelial system (RES).

Cell Based Delivery of Combined Prodrug and Prodrug Activating Enzyme

Irinotecan (CPT-11) is a potent anticancer prodrug that is converted by carboxylesterase (CE) to a topoisomerase I inhibitor, 7-Ethyl-10-hydroxycamptothecin (SN-38). However, the use of this drug is limited since only 2-5% is converted into active SN-38 [5] and because of undesirable off-target effects such as diarrhea and neutropenia [6] as well as inter-patient variability of CE expression [7]. A recent publication described a secretory form of rabbit carboxylesterase, which is much more efficient than human carboxylesterasefor activation of CPT-11 to active SN-38 [8]. This group showed that systemic administration of CPT-11 with neural stem cells containing a secretory form of rabbit CE increased the survival of mice with neuroblastoma. Although rabbit CE is more efficient than human CE, use of rabbit CE to treat humans could result in undesirable immune consequences or deactivation of the enzyme [9]. These unwanted side effects could be reduced if both the prodrug and the prodrug activating enzyme were delivered using a self-contained, targeted cellular delivery system so that the enzyme is not activated until reaching the target. We used RAW264.7 monocyte/macrophage-like cells (Mo/Ma) for delivery of both prodrug and enzyme [10]. We engineered RAW264.7 monocyte/macrophage-like cells (Mo/Ma) to be double stable (DS monocytes) usingTet-On®. Advanced system for intracellular carboxylesterase (CE) expression (i.e., the rabbit carboxylase is not secreted from the cell). This system offers a double layer of protection. It sequesters both the prodrug, CPT-11 (tethered to dextran via a CE cleavable bond), and intracellular prodrug activating enzyme, CE. Once the engineered cells reach the cancer site, systemic administration of doxycycline induces rabbitCE expression and activates CPT-11. We have shown that this gene regulated cytotherapy significantly reduced the tumor weight and number of tumors in lung melanoma in C57Bl/6 mice [10]. This system was also tested in a murine disseminated peritoneal pancreatic cancer model using intracellular CE engineered tumor homing mouse monocyte/macrophage cells as carriers for both prodrug and enzyme. In addition, we have shown a significant increase in the survival time of mice bearing pancreatic tumors [11]. We have also designed a magnetic nanoparticle based SN-38 prodrug, where SN-38 is attached to the surface of magnetic nanoparticles (MNP) with a carboxylesterase cleavable linker [12].

Cell Delivered Chemotherapeutic Agents

Choi and colleagues isolated peritoneal macrophages from mice and loaded them with liposomes containing doxorubicin. The preloaded cells were given intravenously to mice with A549 lung or subcutaneous tumors. Tumor volume was reduced; however, this result was not statistically significant [4]. Mesenchymal stem cells loaded with nanoparticles containing coumarin as an imaging agent were administered ipsilaterally or into the contralateral hemisphere of mice with intracranial gliomas. The tumors were successfully imaged after cell administration [13].

Cell Delivered Magnetic Hyperthermia

Magnetic hyperthermia is receiving considerable attention as a cancer therapy. The primary limitation with magnetic hyperthermia or photoactive hyperthermia is that it requires injection of milligram amounts of nanoparticles directly into the tumors; hence, it is limited to accessible tumors. Cytotherapy could potentially be used to overcome these limitations by specifically delivering nanoparticles to the tumor site.

Our group has demonstrated the utility of this approach by using neural stem cells (NSC) to deliver magnetic nanoparticles to melanomas followed by alternating magnetic field (AMF) exposure to generate hyperthermia. Core/shell iron/iron oxide nanoparticles were loaded into NSC. Mice bearing subcutaneous melanomas were treated with intravenously injected, nanoparticle-loaded NSC five days after tumor transplant. Nine, ten and eleven days after tumor insertion, the mice were treated with AMF for 10 minutes. Nanoparticle-loaded NSC were able to traffic to the tumor and on treatment with AMF a 43% decrease in tumor size was obtained, showing that cell-delivered nanoparticles can be used in vivo to treat malignancies [14].

In another study, the ability of hyperthermia/cytotherapy combinations to treat deep seated tumors was demonstrated by our group. Core/shell iron/iron oxide nanoparticles were loaded into Raw264.7 (monocyte-macrophage-like cells termed 'Mo/Ma' cells). The nanoparticle-loaded Mo/Ma cells were then tested in vivo in a disseminated peritoneal pancreatic cancer model in mice. Tumor-bearing mice were treated with intraperitoneally transplanted, nanoparticle-loaded Mo/Ma five, nine and thirteen days after tumor implantation. Mice were also treated with AMF for twenty minutes on eight, twelve and fifteen days after tumor implantation. The nanoparticle-loaded Mo/Ma migrated to the tumors (but not healthy tissue), and treated mice showed a significant increase in life-expectancy post-tumor transplant [15].

Subsequent to this work, two other reports describing cell-based

***Corresponding author:** Deryl Troyer, Department of Anatomy and Physiology, Kansas State University, Manhattan, KS66506, USA, Tel: 785-532-4509; Fax: 785-532-4557; E-mail: troyer@vet.k-state.edu

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hyperthermia have been published. Ruan, et al. used mesenchymal stem cells (MSC) to deliver iron oxide nanoparticles to subcutaneous gastric tumors in mice. Intravenously injected MSC trafficked well to the tumors delivering the nanoparticles with high specifically. Upon treatment with AMF almost complete inhibition of tumor growth was achieved [16]. Toraya-Brown et al. used tumor associated phagocytes to deliver iron oxide nanoparticles to disseminated peritoneal ovarian cancer in mice. Iron oxide nanoparticles were injected intraperitoneally into mice bearing tumors and the iron was taken up by the phagocytes. Soluble phagocytes were harvested by peritoneal lavage the next day and injected intraperitoneally into other tumor bearing mice. Upon treatment with AMF, cell death was induced specifically in tumors while healthy tissues and other organs were unaffected [17].

Conclusions

There is a growing sense of urgency in developing effective targeted nanotheranostics for clinical trials. Heterogeneous distribution of therapeutics due to physiologic barriers attributable to abnormal tumor vasculature and interstitium remains a major issue. Cell vectors have three distinct advantages, compared to conventional chemotherapeutic strategies: 1) They are capable of penetrating tumors and metastases alike. 2) Depending on the selection of the cell vector, various regions of the tumors (e.g. microvasculature or tumor core) can be targeted. 3) As described here, numerous strategies for cell-based tumor targeting and treatment are being developed.

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