Spring 2025

Biochemistry and Molecular Biology Brown Bag Series

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"TIP60 and ΔNp63α: A therapeutic axis in targeting Cisplatin Resistance in Squamous cell carcinoma"

Tuesday, February 18, 2025

11:00 AM

Location 125 Oelman Hall

Lab: Madhavi Kadakia, Ph.D.

Boonshoft School of Medicine
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https://science-math.wright.edu/biochemistry-and-molecular-biology

Abstract

Cisplatin, a widely used chemotherapeutic agent, is often administered alone or in combination with ionizing radiation (IR) to treat squamous cell carcinoma (SCC). However, many SCC cases fail to respond to therapy, leading to low treatment efficacy and high rates of disease recurrence. The oncogenic protein ΔNp63α, which is overexpressed in SCC, is stabilized and acetylated by TIP60, a histone acetyltransferase. Stabilization of ΔNp63α promotes cell survival, proliferation, and cisplatin resistance. Our previous studies demonstrated that knockdown or inhibition of TIP60 using small molecules reduced ΔNp63α acetylation, sensitized resistant SCC cells to cisplatin, and induced G2/M cell cycle arrest, ultimately leading to increased cell death. These findings suggest that targeting TIP60 could overcome cisplatin resistance and improve treatment outcomes for SCC patients. We hypothesize that TIP60-mediated acetylation of ΔNp63α regulates its stability and transcriptional activity, modulates response to cisplatin, enhance the DNA damage response (DDR), and inhibits apoptotic cell death thereby promoting chemoresistance. This study objective was to determine the role of TIP60 and ΔNp63α in the modulation of cisplatin-DNA adduct kinetics and repair, cisplatin export, and DDR in the promotion of chemoresistance. Our data demonstrate that cisplatin-resistant cells, which express higher levels of ΔNp63α and TIP60, exhibit decreased cisplatin-DNA adduct formation and enhanced DNA repair compared to cisplatin-sensitive cells. Knockdown of either ΔNp63α or TIP60 reduced the expression of ABCC1, a transporter associated with drug efflux, thereby leading to increased cisplatin-DNA adduct accumulation in the cisplatin resistant cells. Consistently, treatment with MK-571, an ABCC1 inhibitor also led to an increase in cisplatin-DNA adducts. Together these results suggests that increased ABCC1 expression by TIP60 and ΔNp63α plays a role in mediating cisplatin resistance. Furthermore, depletion of TIP60 or ΔNp63α impaired the repair of cisplatin-induced DNA adducts and decreased the expression of DDR-related genes. In summary, our study uncovers a novel mechanistic role for TIP60 and ΔNp63α in the regulation of DDR driving cisplatin resistance. These findings highlight TIP60 as a potential therapeutic target, offering a promising strategy to overcome cisplatin resistance and improve SCC treatment outcomes.