Using RNA Editing and ADARs to Increase Cell Sensitivity to Interferon Chemotherapies

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Background and Hypothesis: During viral infection, viral double stranded RNAs (dsRNAs) are bound by and activate pattern recognition receptors (PRRs). Activated PRRs signal several downstream cellular events, including activating transcription of interferon (IFN). IFN-β can bind to cellular receptors and increase transcription of PRRs, interferon stimulated genes (ISGs), activate Protein Kinase R (PKR) and trigger apoptosis. The ability of IFN to trigger apoptosis makes it a potential chemotherapeutic. However, IFN therapy has had mixed efficacy in inducing tumor cell apoptosis. One mechanism for this failure may be intrinsic mechanisms that prevent dsRNA from binding to and activating PRRs. ADAR1 binds to dsRNA and catalyzes deamination of adenosine to inosine, a process known as RNA editing. Normally, ADAR1 inhibits cellular dsRNAs from initiating the IFN response. Recent studies have shown ADAR1 is overexpressed in several cancers and contributes to oncogenic phenotypes, suggesting inhibition of ADAR1 may increase sensitivity to IFN-β. The Hundley lab recently identified an inhibitor of ADAR1 called ADAR3. ADAR3 has no deaminase activity and is highly expressed in glioblastoma (GBM) tumors. We hypothesize that ADAR3 expressing GBM cells should exhibit a greater antiproliferative effect in response to IFN-b treatment compared to control.

Experimental Design or Project Methods: An MTT assay was conducted in which U87 ADAR3 +/- cell lines were exposed to IFN-β after 24 hours. Cell viability was measured for 3 days post-treatment.

Results: U87 ADAR3 + cells are more sensitive to IFN-β treatment (n=2 biological replicates, p-value= 0.04).

Conclusion and Potential Impact: The results suggest a mechanism to enhance IFN therapy for patients with ADAR3 expressing GBM.