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JSM Nanotechnology & Nanomedicine

Letter to the Editor

The EPR Effect as the Critical Event in the Decathlon of Nanoparticle Targeting to Tumors

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Submitted: 10 September 2013
Accepted: 10 September 2013
Published: 12 September 2013

DEAR EDITORS

In the following letter, we would like to share our thoughts with the readers of this Inaugural issue of Nanotechnology and Nanomedicine concerning the Enhanced Permeability and Retention (EPR) effect, and how the drug-delivery field has somewhat drifted in its interpretation of this dynamic property from the context of its original observation.

Materials science strongly supports the ability to develop an almost unlimited array of unique and multi-functional nanoparticles (NP), supported by an arguably misguided and over-interpreted belief that more complexity will provide improved NP performance characteristics. Despite overwhelming validation of the benefits of NP-based drug delivery in pre-clinical settings, the NP drug carriers that are clinically approved are few in number: thus, a serious conundrum. Perhaps this dilemma justifies bold re-examination of the rationale underlying the NP-based drug delivery technology?

It is well-established that because of their low molecular weight, the majority of routinely used cancer drugs are rapidly cleared from systemic circulation and show very limited preferential biodistribution in tumors; combined with their typically high hydrophobicity, they also have a large volume of distribution, resulting in well-known confounding toxicity towards normal tissues and limiting their therapeutic indices: hence, the quest for improved delivery systems, such as NP.

Exploiting the EPR effect-the first phase

The extravasation of NP from the tumor-feeding vasculature to the interstitium of solid tumors is achieved predominantly by the EPR effect, first described about 25 years ago, and the most critical and early step of the metaphoric delivery "decathlon". Very different NP properties/capabilities are required to enable success at each of the multiple steps. This applies to both "passively" (exploiting only patho-physiological properties of tumor tissue) and "actively" (exploiting tumor cell recognition/uptake) targeted NP. The term "EPR effect" has regrettably been over-enthusiastically abused, as though NP will somehow go only to tumors: even under the best of circumstances, far from it---most end up in clearance organs and to a lesser extent in other normal tissues. Further, once NP reaches the tumor site, they have to penetrate the tumor microenvironment, known to be significantly different from that of normal tissues. The dense extracellular matrix (ECM) and elevated interstitial fluid pressure (IFP) of tumors makes drug penetration even more difficult than in normal tissues, and more difficult than for the smaller, free drugs. Thus, we should re-examine both major underlying premises and the results to date associated with the NP delivery approach.

First, at several steps following their intravenous administration, NP diffusion is the sole driving mechanism, and not any propulsive or convective force. An exception to this could be made for magnetically-responsive NP, under the influence of a magnetic field gradient. Thus, what we call targeting, whether passive or active, is secondary to this diffusion, and results in what might be better termed merely "improved" delivery. Exploitation of the EPR effect results in improved delivery by NP as compared with that of free, low molecular weight conventional chemotherapeutic agents; normally, small molecules do not show the EPR effect, because they can freely pass through the blood vessels of either normal or tumor tissue--and even diffuse back into circulation again.

The next steps

Second--and this point is very contrary to widely held and prevailing views--overexpression of receptors or other cell-surface molecular targets does not necessarily increase the likelihood of successful targeting approaches and improved tumor accumulation: in other words, in the early phases post-EPR-mediated extravasation. The flaws in this mindset include the virtual absence of totally exclusive expression of any such molecules only on tumor cells, and--given that--since normal cells

far outnumber tumor cells, much of the affinity-based recognition will be deflected to normal cells and tissues. In fact, this rationale has driven the quest for binding interactions of yet greater and greater affinity/avidity—and may actually result in increased and undesired binding to normal cells sharing a given receptor/determinant, particularly if this occurs prior to EPR-mediated extravasation. Having said that, later post-extravasation stages following tumor accumulation might be enhanced by such interactions, particularly receptor-mediated NP transcytosis and/or internalization/degradation. Nevertheless, compared to tumor cells, macrophages, whether populating normal tissues or infiltrating the tumor, typically exhibit more robust NP uptake, utilizing their Toll-like receptors 4 (TLR-4) or scavenger receptors.

Further, just reaching the tumor tissue is *not* equivalent to improved delivery. Unless the NP are introduced directly to the target cells, as in *in vitro* settings, drug release in the tumor interstitium or following tumor cell uptake of the NP obviously occurs only after the upstream steps of the systemic targeting phase are successfully achieved. Active targeting is generally intended to improve target cell recognition and subsequent uptake and internalization to the cytoplasm, nucleus or other cellular organelles: not necessarily to improve net tumor accumulation. Despite many advances made at the preclinical level with regard to active targeting, for the most part, only antibody-based agents have been approved for clinical use; no actively targeted NP have thus far been approved for clinical use, and few are in clinical trials, although Alchemia's CD44-targeted HA Irinotecan might soon become the first to reach registration. In this setting, the encapsulating 750 kDa HA of the conjugate likely serves a role both as a polymeric NP to exploit the EPR affect and facilitates subsequent uptake by CD44 (+) tumor cells.

Additional constraints may be caused by intra-tumoral transport dynamics that arise from elevated tumor IFP and abnormal ECM structure. The IFP of a solid tumor is at elevated levels compared to vascular pressures—thus creating an upstream gradient against extravasation--and it sharply decreases only at the periphery of the tumor—rendering the core of the tumor less accessible. The high collagen content of the ECM and the consequent dense organization of collagen fibrils, intermingled with proteins such as proteoglycans and glycosaminoglycans, also results in low diffusivity; since diffusion decreases sharply as the molecular weight of the drug increases, transport of NP-bound drugs is comparatively even more impaired in the tumor interstitium. This has prompted development of strategies to normalize the tumor vasculature, to minimize pressure differentials, and to degrade the impeding tumor ECM.

Rapid, premature drug release from a NP while still in circulation will give rise to a biodistribution and toxicity profile that mimics the free drug; further, accumulation of empty NP at tumors may physically overload and impede the desired NP-based drug delivery. Thus, NP-drug constructs that depend on chemadsorptive interactions carry substantial risks in this regard; selection of appropriate bioreversible, covalent linker chemistry that is predominantly stable in plasma and exhibits release profiles preferential for tumor sites, and at tuned levels aligned with therapeutic effects, would be preferential.

Effective NP-mediated drug delivery is the result of multiple distinct, and in some cases, competing dynamics: renal excretion, clearance by mononuclear phagocytes in the liver, spleen and other organs, and as discussed above, uptake, retention and dispersion within the tumor microenvironment itself--all comprise this decathlon. Our use of the decathlon metaphor reflects the fact that NP parameters that may enhance success at one step may be irrelevant or even detrimental at others; further, that failure at early steps also precludes proceeding to later steps. Whereas avoiding renal elimination is virtually assured for any NP larger than the glomerular pores (~5 nm), overwhelming data has indicated that with all EPR effect-based NP, liver and spleen are the two major organs aside from tumors in which NP accumulate. Strategies that limit the binding of NP by serum opsonins and subsequent clearance by the mononuclear phagocyte system (e.g., PEG-ylation) may also serve to limit the interaction of NP with the tumor cell membrane and subsequently reduce internalization and uptake by tumor cells. It is increasingly clear that although the EPR effect is indeed operant in human clinical settings, it is nevertheless highly heterogeneous; no single histiotype of tumor will have broadly predictable responses, nor will pre-clinical models be adequately predictive of clinical outcomes. Due to the differences in growth rates between pre-clinical tumor models, usually xenografts, and most human solid tumors, the vasculature in the latter is more mature and less deranged—making the presence of an EPR effect less certain. Even within a single tumor, there may be marked differences in vascular permeability, dependent on whether or not the endothelial lining is intact, or whether vascular leakiness is affected by the presence of the peri-vascular lining, such as pericytes, smooth muscle cells or fibroblasts. Thus, design and engineering of NP based on the nature of the critical EPR effect in pre-clinical models might be a flawed prism through which to view the path to translation to human clinical applications.

Where we are---and where we need to go

The sequencing of the human genome brought with it the vision that it was only a matter of time and resources before the cancer armamentarium was populated with potent and specific therapeutic agents for each and every genetically deranged pathway. Regrettably, reality has been much different. What has become clear is that tumor cells have inherently high plasticity and heterogeneity, evident in the mutation frequency observed even in a single patient---and that finding specific alterations and gene mutations common among patients has been virtually infeasible; dozens of genetic variants may arise even from a single malignancy. This makes the task of aligning a particular therapeutic to deal with each of these potential drivers a Herculean one. Most of the new agents approved by the FDA for cancer therapy in 2012 cost $100,000 or more for a single course of treatment and, even in pre-selected patients, only improve survival by a matter of months. Thus, the winners among many targeted cancer therapeutics to date are disappointingly few:

arguably, Rituximab, Herceptin and Gleevec. Placed in the context of increasing national and global cost/benefit consciousness, one might justifiably argue that the current approach to targeted cancer therapy needs severe re-evaluation, at the very least.

Thus, with that in mind, the readership of this Journal should also recognize this downturn as a new opportunity to develop future generations of NP-based therapeutic agents, to deliver both current cytotoxic and molecularly targeted agents and those that are in the development pipeline, as well as novel therapeutics directed at cancer stem cells. However, unlike the path that nanotechnologists have taken in the recent decade, greater heed must be taken that a complete and balanced picture is embraced of how NP-based drug delivery can enhance the therapeutic index, and how critical the optimal exploitation and even manipulation of the EPR effect is to this quest.

We can, and must, do better.

Yours Sincerely,

Jim Klostergaard

Cite this article

Alpay NS, Klostergaard J (2013) The EPR Effect as the Critical Event in the Decathlon of Nanoparticle Targeting to Tumors. JSM Nanotechnol Nanomed 1(2): 1011.