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Review

New trends in guided nanotherapies for digestive cancers: A systematic review

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ABSTRACT

Digestive tract tumors are among the most common and deadliest malignancies worldwide, mainly due to late diagnosis and lack of efficient therapeutics. Current treatments essentially rely on surgery associated with (neo)adjuvant chemotherapy agents. Despite an upfront response, conventional drugs often fail to eliminate highly aggressive clones endowed with chemoresistant properties, which are responsible for tumor recurrence and disease dissemination. Synthetic drugs also present severe adverse systemic effects, hampering the administration of biologically effective dosages. Nanoencapsulation of chemotherapeutic agents within biocompatible polymeric or lipid matrices holds great potential to improve the pharmacokinetics and efficacy of conventional chemotherapy while reducing systemic toxicity. Tagging nanoparticle surfaces with specific ligands for cancer cells, namely monoclonal antibodies or antibody fragments, has provided means to target more aggressive clones, further improving the selectivity and efficacy of nanodelivery vehicles. In fact, over the past twenty years, significant research has translated into a wide array of guided nanoparticles, providing the molecular background for a new generation of intelligent and more effective anti-cancer agents. Attempting to bring awareness among the medical community to emerging targeted nanopharmaceuticals and foster advances in the field, we have conducted a systematic review about this matter. Emphasis was set on ongoing preclinical and clinical trials for liver, colorectal, gastric and pancreatic cancers. To the best of our knowledge this is the first systematic and integrated overview on this field. Using a specific query, 433 abstracts were gathered and narrowed to 47 manuscripts when matched against inclusion/exclusion criteria. All studies showed that active targeting improves the effectiveness of the nanodrugs alone, while lowering its side effects. The main focus has been on hepatocarcinomas, mainly by exploring glycans as homing molecules. Other ligands such as peptides/small proteins and antibodies/antibody fragments, with affinity to either tumor vasculature or tumor cells, have also been widely and successfully applied to guide nanodrugs to gastrointestinal carcinomas. Conversely, few solutions have been presented for pancreatic tumors. To this date only three nanocomplexes have progressed beyond pre-clinical stages: i) PK2, a galactosamine-functionalized polymeric-DOX formulation for hepatocarcinomas; ii) MCC-465, an anti-(myosin heavy chain a) immunoliposome for advanced stage metastatic solid tumors; and iii) MBP-426, a transferrin–liposome–oxaliplatin conjugate, also for advanced stage tumors. Still, none has been approved for clinical use. However, based on the high amount of pre-clinical studies showing enthusiastic results, the number of clinical trials is expected to increase in the near future. A more profound understanding about the molecular nature of chemoresistant clones and cancer stem cell biology will also contribute to boost the field of guided nanopharmacology towards more effective solutions.

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Contents

1. Introduction

Gastrointestinal carcinomas are a heterogeneous group of malignancies of the digestive track, which includes namely, esophagus, stomach, liver, pancreas and colorectal tumors, which all together represent one of the major leading causes of death by cancer worldwide [1]. Colorectal, gastric and hepatic cancers not only present the highest incidence but also the most elevated mortality rates [1]. These tumors are often diagnosed in an advanced stage and their rapid metastatic rates constitute a major poor prognosis factor [2]. Furthermore, disease management relies mostly on surgery in association with (neo)adjuvant chemotherapy agents, namely, Anti-metabolites (5-fluorouracil, 5-FU), Topoisomerase inhibitors (Doxorubicin, DOX), Platinum Salts (Cisplatin), Anthracycline drugs (Epirubicin, EPI), Taxanes (Paclitaxel, PTX) and/or radiotherapy [3].

Conventional chemotherapy, while efficient against the tumor bulk, often fails to eliminate subpopulations of highly aggressive cancer cells endowed with chemotherapy resistance, capability of enhance tumor heterogeneity and develop metastasis [4,5]. Drug resistance is considered a multifactorial process highly influenced by inadequate pharmacokinetics of the drugs and abnormal tumor vascularity, resulting in the delivery of suboptimal concentrations of the agents to tumor sites [5,6]. In addition, tumor cells may either present, or develop during the course of treatment, intrinsic molecular mechanisms to overcome the chemotherapeutic challenge [7–9]. Conventional chemotherapeutic agents are highly toxic, therefore limiting the dosage that can be administered to patients, and reducing the efficacy of the treatment [10–12]. Toxicity is a particularly critical matter for the elder population that constitute the majority of the patients diagnosed with gastrointestinal malignancies [13,14], urging the introduction of less toxic and more effective drugs.

Nanoencapsulation of chemotherapeutic agents by biocompatible molecules holds great potential to exceed some of the limitations of conventional chemotherapeutic agents, namely by enhancing the pharmacokinetics and efficacy of the drugs while reducing systemic toxicity [15,16]. Moreover, nanoencapsulation may improve the solubility of poorly water-soluble compounds and has the ability to deliver two or more drugs simultaneously upon co-encapsulation in the same nanocarrier [17]. Due to their nanoscale dimensions, nanomedicines preferentially target solid tumors in comparison to healthy tissues by exploiting vasculature imperfections [18]. Solid tumors present tortuous and poorly differentiated blood vessels (100–600 nm fenestrations), that in contrast to healthy vasculature (1–2 nm fenestrations) allow the extravasation of drugs with sizes up to several hundreds of nanometers [19,20]. Tumors also lack functional lymphatic drainage, making them unable to eliminate extravased nanomaterials. As a result, long-circulating nanoparticles (NPs) tend to accumulate in tumors over time, a mechanism known as enhanced permeability and retention (EPR) effect ((see Fig. 1A) revised by Maeda et al. [21]).

There are a variety of NP systems currently being explored for cancer therapeutics [22], including biodegradable nanocarriers as lipid-based [23], polymeric nanoparticles [24], dendrimers [25], micelles [26], and nondegradable nanocarriers, namely carbon nanotubes [27], mesoporous silica [28] and magnetic nanoparticles [29]. Cationic liposomes and biopolymers (Fig. 1B) are currently the two major carriers used to complex therapeutic payloads [30,31]. Functionalization of liposomes with polyethylene glycol (PEG) (Fig. 1B) or other inert hydrophilic polymers has allowed to reduce their negative-charged surface, and consequently the opsonization and clearance from the blood stream, increasing nanocarrier circulation half-lives [3,32]. Accordingly, Abraxane, a PTX albumin-stabilized nanoparticle formulation, has already been approved for breast, lung and pancreatic cancers and many others face late stage clinical trials [revised by Stirland et al. [33]]. Recently, several molecular strategies have been developed to overcome other physiological barriers posed by solid tumors. Namely, some effects derived from the tumor microenvironment, such as high interstitial fluid pressure and low extracellular pH, commonly presented by hypoxic niches. Furthermore NP biocompatibilization has allowed overcoming the selective permeability of cell membranes and endosomal sequestration and allowed specific organelle targeting [34,35].

Drug-loaded nanoparticles may accumulate in tumor tissues solely due to the EPR effect (passive nanocarriers) [36,37] or may actively target cancer cells [22,38]. Active targeting is achieved by functionalization of the nanocarrier surface with ligands that specifically recognize and bind to receptors overexpressed on the surface of tumor cells [22,39]. The most common homing molecules include monoclonal antibodies (mAb) or antibody fragments (such as antigen-binding (Fab′) or single chain variable fragments (scFv)) [40], peptides and proteins [41], carbohydrates [42] and, more recently, aptamers [43]. This new generation of "intelligent" anti-cancer agents has enhanced target cell recognition, cell uptake and tissue microdistribution in comparison to non-guided nanotherapeutics [6–9,14]. Namely, several reports show that targeted nanoencapsulated drugs preferentially bind to cancer cells within the tumor bulk, whereas non-targeted vehicles accumulated in the tumor stroma, limiting their action [44,45]. The affinity of guided nanodrugs to tumor cells also avoids their translocation back to the circulation, thereby improving their efficacy [39]. Ideal targeted cell receptors should be tumor specific, homogeneously expressed on the tumor cell surface and should not be shed into the blood circulation, which would contribute to reduce the nanodrug bioavailability [22,46]. Moreover, internalization of targeting conjugates must also occur by receptor-mediated endocytosis after binding to target cells, facilitating drug release inside malignant cells [47–49].