EXTERNAL SEMINAR

"Maternal transmission of mammalian mtDNA is dependent on an interaction between the germline bottleneck and purifying selection"

Prof. Nils-Göran Larsson

Karolinska Institutet, Stockholm, Sweden

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Amphithéâtre Bât. 21, I2BC, Gif-sur-Yvette

Mammalian mtDNA has a high mutation rate and is maternally transmitted without germline recombination. This asexual mode of transmission should theoretically lead to a mutational meltdown over generations, the so-called Muller ratchet effect. To combat this threat, at least two key mechanisms are operational: the mtDNA bottleneck, a stochastic process that reduces the number of mtDNA molecules passed to the next generation, and purifying selection, which actively eliminates mtDNA molecules with harmful mutations. Despite their importance, it has remained unclear whether both mechanisms act independently or if they are functionally linked. By using genetic mouse models, we demonstrate that tightening the mtDNA bottleneck increases heteroplasmic variance between individuals causing lower mutational burden and nonsynonymous-to-synonymous ratios. In contrast, reduced autophagy weakens purifying selection leading to decreased inter-offspring heteroplasmic variance and increased mutational burden with higher nonsynonymous-to-synonymous ratios. These findings provide experimental evidence that the mtDNA bottleneck size modulates the efficacy of purifying selection. Our results suggest that pharmacological modulation of autophagy or mtDNA copy number may provide future avenues to limit the spread of mtDNA mutations.

Contact: Inge Kühl; inge.kuhl@i2bc.paris-saclay.fr

Club Mitochondrie - Cell Biology department