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Study of a damaged chromatin-induced cellular mechanism triggered by the viral protein ICP0

Project coordinator : **Patrick Lomonte**

Centre de génétique Moléculaire et Cellulaire - UMR 5534 – CNRS - UCBL1

Lomonte@cgmc.univ-lyon1.fr

We have recently discovered a new cellular response triggered by damaged interphase centromeres (Morency et al., 2007). This response, that we named iCDR (for interphase Centromere Damage Response), results in the accumulation at damaged centromeres of coilin, fibrillarin, and SMN (Survival Motor Neuron) three of the most abundant proteins of Cajal bodies/gems nuclear domains. The iCDR is set off by the destabilization of the centromeric chromatin by the ICP0 protein of the herpes simplex virus type 1 (HSV-1). ICP0 is a nuclear RING finger protein with characterized E3 ubiquitin ligase activity. ICP0 induces the proteasomal degradation of several centromeric proteins (CENPs), such as, the histone H3 centromeric variant CENP-A, but also CENP-B, and –C, all essential for the structure of the centromere chromatin. This activity of ICP0 probably results in the formation of an aberrant chromatin fibre. We have now additional data that highly suggest that the iCDR might be only one aspect of a broader mechanism triggered by the destabilization of the chromatin whatever it is centromeric or not.

In the chromatin fibre, the nucleosome positioning is tightly control by chromatin remodelling factors in physiological processes such as transcription, replication, reparation, epigenetic controls… Likewise, the induction of DNA damage following genotoxic stresses leads to the remodelling of the chromatin structure at the sites of the lesions. Therefore, the capacity of the cell to organize the chromatin structure, and nucleosome positioning is a common aspect of both physiological and pathological processes. Any defect in the process of remodelling would have dramatic consequences for the biology of the cell, and the existence a mechanism dedicated to detect, signal, and repair aberrant chromatin structure and irregular nucleosome positioning might be anticipated.

Our project aims to characterize the first steps of such a mechanism by analyzing the binding properties of the coilin protein to chromatin using combined *in vitro* and *in cellulo* approaches. We will use microinjection technology to introduce, in nuclei, *in vitro* reconstituted chromatin containing various modifications. This approach will enable to analyze specifically the triggering of the iCDR with respect to the modified chromatin. The final aim of the project being to understand the role of the iCDR in the biology of HSV-1.

Morency, E., Sabra, M., Catez, F., Texier, P., and Lomonte, P. 2007. A novel cell response triggered by interphase centromere structural instability (iCDR). J Cell Biol 177, 757-768.