Title: NF-κB Decoy Polyplexes Decrease P-Glycoprotein-Mediated Multidrug Resistance in Colorectal Cancer Cells

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Multidrug resistance (MDR), a major cause for chemotherapy failure, has been linked to upregulation of ATP-dependent membrane efflux systems that limit intracellular accumulation of cytotoxic anticancer agents. P-glycoprotein (P-gp) encoded by the human ABCB1 gene was the first efflux transporter identified to contribute to MDR. ABCB1 gene expression is correlated with constitutive activation of the NF-κB signaling pathway in tumor cells. The objective of this research is to modulate P-gp activity in colon cancer cells using NF-κB decoy oligodeoxynucleotides (ODNs) that are effectively delivered into the nucleus of colorectal cancer cells by self-assembling nonviral nanoparticles comprising the
novel poly[N-(2-hydroxypropyl)methacrylamide]-poly(N,N-dimethylaminoethylmethacrylate) diblock copolymer (pHPMA-b-pDMAEMA). Ethidium bromide intercalation and gel retardation assays demonstrated high DNA condensation capacity of pHPMA-b-pDMAEMA. Nanoparticles prepared with and without decoy ODNs did not significantly compromise cellular safety at N/P ratios ≤ 4. Transfection efficiency of pHPMA-b-pDMAEMA polyplexes (N/P = 4) in Caco-2 cells was comparable to TurboFect transfection standard, resulting in a 98% reduction in P-gp protein levels. As a pharmacodynamic consequence, intracellular accumulation of the P-gp substrate Rhodamine123 significantly increased by almost twofold. In conclusion, NF-κB ODN polyplexes fabricated with pHPMA-b-pDMAEMA polymer effectively reduced P-gp-mediated efflux activity in Caco-2 cells, suggesting successful interference with NF-κB-binding sites in the promoter region of the ABCB1 gene.