

Aptamer Functionalized Nanoparticles for Cancer Targeting

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Changes in the expression of key proteins of the cellular signaling pathways are at the forefront of molecular abnormalities found in cancer. An increasing number of proteins involved in cell growth, including growth factors, receptors, intracellular mediators and transcription factors have been found to be altered through multiple mechanisms of oncogene activation [1]. These abnormal membrane proteins serve as ideal biomarkers for disease diagnoses, therapeutics and prognosis. Hence, finding specific ligands capable to detect and measure their expression is a strategic objective for the diagnosis and therapy of cancer. These ligands should be able to bind and recognize with high affinity and specificity to surface receptors of tumor cells. Different types of molecules have shown great potential in achieving this goal, such as antibodies [2], folic acid [3], peptides [4,5], and aptamers [6].

Aptamers are short single-stranded nucleic acid oligomers (ssDNA or RNA) that can form specific and complex three-dimensional structures which can bind with high affinity to specific targets, including cancer cells. The term 'aptamer' is derived from the Latin word *aptus* meaning "to fit" [7]. A procedure to derive sequences recognizing specific targets was first described under the name of Systematic Evolution of Ligands by Exponential Enrichment (SELEX). The method enables isolating an aptamer of interest from a pool of randomized molecules by repeated steps of incubation with the target, partitioning and amplification, until the pool of molecules becomes enriched in a particular clone [8]. Aptamers have been selected against a wide variety of targets, from small molecules to proteins and even whole organisms [9,10] and present the same high specificity and affinity for their targets as antibodies. In addition to efficient binding, aptamers have seem to lack immunogenicity, can be chemically modified in order to improve their stability against nucleases or to modify their pharmacokinetics, can have inhibitory activity on their targets, and also straightforward modifications and functionalizations of aptamers make them ideal targeting agents.

The potential clinical utility of aptamers might be best appreciated by considering that an aptamer-based therapeutic (known as Macugen) has been approved by US FDA for the treatment of age-related macular degeneration [11].

The development of aptamers as therapeutic agents has primarily involved aptamers that bind and inhibit the activity of their protein targets, leading to desired antitumor activity. Another promising application of aptamers is to use their high binding specificity for designing targeting moieties to deliver any kind of imaging probes or secondary reagents to a given cancer cell or tissue, that is, the aptamer portion is designed to drive the complex containing a therapeutic or imaging agent toward the surface of the targeted ill cell. Once delivered, the functional complex, then impart their imaging or therapeutic effect selectively to the cancer cells of the patient. Despite the fact that non-targeted cells are exposed to the secondary reagent, the potential for unwanted side effects, such as death of normal cells is substantially reduced [12]. Due to the abovementioned promising characteristics

of aptamers, these molecules have been considered being an exquisite alternative to improve specificity of nanoparticles for both therapeutic and diagnostic applications.

Nanoparticles are defined as structures in a nanometer range (frequently less than 100nm) that can be able to extravasate through vessels accumulating in affected areas. Differently from other particles or molecules, nanoparticles present a huge surface area being able to achieve high payloads for therapeutic or diagnostic agents [13]. Two approaches can be used by these nanostructures to access tumor areas. First, nanoparticles can take advantage of the large fenestrations presented by tumor vessels in comparison to normal ones. As a result, particles in nanometer scale might be capable to leak from those vessels, accumulating in the tumor tissue. This phenomenon is known as Enhanced Permeability and Retention (EPR effect). In addition to the passive targeting, molecules can be attached onto the surface of such particles to provide higher specificity. This strategy is known as active targeting. Several molecules might be used to attain higher drug concentration in diseased tissues, such as aptamers [14].

Aptamer-conjugated nanostructures include iron oxide nanoparticles, gold nanoparticles, carbon nanotubes, dendrimers, quantum dots, liposomes, as well as soft and hard nanoparticles [14-21]. The key advantage of these drug delivery systems is their ability to alter the pharmacokinetics and biodistribution of a drug, reducing the effects on non-target tissues. Combining these delivery systems with aptamers provides the additional advantage of specificity. Unlike antibodies, aptamers can be chemically synthesized, making it feasible to add functional groups to their ends in order to facilitate linkage to nanoparticles. Moreover, aptamers, being nanoscale molecules, contribute little to the overall size of the nano-drug delivery composite, which is important for the passive uptake and transport of the nanoparticle drug delivery system through the microvasculature [22].

By integrating the advantages of nanoparticles with the cell-targeting capabilities of aptamers, aptamer-functionalized nanoparticles may afford a new path of designing solutions for biomedical applications. Bagalkot et al. [16] were the first to demonstrate aptamer based drug delivery *in vivo*. They showed that docetaxel (Dtxl) containing di-block copolymer nanoparticles functionalized with RNA aptamers could significantly decrease tumor with reduced toxicity compared to Dtxl alone [23]. Jianwei Guo et al. [24] developed a nanoparticulate

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drug delivery system (Ap-PTX-NP) decorated with AS1411, a DNA aptamer specifically binding to nucleolin, which was highly expressed in the plasma membrane of cancer cells, as the targeting ligand to improve the anti-glioma efficacy of paclitaxel (PTX), a widely used chemotherapeutic agent. Biodistribution study in xenograft nude mice models showed that at all time points, PTX concentrations determined in the tumor were higher for those animals that received Ap-PTX-NP than those who received PTX-nanoparticle or only PTX, and the accurate *in vivo* tumor targeting improved anti-glioma efficacy for PTX on rats-bearing intracranial C6 gliomas. In another study, Jalalian et al. [25] evaluated the use of 5TR1 aptamer – super paramagnetic iron oxide nanoparticles (SPIO) loaded with Epirubicin (therapeutic agent) for the imaging and treatment of murine colon carcinoma cells, showing that the complex was less cytotoxic to nontarget cells when compared to Epirubicin alone. Furthermore, Kim et al. [26] developed a cancer targeting theranostics probe in a single system using an AS1411 aptamer - and miRNA 221 molecular beacon conjugated magnetic fluorescence (MF) nanoparticle (MFAS miR-221 MB) to simultaneously target to cancer tissue, image intracellularly expressed miRNA-221 and treat miRNA-221- involved carcinogenesis. AS1411 aptamer-conjugated MF nanoparticles displayed a great selectivity and delivery into various cancer cell lines. The miR-221 MB detached from the MFAS miR-221 MB in the cytoplasm of C6 cells clearly imaged miRNA-221 biogenesis and simultaneously resulted in antitumor therapeutic effects by inhibiting miRNA function, indicating a successful astrocytoma targeting theranostics. Cao et al. [27] also recently reported cell specific drug delivery based on aptamer functionalized liposomes.

In conclusion, aptamers possess several advantages as specific targeted molecules when compared with other traditional substances used to this aim, such as antibodies, and peptides. Aptamers might overcome the drawbacks presented by antibodies (immunogenicity) and peptides (degradation) leading to high-specificity molecules for delivering nanoparticles into targeted area. These new nanoplatforms may be used as diagnostic probes, therapeutic agents, or even for both applications in multimodal nanostructures, as already published by some groups. Although much remain to be done to effectively translate those aptamers-functionalized nanoparticles to clinic, such as nanotoxicity studies, it is clear that conjugation of a high-specificity molecule, i.e. aptamer, poses many advantages over conventional approaches. We believe that due to their unusual characteristics, including extraordinary specificity conferred by aptamers is likely that such formulations will have major impact in the nanomedicine field in the near future.

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