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Invited critical review

Targeted anticancer therapy: Overexpressed receptors and nanotechnology

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ABSTRACT

Targeted delivery of anticancer drugs to cancer cells and tissues is a promising field due to its potential to spare unaffected cells and tissues, but it has been a major challenge to achieve success in these therapeutic approaches. Several innovative approaches to targeted drug delivery have been devised based on available knowledge in cancer biology and on technological advancements. To achieve the desired selectivity of drug delivery, nanotechnology has enabled researchers to design nanoparticles (NPs) to incorporate anticancer drugs and act as nanocarriers. Recently, many receptor molecules known to be overexpressed in cancer have been explored as docking sites for the targeting of anticancer drugs. In principle, anticancer drugs can be concentrated specifically in cancer cells and tissues by conjugating drug-containing nanocarriers with ligands against these receptors. Several mechanisms can be employed to induce triggered drug release in response to either endogenous trigger or exogenous trigger so that the anticancer drug is only released upon reaching and preferentially accumulating in the tumor tissue. This review focuses on overexpressed receptors exploited in targeting drugs to cancerous tissues and the tumor microenvironment. We briefly evaluate the structure and function of these receptor molecules, emphasizing the elegant mechanisms by which certain characteristics of cancer can be exploited in cancer treatment. After this discussion of receptors, we review their respective ligands and then the anticancer drugs delivered by nanotechnology in preclinical models of cancer. Ligand-functionalized nanocarriers have delivered significantly higher amounts of anticancer drugs in many *in vitro* and *in vivo* models of cancer compared to cancer models lacking such receptors or drug carrying nanocarriers devoid of ligand. This increased concentration of anticancer drug in the tumor site enabled by nanotechnology could have a major impact on the efficiency of cancer treatment while reducing systemic side effects.

Contents

Abbreviations: Bn, bombesin; BnR, bombesin receptor; BR, biotin receptor; c(RGD-K), cyclic {Arginine-Glycine-Aspartic acid (RGD)} containing peptide; CA, cholic acid; DOX, doxorubicin; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ETRB, endothelin receptor B; FA, folic acid; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FR, folate receptor; FSH, follicle stimulating hormone; FSHR, follicle stimulating hormone receptor; NPs, nanoparticles; Nrp-1, neuropilin receptor-1; PEG, poly(ethylene glycol); PLA, poly(lactic acid); PTMC, poly(trimethylene carbonate); PTX, paclitaxel; QDs, quantum dots; S1R, sigma receptor 1; S2R, sigma receptor 2; SRs, sigma receptors; SSTRs, somatostatin receptors; Tf, transferrin; TfR, transferrin receptor.

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1. Introduction

More than 10 million patients are diagnosed with new cases of cancer every year, and approximately 27 million new cases of cancer will have been recorded by 2030 [1,2]. While cytotoxic chemotherapeutic agents such as paclitaxel (PTX) and doxorubicin (DOX) effectively kill cancer cells, they cannot distinguish cancer cells from normal cells. This lack of selectivity leads to undesirable systemic toxicity when patients are exposed to the high dosages of cytotoxic agents required to eradicate the tumor. Improving the selectivity of anticancer drug delivery to cancer cells and the tumor microenvironment while sparing normal cells and tissues is a major challenge in the effective treatment of cancers of various tissues and organs. Marked differences are found in cancer cells and tissues in terms of biochemical, molecular and physiological features when compared with normal cells and tissues such as differences in redox status, pH levels, expression of certain cell membrane receptors, the leakiness of tumor tissues and the tumor vasculature. Therefore, cancer stands out as a disease likely to benefit from targeted drug delivery approaches exploiting these differences. These differences between healthy and cancerous cells and tissues, or hallmarks of cancer, have recently been reviewed [3].

Differences in normal and cancer biology are found at the level of anatomy, biochemistry and molecular biology. The characteristic anatomic features of tumor biology include the leakiness of blood vessels and poor lymphatic drainage in tumor tissues. The morphology and shape of blood endothelial cells are different in cancer vasculature due to the presence of fenestrae between adjacent cells, and thus the lack of contact inhibition. Most solid tumors, upon reaching a certain level of growth, exhibit enhanced vascular permeability, ensuring a sufficient supply of nutrients and oxygen to tumor tissues and outpacing the growth of surrounding tissues. Blood vessels in tumors are often dilated and convoluted, and compared with normal tissues, exhibit branching patterns that feature excessive loops and arteriolar–venous shunts [4]. All these features enhance the permeability of blood vessels in tumors compared with the vasculature in normal tissues, enabling the delivery and accumulation of molecules and other substances in tumor tissues that are generally not able to enter the vasculature in normal tissues. This is called the enhanced permeability and retention (EPR) effect, a phenomenon associated with the tumor vasculature. The net result of the EPR effect for circulating molecules depends on their properties including size, shape, charge, and polarity. The principal difference between EPR and passive localization lies in the characteristics of retention and tissue clearance rather than uptake. Small drug molecules rapidly penetrate into the tumor interstitial space, but in the absence of specific binding to cellular proteins, drug is not retained and may be free to diffuse out of the tissue back into the blood pool or the lymphatic system. In contrast, macromolecules have smaller diffusion constants, reducing the initial rate of tumor uptake but also tending to increase the half-life of blood-pool circulation by enhancing tissue retention and decreasing the rate of clearance [5]. Therefore, receptor–ligand interactions are the most important aspect of active targeting of nanocarriers (or nanoconjugates or macromolecules) and could be further potentiated by EPR (Fig. 1). The biochemical conditions of acidity (lower pH value) and hypoxia (lower concentration of oxygen) generally prevail in cancer cells and tumor tissues. The extracellular pH in tumor tissue is slightly lower than that in normal tissue, and this difference has been exploited to achieve pH-triggered drug release in tumor tissue [6]. A diverse group of functional materials has been designed to accomplish triggered drug release in response to other stimuli such as temperature [7,8], redox potential [9], ultrasound [10], and light [11]. These mechanisms of endogenously or exogenously triggered drug release [12] can only be applied once the anticancer drug reaches and accumulates at the desired site, *i.e.*, tumor tissues. Molecular markers of cancer include the differential expression of proteins residing in the cytosol, organelles or membrane. The group of differentially expressed proteins includes receptors that are specifically expressed or overexpressed in cancer cells compared to normal cells. These overexpressed receptors have provided important endogenous tools for exploitation in the active targeting of drugs to cancer cells. Targeting nanocarriers to a particular organ or tissue through the blood or lymph circulation is referred to as primary targeting, while the accumulation around a cancer cell is named secondary targeting and manipulating the uptake of nanocarriers/drugs by cells and cellular compartments is known as tertiary targeting [13]. This review focuses on overexpressed receptors exploited for targeting drugs to cancer and the tumor microenvironment (Table 1). We briefly evaluate the structure and function of these receptor molecules, emphasizing the elegance of exploiting characteristics of cancer in cancer treatment. After discussing these receptors, their respective ligands are mentioned, followed by a review of the anticancer drugs that have been delivered by nanotechnology in preclinical models of cancer (Table 2).

2. Overexpressed receptors, their ligands, and drug delivery to cancer using nanotechnology

Receptors overexpressed or specifically expressed in cancers of various tissues and cells are listed in Table 1. These receptors provide unique opportunities to understand cancer biology and its treatment. In attempts to treat cancer, overexpressed receptors are directly modulated/inhibited by agents such as antibodies or antibody fragments, and also by other small chemicals that directly bind these receptors and block their activities. These treatment strategies thus block the consistent unwanted stimulus for uncontrolled cell division, thus blocking cancer progression. Other approaches to cancer therapy do not intentionally interfere with receptor function, but rather exploit *receptor overexpression* for the targeted delivery of effective anticancer drugs that do not discriminate between cancer and normal cells. These drugs can be guided by linking them to suitable ligands against such overexpressed receptors. The field of nanotechnology has developed the ability to synthesize an enormous variety of NPs, providing a platform for guiding and carrying drugs to cancer cells and tumor tissues. These NPs can be loaded with anticancer drugs and conjugated with ligands. Nanosized liposomes, dendrimers, micelles, metals, alloys, mixtures of inorganics and organics, and other materials have been synthesized by nanotechnology for use in diverse applications such as catalysis, sensing and medicine. NPs loaded with drug molecules and conjugated with receptor ligands have been variously termed as nanoconjugates, nano-formulations, nano-carriers, *etc*. Table 2 summarizes some recent outcomes of the nanotechnology-based interventions in the targeting of anticancer drugs in preclinical *in vitro* and *in vivo*