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Role of spatial chromatin organization in recombinational DNA repair and genomic stability

Abstract

Homologous recombination (HR) templates DNA double-strand break (DSB) repair off an intact homologous dsDNA "donor"molecule, which can exist in the form of a sister chromatid, a homologous chromosome, or dispersed repeats. HR fidelity partly depends on this competitive donor selection process, which embeds homology sampling by the RecA/Rad51-ssDNA nucleoprotein filament (NPF), DNA joint molecules reversal by ancillary HR factors and, presumably, regulation of the spatial collisions between the NPF and any given genomic loci (Savocco and Piazza, 2021). We developed various proximity ligation-based methodologies enabling detection of transient NPF-dsDNA interactions and early DNA joint molecules (as-of-yet recalcitrant to molecular detection) which granted direct study of these core HR steps and their regulation in S. cerevisiae (Piazza et al., 2017, 2018, 2019, 2021a). In collaboration with the Koszul lab, we recently identified two main ways by which cohesin bias ectopic donor identification, promoting it in cis and inhibiting it in trans (Piazza et al., 2021b). We present here additional mechanistic insights into the promotion of cis-sampling by the NPF. Mutation accumulation experiments in genotoxic conditions reveals that perturbation of chromatin loop folding in hypomorph mutants of cohesin regulators leads to repeat-mediated genome instability. This preliminary work furthers the characterization of the cohesin-mediated regulation of homology search during HR and its role as a suppressor of genomic instability.

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Auteurs principaux: Dr BORDELET, Helene (ENS Lyon - Institut Pasteur); Mme DUMONT, Agnès (ENS Lyon); Dr SAVOCCO, Jérôme (ENS Lyon); Mme PIVETEAU, Vinciane (ENS Lyon); Dr KOSZUL, Romain (Institut Pasteur); Dr PIAZZA, Aurele (ENS Lyon)

Orateur: Dr PIAZZA, Aurele (ENS Lyon)