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Remodelers move chromatin in response to DNA damage

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DNA double-strand breaks (DSBs) are dangerous lesions that occur when both strands of the DNA double helix are broken. Repair of DSBs occurs either by homologous recombination (HR) or non-homologous end-joining (NHEJ). A fundamental distinction between the 2 pathways lies in the requirement for a homologous sequence that templates the repair: this is needed for HR but not for NHEJ. In S-phase cells, the template most often used is the sister chromatid. If the break occurs in G_1 phase (particularly in haploid cells, like yeast) or if both sisters are damaged, the homolog or an ectopic sequence with appropriate homology must be used as a template. For that to occur, the damage and the intact homologous sequence must first physically meet, through a process called homology search. In mammalian nuclei this would involve the scanning of thousands of millions of base pairs for an exact copy of the damaged site. Not surprisingly, ectopic recombination (i.e., recombination with a homolog or a non-sister chromosome) is relatively rare in complex genomes, while it occurs quite efficiently in yeast.

Given the spatial constraint that restricts the mobility of chromosomal loci,[1] it is not surprising that the time it takes for 2 specific sites to collide is rate limiting for HR. Both computer simulations and experiments that monitored recombination rates in yeast support this notion.[2,3]

Intriguingly, last year it was shown, through single-particle tracking with high-resolution time-lapse microscopy in yeast, that fluorescently tagged sites of DSBs move within a larger radius than the same tagged site when it is undamaged.[4,5] Notably, the volume explored increased by ~4-fold. Mutations in repair proteins such as Rad51 and Rad54 or in the DNA damage checkpoint kinase Mec1 (ATR) were shown to be important for the increased mobility. Two studies reported similar phenomena, yet they differed in one aspect: one suggested that loci unlinked to the damage might also increase in mobility after exposure to ionizing irradiation, while the other did not observe this after induction of a single DSB or on low level Zeocin. The discrepancy was recently resolved by showing that the genome-wide response to damage that leads to increased chromatin mobility depends on the activation of the DNA damage checkpoint response (DDR).[6] The DDR is not immediately induced in the presence of a single DSB, nor in the presence of low levels of Zeocin, while higher levels of Zeocin activate the DDR rapidly and, indeed, induce the general chromatin response.[6]

Genetic dependence on DNA damage checkpoint kinases was shown by mutating either Mec1 and/or its downstream target kinase Rad53. In both mutants, the ectopic or general increase in mobility was impaired. Remarkably, an artificial activation of Mec1 kinase by juxtaposition of its binding partner Ddc2 and the kinase co-activator Ddc1 led to a similar increase in chromatin mobility in the absence of DNA damage, ruling out potential indirect effects of Zeocin and/or DNA damage.

In contrast to the increased movement scored for the DSB site itself, this general increase in mobility was not dependent on Rad51. Thus the mechanism that acts at the site of damage (in cis) differs at least in part from that which increases chromatin mobility in trans.[6]

Increases in chromatin mobility could be a direct consequence of nucleosome remodeling that would change the flexibility of a chromatin fiber. Previous work has shown that the targeting of the INO80 nucleosome remodeling complex leads to an increase in the mobility of an intact locus. Studies of the yeast *PHO5* promoter showed that the INO80-dependent increase in mobility correlated with the removal of nucleosomes. Since the INO80 complex is a known target of the DDR, the INO80 complex was tested for contributions to the DDR-induced increase in chromatin mobility. Indeed, deletion of INO80 subunits that compromise its ATP-dependent nucleosome remodeling activity reduced the DDR-induced increase in chromatin mobility at ectopic sites. Ablation of other remodelers, such as Chd1 and Swr1, did not.[6]

A number of open questions remain (**Fig. 1**). First and foremost, what is the structural change in chromatin that leads to increased mobility of a given tagged locus? Does the increased mobility correlate with nucleosome displacement, loss of other factors, or disruption of an anchor? Finally, how do checkpoint kinases regulate INO80?

Whereas both homology search and the flexibility of the chromatin fiber may be different in mammalian cells, it is nonetheless plausible that the effects observed are relevant beyond yeast. For instance, a DSB array that leads to a translocation in mouse fibroblasts has a higher mobility than that of a non-translocating array.[7]

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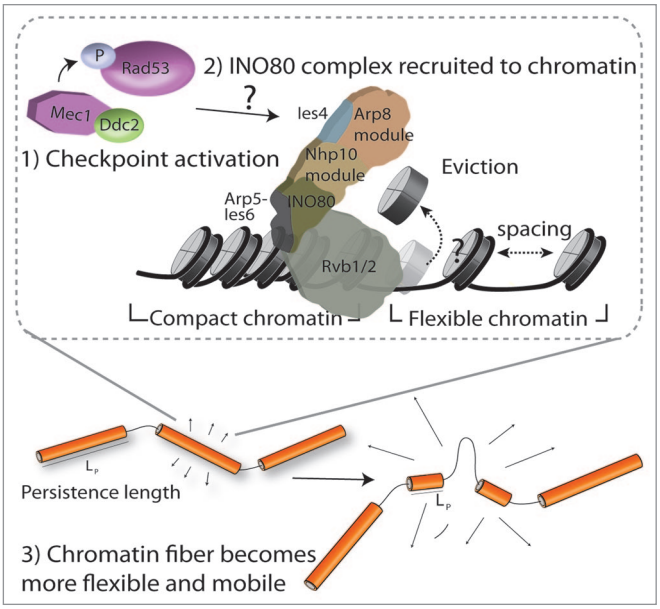

Figure 1. Hypothetical model of INO80 mediated enhanced chromatin mobility. Checkpoint activation due to DNA damage targets the INO80 nucleosome remodelling complex to chromatin. INO80 evicts nucleosomes and makes chromatin more flexible. Due to the actions of INO80 the persistence length of the chromatin fiber is reduced allowing for chromatin to move more freely.

Since NHEJ is the preferred mode of repair in mammalian cells, and not HR, it may only be an exceptional type of break that requires a homology search, and therefore enhanced movement. Indeed, homology search in mammals may normally be actively suppressed to prevent unwanted translocations or deletions. It will be intriguing to see if remodelers that favor NHEJ, such as the SWI/SNF remodeler BRM,[8] antagonize movement in mammalian cells, by perhaps counteracting the activity of INO80. Fortunately the tools are in hand to test such hypotheses, both in mammalian and yeast cells.

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