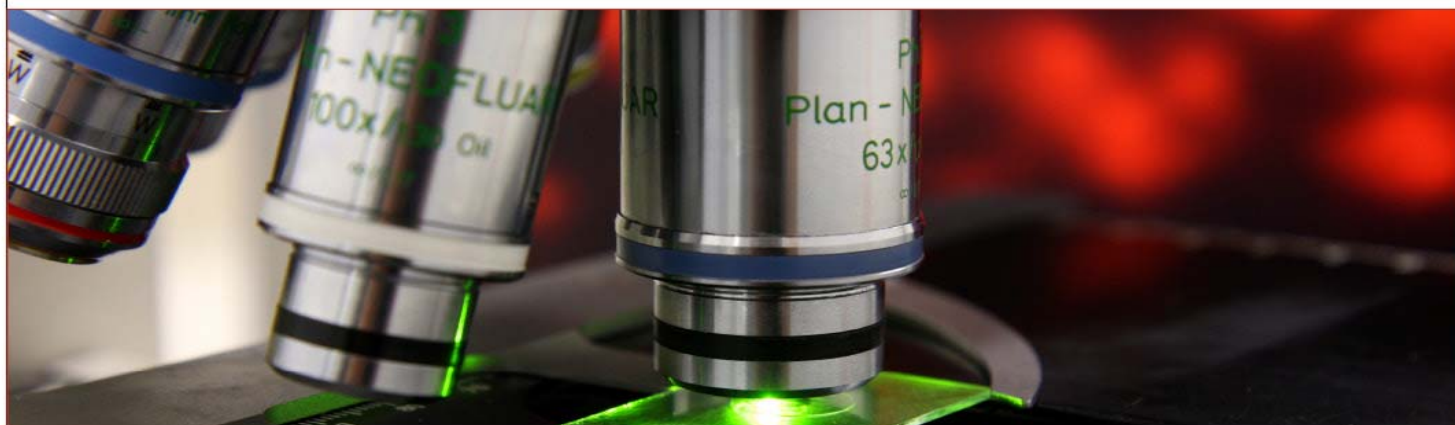


SÉMINAIRES ET CONFÉRENCES



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« MECHANISMS REGULATING POLY(ADP-RIBOSE) POLYMERASE ENZYMES »

Poly(ADP-ribose) polymerases (PARPs) use the ADP-ribose posttranslational modification to regulate diverse aspects of cell biology, most notably the cellular response to DNA damage. Our laboratory has focused on the structural biology and biochemistry of PARP family members, addressing key questions regarding the mechanisms regulating poly(ADP-ribose) production in cells. Much of our work has centered on PARPs involved in the cellular response to DNA damage (human PARPs 1, 2, and 3), where we have illustrated the fundamental aspects of how PARPs recognize DNA damage and how damage detection is coupled to poly(ADP-ribose) production. Our model for DNA damage-dependent PARP-1 activation indicates a monomeric interaction with DNA damage that conformationally positions the multi-domain architecture of PARP-1 for in cis automodification. In addition to the major global changes in PARP-1 structure upon detecting DNA damage, we have identified a major change in the local structure of the catalytic domain; specifically, a dramatic unfolding transition in a helix that we have shown to autoinhibit PARP-1 activity. Notably, the local structural change occurs in a catalytic domain region that partially forms the binding site for certain PARP inhibitors used to treat cancer, suggesting that these inhibitors could directly engage the PARP-1 allosteric activation mechanism and influence PARP-1 activity in distinct ways.



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