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Nanotechnology-mediated targeting of tumor angiogenesis

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Abstract

Angiogenesis is disregulated in many diseased states, most notably in cancer. An emerging strategy for the development of therapies targeting tumor-associated angiogenesis is to harness the potential of nanotechnology to improve the pharmacology of chemotherapeutics, including anti-angiogenic agents. Nanoparticles confer several advantages over that of free drugs, including their capability to carry high payloads of therapeutic agents, confer increased half-life and reduced toxicity to the drugs, and provide means for selective targeting of the tumor tissue and vasculature. The plethora of nanovectors available, in addition to the various methods available to combine them with anti-angiogenic drugs, allows researchers to fine-tune the pharmacological profile of the drugs *ad infinitum* . Use of nanovectors has also opened up novel avenues for non-invasive imaging of tumor angiogenesis. Herein, we review the types of nanovector and therapeutic/diagnostic agent combinations used in targeting tumor angiogenesis.

Introduction

Since Judah Folkman emphasized the 'angiogenic switch' hypothesis for tumor progression in 1991, there has been a tremendous surge in targeting angiogenesis for cancer therapeutics [1]. In the past 30 years, many advances have been made in the field, with the elucidation of various angiogenic molecules that could be targeted to halt angiogenesis, and hence, tumor progression. Angiogenesis, the formation of new capillaries from preexisting vessels, is crucial for ensuring normal embryonic vascular development of all vertebrates, as well as regulating physiological processes such as menses and wound healing in adults [2– 4]. Deregulation of angiogenesis hence underlies pathologies characterized by vessel overgrowth (e.g. cancer) as well as vessel insufficiency (e.g. cardiovascular disease, CVD) [4].

It is now well-established that without angiogenesis, tumors cannot grow more than 2 mm in diameter [5– 7]. Studies in breast cancer patients have showed that angiogenesis positively correlates with the degree of metastasis, tumor recurrence and shorter survival rates, thus demonstrating the value of angiogenesis as a prognostic cancer marker [1, 8]. Tumor angiogenesis essentially entails the same sequences of events as physiological angiogenesis, however, the latter proceeds in an uncontrolled and excessive manner giving rise to leaky and tortuous vessels that are in a constant state of inflammation [6, 9]. This is mainly due by an

upregulation of angiogenic cytokines and growth factors, most notably the vascular endothelial cell growth factor (VEGF) and Angiopoietin (Ang) families, as well as integrins [10– 12]. Integrin $\alpha_v\beta_3$ is the best-characterized heterodimer that is upregulated in most cancer settings, both on the vasculature and on the tumor cells themselves [13, 14]. It is hence not surprising that these molecules are often targeted in both experimental and clinical cancer settings.

As such, the first U.S. Food and Drug Administration (FDA) approved anti-angiogenic therapy was the monoclonal antibody Bevacizumab (Avastin), that targets VEGF proteins overexpressed on colorectal cancer cells and their vasculature [15, 16]. In spite of the clinical success of Avastin, the majority of other such anti-angiogenic therapeutic agents have yet to pass phase II clinical trials, suggesting a new paradigm is essential to target aberrant angiogenesis.

Moving away from conventional chemotherapy

Engineering anti-angiogenic nanoparticles to suit our needs: Playing with nanovector backbone and drug coupling for therapeutic and imaging purposes

Since nanoparticles were first proposed by Marty JJ. *et al* . in 1978 as novel drug-delivery systems [39], their use as anti-cancer agents exploded during the 1980 s. However, only more recently (1995) have they been used to target angiogenesis [40]. Several nanovectors have been reported thus far in mediating anti-angiogenesis therapy and imaging of the tumor vasculature. These include an arsenal of synthetic and natural nanoparticles such as polymeric conjugates and polymeric nanoparticles; liposomes and micelles; synthetic organic nanoparticles such as dendrimers; carbon-based nanostructures such as carbon nanotubes and polyhydroxylated fullerenes; inorganic nanoparticles of gold, silver and iron-oxide; quantum dots; viral capsids and ferritin. The plethora of nanovectors allows researchers to fine-tune the properties of the drugs depending on their target. Further fine-tuning is also possible depending on the method of drug-nanovector coupling, thus offering the potential to engineer revolutionary therapeutics in the field of angiogenesis. Herein, we review the different types of nanovectors that have been studied to formulate anti-angiogenic agents for imaging and therapeutic purposes, their main modifications, as well as their advantages and limitations.

New generation research in anti-angiogenesis therapy

Apart from the more conventional approaches of arraying small molecule chemotherapeutic drugs or antibodies on different synthetic or natural nanovectors to achieve anti-angiogenic effects, new research reports are emerging that target the molecular mechanism of angiogenesis by using approaches such as gene silencing and others. In the following sections, we will review some of these emerging new strategies.

Concluding Remarks and Future Directions

The tumor neovasculature is an attractive target for anti-angiogenic therapy as well as non-invasive imaging studies. Nanotechnology has emerged as an exciting field in this area of research due to multiple advantages, including the capacity of nanoparticles to carry multiple moities of therapeutic and imaging agents, offer longer circulation time and increase the therapeutic index of chemotherapeutcs, to name a few. Moreover, with the various types of nanovectors available, many of which are FDA-approved, along with the various methods for coupling them to drugs and diagnostic agents, there is an endless opportunity to fine-tune nanotherapeutics depending on the task needed. Clearly, the advent of nanothechnology provides a huge potential for devising increasingly novel anti-angiogenic therapeutics that can eventually be translated from bench to bed-side.

Declarations

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DB and RH collected the references and compiled the manuscript; DB, RH and SS edited the manuscript. All authors read and approved the final manuscript.

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