CRBM external seminar
Thursday Dec 8th 11:00 am Salle Marcel Dorée

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« Size matters »: How genetic stability and nuclear architecture respond to changes in DNA content.

Simon GEMBLE is a postdoctoral researcher working in the team of Renata Basto at the Curie Institute in Paris. After a PhD in the team Amor-Gueret working on genetic instability and carcinogenesis, he joined the Basto team to work on a collaborative project with Daniele Fachinetti on the functional relationship between centromeres and centrosomes during the cell cycle. He is now investigating the consequence of polyploidy on genetic stability.

Whole genome duplication (WGD) results from the gain of complete chromosome sets. WGD can be developmentally programmed to sustain cell and tissue functions. Conversely, when non-programmed, WGD can generate genetic instability. Indeed, it has been assessed that 40% of human tumors are tetraploid, due to at least one event of WGD. Tetraploid content appears to fuel abnormal karyotypes favoring tumorigenesis. However, little is known about how tetraploidization generates genetic instability. To investigate this question, we have induced WGD in diploid human cell lines using multiple means and found that both (1) genetic stability and (2) nuclear architecture are impaired within the first cell cycle upon WGD. Indeed, (1) we demonstrated that high levels of DNA damage are generated in a DNA-replication manner within the first S-phase following WGD. This is resulting from a lack of scaling up of multiple replication factors that creates an imbalance between the amount of replication machineries and DNA content, generating replication stress (Gemble *et al.,* Nature, 2022). Moreover, (2) we observed the appearance of nuclear deformations in the first G1 upon WGD. These abnormal nuclear shapes are due to the microtubule cytoskeleton that are generating nuclear invaginations during G1. We are now investigating the subsequent consequences of nuclear deformations on tetraploid cell (Unpublished data). Our results provide a new framework to unravel the multiple ways by which non-programmed WGD can impact genetic stability and contribute to cancer.

Genetic instability from a single S phase after whole-genome duplication. Gemble S et al. **Nature.** 2022 doi: 10.1038/s41586-022-04578-4.

CHRONOCRISIS: When Cell Cycle Asynchrony Generates DNA Damage in Polyploid Cells. Gemble S, Basto R. **Bioessays.** 2020 doi: 10.1002/bies.202000105.