CRBM external seminar
Thursday, October 26th 11:00 am Salle Marcel Dorée

Deciphering the molecular mechanisms linking mitochondrial homeostasis to cell division

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Eva PANGOU got her PhD thesis in Biochemistry in Prof. George Simos laboratory in Greece, studying phosphorylation-dependent signaling pathways in cancer cells in response to hypoxic stress. Through a FRM fellowship she then joined the group of Izabela Sumara at the Institute of Genetics and Molecular and Cellular Biology (IGBMC) in Strasbourg focusing on mechanisms that regulate mammalian cell division. This has led to her recent discoveries on signals connecting mitotic surveillance mechanisms to balanced mitochondrial function that ensure genome fidelity.

Abstract

Mitosis, the process of cell division in eukaryotes, is regulated by the spindle assembly checkpoint (SAC) to ensure faithful chromosome segregation. Mitotic slippage, an escape from SAC-mediated arrest, is frequently observed in aneuploid cancer cells. While the fidelity of chromosome division is essential, the role of subcellular organelles, particularly mitochondria, and their dynamic behaviour of undergoing cycles of fission, fusion and transport during cell division, remains poorly understood. Recently, I identified a novel regulatory mechanism upstream of the Mitochondrial Fission Factor (MFF) based on its phosphorylation by Protein Kinase D (PKD), which occurs specifically during mitosis. MFF phosphorylation by PKD is directly coupled to fidelity of chromosome segregation and protects cells from SAC adaptation. Cells with a defective PKD-MFF pathway are characterized by a highly fused mitochondrial network, premature anaphase initiation, mitotic slippage, polyploidy and reduced long-term proliferative capacity. My discovery has raised important questions and challenged our current knowledge of how signals linking mitotic surveillance mechanisms to balanced mitochondrial function maintain genome fidelity.To gain further insights into the signaling networks that couple mitochondrial division to the mitotic machinery of mammalian cells, I plan to develop a research plan that focuses on identifying: (a) Signaling pathways that regulate mitochondrial fission/fusion factors specifically during mitosis with an emphasis on phosphorylation and ubiquitylation, (b) How remodeling of the mitochondrial network can be spatiotemporally coordinated with mitotic surveillance pathways and (c) How reorganization of the mitochondrial network synchronizes with the process of cytokinesis. Characterization of novel targets that directly couple imbalanced mitochondrial dynamics to defective cell cycle checkpoints could in the long-term improve our understanding of the pathophysiology of mitochondrial-related diseases and/or cancer.

Selected publications

Vivot K, Meszaros G, **Pangou E**, Zhang Z, Qu M, Erbs E, Yeghiazaryan G, Quiñones M, Grandgirard E, Schneider A, Clauss-Creusot E, Charlet A, Faour M, Martin C, Berditchevski F, Sumara I, Luquet S, Kloppenburg P, Nogueiras R, Ricci R. "CaMK1D signaling in AgRP neurons promotes ghrelin-mediated food intake". **Nature Metabolism, 2023**

Guerber L, Vuidel A, Liao Y, Kleiss C, Grandgirard E, Sumara I, **Pangou E**. "UBAP2L-dependent coupling of PLK1 localization and stability during mitosis". **EMBO Reports, 2023**

Compe E, **Pangou E,** Le May N, Elly C, Braun C, Hwang J, Coin F, Sumara I, Choi KW and Egly JM. "Phosphorylation of XPD drives its mitotic role independently of its DNA repair and transcription functions". **Science Advances**, **2022**

Pangou E, Bielska O, Guerber L, Schmucker S, Agote-Arán A, Ye T, Liao Y, Puig-Gamez M, Liu Y, Compe E, Zhang, Z, Grandgirard E, Kleiss, C, Aebersold R, Ricci R and Sumara I. "A PKD-MFF signaling axis couples mitochondrial fission to mitotic progression". **Cell Reports**, **2021**