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Arsenic mediated disruption of promyelocytic leukemia protein nuclear bodies induces Ganciclovir susceptibility in Epstein-Barr positive nasopharyngeal carcinoma cells

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Background: The Epstein - Barr virus (EBV) is highly correlated with the pathology and progression of anaplastic nasopharyngeal carcinoma (NPC). Promyelocytic leukemia protein nuclear bodies (PML NBs) have been implicated in the host immune response to viral infection. PML NBs are targeted for degradation during reactivation of herpes viruses, suggesting that disruption of PML NB function supports this aspect of the viral life cycle.

Objectives: Our finding that the EBV encoded Latent Membrane Protein 1 (LMP1) induces PML NB immunofluorescence intensity led to the hypothesis that LMP1 may upregulate PML NBs as a means of maintaining EBV latency. Further, that disruption of PML NBs may induce EBV lytic protein expression and ganciclovir (GCV) susceptibility.

Methods: A549 and CNE1 cells were infected with the BX1 recombinant strain of EBV and latency was established. Cells were treated with 1-10nM arsenic trioxide (ATO) and/or 40uM GCV. Cell viability and EBV lytic protein expression was assessed.

Results: Increased PML protein and morphometric changes in PML NBs were observed in EBV infected alveolar epithelial and NPC cells. Treatment with ATO disrupted PML NBs, reactivated the EBV lytic cycle, and conferred susceptibility to ganciclovir in EBV positive NPC cells, but not in uninfected parental control cells. Similar results were obtained when PML siRNA was use in place of ATO.

Conclusions: This study introduces a possible method for treating EBV positive tumors by combining two FDA-approved agents. Targeting EBV positivity rather than the rapid replication of the cancer cell may provide an additional tool for the treatment of EBV positive tumors. Data regarding GCV+ATO co-treatment using the xenograft model of NPC will be presented.