REGIONAL CENTRE FOR BIOTECHNOLOGY

Seminar series

Application of Aptamers for Therapeutics

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Abstract

Aptamers are a class of oligonucleotide (RNA or DNA) ligands that share the same virtue of high affinity for their specific binders as antibodies and are generated by using SELEX (Systematic Evolution of Ligands by Exponential Enrichment). We devised an in vitro positive/negative selection strategy to identify RNA aptamers that could detect structural differences between the secretomes of pancreatic cancer and non-cancerous cells. Using this molecular recognition approach, we identified an aptamer (M9-5) that differentially bound conditioned media from cancerous and non-cancerous human pancreatic cell lines. This aptamer further discriminated between the sera of pancreatic cancer patients and healthy volunteers with high sensitivity and specificity. We utilized biochemical purification methods and mass-spectrometric analysis to identify the M9-5 target as cyclophilin B (CypB). This molecular recognition–based strategy simultaneously identified CypB as a serum biomarker and generated a new reagent to recognize it in body fluids. Moreover, this approach should be generalizable to other diseases and complementary to traditional approaches that focus on differences in expression level between samples.

Aptamers can also be used for the targeted delivery of drugs into diseased cells. Gemcitabine is a nucleoside analog that is currently the best available single-agent chemotherapeutic drug for pancreatic cancer. However, efficacy is limited by our inability to deliver sufficient active metabolite into cancer cells without toxic effects on normal tissues. Targeted delivery of gemcitabine into cancer cells could maximize effectiveness and concurrently minimize toxic side effects by reducing uptake into normal cells. Most pancreatic cancers overexpress epidermal growth factor receptor (EGFR), a trans-membrane receptor tyrosine kinase. We utilized a nuclease resistant RNA aptamer that binds and is internalized by EGFR on pancreatic cancer cells to deliver gemcitabine-containing polymers into EGFR-expressing cells and inhibit cell proliferation in vitro. This approach to cell type–specific therapy can be adapted to other targets and to other types of therapeutic cargo.