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"Ancient Intruders: Human Endogenous Retroviruses (HERVs) in Glioblastoma"

Human endogenous retroviruses (HERVs) are ancient retroviral sequences that integrated into the primates' genome millions of years ago. HERV sequences account for about 8% of the human genome. Over evolutionary time, most HERVs have become highly mutated and no longer encode functional genes; however, the more recently introduced HERV-K family contains intact open reading frames and expresses viral proteins. During early human development and in the *in vitro* model of induced pluripotent stem cells, HERVs activation and expression can occur due to loss of epigenetic silencing. Interestingly, expression of HERVs has also been observed in various human cancers. In glioblastoma multiforme (GBM), one of the most aggressive human cancers, expression from HERV loci is linked to cancer stemness and drug resistance. Because GBM has limited treatment options, especially for recurrent tumors resistant to Temozolomide (TMZ; used in the current standard of care), deciphering connections between HERV-K and GBM development, progression, stemness, and drug resistance could prompt new therapeutic strategies.

This study aims to 1) characterize HERV-K expression in multiple human GBM cell lines compared to normal human astrocytes (NHA), and 2) compare HERV-K expression in GBM cell lines sensitive and resistant to TMZ.

Cells used in the project are: NHA, GBM cell lines sensitive to TMZ: LN229, U87MG, and TMZ resistant cell lines: U118MG, T98G. HERV-K expression in each cell line is determined using quantitative real-time PCR (RT-qPCR) and Western blot techniques. These methods measure the expression of established HERV-K RNA sequences (RT-qPCR) and associated proteins (Western blot): Env, Gag, and Pro.

Our findings show detectable HERV-K expression on both the RNA and protein levels in all tested cell lines. We observed statistically significant differences in HERV-K gene expression between NHA and GBM. Our data surprisingly show higher HERV-K expression levels in NHA vs. GBM cell lines. Our initial results show differences in HERV-K expression between TMZ-resistant and TMZ-sensitive GBM, and experiments aiming to determine statistical significance are ongoing. The contribution of HERV-K expression to cell phenotype will be further addressed with a CRISPR gRNA multiplexing method to induce or silence HERV-K expression.

In conclusion, our data indicates that HERV-K may be involved in GBM biology and suggests the potential use of HERV-K expression in diagnostic and/or therapeutic strategies.