Advancements in Genetic Engineering

Editorial

pH-sensitive Covalent Linkages in Dimeric DNA Aptamer Complexes for High-capacity–targeted Drug Delivery

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To improve cancer chemotherapy, cell-specific delivery of cytotoxic drugs through passive and active targeting is a key goal. The targeting vehicle must have the required dimensions for tumour localization through the enhanced permeability and retention effect, as well as bind to an antigen that is specifically expressed by targeted cells with high affinity. Drug delivery through a targeted approach has additional requirements in terms of drug complex stability: the drug must be held in the complex during targeting, which can take several hours, but released after binding to the targeted cell. Drug delivery should also be effective, with several drugs released for each complex that is successfully targeted. New targeted drug delivery methods that are stable and deliver a large payload are desperately needed.

Because of its elevated expression on the apical plasma membrane of prostate cancer (PCa) cells and in endothelial cells of the vasculature from various malignancies, prostate-specific membrane antigen (PSMA) is of importance for selective delivery of therapeutics for cancer treatment. PSMA is a folate hydrolase and NAALADase (N-acetylated-linked acidic dipeptidase) activities exopeptidase. PSMA is also a member of the anaphase-promoting complex, and its presence may contribute to aneuploidy. PSMA expression is expressed by prostate epithelial cells, but it is elevated in advanced PCa, like bone metastases, and PSMA expression levels are an independent predictor of PCa recurrence.

PSMA is found in the vasculature of a variety of cancers, including a high proportion of bladder, gastric, and colorectal cancers, as well as hepatocellular, renal, breast, and ovarian cancers. PSMA exists as a dimer, and dimerized ligands that target the PSMA dimer have higher activity than monovalent ligands.

Due to PSMA's limited expression, several attempts have been made to image and treat cancer using PSMA-targeted diagnostic and therapeutic modalities. Monoclonal antibodies like J591, RNA aptamers like A10-3, and small molecule inhibitors of PSMA enzymatic activity are the most commonly used molecules in these targeted applications. J591 radiolabeled conjugates are being studied for the treatment of advanced PCa and have previously been used for cancer imaging. Theranostic nanoparticles have been delivered to cancer cells using PSMA inhibitors. The A10-3 RNA aptamer to PSMA has been used to deliver cisplatin functionalized nanoparticles a micelle-encapsulated PI3K inhibitor toxins and small interfering RNA to cancer cells selectively. Aptamer targeting of PSMA may be particularly useful for anticancer drugs with severe systemic side effects, such as doxorubicin (Dox). Dox is one of the most commonly used chemotherapy drugs; however, it causes severe, often fatal cardiotoxicity that can manifest years after treatment, necessitating the creation of more targeted delivery methods.

There are some drawbacks to the existing approaches to Dox delivery using RNA aptamers that could be solved to boost patient outcomes. RNA aptamers are currently expensive to manufacture, require modified nucleotides for nuclease stability, and are commonly noncovalently associated with Dox. Noncovalent Dox complexes with duplex DNA are unstable, with half-lives of just a few minutes (or less), and noncovalent Dox complexes with aptamers are unlikely to be stable enough for optimal in vivo action. PSMA is expressed as a dimer on the plasma membrane, and dimerized ligands targeting PSMA have higher activity than monovalent ligands.