CRBM External Seminars 2024
Thursday, February 8th at 11:00 am Salle Marcel Dorée

Precise control of autophagy activity facilitates accurate cell division

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Caroline MAUVEZIN long-standing research interests focus on autophagy, a catabolic process fundamental for cellular homeostasis, with links to many human diseases including cancer. During her PhD at IRB Barcelona (2006-2011) supervised by Dr. ZORZANO, her work brought together, for the first time, two previously unrelated areas: nuclear co-factor signaling and autophagy. She uncovered a novel function for the transcription co-factor TP53INP2/DOR as an autophagy activator. In 2011, she joined Dr. NEUFELD's lab at the University of Minnesota to continue her training on autophagy and learn the Drosophila model system. There, her research focused on determining the mechanisms driving autophagosome-lysosome fusion and acidification. Resolving a long-standing controversy in the field, she revealed that lysosomal acidification is not a prerequisite for fusion, in contrast to previous beliefs. Particularly important to the autophagy field, this prompted re-evaluation of studies whose interpretation depends on selective inhibition of lysosome acidification by lysosomotropic drugs. She also led a collaborative project aiming to determine the involvement of lipid-interacting proteins in autophagy and identified a novel complex essential for accurate autophagy. From 2015 to 2021, she was a senior postdoctoral associate at IDIBELL in the Laboratory of Cancer Metabolism, Barcelona. She was awarded 2 prestigious research grants: Juan de la Cierva fellowship, to characterize the role of lysosomes in E2F1-induced mTOR activation in cancer cells, and the European fellowship Marie Curie to support her innovative project focused on the role of autophagy during mitosis. Her findings revealed that efficient autophagy and lysosome degradation during mitosis protects against chromosomal instability (CIN), a hallmark of cancer, and revealed an atypical nuclear phenotype, the toroidal nucleus, as a useful biomarker for CIN. Since 2021, she is a junior group leader at the University of Barcelona and the recipient of 2 prestigious research grants, JIN-MINECO and LAB AECC, to define novel personalized cancer therapies based on autophagy modulation.

Abstract

Mitosis dictates the faithful transmission of the genetic material among generations, which precludes chromosomal instability, a hallmark of cancer. Correct mitotic progression relies on the orchestrated degradation of mitotic factors, and whether autophagy and lysosome-dependent degradation are involved in mitotic coordination remains a controversial question. We recently established that lysosome-dependent degradation is an essential process which prevents chromosomal instability (Almacellas et al., 2021), providing new perspectives in cancer therapeutics. Our study resulted in the demonstration that lysosomes and autophagy are active during mitosis, and that their impairment increased mitotic timing and mitotic errors, thus promoting chromosomal instability. We also observed that cells that endured mitotic errors resulted in daughter cells with a toroidal nucleus, a unique phenotype highlighted by a perforated nucleus. We characterized the toroidal nucleus as a novel biomarker for the identification of chromosomal instability, inherent in cancer cells. Recently, we explored whether acute activation of mitotic autophagy could reverse chromosomal instability. Interestingly, our findings are establishing a novel connection between two influential fields in cancer research - autophagy and chromosomal instability - and indicate that a tight regulation of autophagy is important for genomic stability.

Selected publications

Almacellas E, **Mauvezin C**. (2022) Emerging roles of mitotic autophagy. **J Cell Sci**.;135(11):jcs255802.

Almacellas E, Pelletier J, Day C, Ambrosio S, Tauler A, **Mauvezin C**. (2021) Lysosomal degradation ensures accurate chromosomal segregation to prevent chromosomal instability. **Autophagy**, 17(3), 796–813.