

There is Plenty of Room at the Bottom for Improving Chemotherapy: Exploiting the EPR Effect with Nanotechnology

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Despite the efforts made by countless researchers worldwide on improving anticancer therapies, the treatment of several kinds of cancers is still a major challenge in medicine. For some types of malignant tumors such as those of the oral cavity [1], the patients' survival rates have not significantly increased over the last decades. One reason for this is that chemotherapy, one of the main options for treating cancer, has not been significantly improved since its inception more than 70 years ago [2]. The therapeutic indexes of anticancer drugs are generally low [3], well below those observed for most of the drugs. Their toxicity severely limits their dose. Although a few good exceptions exist such as imatinib (Glivec[®]), which is effective and particularly selective to chronic myelogenous leukemia cells, an ideal drug to treat malignant tumors is not yet available [2].

The pertinent literature clearly shows that the toxicity of chemotherapeutic agents towards healthy tissues is one of the main factors limiting the success of chemotherapy [3,4]. Thus, one could reasonably expect that increasing the selectivity of anticancer drugs to the tumor would significantly improve chemotherapy outcomes. Not only new drugs are necessary, but also new formulations.

Indeed this is what many researchers have been looking for, mainly over the last two decades. It was found out that by associating drugs to certain macromolecules, macromolecular complexes or particles known as drug delivery systems (DDS), it was possible to increase the tumor selectivity in comparison to conventional formulations. A review on this issue can be found elsewhere [4].

Since the first seminal studies on anticancer DDS [5], pharmaceutical technology has brought to light a plenty of possibilities for improving selectivity of chemotherapeutic drugs to tumors. But, how do these DDS work? In chemotherapy, an ideal DDS delivers an anticancer drug to the tumor tissue while preventing it to reach healthy, non-target tissues. Such a system may be designed on the basis of a careful analysis of tumor pathophysiology. In this context, it is known that solid tumors often present a defective vascular architecture, with a more permeable endothelial lining than that of healthy tissues. Generally, this leaky, tumor-associated vasculature but not that of healthy tissues, allows for particles ranging from 200 to 800 nm in diameter to reach the interstitial space [6]. Moreover, particles stay longer in the tumor than in healthy tissue interstitium because of the impaired lymphatic drainage, commonly observed in solid tumors. This phenomenon is known as the enhanced permeation and retention (EPR) effect. It allows for DDS to passively accumulate in solid tumors, provided they are small enough to permeate tumor vasculature; large enough to be incapable of crossing walls vessels of healthy tissues and present a sufficiently long circulation time.

Nanostructures can be easily designed to have those characteristics. Nanotechnology offers tools for controlling DDS size at the nanoscale, and to prolong their circulation time in the bloodstream [7]. Thus, exploiting the EPR effect should be viewed as a fundamental point

to be taken into account, when one designs a nanostructured DDS. It is really not difficult in nanotechnology. Moreover, there are plenty of methods that allow for the association of virtually every chemotherapeutic drug to a nanostructure. The compartmentalized nature of a nanostructure can also be used for associating different synergic drugs in a single DDS, and to functionalize its surface in order to achieve active targeting of tumors [8]. Controlled drug release can be also achieved with nanostructures, if necessary.

Thus, it is possible to improve chemotherapy with nanotechnology. Although some problems presented by nano-based DDS, mainly related to the tumor idiosyncrasy still remain to be solved, solid laboratory and clinical evidences already show that nanostructures have the potential to revolutionize chemotherapy [2,6]. The dose-limiting toxicity presented by classical anticancer drugs may be circumvented with nano-based solution. As Richard Feynman said, "there is plenty of room at the bottom". Taking advantage of what is down; there may be a way to really improve chemotherapy.

References

1. Sargeran K, Murtomaa H, Safavi SM, Vehkalahti MM, Teronen O (2008) Survival after diagnosis of cancer of the oral cavity. *Br J Oral Maxillofac Surg* 46: 187-191.
2. Maeda H (2012) Macromolecular therapeutics in cancer treatment: The EPR effect and beyond. *J Control Release*.
3. McGuire WP 3rd, Markman M (2003) Primary ovarian cancer chemotherapy: current standards of care. *Br J Cancer* 89: S3-S8.
4. Brannon-Peppas L, Blanchette JO (2004) Nanoparticle and targeted systems for cancer therapy. *Advanced drug delivery reviews* 56: 1649-1659.
5. Bresseur F, Couvreur P, Kante B, Deckers-Passau L, Roland M, et al. (1980) Actinomycin D adsorbed on polymethylcyanoacrylate nanoparticles: increased efficiency against an experimental tumor. *Eur J Cancer* 16: 1441-1445.
6. Torchilin V (2011) Tumor delivery of macromolecular drugs based on the EPR effect. *Adv Drug Deliv Rev* 63: 131-135.
7. Muehlmann LA, Joanitti GA, Silva JR, Longo JP, Azevedo RB (2011) Liposomal photosensitizers: potential platforms for anticancer photodynamic therapy. *Braz J Med Biol Res* 44: 729-737.
8. Marcucci F, Lefoulon F (2004) Active targeting with particulate drug carriers in tumor therapy: fundamentals and recent progress. *Drug Discov Today* 9: 219-228.

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