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# Chromatin yo-yo: expansion and condensation during DNA repair

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## Abstract

DNA double-strand breaks are repaired by nonhomologous end-joining (NHEJ) and homologous recombination (HR). Disrupting the balance between these pathways results in toxic chromosomal rearrangements. Several recent studies are revealing that dynamic changes in chromatin conformation can regulate DNA repair pathway choice both spatially and temporally.

### Keywords

chromatin; DNA repair; homologous recombination

Unrepaired DNA double-strand breaks (DSBs) can result in cell death or widespread genomic instability that predisposes to cancer. DSBs are repaired through a combination of homologous recombination (HR) and nonhomologous end-joining (NHEJ) pathways. DNA end resection and single strand DNA generation promotes HR usage, while conditions that prevent end resection favor NHEJ. Balance between the two competing processes is critical for genome stability as evidenced by a striking genetic interaction involving BRCA1 and 53BP1. Defective HR in the case of BRCA1 deficiency is strongly mitigated by concomitant disruption of the NHEJ-promoting 53BP1 gene, due in part to elevated end resection [1]. While the protein machinery that defines each pathway has been extensively dissected, evidence that chromatin dynamics can regulate pathway choice has only emerged in the last few years.



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Recent studies suggest differences in DSB repair between euchromatin and heterochromatin. Using fluorescence imaging in mammalian and insect cells exposed to ionizing radiation, several groups inferred that DSBs within heterochromatin are preferentially repaired by HR [2]. Interestingly, one study documented heterochromatin expansion and DSB relocalization outside of the HP1a domain, which coincided with Rad51 [3]. This dynamic change in chromatin conformation, from a compact to more diffuse state, was thought to be necessary for the HR repair of DSBs in heterochromatin.

There is, however, considerable evidence for euchromatin-associated modifications as a key characteristic of DSBs undergoing HR. Notably, meiotic recombination hotspots occur at sites enriched for H3K4me3, a mark associated with transcriptional start sites, and there is a dedicated histone methyltransferase responsible for this predilection. In its absence, meiotic recombination is redirected to H3K4me3 within active genes [4]. Histone acetylation has also been intimately associated with active HR. Acetylation of H4K16 was found to antagonize 53BP1 ionizing radiation-induced foci formation in part by reducing affinity between the 53BP1 Tudor domains and the H4K20me2 mark [5,6]. Not only did acetylation promote BRCA1 DSB localization at the expense of 53BP1, active transcription near the DSB did likewise in several independent studies [5,7,8]. HR and NHEJ pathway effector proteins were differentially distributed across the entire genome in response to site-specific DSBs. Rad51 predominantly localized at transcriptionally active regions while XRCC4 did not [7]. This was thought to be mediated by SETD2-dependent H3K36 trimethylation, which recruits LEDGF and CtIP for endresection [8]. Both reports suggest a critical function of H3K36me3 in DSB repair by HR at transcriptionally active regions, and they confirmed that H3K36me3 around DSB sites preceded DSB formation, consistent with a role of chromatin context in DSB repair pathway choice. Thus, active transcription-associated marks function during the early stages of HR in both meiotic and mitotic cells, suggesting a requirement of open chromatin conformation.

Although evidence exists for both heterochromatic and euchromatic marks promoting HR, it is unclear how these disparate states could function together to achieve a repair process that requires similar protein effectors. Perhaps these can be explained by the historical “prime, repair, restore” model of chromatin dynamics during DNA repair [2], in which an initial chromatin expansion is thought to enable DNA repair protein access, followed by restoration of chromatin structure during the latter stages of repair. It is, however, unclear whether expansion and restoration occur simultaneously and whether they cooperate or compete.

In this light, a new study from Khurana et al. demonstrates that initial chromatin expansion is followed by gradual condensation [9]. The dynamic switch between expansion and compaction after damage may explain the previously reported requirement for marks associated with both open and closed chromatin. The authors of this study describe contributions of histone variant macroH2A1 and the H3K9 methyltransferase PRDM2 in HR repair of DSBs. In an RNAi screen for chromatin factors that affect HR, they identified macroH2A1 knockdown as reducing homology directed repair. Since macroH2A1 was reported to associate with heterochromatin, Khurana et al. investigated whether repressive chromatin marks accumulate at damage sites, and discovered that H3K9me2 is enriched near DSBs. This dimethylation event is mediated by the PRDM2 methyltransferase, which is

recruited to DSBs by macroH2A1 to promote HR. Both macroH2A1 and PRDM2 appear to mediate the gradual chromatin compaction phase following the initial rapid expansion that occurs after damage. Furthermore, both promote the accumulation of pro-HR BRCA1 protein at DSBs. Taken together, the findings suggest that the condensation phase is important for repair by HR. Thus euchromatic marks and the initial relaxation may be important for "priming" the chromatin near DSBs, while the acquisition of heterochromatic marks could facilitate repair by HR in the "prime, repair, restore" model (Figure 1). An important note of caution when interpreting these findings, however, is the striking differences between double knockout macroH2A mice in comparison to BRCA1 or BRCA2 knockouts. Double knockout macroH2A mice are viable and without obvious developmental defects [10], which is in stark contrast to null phenotypes in either BRCA1 or BRCA2 knockout mice, both of which result in embryonic lethality commensurate with rampant genomic instability. It is thus unclear the extent to which these histone variants contribute to BRCA-dependent HR repair in physiologic settings.

An interesting area for future exploration is the significance of the open to closed chromatin transition, and whether the two phases indeed serve different purposes in the damage response. A second aspect worthy of consideration is that PRDM2 is frequently mutated in cancers, raising the possibility that its role in HR is relevant to tumor suppression.

## References


1. Chapman JR, et al. Playing the end game: DNA double-strand break repair pathway choice. MOLCEL. 2012; 47:497–510.
2. Soria G, et al. Prime, repair, restore: the active role of chromatin in the DNA damage response. Molecular Cell. 2012; 46:722–734. [PubMed: 22749398]
3. Chiolo I, et al. Double-strand breaks in heterochromatin move outside of a dynamic HP1a domain to complete recombinational repair. Cell. 2011; 144:732–744. [PubMed: 21353298]
4. Brick K, et al. Genetic recombination is directed away from functional genomic elements in mice. Nature. 2013; 485:642–645. [PubMed: 22660327]
5. Tang J, et al. Acetylation limits 53BP1 association with damaged chromatin to promote homologous recombination. Nature Structural & Molecular Biology. 2013; 20:317–325.
6. Hsiao K-Y, Mizzen CA. Histone H4 deacetylation facilitates 53BP1 DNA damage signaling and double-strand break repair. J Mol Cell Biol. 2013; 5:157–165. [PubMed: 23329852]
7. Aymard F, et al. Transcriptionally active chromatin recruits homologous recombination at DNA double-strand breaks. Nature Structural & Molecular Biology. 2014; 21:366–374.
8. Pfister SX, et al. SETD2-dependent histone H3K36 trimethylation is required for homologous recombination repair and genome stability. Cell Rep. 2014; 7:2006–2018. [PubMed: 24931610]
9. Khurana S, et al. A macrohistone variant links dynamic chromatin compaction to BRCA1-dependent genome maintenance. Cell. 2014 Rep DOI: 10.1016/j.celrep.2014.07.024.
10. Gaspar-Maia A, et al. MacroH2A histone variants act as a barrier upon reprogramming towards pluripotency. Nature Communications. 2013; 4:1565.

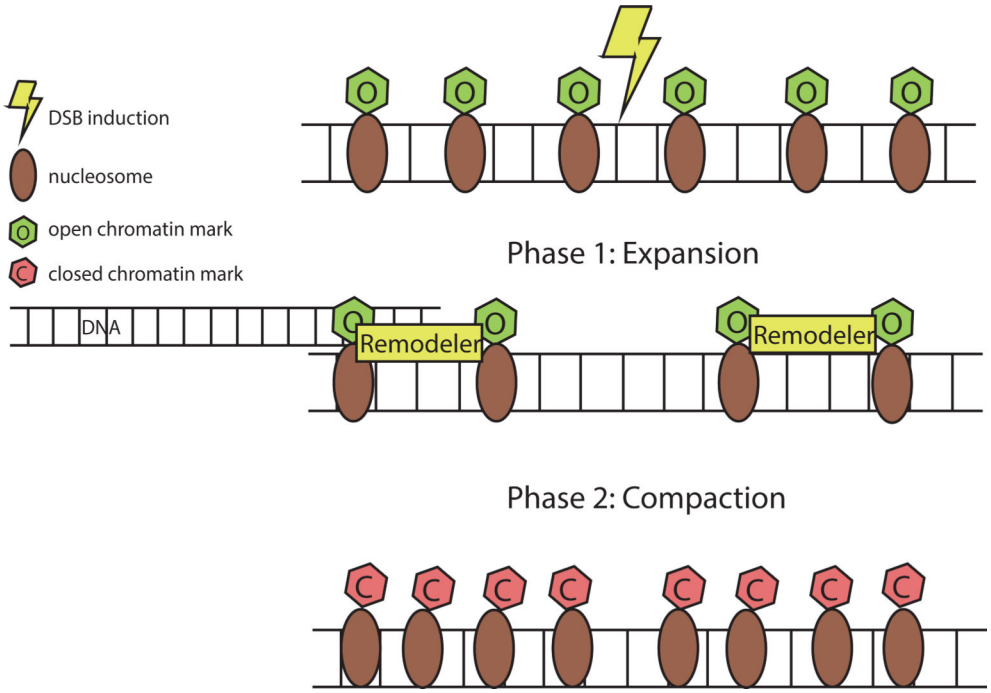


**Figure 1. Chromatin dynamics during HR at actively transcribed regions**

Histone modifications that mark open chromatin are deposited during transcription. After double-strand break (DSB) occurs at these regions, the pre-existing marks of open chromatin recruit repair machinery and remodeling complexes to the DSB to rapidly mediate chromatin relaxation. This is followed by prolonged gradual compaction of the chromatin, along with the deposition of histone marks associated with closed chromatin.