Blocking Multidrug Resistance in Cancer Cells with MicroRNA Mimics

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Chemotherapy, a major cancer treatment approach, suffers seriously from multidrug resistance (MDR), generally caused by innate DNA repair proteins or transmembrane efflux proteins that remove chemotherapeutics. This project focused on finding microRNAs that can regulate MDR proteins by managing corresponding mRNA levels through post-transcriptional regulation. Last year, screening was done with bioinformatics databases for unpublished/unexplored microRNAs with high nucleotide sequence correspondence to two representative MDR proteins, MGMT (a DNA repair protein) and ABCB1 (an efflux protein), revealing microRNA-4539 and microRNA-4261 respectively. This year, T98G (glioblastoma) cell line – with high levels of MGMT - was administered varying concentrations of Temozolomide and microRNA-4261, while MDA-MB-231-luc (triple-negative breast cancer) cell line – with high levels of ABCB1 - was administered varying concentrations of doxorubicin and microRNA-4539. First, fluorescent light imaging was used to show the uptake of nanoparticles with microRNA into cancer cells and found them clustered around the nuclei, ensuring effective microRNA delivery. The cytotoxicity of various combinations of chemotherapeutic dosages and microRNA concentrations was evaluated with an MTT assay. Finally, the suppression of ABCB1 and MGMT expression with an increase in microRNA concentration was also confirmed by Western blotting. The downregulation of MDR proteins enhanced the response to anti-cancer therapeutics and effective cell death, proving that the selected microRNAs could be used to assist anti-cancer therapeutics for the prevention of MDR, and that the nucleotide sequence matching of microRNA and targeted mRNA can lead to the experimentally shown regulation of protein expression.

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