Tousled Like Kinase As A New Drug Target Towards Prostate Cancer Therapy

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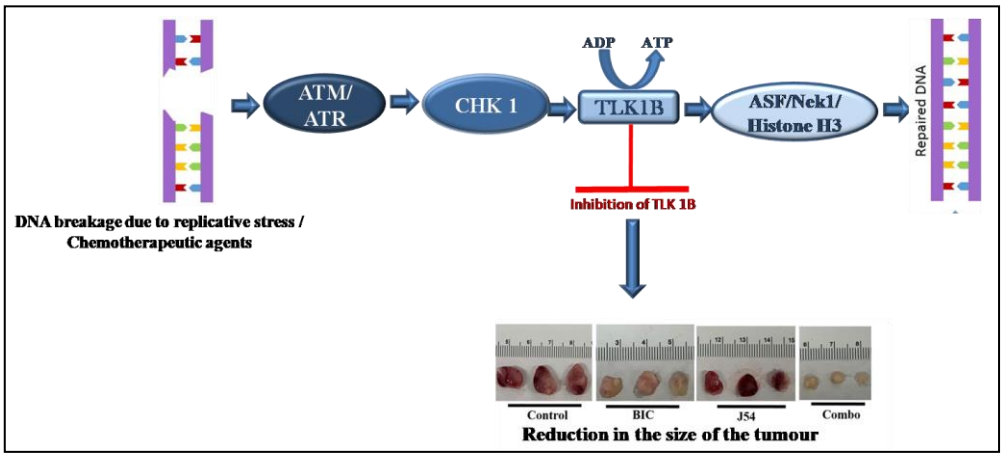
Abstract: Cancer, characterized by abnormal growth of cells, shows mutation in DNA repair genes. This causes the tumor to develop multiple pathways to survive radiation stress (radiotherapy), through a fast mechanism of DNA Damage Response (DDR) pathway[1]. Tousled like kinases (TLKs) have been implicated in chromatin assembly, DNA repair, DNA replication and transcription with highest activity levels in the S-phase of cell cycle[2]. TLK belongs to a class of serine-threonine kinases that phosphorylates important DDR proteins like Asf1, RAD9, Histone H3 and Nek1[3]. TLK activity is attenuated during the DDR activation via the ATM-Chk1 downstream kinase pathway[4]. This suggests that TLK can be used as a drug-target, to hinder the DDR pathway specific for cancer cells.
The main focus of our study was to develop effective inhibitors against the splice variant of TLK-TLK1B and to hypothesis that the pre-emptive inhibition of the kinase could choke the crucial steps towards the formation of the tumors. As an initial step towards the drug discovery for this kinase, we reported the bacterial expression and purification of the wild type-TLK1B and produced the unphosphorylated form the kinase in high yields for structural and biochemical studies. Our experimental results shows a novel phenothiazine based inhibitor J54, to have promising results during the *in vivo* xenograft studies and suggests that the combinatorial treatment of J54 along with Bicaltuamide will be successful over similar DDR-based strategies in prostate cancer therapy.

Figure:



References and Notes:

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Dr. Sivapriya Kirubakaran did her Ph.D (Organic chemistry) from Indian Institute of Science, Bangalore and Postdoctoral fellowship From Harvard Medical School and Whitehead Institute, MIT. She is an associate professor in chemistry at Indian Institute of Technology, Gandhinagar. She has co-authored about 41 publications, 1 book chapter and have 8 US and 11 Indian patents to her credit. She is also a recipient of prestigious DST Ramanujan Fellowship. Her current areas on interest include targeted drug discovery and medicinal chemistry. She is studying mechanistic pathways of DDR kinases using small molecules to develop novel therapeutics for cancer as well exploring H. pylori survival pathways for developing drugs against the infection. Her long-term goal would be to make affordable medicines for cancer.