Identification of E3 Ligases Involved in UBBP4-Mediated Modification

Record number : OPR-1379

Overview

RESEARCH DIRECTION

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INFORMATION

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ADMINISTRATIVE UNIT(S)

Faculté de médecine et des sciences de la santé

LEVEL(S)

2e cycle
3e cycle

LOCATION(S)

Campus de la santé

Project Description

Post-translational modification by ubiquitin corresponds to the covalent addition of this small protein to lysine residues on target proteins. Beyond its well-known role in protein degradation, ubiquitylation regulates subcellular localization, protein–protein interactions, and many essential cellular functions. Dysregulation of this system is associated with multiple pathologies, including cancer and neurodegenerative diseases. In mammals, ubiquitin is classically produced from four genes (UBA52, RPS27A, UBB, and UBC), generating proteins with identical amino acid sequences. However, recent large-scale proteomics and RNA sequencing analyses have revealed the expression of UBBP4, a pseudogene of UBB, which produces a functional ubiquitin variant with slight sequence differences.

Our results demonstrate that this ubiquitin variant modifies a distinct set of protein substrates, notably proteins involved in DNA replication and cell cycle control, and is not associated with classical proteasomal pathways, suggesting a specialized function. Substrate specificity in ubiquitylation largely depends on E3 ligases, which recognize target proteins and catalyze ubiquitin transfer. However, the E3 ligases responsible for UBBP4 conjugation remain completely unknown. Our hypothesis is that UBBP4-mediated modification is driven by a specific subset of E3 ligases that are distinct from — or show preferential affinity compared to — those involved in canonical ubiquitylation, thereby defining a new functional branch of the ubiquitin system.

To test this hypothesis, the thesis project will pursue the following objectives:

Objective 1: Identify the E3 ligases involved in UBBP4 conjugation.

We will use interaction proteomics, co-immunoprecipitation, proximity labeling, and quantitative mass spectrometry to identify E3 ligases associated with UBBP4 or with UBBP4-modified substrates. Targeted loss-of-function screens (CRISPR/siRNA) of candidate E3 ligase families will be performed to determine their contribution to UBBP4 conjugate formation.

Objective 2: Characterize enzymatic specificity and E3 ligase–dependent substrates of UBBP4.

Cellular and biochemical assays will be used to validate identified E3 ligases and compare their ability to transfer canonical ubiquitin versus UBBP4. Proteomic mapping of substrates dependent on these E3 ligases will define the cellular pathways they regulate.

Objective 3: Determine the functional impact of UBBP4-dependent E3 ligases on DNA replication and the cell cycle.

Knockout/knockdown cell lines for UBBP4 and candidate E3 ligases will be generated to assess effects on cell growth, replication stress responses, and cell cycle dynamics.

This project will identify, for the first time, the E3 ligases responsible for UBBP4-mediated modification and define a new specificity module within the ubiquitin system. These studies will transform our understanding of the functional diversity of ubiquitin variants and may open the way to new strategies for selectively targeting specialized ubiquitylation pathways for therapeutic purposes

Discipline(s) by sector

Sciences de la santé

Biochimie, Biologie cellulaire, Biologie moléculaire, Immunologie, Microbiologie, Pharmacologie

Funding offered

Yes

29 000$/year

The last update was on 11 February 2026. The University reserves the right to modify its projects without notice.