World Academy of Science, Engineering and Technology
International Journal of Medical and Health Sciences
Vol:17, No:07, 2023

New Targets Promoting Oncolytic Virotherapy

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Abstract : The entry of oncolytic viruses (OVs) into clinical application opens groundbreaking changes in current and future treatment regimens. However, despite their potent anti-cancer activity in vitro, clinical studies revealed limitations of OVs as monotherapy. The same applies to CDK 4/6 inhibitors (CDK4/6i) targeting cell cycle as well as bromodomain and extra-terminal domain inhibitors (BETi) targeting gene expression. In this study, the anti-tumoral effect of XVir-N-31, an YB-1 dependent oncolytic adenovirus, was evaluated in combination with Ribociclib, a CDK4/6i, and JQ1, a BETi. The head and neck squamous cell carcinoma (HNSCC) cell lines Fadu, SAS, and Cal-33 were used. DNA replication and gene expression of XVir-N-31 was measured by RT-qPCR, protein expression by western blotting, and cell lysis by SRB assays. Treatment with CDK4/6i and BETi increased viral gene expression, viral DNA replication, and viral particle formation. The data show that the combination of oncolytic adenovirus XVir-N-31 with CDK4/6i & BETi acts highly synergistic in cancer cell lysis. Furthermore, additional molecular analyses on this subject demonstrate that the positive transcription elongation factor P-TEFb plays a decisive role in this regard, indicating an influence of the combinational therapy on gene transcription control. The combination of CDK4/6i & BETi and XVir-N-31 is an attractive strategy to achieve substantial cancer cell killing and is highly suitable for clinical testing.

Keywords : adenovirus, BET, CDK4/6, HNSCC, P-TEFb, YB-1
Conference Title : ICOVV 2023 : International Conference on Oncolytic Viruses and Virotherapy
Conference Location : Copenhagen, Denmark
Conference Dates : July 10-11, 2023