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Characterizing an oncolytic virotherapy targeted towards brain tumor stem cells

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Recent evidence suggests that neoplastic tumors are initiated and maintained exclusively by a rare fraction of cancer cells with stem cell properties (cancer stem cells). Several groups of investigators reported the presence of stem cell-like cells in human brain tumor specimens, and Dirks and his colleagues nicely demonstrated that only the CD133⁺ fraction of human brain tumor cells has potential to develop brain tumors in SCID mice. The cancer stem cell theory emphasizes the importance of developing effective therapeutics directed towards cancer stem cells. However, most conventional cancer therapies, such as chemotherapy and radiation are likely to be refractory to these cells because they often express high levels of anti-apoptotic proteins, DNA repair enzymes and ABC transporters. In this study, we hypothesized that our recently developed oncolytic HSV mutant rQNestin34.5, which has a deletion in the ICP6 gene and expresses the ICP34.5 virulent gene under the control of a nestin/hsp68 chimeric promoter, could replicate in and kill CD133⁺ brain tumor stem cells more effectively than a control HSV mutant (rHSVQ1) with deletions in both ICP6 and ICP34.5 genes. We also reasoned that a majority of CD133⁺ brain tumor stem cells are infectable with HSV, much like normal human neural stem/progenitor cells and that upregulated expression of anti-apoptotic proteins and DNA repair enzymes would promote replication of HSV mutants in these cells. To characterize the oncolytic activity of rQNestin34.5 in brain tumor stem cells, rQNestin34.5 and rHSVQ1 were compared using human glioblastoma multiforme (GBM) stem cell fractions separated from xenograft cell lines (kindly provided by Dr. C. David James, Mayo Clinic, Rochester MN). The glioma cells were confirmed to form tumor spheres when cultured with growth factors. When the growth factors were removed from the culture, they showed morphological changes suggesting differentiation. The rQNestin34.5 showed enhanced propagation and cytotoxicity to these tumor sphere cells compared to rHSVQ1. This result indicates that rQNestin34.5 has an enhanced oncolytic activity against brain tumor stem cells and possesses great potential in treating brain tumors.

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