Md. Hafiz Uddin et al., Madridge J Cancer Stud Res. 2020
DOI: dx.doi.org/10.18689/2640-5180.a5.004

madridge CONFERENCES

6th International

CANCER STUDY & THERAPY CONFERENCE

October 01, 2020 | Virtual Conference

Inhibition of Nuclear Exports Demonstrates a Novel Synergy with PARPinhibitors in Castration Resistant Metastatic Prostate Cancer

Md. Hafiz Uddin*, Yiwei Li, AmroAboukameel, Asfar S. Azmi and Elisabeth I. Heath
Wayne State University, USA

Impaired nuclear protein transport, often observed in cancer, causes mislocalization dependent inactivation of critical cellular proteins. Earlier we showed that nuclear exporter protein exportin 1 (XPO1) is over-expressed in metastatic castration resistant prostate cancer (mCRPC). We also showed that targeted inhibition of XPO1 by crispr/cas9 validated specific inhibitor of nuclear export compounds (SINE) selinexor or next generation compound eltanexor could suppress CRPC cellular proliferation and xenograft tumor growth. XPO1 inhibition reduces total androgen receptor (AR) levels, including AR variant 7 (ARv7), via eIF4E inhibition and may re-sensitize prostate cancer cells to androgen deprivation therapy. Selinexor, the first-in-class, orally bioavailable reversible covalent XPO1 inhibitor, showed anticancer activity in patients (pts) with solid tumors including mCRPC.Here we evaluate the combination of SINE with PARP inhibitors (rucaparib, veliparib and olaparib). SINE synergize with three PARPi (CI<1) at pharmacologically relevant concentrations. SINE-PARPi showed superior induction of apoptosis compared to single agent treatment. Molecular analysis using RT-PCR revealed that SINE-PARPi suppressed AR, PSA and AR targets UBE2C and FOXA1. SINE-PARPi caused down-regulation of pro-survival factor Bcl-2 with simultaneous activation of pro-apoptotic caspases. Western blot analysis revealed similar results with significant down-regulation of AR, Arv, UBE2C, SAM68 and FOXA1. Crispr/cas9 edited cells lacking SINE binding site were not responsive to SINE treatment confirming a XPO1 inhibition dependent synergy. Pre-clinical evaluation of the efficacy of SINE-PARPi in xenograft of CRPC are currently ongoing. Our studies bring forward a novel and effective combination regimen targeting prostate cancer at the nuclear pore.

Biography:

Md. Hafiz Uddin is a postdoctoral fellow at the Department of Oncology, Wayne State University. He was awarded the prestigious Graduate Scholarship for Excellent Foreign Student (GSFS) fellowship for his Ph.D. program at Seoul National University, South Korea. During his Ph.D., he worked on the mechanism of carcinogen-parasite induced bile duct cancer in hamster model. In his postdoctoral research, he focused on the mechanism of chemoresistance and molecular targets in ovarian, breast and prostate cancer and their association with cancer stem cells, unfolded protein response,drug synergy, TRAIL,MAPK and DNA damage pathways.