SCIENCES & BIOENGINEERING SCIENCES

The Research Group
Molecular and Cellular Life Sciences

has the honor to invite you to the public defense of the PhD thesis of

Mara Esposito

to obtain the degree of Doctor of Sciences

Multipronged Regulation of Cell Cycle Proteins by the Deubiquitinase USP13

Promotors:
Prof. dr. Gustavo Gutierrez Gonzalez

The defense will take place on

Wednesday, October 21, 2020 at 16h00

The defense can be followed through a live stream. Contact mara.esposito@vub.be for more information

Members of the jury

Prof. dr. Sophie De Buyl (VUB, chair)
Prof. dr. Eveline Peeters (VUB, secretary)
Prof. dr. Peter Tompa (VUB)
Prof. dr. Catherine Lindon (Cambridge University, UK)
Prof. dr. Sonja Lorenz (Universität Würzburg, DE)

Curriculum vitae

Mara Esposito graduated at University of Milano-Bicocca (Italy) as Biotechnologist (BSc Industrial Biotechnology) and worked as a technician in the laboratory of cellular biology at ABICH Srl. Then, she graduated at University of Milano-Bicocca (Italy) as Biologist (MSs Biology) and performed her master thesis at the research laboratory of repair and transcription in hematopoietic stem cells (LRTS) of CEA (Atomic Energy and Alternative Energies Commission) in France. In 2015, she started her PhD research at Laboratory of Pathophysiological Cell Signalling (PACS) of VUB.

Abstract of the PhD research

Post-translational modifications (PTMs) of proteins are essential regulatory mechanisms of cellular pathways such as the cell division cycle. One of the most common PTMs occurring to cell cycle proteins is their conjugation to ubiquitin, a process known as ubiquitination. Ubiquitination can lead to different cellular outcomes but in many cases, to the proteasome-mediated degradation of the ubiquitinated substrate. Ubiquitination is counteracted by deubiquitinating enzymes (DUBs), a class of enzymes that can remove ubiquitin signals from ubiquitinated substrates. The human genome encodes ~100 DUBs which are classified in different families. USP13 is a member of the USP family that directly controls the stability of several target proteins involved in cancer pathways.

In this PhD thesis, we have identified and characterized the molecular/cellular regulation of two novel substrates of USP13: Aurora B and CDH1 (cell division cycle (CDC20)-homologue 1). Aurora B is a master regulator of the cell cycle. Proper localization of Aurora B and its protein levels regulation during mitosis is crucial for its function during the cell cycle and is in part regulated by ubiquitination. We found that USP13 associates with and stabilizes Aurora B in cells, especially before their entry into mitosis. We also present evidence that USP13 promotes Aurora B deubiquitination and/or protect it from degradation in a non-catalytic manner. Furthermore, we found that USP13 controls Aurora B localization during entry into mitosis.

CDH1 is one of the adaptors/activators of the anaphase-promoting complex/cyclosome (APC/C) E3 ubiquitin ligase, which regulates mitotic progression and exit from mitosis. CDH1 protein levels are tightly regulated in time and space during mitosis. We found that USP13 binds and stabilizes CDH1 in cells. We show that downregulation of USP13 expression results in CDH1 destabilization whereas overexpression of USP13 induces CDH1 accumulation. Accordingly, CDH1 half-life is increased under USP13 overexpression.

Finally, we report data indicating that genetic or chemical modulation of the cellular levels/activity of USP13 affects unperturbed cell cycle progression. Overall, this PhD thesis unveiled molecular and cellular connections between USP13 and the cell cycle regulators Aurora B and CDH1, which are potentially implicated in the rewiring of the cell cycle in cancer cells.