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Review

Towards targeted cancer therapy: Aptamer or oncolytic virus?

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ABSTRACT

Cancer is a leading cause of global mortality. Whilst anticancer awareness programs have increased significantly over the years, scientific research into the development of efficient and specific drugs to target cancerous cells for enhanced therapeutic effects has not received much clinical success. Chemotherapeutic agents are incapable of acting specifically on cancerous cells, thus causing low therapeutic effects accompanied by toxicity to surrounding normal tissues. The search for smart, highly specific and efficient cancer treatments and delivery systems continues to be a significant research endeavor.

Targeted cancer therapy is an evolving treatment approach with great promise in enhancing the efficacy of cancer therapies via the delivery of therapeutic agents specifically to and into desired tumor cells using viral or non-viral targeting elements. Viral oncotherapy is an advanced cancer therapy based on the use of oncolytic viruses (OV) as elements to specifically target, replicate and kill malignant cancer cells selectively without affecting surrounding healthy cells. Aptamers, on the other hand, are non-viral targeting elements that are single-stranded nucleic acids with high specificity, selectivity and binding affinity towards their cognate targets. Aptamers have emerged as a new class of bioaffinity targeting elements can be generated and molecularly engineered to selectively bind to diverse targets including proteins, cells and tissues. This article discusses, comparatively, the potentials and impacts of both viral and aptamer-mediated targeted cancer therapies in advancing conventional drug delivery systems through enhanced target specificity, therapeutic payload, bioavailability of the therapeutic agents at the target sites whilst minimizing systemic cytotoxicity. This article emphasizes on effective site-directed targeting mechanisms and efficacy issues that impact on clinical applications.

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1. Introduction

Cancer continues to be one of the primary causes of global mortality. It is estimated that approximately 1.6 million new cancer cases with around 580 thousands deaths were recorded in the United States in 2015 (Siegel et al., 2015). Cancer originates from uncontrolled cell division with potential metastasis into other normal neighboring tissues. It is caused by internal factors (such as extreme hormonal changes, inherited genetic disorders, immunity, and family history), external factors (such as poor diet, unhealthy lifestyles, tobacco, and alcohol), and environmental factors (such as exposure to chemicals, ultraviolet light, radiation, pollution, and infectious organisms) (Ferlay et al., 2015; American Cancer Society, 2015), and it is often diagnosed only after years of exposure to these factors. Cancerous cells differ from other normal cells by unlimited replication and proliferation, persistent angiogenesis, metastasis, evading apoptosis, and invading tissues (Li et al., 2014a, 2014b; Singh et al., 2012). These cancerous/tumor cells can survive even with redundant signaling pathways (Li et al., 2014a, 2014b).

Today, there are various cancer treatments available. These include surgery, chemotherapy, radiotherapy, immune therapy, and targeted therapy. Although recent advances in medicine have resulted in increased patient survival rates, cancer recurrence after recovery still persists, and this is a key hindrance to long-term survival (Smith et al., 2013). Targeted therapy is the most advanced form of cancer therapies aimed at delivering treatment to specific and targeted cancerous cells with minimal cytotoxic effects (Shaikh, 2012). It makes use of targeting agents which are either viral or non-viral elements with specific functional features (Kim et al., 2011b).

Viruses have been demonstrated as effective vaccination vectors and are now developed as novel antitumor agents with the capability of activating lytic activity and antitumor immune responses (Woller et al., 2014). They can kill cancerous cells via diverse mechanisms including apoptosis, autophagy, direct lysis, necrosis, toxic protein expression and immune response stimulation (Wong et al., 2010). Viral vectors are widely used as effective therapeutic delivery vehicles for both in vitro and in vivo gene expression for cancer treatment (Giacca and Zacchigna, 2012). Examples include the activation of the immune system by delivering genes that encode for co-stimulatory proteins into tumor cells; and the inhibition of tumor cell proliferation by hindering the regulatory proteins of the cell cycle (Giacca and Zacchigna, 2012). Over the past decades, viral oncotherapy has been used widely in cancer treatments for specific tumor targeting and inactivation due to the inherent anticancer properties of oncolytic viruses (OV) that enable them to replicate, spread and kill tumor cells without damaging surrounding normal non-cancerous cells (Singh et al., 2012; Russell and Peng, 2007; Lu et al., 2012; Chiocca and Rabkin, 2014). OVs are made of DNA and RNA viruses that are either tumor selective by nature or genetically-engineered (Chiocca and Rabkin, 2014). OVs employed in cancer treatments are often non-pathogenic naturally occurring viruses of either the wild-type that are only cytotoxic to malignant cells (Cripe et al., 2009), or naturally-existing mutants that are attenuated (Eager and Nemunaitis, 2011). The first commercialized OV anticancer drug is the H101 type 5 adenovirus with E1B-55KD and partial deletions of E3 gene. This OV anticancer drug was granted in 2005 by Chinese regulators as a result of its safety and superior anti-tumor performance in treating head and neck cancer when combined with chemotherapy (Russell and Peng, 2007; Vähä-Koskela et al., 2007).

Non-viral targeting elements such as aptamers show significant therapeutic potential due to their favorable biophysical and biochemical characteristics such as low immunogenicity, high productivity, biodegradability and biocompatibility (Kim et al., 2011b). Aptamers are oligonucleotides which can either be single-stranded deoxyribonucleic acid (ssDNA) or ribonucleic acid (ssRNA) molecules (Sun et al., 2014). They are widely used as advanced cell targeting elements in clinical diagnostics and targeted therapeutic delivery due to their high selectivity, specificity and binding affinity to their targets (McKeague and DeRosa, 2012). Aptamers fold into specific 3-D structures (Song et al., 2012; Baird, 2010) to bind to their targets via hydrogen bonding, Van der Waal interactions, electrostatic interaction and/or hydrophobic interactions (McKeague and DeRosa, 2012; Upadhyay et al., 2013; Witt et al., 2015). The conformation of the interactions between an aptamer and its target is based on the 3-D structure of the aptamer. Systematic Evolution of Ligands by Exponential enrichment (SELEX) technology is an in vitro iterative selection process used to generate aptamers specific for a desired target with high binding affinity. The SELEX methodology comprises of repetitive selection, amplification and enrichment schemes until the library is enriched with a specific target clone to derive the aptameric sequence (Radom et al., 2013; Orava et al., 2010; Alibolandi et al., 2015). The emergence of several SELEX modifications allows the generation of aptamers with high specificity towards a wide range of targets including proteins, cells and tissues (Ye et al., 2012; Tan et al., 2016; Santosh and Yadava, 2014). Hence, they are often experimented and used as drug carriers for targeted pharmaceutical delivery and as biological drugs for therapeutic treatments. The approval of pegatanib aptamer by US Food and Drug Administration (FDA) in 2004 for the treatment of vascular age-related macular degeneration has become the landmark in the clinical applications of aptamers (Song et al., 2012). There are a number of therapeutic aptamers in clinical trials. For example, the nucleolin-specific AS1411 aptamer for treating acute myeloid leukemia and renal cell carcinoma (Sun et al., 2014), and the NU172 aptamer for targeting thrombin molecules to treat anticoagulation in heart disease (Song et al., 2012). This article discusses the prospects of aptamer-mediated targeted cancer therapies for enhanced cancer treatment in juxtaposition with viral oncotherapy. It focuses on the targeting mechanisms, challenges faced and milestones achieved by both OVs and aptamers as targeting agents for effective pharmaceutical delivery for cancer treatment.

2. Global cancer scenario

Cancer is a major global health problem causing about one in every seven deaths worldwide (American Cancer Society, 2015). The high mortality rate of cancer persists regardless of the significant developments in cancer therapies over the past few decades (Singh et al., 2012). It has been reported that over 60% of cancer deaths happen in low-medium resource economies due to poverty, ignorance, environmental pollution, and poor medical and health systems (Siegel et al., 2015). Notwithstanding the advancements in modern medicine, the global cancer 'epidemic' is increasing significantly. The American Cancer Society predicts that there will be approximately 21.7 million of new cancer cases with 13 million deaths in 2030 (American Cancer Society, 2015). According to GLOBOCAN, about 15 million new cancer cases and 8.8 million cancer mortality cases, excluding non-melanoma skin cancer, are expected globally in 2015 (Ferlay et al., 2013). It has been reported that about one-third of cancer cases in developed nations are due to unhealthy behaviors including poor nutrition, obesity, and physical inactivity (American Cancer Society, 2015). Cancers that are common in men are lung and bronchus, colorectal, prostate, pancreas and liver cancers whilst women are mostly diagnosed with breast, colorectum, pancreas, ovary, and lung and bronchus cancers (Siegel et al., 2015; Ferlay et al., 2015). According to American Cancer Society, the top five cancers in both men and women are breast, prostate, cervix uteri, lung and colorectal cancers (Siegel et al., 2015; Saranath and Khanna, 2014). Globally, most of the cancer related deaths are caused by lung, stomach and liver cancers (Sharma et al., 2014) (See Table 1.).

Cancer cases are expected to increase, and the challenge is to develop effective medical interventions to address this top public health concern. Cancer therapies such as chemotherapy and radiotherapy provide immediate pathways to treat cancerous cells, and have been partially or completely successful in many cases. However, these therapies are challenged with low therapeutic index due to their infectiveness to