ID de Contribution: **2** Type: **Non spécifié**

Does the nuclear envelope's structure and lipid composition impact genome stability?

The genome is compartmentalized from the rest of the cell by the nuclear envelope (NE), which consists of two concentric lipid bilayers separated by an inter-membrane space (IMS). The inner and the outer nuclear membranes (INM, ONM) face the nucleoplasm and the cytoplasm, respectively, and are maintained at a constant distance by bridging proteins demarcating the IMS. In humans, this bridging complex is known as **LINC** (LInker of Nucleoskeleton and Cytoskeleton). It takes its name from its most studied function, allowing to transmit forces between the nuclear and cytoplasmic skeletons. This latter function is well studied in cancer, where its dysregulation underlies increased cell migration thus metastatic capacity. Cancer state is also associated with genomic instability as DNA breaks, mutations or repair defects. In the case of LINC, its absence notably correlates with anarchic DNA repair and repair pathways dysregulation in C. elegans, S. pombe and Human cells and chromatin rearrangement in Human cells.

However, it is impossible, in human cells, to distinguish whether this anarchy is caused by the loss of transmission of mechanical forces through the nuclear membranes, or by the loss of morphology of the inter-membrane space. This latter hypothesis has never been explored.

To this end, I use the yeast model Saccharomyces cerevisiae where, in contrast to human cells, the two functions of LINC, namely transmission of forces and the maintenance of IMS width, can be easily uncoupled. This is possible thanks to a LINC-like protein, **Nvj1**, present at a NE subdomain where it establishes contact between the ONM and the yeast lysosome-like organelle, the vacuole. Indeed, Nvj1 separation-of-function mutants provide us with this opportunity.

Dissecting the role of Nvj1, my preliminary data suggest that the inter-membrane distance ensured by LINC and LINC-like proteins imparts, both, an accurate control of the repair of DNA double strand breaks and a regulation of chromatin dynamics. Indeed, when I delete NVJ1, cells become hyper-recombinant and the movement of a repetitive locus, erratic. I purport that the physical tethering of both membranes together imposes a specific lipidome and proteome, both important to these tasks. To explore this, I also study, by deleting lipid enzyme genes, how DNA recombination pathways react to global or specific lipid imbalance. My ongoing educated-guess screen already firmly implicates the metabolism of sterols.
In sum, I aim at providing pioneer insights into how NE morphology and composition matter in responding to DNA damage.

Auteurs principaux: BÂCLE, Janélie (CRBM, cnrs, Université de Montpellier); Dr MORIEL CARRETERO, María (CRBM, CNRS)

Orateur: BÂCLE, Janélie (CRBM, cnrs, Université de Montpellier)