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Cancer nanotechnology: The impact of passive and active targeting in the era of modern cancer biology ☆

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ABSTRACT

Cancer nanotherapeutics are progressing at a steady rate; research and development in the field has experienced an exponential growth since early 2000's. The path to the commercialization of oncology drugs is long and carries significant risk; however, there is considerable excitement that nanoparticle technologies may contribute to the success of cancer drug development. The pace at which pharmaceutical companies have formed partnerships to use proprietary nanoparticle technologies has considerably accelerated. It is now recognized that by enhancing the efficacy and/or tolerability of new drug candidates, nanotechnology can meaningfully contribute to create differentiated products and improve clinical outcome. This review describes the lessons learned since the commercialization of the first-generation nanomedicines including DOXIL® and Abraxane®. It explores our current understanding of targeted and non-targeted nanoparticles that are under various stages of development, including BIND-014 and MM-398. It highlights the opportunities and challenges faced by nanomedicines in contemporary oncology, where personalized medicine is increasingly the mainstay of cancer therapy. We revisit the fundamental concepts of enhanced permeability and retention effect (EPR) and explore the mechanisms proposed to enhance preferential "retention" in the tumor, whether using active targeting of nanoparticles, binding of drugs to their tumoral targets or the presence of tumor associated macrophages. The overall objective of this review is to enhance our understanding in the design and development of therapeutic nanoparticles for treatment of cancers.

Contents

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1. Introduction

More than 40 years ago, the foundations were laid down for nanotechnologies to deliver therapeutic and diagnostic agents in a safer and more efficient manner [1]. Achieving this vision became more realistic in recent years, with increasing numbers of nanotherapeutics and nanodiagnostics being commercialized or having reached clinical stage. In addition other important bench-to-bedside milestones are being achieved. In 2010, the first clinical evidence of gene silencing was obtained by systemically-administered targeted nanoparticles (NPs) delivering siRNA therapeutics [2]. Other clinical evidences of RNA interference have been obtained since then [3]. In parallel, clinical investigation of the first actively-targeted polymeric NPs, BIND-014, for the delivery of a small molecule drug (docetaxel) was reported [4]. Although only a relatively small number of nanosized drug delivery carriers have been approved for human use so far, it is now accepted that nanotechnologies will likely constitute a growing share of the oncologist's therapeutic arsenal over the next decades to come [5–7]. There are many nanoparticle technologies under development and a great majority are still without preclinical proof of concept. However, what is exciting is the momentum in this field: of the 81,000 articles on "nanoparticle" reported in Pubmed as of November 2013, more than half were published since 2010, emphasizing that research efforts are growing exponentially.

Nanoparticles offer the possibility to encapsulate poorly soluble drugs [8,9], protect therapeutic molecules [10], and modify their blood circulation and tissue distribution [11,12]. These properties are attractive in oncology in order to encapsulate cytotoxics exhibiting wide-ranging toxicities and physicochemical properties. For instance, liposome-encapsulated doxorubicin (DOX) decreases cardiac toxicity of the cytotoxic drug [13,14], and albumin-stabilized paclitaxel (nab-PTX) allows higher tolerated doses in patients [15]. Lately, drugs that modulate cancer signaling pathways (*i.e.*, molecularly targeted therapies) have shifted the paradigm of cancer treatment in patients exhibiting specific genetic mutations [16]. Like their cytotoxic counterparts these targeted drugs have toxicities and suboptimal tumor distributions that motivate their encapsulation in therapeutic NPs [17]. Furthermore, the robustness and redundancy of the signaling networks as well as the cross-talk between molecular pathways often promote resistance in cancers treated with molecularly targeted therapies [18,19]. For many kinase inhibitors on-target activity requires sufficient plasma concentrations of the drug and molecular pathways can reactivate as plasma concentrations decline [20]. Using NPs to precisely control the tumor levels of protein kinase inhibitors could theoretically circumvent that problem and result in improved efficacy.

Nanotechnologies are also appealing because they can facilitate the combination regimens which are commonly practiced in cancer therapy. Having a single NP encapsulating multiple active pharmaceutical ingredients (API) could potentially offer synergistic effects to promote the efficacy of therapies, while limiting the risk of resistance. When multiple drugs are administered separately, each API acts according to its own distinct pharmacology. Because drugs differ in their pharmacokinetic and pharmacodynamic properties, there is no certitude that target cells or tissues will synchronously receive optimal levels of each therapeutic entity. Conversely, when drugs are combined in a single NP carrier, the spatiotemporal exposure of each drug can be controlled more precisely and this may translate to a synergistic action among the API. The timely co-delivery to cancer cells of multiple agents inhibiting distinct, essential pathways could provide improved anticancer effects. This synergy has been demonstrated for combinations of small molecular weight drugs *in vitro* [21], combinations of a cisplatin prodrug and siRNA *in vivo* [22] or the combination of siRNA targeting 2 different genes in humans [3], highlighting the potential of encapsulating multiple API in a single carrier. Nevertheless, the determination of optimal therapeutic combinations using NPs is challenging. In opposition to conventional anticancer regimens where the dose of each single drug can be adjusted individually in patients (*i.e.*, based on their response or susceptibility to toxicities), the ratios of the different APIs encapsulated in a NP need to be optimized *a priori*, during the development phase. The large diversity of regimens possible makes the selection of ideal combinations difficult. Furthermore, temporal exposure to the different therapeutic components might also be important to maximize efficacy and avoid syngerstic toxicities. Anticancer treatments undeniably impact transcriptional response in the tumor microenvironment and cancer cells, sometimes with important impact on subsequent response to chemotherapy (for example through p53 gene down-regulation or WNT16B expression) [23,24]. Combination regimens must therefore be designed so that the chronology of exposure to one agent does not affect the efficacy of the second drug. This might be particularly true for antiangiogenic agents where the shutdown of oxygen supplies has been shown to significantly reduce susceptibility of cancer cells to other chemotherapeutics [23]. Although it is feasible to independently control the release of APIs from a NP, the sequence of exposure must be specifically considered to maximize therapeutic synergism [25]. Robust chemistry, manufacturing and control processes also need to devised to address the complexities of the multi-API therapeutics for successful development and commercialization.

Currently, despite the broad interest surrounding nanomedicines, the development and clinical translation of NPs remain laborious.