University of Cyprus
Department of Biological Sciences

## Ph.D. Thesis Defense

# Student Presentation

**Wednesday, 27 November 2024 at 10:30**
**UCY Library, Room LRC014, Panepistimioupoli Campus**

***This seminar is open to the public also via Zoom***

***https://ucy.zoom.us/j/62412528088?pwd=CcKmSoUco5OrjHGBy2Ubf0ADlahu64.1***


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## "UNVEILING YEAST N-TERMINAL ACETYLTRANSFERASE NAT4 AS A NEW PLAYER IN THE DNA DAMAGE RESPONSE"


The DNA damage response constitutes a vital cellular process that safeguards genome integrity by detecting and repairing DNA lesions. This intricate biological process involves substantial alterations in chromatin structure, commonly orchestrated by epigenetic enzymes. In this study, we show that the epigenetic modifier N-terminal acetyltransferase 4 (Nat4), known to acetylate the alpha-amino group of serine 1 on histones H4 and H2A, is implicated in the response to DNA damage in *S. cerevisiae*. Notably, Nat4 has been previously shown to impact various biological processes, including cellular aging, metabolism and carcinogenesis. However, whether it plays a role in DNA damage response pathways remained elusive until now. Initially, we demonstrate that yeast cells lacking Nat4 exhibit increased sensitivity when exposed to DNA damage and accumulate more DNA breaks than wild-type cells. Accordingly, upon DNA damage, *NAT4* gene expression is significantly elevated, and the enzyme is specifically recruited to sites of double-strand breaks. Delving deeper into its molecular effects on the DNA damage signaling cascade, *nat4*-deleted cells exhibit lower levels of the damage-induced modification H2AS129ph (γH2A). This reduction is accompanied by diminished binding

of the checkpoint control protein Rad9 surrounding the double-strand break, indicating impaired checkpoint signaling. Consistently, Mec1 kinase recruitment at double-strand breaks, critical for H2AS129ph deposition and Rad9 retention, is significantly impaired in *nat4*Δ cells. Consequently, Mec1-dependent phosphorylation of downstream effector kinase Rad53, indicative of DNA damage checkpoint activation, is reduced. Importantly, our findings reveal that the regulatory effects of Nat4 on the checkpoint signaling cascade are mediated through its N-terminal acetyltransferase activity targeted specifically towards histone H4. Overall, this study points towards a novel functional link between histone N-terminal acetyltransferase Nat4 and the DNA damage response, associating a new histone-modifying activity in the maintenance of genome integrity.