

Abstract 335: Ubiquitin Specific Peptidase 37 promotes Osteosarcoma oncogenesis by interacting with PCNA and impacting constitutive replication fork movement. **FREE**

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Abstract

Osteosarcoma is the heterogeneous primary malignancy of bone which is most commonly found among children and adolescents. Recent data related to treatment of osteosarcoma indicates the lack information about the progression of the disease. Osteosarcoma has been a challenge for the oncologist because even after surgical removal of primary tumors many patients go on to develop pulmonary metastasis. Protein deubiquitination controls many intracellular processes, including cell cycle progression, transcriptional activation, and signal transduction. Ubiquitin specific peptidases (USPs) remove ubiquitin tags from target proteins to alter protein configuration and function. Recent studies have revealed that Ubiquitin specific peptidase 37 (UPS37) regulates replication stress by regulating important protein involved in several important cellular functions. Analysis of TCGA data indicated that overexpression of USP37 correlated with reduced progression free survival (PFS) in osteosarcoma patients. Next generation sequencing (NGS) analysis of osteosarcoma cells indicated that distinct set of genes were altered on overexpression or knockdown of USP37. Our data indicate that USP37 overexpression confers survival advantage while its depletion enhances sensitivity for cell killing in osteosarcoma cells due to replication stress. USP37 overexpressing cells were able to resolve DNA damage foci much more rapidly than the control cells or cells in which USP37 was depleted in response to genotoxic stress. USP37 depletion results in reduced resolution of γ H2AX and 53BP1 DNA damage foci and increase in number of collapsed replication fork which indicates the reduced ability of cells to carry out constitutive DNA replication. USP37 was found to interact with PCNA

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tolerance of replication stress as it interacts with PCNA which is required to dock additional replication factors and stabilize DNA replication fork. The current data provides new mechanistic details for the regulation of replication stress by USP37 which merits the development of targeting strategies to explore its therapeutic potential in osteosarcoma by inducing synthetic lethality.

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