Adel Galal El-Shemi et al., J Cancer Sci Ther 2014, 7:10
http://dx.doi.org/10.4172/1948-5956.C1.060

OMICS International
conferenceseries.com

8th Euro Global Summit on
Cancer Therapy
November 03-05, 2015 Valencia, Spain

Novel preclinical study of cancer targeting oncolytic adenoviruses co-expressing ING4 and TRAIL genes for treatment of hepatocelluar carcinoma

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Hepato-cellular carcinoma (HCC) is one of the world's deadliest cancers and efforts to improve its therapy have not yet impacted its poor prognosis and high associated mortality. Limited therapeutic efficacy, high rate of resistance and significant toxicity of current HCC conventional therapy constitutes the most important challenge. In turn, development of more effective and highly selective alternative new therapeutic approach is a critical medical need. Interestingly, application of cancer targeting gene-viro-therapy (CTGVT), in which an anti-tumor gene is inserted into an oncolytic viral vector, has shown much better anti-tumor activity than that of respective gene therapy alone or oncolytic virus (e.g. oncolytic adenovirus, OAd) therapy alone. More importantly, further modification of this strategy to a novel one called the cancer-targeting dual gene viro-therapy (CTDGVT), in which an excellent triplex anticancer effect can be achieved by the oncolytic effect of AOd and the additive or synergetic interaction between two anti-tumor genes encoded by this vector. Therefore, the present research work was designed to investigate the therapeutic potential and possible synergy of this CTDGVT strategy in treatment of HCC. As the remarkable tumoricidal effects of ING4 gene; a new member of tumor suppressor genes, and TRAIL gene; an apoptotic ligand induces apoptosis in tumor cells, have been recently documented, herein we investigated the therapeutic efficacy of CTDGVT strategy composed of co-administration of OAd-ING4 plus OAd-TRAIL. To achieve these objectives, we firstly constructed and generated the followings 3 OAds: OAd alone (i.e., not carrying any therapeutic gene), OAd- expressing ING4 gene, and OAd- expressing TRAIL gene. Next, the tumoricidal effect of OAd alone, OAd-ING4, OAd-TRAIL, and OAd-ING4 plus OAd-TRAIL were tested and evaluated both in vitro and in vivo, using universal human HCC cell lines and xenograft mouse model of human HCC. Results showed that each tested strategy (OAd alone, OAd-ING4, OAd-TRAIL and OAd-ING4 plus OAd-TRAIL) had resulted in significant cytotoxic and inhibitory effects on both human cell lines and xenograft model of HCC; however, the highest efficient effect was achieved by OAd-ING4 plus OAd-TRAIL combination therapy, and this advantage of CTDGVT strategy was confirmed by the gross, histopathological, immunohistochemical, ELISA and qRT-PCR findings. The present new preclinical data of HCC-targeting CTDGVT strategy, which composed of OAd carrying ING4 and TRAIL tumor-suppressor genes, may provide a promising approach for liver cancer gene therapy.

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