Peptide Targeting of the Glucose Regulated Protein of 78 kilodalton for Gene Delivery and Therapy Applications

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The Glucose Regulated Protein of 78 kilodalton (GRP78) is a main chaperone assisting in protein folding in the endoplasmic reticulum (ER) during cell stress conditions. Furthermore, GRP78 is overexpressed and translocated to the cell surface of cancer but is absent (or minimally expressed) on normal tissues, acting as a clinical biological marker (biomarker) for cancer-targeted therapy. This research is based on the discovery of cell surface (cs)GRP78 peptide binding ligands for cancer-targeted gene (short interfering RNA, siRNA, and plasmid DNA, pDNA) delivery and therapy applications. Synthetic fluorescein-labeled amphiphilic peptides composed of csGRP78 targeting and penetrating domains were investigated for anti-cancer utility. These peptides folded into unusual helical-coiled structures that enabled self-assembly into nanofibers. The peptides also displayed GRP78-dependent cell uptake in a representative GRP78 overexpressing prostate cancer (DU145) cell line. The detected cytosolic and nuclear accumulation of fluorescein-labeled peptides underscored their utility in gene delivery applications. Transfections (siRNA and pDNA) in the DU145 cells indicated the potential to silence (*e.g.*, GRP78 siRNA) and activate (*e.g.*, p53 pDNA) key biomarkers implicated in the cancer cell death response. This presentation will thus serve to highlight the importance of targeted gene delivery approaches for precision oncology applications.