Designing a Tumor-Specific Oncolytic Virus to Induce Suicide Gene Expression

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Glioblastoma multiforme is the most aggressive form of brain cancer where <5% of patients live longer than 5 years. Metastatic cancer remains difficult to treat effectively and treatments are not curative and cause deadly side effects. Genetically engineered viruses can cross the blood-brain barrier and selectively target tumor cells with tumor-specific promoters. These promoters allow cytotoxicity to be limited towards cancer cells without damaging neurons. Studies are looking towards employing a multimodal approach to targeting cancer by attacking multiple pathways at once. In this research, a dual promoter system using HMGB2 and VEGF promoters to drive suicide gene HSVtk was constructed. This simultaneously targets two key characteristics of glioblastoma—the HMGB2 pathway and hypoxia—using tumor-specific promoters. To prepare the treatment, HMGB2 and VEGF promoters were subcloned into a GFP-HSVtk plasmid using restriction digestion, PCR amplification, and ligation. Final plasmids (HMGB2, VEGF, HMGB2-VEGF, and GFP-HSVtk control) were transfected into glioblastoma and fibroblast cells. Cytotoxicity and protein expression were analyzed using four assays over 10 days. Results showed that tumor specific plasmids were successful in killing glioblastoma stem cells, but not healthy fibroblast stem cells. As hypothesized, the HMGB2-VEGF dual promoter system killed the fewest healthy cells but rapidly killed glioblastoma cells. For further analysis, HMGB2-VEGF treatment was compared to Temozolomide (TMZ), the drug typically prescribed for glioblastoma, and empirically proven to be safer. This research proposes HMGB2-VEGF dual promoter system as a safe and effective treatment in-vitro. Future research can expand this treatment to other cancers (breast, lung, pancreatic).

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