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Ubiquitin specific peptidase 37 and PCNA interaction promotes osteosarcoma pathogenesis by modulating replication fork progression

Ravi Chauhan[1], Ashna Gupta[1], Lakshay Malhotra[2], Ajaz A. Bhat[3], Raj K. Pandita[4], Tariq Masoodi[5], Gunjan Dagar[1], Hana Q. Sadida[3], Sara K. Al-Marzooqi[3], Atul Batra[6], Sameer Bakhshi[6], Mehar Chand Sharma[7], Pranay Tanwar[8], Shah Alam Khan[9], Ethayathulla Abdul Samath[2], Shahab Uddin[10], Ammira S. Al-Shabeeb Akil[3], Mohammad Haris[11], Muzafar A. Macha[12], Tej K. Pandita[4] and Mayank Singh[1*]

Abstract

Background Osteosarcoma is a type of bone cancer that predominantly affects young individuals, including children and adolescents. The disease progresses through heterogeneous genetic alterations, and patients often develop pulmonary metastases even after the primary tumors have been surgically removed. Ubiquitin-specific peptidases (USPs) regulate several critical cellular processes, such as cell cycle progression, transcriptional activation, and signal transduction. Various studies have revealed the significance of USP37 in the regulation of replication stress and oncogenesis.

Methods In this study, the Cancer Genome Atlas (TCGA) database was analyzed to investigate USP37 expression. RNA sequencing was utilized to assess the impact of USP37 overexpression and depletion on gene expression in osteosarcoma cells. Various molecular assays, including colony formation, immunofluorescence, immunoprecipitation, and DNA replication restart, were employed to examine the physical interaction between USP37 and PCNA, as well as its physiological effects in osteosarcoma cells. Additionally, molecular docking studies were conducted to gain insight into the nature of the interaction between USP37 and PCNA. Furthermore, immunohistochemistry was performed on archived tissue blocks from osteosarcoma patients to establish a correlation between USP37 and PCNA expression.

Results Analysis of the TCGA database revealed that increased expression of USP37 was linked to decreased progression-free survival (PFS) in osteosarcoma patients. Next-generation sequencing analysis of osteosarcoma cells demonstrated that overexpression or knockdown of USP37 led to the expression of different sets of genes. USP37 overexpression provided a survival advantage, while its depletion heightened sensitivity to replication stress in osteosarcoma cells. USP37 was found to physically interact with PCNA, and molecular docking studies indicated that the interaction occurs through unique residues. In response to genotoxic stress, cells that overexpressed USP37 resolved DNA damage foci more quickly than control cells or cells in which USP37 was depleted. The expression of USP37 varied in archived osteosarcoma tissues, with intermediate expression seen in 52% of cases in the cohort examined.

*Correspondence:
Mayank Singh
mayank.osu@gmail.com
Full list of author information is available at the end of the article