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Research review paper

Cancer hallmarks and malignancy features: Gateway for improved targeted drug delivery

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ABSTRACT

Cancer chemotherapy is mainly based on the use of cytotoxic compounds that often affect other tissues, generating serious side effects which deteriorate the quality of life of patients. Recent advancements in targeted drug delivery systems offer opportunities to improve the efficiency of chemotherapy, by the use of smaller drug doses with reduced side effects. In the gene therapy approach, this consists in improving the transformation potential of the gene delivery system. Interestingly, these systems further provide good platforms for the delivery of hydrophobic and low-bioavailability compounds, while facilitating the penetration of the blood-brain barrier. The present report provides an overview of biologically relevant cancer hallmarks that can be exploited to design effective delivery vehicles that release cytotoxic compounds specifically in cancer tissues, in a targeted manner. The relevance of each cancer marker is presented, with particular emphasis on the generation of these hallmarks and their importance in cancer cell biology.

1. Introduction

Cancer is one of the most serious health burdens in the world. According to the World Health Organization estimates, it causes more than 8.9 million deaths every year (Fitzmaurice et al., 2018). Affecting almost all types of tissues in the body, cancers are caused by a variety of factors, and more than 17.2 million new cases are diagnosed every year, which affects the lives of many more families (Forouzanfar et al., 2016; Fitzmaurice et al., 2018). Hence, developing effective approaches for cancer prevention, diagnosis and therapy is currently the focus of many research teams and clinicians across the world. In this quest, advancements in nanotechnology enable the use of nanomaterials as promising tools for both cancer diagnosis and therapy, especially as carriers for bioactive molecules or imaging probes (Lacombe et al., 2017). In fact, nanomaterials have been used to specifically modify the tumor microenvironment, regulate nutrients supply, and/or facilitate tissue repair following surgical resection (Hinderer et al., 2016; Springer and Fischbach, 2016). Moreover, some of these biomaterials exhibit cytotoxicity directed against tumor cells (Kaewkorn et al., 2012).

Cancer chemotherapy is based on the use of cytotoxic molecules that have the inherent ability to also affect normal cells, causing tremendous side effects that degrade the quality of life of patients, especially in the case of systemic chemotherapy (Brown et al., 2015). In addition, most effective cancer cell-killing compounds are hydrophobic, with poor solubility and low bioavailability in the biological milieu. Interestingly, using nanotechnology, targeted drug delivery strategies can be applied to circumvent these significantly limiting factors (Peer et al., 2007; Davis et al., 2008; Kakkar et al., 2017). Considered prodrugs, drug delivery systems are assemblies composed of bioactive molecules carried by/within a biomaterial associated with a targeting ligand, the whole system being capable to achieve appropriate spatiotemporal drug release (Srinivasarao et al., 2015). The carrier supports and ensures appropriate cohesion between the different elements of the complex, whereas the targeting ligand appears as the most important element of the system, as it guides the prodrug to the tumor cells where the bioactive compound is to be released (Kakkar et al., 2017; Shi et al., 2017). Therefore, the targeting ligand must be a molecule that specifically interacts with cancer cells, while sparing normal cells. To achieve this specific recognition, ligands are conceived based on specific phenotypes of cancer cells and their biology (Srinivasarao et al., 2015; Lin et al., 2017). In fact, during the transformation process that leads to malignant proliferation, cancer cells acquire several attributes that can be targeted in the design of drug delivery systems. These encompass modifications in metabolism, interactions with other cells, and the expression of membrane proteins along with regulating elements of

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the cell microenvironment (Hanahan and Weinberg, 2011).

Regardless of the cause or genotype of a cancer, the malignancy phenotype at the cellular level results in observable physicochemical modifications and distinct expression profile of membrane and cytoplasmic proteins, which can be used as markers for targeted cancer drug delivery. The main principles dictating the design of targeted drug delivery systems, along with their respective characteristics, were well-summarized by Srinivasarao et al. (2015); Srinivasarao and Low, 2017). Moreover, advancements in drug delivery systems have been discussed at tissue, cellular and subcellular levels, as well as in terms of system chemistry (Petros and DeSimone, 2010; Wang et al., 2015a, 2015b; Shen et al., 2017). In order to provide a comprehensive view of the importance of cancer biomarkers in cancer biology and their usefulness in targeted drug delivery, the present paper overviews the most significant cancer markers, with particular focus on their biological function in the malignancy phenotype. Moreover, the addressing systems utilized in the design of effective targeting systems are discussed.

2. Passive drug delivery systems

Oncogenesis is a transformation process during which normal cells undergo various changes to become cancerous, with overly increased proliferation (Hanahan and Weinberg, 2011). For the purpose of eradicating the transformed cells, each of the abnormal features can be subjected to a particular targeting strategy in the design of drug delivery vehicles. Passive delivery strategies consist in the use of drug delivery cargoes with the sole function of releasing drugs or imaging probes under physicochemical conditions that are particular to tumors or tumor microenvironments (Fig. 1). These systems can be qualified as targeted drug release rather than targeted drug delivery systems because they are passively transported to tumors. The transport of such systems to tumors takes advantage of the enhanced permeability and retention effect (EPR), which promotes the accumulation of particles and other small molecules in cancer tissues rather than healthy tissues (Maeda, 2010; Abdalla et al., 2018; Poudel et al., 2018). The EPR effect arises from the uncontrolled and rapid vascularisation of tumors. Due to accelerated angiogenesis, blood vessels in tumors present a leaky structure, thereby enhancing the penetration of nanoparticles (Greish, 2007). Furthermore, tumor cells exhibit poor lymphatic drainage, which likewise increases the accumulation of nanoparticles (Cairns et al., 2006; Kobayashi et al., 2014). When applied as targeted drug release systems, these particles discharge cytotoxic compounds that in turn induce the death of cancer cells. In this goal several release mechanisms may be exploited, by engaging pH-sensitive bonds, redox-sensitive bonds, or specific enzyme-cleavable bonds.

2.1. pH-sensitive drug release systems

Cancer cells are characterized by a typical metabolism that leads to a significantly lower cellular pH, distinguishing them from healthy cells. Indeed, in cancer cells, the increased proliferation rate demands high nutrient support, which causes a metabolic shift towards increased nutrient diffusion and accelerated anabolism (Gatenby and Gillies, 2008). This metabolic rewiring involves a preference for glucose as the carbon and energy source, with its overconsumption even in presence of oxygen via a phenomenon known as the Warburg effect (Warburg et al., 1927). The oxidative metabolism then results in a high rate of acidic by-product formation that contributes to the acidification of the tumor microenvironment, namely the extracellular matrix (ECM), the cytoplasm, and the endocytic vesicles (Asgharzadeh et al., 2017; Fouad and Aanei, 2017). Such metabolic deregulation is observed in all solid tumors, qualifying the acidic pH as an appropriate marker for the design of targeted drug release systems able to deliver cytotoxic molecules locally in cancer cells.

Based on pH sensitivity, various drug-releasing particles may be obtained by varying the type of carrier employed in the system, or by exploiting the array of pH-sensitive bonds that may be formed between the different elements of the system. For this purpose, the nanoparticle configuration is preferred (Ganta et al., 2008). Acetal and hydrazone bonds between drugs and biomaterials, or the use of acetal bonds between two different polymers have been reported for the design of such particles, to allow pH-dependent drug release (Yu et al., 2014; Xiao et al., 2017a, 2017b). These particles enabled the effective release of the anti-cancer drugs daunorubicin, docetaxel, and paclitaxel under acidic conditions (pH ~ 5.5), leading to cytotoxicity in cancer cell lines and xenograft tumors (Zhang et al., 2016). Moreover, a pH-sensitive system based on hydrazone bonds was also designed both for the delivery of doxorubicin and for the preparation of magnetic resonance probes for enhanced MRI contrast (Chang et al., 2011; Etrych et al., 2011). Particles exploiting the instability of orthoester and diorthoester bonds under acidic conditions were also fabricated and were able to successfully deliver doxorubicin with enhanced cytotoxicity (Zha et al., 2017). Other functional groups exploited include vinyl ether, phosphoramidate and β-thiopropionate linkers, which have shown pH sensitivity in cancer cells, as reviewed by Romberg et al. (2008). Besides, a high protonation level of basic functional groups on the surface of materials such as poly(amidoamine) dendrimers (PAMAM) and polyhistidine may be harnessed for the pH-dependent release of drugs bound via electrostatic interactions, or nucleic acids (DNA plasmids and siRNAs) adsorbed by complexation (Wang et al., 2013; Zhang et al., 2015).

2.2. Redox-sensitive drug delivery systems

As another form of passive drug release, redox-sensitive systems are based on the use of cargoes built with specific bonds that can be broken under particular redox conditions (Ganta et al., 2008). The unique ability of cancer cells to produce larger amounts of glutathione (GSH) as compared to normal cells is exploited in this context. The most common approach for the design of such systems is the use of disulfide bonds, sensitive to GSH activity (Saito et al., 2003).

In healthy cells, the balance between the amount of reactive oxygen species and antioxydant molecules maintains an overall redox potential in the cytoplasm necessary for the normal function of every cellular component and macromolecule. Any alteration in this equilibrium through excessive oxidative stress is one of the most commonly observed scenarios in cancer. Oxidative stress actually causes various deleterious effects, among which DNA damage inducing cellular transformations, chronic inflammation, and cancerous differentiation (Reuter et al., 2010). Furthermore, in cancer cells, the sustained oxidative stress results in the overexpression of GSH, one of the key elements involved in the maintenance of the redox equilibrium. Additionally, glutathione peroxidase, an enzyme that converts GSH to GSSG, the oxidized form of glutathione, is down-regulated in cancer cells, which also leads to an accumulation of GSH (Chen et al., 2017a, 2017b). Under such conditions, due to the ability of GSH to disrupt disulfide bonds, drug release systems presenting these bonds are more likely to be cleaved in cancerous tissues rather than normal cells, thus activating the localized release of toxic molecules. This strategy proved efficient in the delivery of various chemotherapeutic agents contained in nanogels, micelles and nanoparticles (Chen et al., 2016a; Kumar et al., 2017). For example, in combination with a tumor-penetrating cyclopeptide, glutathione-based redox-sensitive nanoparticles were fabricated that delivered interfering RNAs in cancer cells both *in vitro* and *in vivo* (An et al., 2015). Aside the accumulated GSH, another facet of oxidative stress in cancer cells may also be exploited, through the use of intracellular reactive oxygen species-sensitive bonds such as thioketals (Xu et al., 2017).

2.3. Enzyme-dependent targeted release

Proteases and peptidases are hydrolytic enzymes that fulfil various