

Published in final edited form as:

Mol Cell. 2016 June 02; 62(5): 712–727. doi:10.1016/j.molcel.2016.04.006.

Epigenome maintenance in response to DNA damage

Juliette Dabin^{1,2}, Anna Fortuny^{1,2}, and Sophie E. Polo^{1,*}

¹Epigenome Integrity group, UMR 7216 CNRS, Paris Diderot University, Sorbonne Paris Cité, Paris cedex 13, France

Summary

Organism viability relies on the stable maintenance of specific chromatin landscapes, established during development, that shape cell functions and identities by driving distinct gene expression programs. Yet, epigenome maintenance is challenged during transcription, replication and repair of DNA damage, all of which elicit dynamic changes in chromatin organization. Here, we review recent advances that have shed light on the specialized mechanisms contributing to the restoration of epigenome structure and function after DNA damage in the mammalian cell nucleus. By drawing a parallel with epigenome maintenance during replication, we explore emerging concepts and highlight open issues in this rapidly growing field. In particular, we present our current knowledge of molecular players that support the coordinated maintenance of genome and epigenome integrity in response to DNA damage, and we highlight how nuclear organization impacts genome stability. Finally, we discuss possible functional implications of epigenome plasticity in response to genotoxic stress.

Introduction: functional importance of epigenome integrity

The diversity of cell types in multicellular organisms is established during development through fine-tuned cell differentiation processes, consisting in the activation and repression of specific transcription programs (Semrau and van Oudenaarden, 2015). Differential gene expression thus contributes to defining specialized functions and identities in cells sharing the same genome. It relies on epigenetic modifications acquired during development and stably inherited through cell divisions.

The epigenome, which supports such heritable changes in gene expression, consists in genome packaging into chromatin in the cell nucleus, where DNA is wrapped around histone proteins to form nucleosomes (Kornberg, 1977; Luger et al., 1997). DNA methylation (Schübeler, 2015), histone post-translational modifications (Bannister and Kouzarides, 2011) and the existence of histone variants that differ in their protein sequences (Maze et al., 2014) confer variability at the nucleosome level. Variations in nucleosome positioning, non-histone chromatin components, and higher-order chromatin folding further contribute to chromatin plasticity (Li and Reinberg, 2011). Chromatin can thus be viewed as

This manuscript version is made available under the CC-BY-NC-ND 4.0 license <http://creativecommons.org/licenses/by-nc-nd/4.0/>

*Correspondence: sophie.polo@univ-paris-diderot.fr.

²Co-first author

a multifaceted signal integration platform that responds to intracellular and environmental cues by dynamic changes in epigenetic marks (Badeaux and Shi, 2013).

While epigenome plasticity is a key feature underpinning cell differentiation, epigenome maintenance is critical for the robustness of phenotypic traits, which is of fundamental importance not only during embryonic development but also for adult tissue homeostasis. Accordingly, failure to maintain epigenome integrity can have deleterious consequences for the organism, resulting in aging and disease (Zane et al., 2014).

However, DNA metabolic activities, such as transcription, replication and repair, trigger dramatic chromatin alterations and thus pose a major challenge to epigenome maintenance. Among them, DNA damage repair is unique in the sense that it is generally non-programmed, DNA damage occurring anywhere in the genome at any time, and also versatile, owing to the variety of DNA lesions (Ciccio and Elledge, 2010; Hoeijmakers, 2009; Jackson and Bartek, 2009). Here, we focus on chromatin dynamics during the repair response in the mammalian cell nucleus. We review recent progress in delineating by which mechanisms and to which extent epigenome integrity is affected and restored after DNA damage, underlying cell fate maintenance.

DNA damage challenges epigenome integrity

DNA damage poses a serious threat to cell viability by compromising both genome and epigenome integrity. Indeed, the DNA damage response (DDR) is accompanied by significant alterations of chromatin structure, affecting intrinsic chromatin components and epigenetic marks, with major implications for epigenome functions.

Chromatin rearrangements in response to DNA damage

A large number of studies, based on biochemical and imaging approaches in several eukaryotic cell systems, highlight the marked rearrangements of damaged chromatin (Figure 1A). In particular, chromatin decondensation, accompanied by a loss of density of core and linker histones, has been reported in human cells exposed to local UVC irradiation (Luijsterburg et al., 2012) or to laser micro-irradiation-induced DNA breaks (Kruhlak et al., 2006; Smeenk et al., 2013; Strickfaden et al., 2015), in a Poly(ADP)Ribose Polymerase (PARP)-dependent manner. Moreover, there is accumulating evidence for nucleosome loss from the damaged region, increase in core histone extractability, and even histone eviction from damaged chromatin, with partial or complete nucleosome disruption (reviewed in Adam et al., 2015a; Bakkenist and Kastan, 2015; Rodriguez et al., 2015). Epigenome perturbations after DNA damage culminate with the degradation of chromatin components, as described for acetylated histones in yeast and mouse cells exposed to alkylating damage or Ionizing Radiation (IR) (Qian et al., 2013).

Likely candidates for promoting histone mobility in response to DNA damage are chromatin remodeling factors, which use the energy of ATP hydrolysis to slide, exchange and/or evict histone proteins from chromatin (Bartholomew, 2014). Indeed, all major families of remodelers are recruited to damaged chromatin and contribute to DNA damage repair (reviewed in Aydin et al., 2014b; Lans et al., 2012; Seeber et al., 2013). Furthermore,

remodelers can have a direct effect on chromatin compaction and histone mobilization at sites of DNA damage, as recently shown for the human remodeling factor Chromodomain Helicase DNA binding protein 2 (CHD2) in response to DNA Double-Strand Breaks (DSBs) (Luijsterburg et al., 2016). In parallel, and independently of ATP hydrolysis, histone chaperones (Gurard-Levin et al., 2014) contribute to histone dynamics in damaged chromatin. This is exemplified at DSBs induced by the site-specific endonuclease I-PpoI in human cells, where the Nucleolin and Anti-Silencing Function 1 (ASF1) chaperones promote nucleosome disassembly by evicting outer and inner core histones, respectively (Goldstein et al., 2013). It is important to stress that, while the alteration of chromatin organization is a general response to DNA damage, different types of DNA lesions likely involve distinct chromatin rearrangements and underlying mechanisms.

Non-histone chromatin components also undergo dynamic changes upon DDR activation in mammalian cells, with the accumulation of silencing factors like Heterochromatin Protein 1 (HP1), Polycomb Group proteins, histone deacetylases, histone methyltransferases and DNA MethylTransferases (DNMTs) at sites of DNA damage, accompanied by chromatin modifications including DNA methylation and repressive histone marks (Alagoz et al., 2015; Dinant and Luijsterburg, 2009; Gong and Miller, 2013; Gursoy-Yuzugullu et al., 2015b; O'Hagan, 2014; Soria et al., 2012; Vissers et al., 2012).

More generally, a plethora of damage-induced post-translational modifications, affecting histone proteins and chromatin-associated components, have been identified (reviewed in Dantuma and van Attikum, 2015). Among them, phosphorylation, acetylation, ubiquitylation and PARylation are the best studied, a prominent example being the evolutionarily conserved phosphorylation of a carboxy-terminal Serine in the H2AX variant - so-called γ H2AX - which plays a pivotal role in response to DSBs (reviewed in Scully and Xie, 2013). Proteomic screens have been instrumental for identifying the multiple targets of post-translational modifications occurring in response to UV, IR, oxidative and alkylation damage in human cells (Elia et al., 2015; Jungmichel et al., 2013; Matsuoka et al., 2007; Povlsen et al., 2012). However, much remains to be learned about the specific, and possibly combinatorial roles of chromatin modifications after a genotoxic stress challenge, especially when considering that several of these modifications are not necessarily unique to the DDR.

Spatio-temporal regulation of chromatin alterations

Chromatin alterations in response to DNA damage undergo a tight spatio-temporal regulation that only begins to be unraveled. Indeed, several recent studies in human cells have shown that transient compaction follows chromatin relaxation at sites of DNA breaks (Ayrapetov et al., 2014; Burgess et al., 2014; Khurana et al., 2014; Strickfaden et al., 2015), which could be driven by the antagonistic activities of chromatin remodeling complexes as proposed for CHD3 and Imitation Switch (ISWI) in response to heterochromatic DSBs (Klement et al., 2014). The temporal dynamics of chromatin changes following DNA damage further emphasizes the fluid nature of chromatin organization during repair. Rearrangements of damaged chromatin are also regulated during the cell cycle: a complete disruption of nucleosomes has been observed around DSBs in asynchronous human cells, with a loss of all core histones, while nucleosomes are only partially disrupted in G1-

arrested cells (Goldstein et al., 2013). This disparity likely reflects the predominance of distinct DSB repair pathways in different cell cycle stages, Non-Homologous End-Joining (NHEJ) being the preferred repair pathway in G1, while Homologous Recombination (HR) predominates in S/G2 (Ceccaldi et al., 2016).

In addition, chromatin dynamics in response to DNA damage are spatially regulated. Indeed, it has been shown in human cells that chromatin is more accessible at laser damage sites and more compact in adjacent regions (Hinde et al., 2014). This observation emphasizes that changes in chromatin organization are not restricted to the damaged area. Genome-wide rearrangements of the epigenetic landscape also take place during the DDR, such as global reprogramming of H3K27ac upon UV irradiation in mammalian cells, which underlies expression changes of critical genes during the stress response (Schick et al., 2015). Similarly UV irradiation triggers genome-wide hyperacetylation on H3 and H4 in budding yeast (Yu et al., 2005). Further highlighting that the response to DNA damage is integrated in the nuclear space, an increased mobility of chromatin surrounding DSBs has been reported in yeast (Dion and Gasser, 2013; Miné-Hattab and Rothstein, 2013), for heterochromatic breaks in *Drosophila* (Ryu et al., 2015) and for damaged or uncapped telomeres in mammalian cells (Chen et al., 2013; Cho et al., 2014; Dimitrova et al., 2008) in a microtubule-dependent manner (Lottersberger et al., 2015).

Functional relevance of chromatin alterations

The above-described changes in chromatin organization after DNA damage have important functional consequences on DNA damage signaling and repair. As proposed several decades ago in the Access-Repair-Restore (ARR) model (Polo and Almouzni, 2015; Smerdon, 1991), transient disruption of chromatin organization is thought to facilitate access of the repair machinery to damaged DNA. Recent work in human cells supports this hypothesis by showing that CHD2 remodeling activity promotes chromatin expansion at DSBs and the recruitment of NHEJ factors (Luijsterburg et al., 2016). Furthermore, damage-induced histone modifications, including γ H2AX, H2AK15 ubiquitination, and H4K20 methylation, are critical for DNA damage signaling and repair progression as they provide a structural basis for the coordinated recruitment of DDR effectors through the binding of histone readers (Figure 2; reviewed in Dantuma and van Attikum, 2015; Smeenk and van Attikum, 2013). Noteworthy, such modifications are not restricted to core histones as linker histone ubiquitylation was recently identified as a key player in DNA damage signaling in response to IR in human cells (Thorslund et al., 2015). The prominent role of histone modifications in this process highlights the importance of the balance between histone modifying enzymes - writers and erasers - in fine-tuning the DDR. Histone dynamics also contribute to regulating repair pathway choice and repair efficiency, as reported for H2A.Z whose dynamic exchange at DSBs in human cells appears to control DNA end resection, DSB repair by HR and NHEJ (Alatwi and Downs, 2015; Gursoy-Yuzugullu et al., 2015a; Xu et al., 2012). Similarly, the dynamics of silencing factors like HP1 and the co-repressor KRAB-Associated Protein 1 (KAP1) are of major importance as their sustained retention on chromatin impairs DSB repair by HR (Kalouisi et al., 2015).

While one can appreciate the functional relevance of chromatin opening and dynamics in the DDR, it was not straightforward to understand the role of chromatin compaction that precedes its relaxation and was also observed at the periphery of damaged areas. Recent studies have demonstrated that transient chromatin condensation is actually necessary and sufficient for stimulating DNA damage signaling in human cells (Burgess et al., 2014). It is also conceivable that local chromatin compaction can facilitate the ligation of broken DNA ends by keeping them in close proximity. Finally, the recruitment of silencing factors and the establishment of repressive histone marks on damaged chromatin can participate in silencing transcription at sites of DNA damage, thus avoiding deleterious interference between transcription and repair machineries (Chou et al., 2010; Gong et al., 2015; Kakaroungkas et al., 2014; Ui et al., 2015).

Restoration of epigenome integrity after DNA damage

New histone deposition

In order to preserve cell identity and function, epigenome integrity must be restored after DNA damage repair. A salient feature of this restoration step is the deposition of newly synthesized histones into damaged chromatin, as first characterized in response to local UVC damage in human cells (Figure 1A). Transient transfection of cells with epitope-tagged histones indeed revealed the *de novo* incorporation of the H3.1 histone variant and of the outer core histone H2A at sites of local UVC irradiation (Dinant et al., 2013; Polo et al., 2006). Combination of local UVC damage with specific tracking of newly synthesized histones using the SNAP-tag technology (Adam et al., 2015b) then established that the histone variant H3.3, but not the centromeric H3 variant Centromeric Protein A (CENPA), was also deposited *de novo* in damaged chromatin (Adam et al., 2013). Notably, both high-frequency point mutations and transcription repression of genes encoding H3.3 have been uncovered in several human cancers, particularly in brain tumors (Gallo et al., 2015; Kallappagoudar et al., 2015). It will be interesting to investigate whether these alterations impact epigenome restoration after DNA damage, thus contributing to tumorigenesis. More generally, how cancer-associated chromatin alterations (Zane et al., 2014) may affect DNA repair and the resetting of epigenetic marks during repair deserves to be explored.

Among the molecular players in repair-coupled chromatin assembly, histone chaperones play pivotal roles in the restoration of chromatin integrity after DNA damage by promoting new histone deposition. In particular, the histone chaperone Chromatin Assembly Factor-1 (CAF-1) escorts H3.1 in human cells (Tagami et al., 2004) and stimulates its *de novo* incorporation into UVC-damaged chromatin in a manner coupled to repair synthesis (Polo et al., 2006). *In vitro* experiments, revealing the direct interaction and functional synergy between the human chaperones CAF-1 and ASF1 during UVC damage repair, raise the possibility that ASF1 could also be involved in new histone deposition upon cell exposure to damaging agents, potentially as a histone donor for CAF-1 (Mello et al., 2002). Furthermore, the recent identification of CAF-1 as a chaperone for the H3.2 histone variant (Latreille et al., 2014) suggests an even wider role for CAF-1 in depositing newly synthesized H3 variants during UV-damaged chromatin restoration. Contrary to CAF-1-mediated H3.1 deposition that is coupled to late repair steps, newly synthesized H3.3

histones are deposited early after damage by the H3.3-specific chaperone Histone Regulator A (HIRA), which is recruited to UVC-damaged chromatin in response to Cullin4-dependent ubiquitylation events occurring upon damage detection (Adam et al., 2013). Intriguingly, HIRA is also required for the deposition of new H3.1, thus revealing a possible crosstalk between H3 variant deposition pathways at repair sites. Finally, the histone chaperone Facilitates Chromatin Transcription (FACT) presumably stimulates new H2A deposition in damaged chromatin because it is responsible for the accelerated turnover of H2A at sites of UVC irradiation (Dinant et al., 2013). Notably, FACT-mediated H2A exchange and HIRA-dependent H3.3 incorporation at damaged sites are shared mechanisms between UVC damage and DSB responses in human cells (Heo et al., 2008; Yang et al., 2013). Furthermore, the budding yeast orthologs of CAF-1 and HIRA likely contribute to chromatin restoration also at meiotic DSBs (Brachet et al., 2015).

Moreover, there is now compelling evidence for an important role of ATP-dependent chromatin remodelers at damage sites (reviewed in Lans et al., 2012; Smeenk and van Attikum, 2013). Current evidence suggests that chromatin remodelers function mostly in providing access to chromatin and regulating repair. These remodelers may also assist histone chaperones and/or directly participate in new histone deposition coupled to repair, as observed during transcription. For example, p400, CHD1 and CHD2 deposit H3.3 in transcriptionally active chromatin regions in mammalian cells (Harada et al., 2012; Pradhan et al., 2016; Siggins et al., 2015). Interestingly, the CHD2 remodeler was recently shown to promote new H3.3 accumulation at sites of laser micro-irradiation-induced damage in human cells (Luijsterburg et al., 2016). One can also hypothesize that chromatin remodelers may help restoring nucleosome positioning/spacing after damage.

Beyond the restoration of chromatin structure by new histone deposition, histone chaperones also contribute to the re-establishment of a transcriptional program after UVC damage, as shown for HIRA (Adam et al., 2013) and FACT in human cells (Dinant et al., 2013). Besides histone chaperones, the histone modifying enzyme DOT1-Like H3K79 methyltransferase (DOT1L) is also required for transcription recovery after UVC damage in mouse cells (Oksenych et al., 2013). However, the molecular bases for how histone dynamics mediated by these chromatin-associated factors contribute to transcription restart are still under investigation. Interestingly, the significant delay observed between HIRA release from damaged chromatin and transcription restart opens up the possibility that new H3.3 histones deposited by HIRA in damaged chromatin could act as a bookmark, licensing chromatin for transcription restart once repair is complete (Adam et al., 2013).

The deposition of new histones at damaged sites also raises the fundamental question of the contribution of parental histones to chromatin restoration after repair. Since parental histones are present in chromatin before damage and carry the original epigenetic information, it will be important to investigate whether they are replaced by newly synthesized histones during chromatin repair and to which extent they participate in the maintenance of epigenome integrity after damage.

DNA and histone modifications

While deciphering the contribution of histone dynamics to restoring chromatin integrity is in progress, how the parental histone and DNA modifications are maintained in response to damage is still uncharacterized. The recruitment of the maintenance DNA (Cytosine-5-)-Methyltransferase 1 (DNMT1) to repair sites upon UVA laser micro-irradiation (Mortusewicz et al., 2005), oxidative damage (O'Hagan et al., 2011) and site-specific DSBs in human cells (O'Hagan et al., 2008) suggests that, like during DNA replication, DNMT1 may contribute to methylating newly synthesized DNA at repair sites. Another key epigenetic regulator of DNA methylation, Ubiquitin-like with PHD and Ring Finger domains 1 (UHRF1), which maintains cytosine methylation and facilitates DNMT1 accumulation, is recruited to DNA inter-strand crosslinks and DSBs in human cells (Liang et al., 2015; Tian et al., 2015; Zhang et al., 2016). Although no evidence for UHRF1 involvement in DNA methylation maintenance at repair sites has been provided so far, UHRF1 interacts with repair factors and regulates lesion processing.

Even less is known about the maintenance of histone modifications at sites of DNA damage repair. Since histone Post-Translational Modifications (PTMs) are key epigenetic marks in the control of gene expression and are challenged by DNA damage, it is important that DNA damage-induced changes in histone PTMs are erased and original PTMs are re-established. However, whether and by which mechanisms this actually occurs is still an open question. Moreover, the fact that newly synthesized histones deposited into chromatin during repair come with their own set of modifications (Loyola et al., 2006) further complicates the maintenance of the original histone PTM landscape. Future work will determine if parental histone marks are transferred to newly deposited histones after repair.

Altogether, this illustrates the lack of mechanistic insights into how DNA and histone modifications are preserved after DNA damage, a question that has been approached in the context of DNA replication.

Lessons from chromatin replication

During the duplication of the genetic material in S phase of the cell cycle, chromatin undergoes dramatic alterations (reviewed in Alabert and Groth, 2012; Annunziato, 2015; Ramachandran and Henikoff, 2015), which bear striking similarity with chromatin rearrangements that occur during DNA damage repair (Figure 1).

Parallel between epigenome maintenance during replication and repair

Similar to the transient chromatin rearrangements observed at sites of DNA damage, DNA replication leads first to the disruption of pre-existing nucleosomes ahead of the replication fork. Parental histones then symmetrically segregate between the leading and lagging DNA strands, and contribute to nucleosome reassembly downstream of the replication fork together with newly synthesized histones. New histones are deposited onto replicating DNA by a replication-coupled nucleosome assembly process (reviewed in Alabert and Groth, 2012; Ramachandran and Henikoff, 2015), which resembles the repair synthesis-coupled deposition of new histones after damage. Noteworthy, the coupling between chromatin

assembly and DNA replication also applies to lagging strand synthesis as new histone deposition is required for the termination of Okazaki fragments in budding yeast (Smith and Whitehouse, 2012). However, while the replication process results into a semi-conservative mode of inheritance at the genome and epigenome levels with a two-fold dilution of parental histones (Alabert et al., 2015), the relative contributions of parental and new histones to the composition of repaired chromatin are still to be determined. Furthermore, in contrast to the massive synthesis of canonical replicative histone variants that occurs in S phase and provides the necessary supply for new histone deposition at the replication fork (Marzluff et al., 2008), there is no evidence for an induction of histone synthesis in response to DNA damage. Canonical histone synthesis is even inhibited due to DNA damage checkpoint activation, as described in human cells exposed to IR (Su et al., 2004). Despite these discrepancies, epigenome maintenance during replication and repair have much in common. Studying chromatin duplication can thus give interesting insights into how chromatin integrity is preserved in response to DNA damage.

Shared molecular players: focus on histone chaperones

Chromatin dynamics during replication and repair share several molecular players (Figure 1), in particular histone chaperones and chromatin remodelers. Indeed, as it is the case at repair sites, the histone chaperone CAF-1 deposits new H3.1 at replication foci in human cells (Ray-Gallet et al., 2011; Smith and Stillman, 1991). Furthermore, the direct interaction of CAF-1 with the polymerase sliding clamp Proliferating Cell Nuclear Antigen (PCNA) ensures proper coordination between new histone deposition and DNA synthesis both at replication (Shibahara and Stillman, 1999) and repair sites (Moggs et al., 2000). Similarly, the interaction of the histone chaperone ASF1 with the replicative helicase subunit MCM2 (MiniChromosome Maintenance 2) through a H3-H4 histone bridge likely coordinates replication fork progression with parental histone transfer in human cells (Groth et al., 2007; Huang et al., 2015; Richet et al., 2015; Wang et al., 2015). Interestingly, human ASF1 participates in parental H3-H4 histone eviction at I-PpoI cut sites (Goldstein et al., 2013). It is thus tempting to speculate that this chaperone could play a central role in parental histone recycling in response to DNA damage, as proposed at the replication fork. In addition, human ASF1 functions as a histone buffer upon replication fork stalling, chaperoning H3-H4 histones within a multi-chaperone complex also containing the histone chaperone Nuclear Autoantigenic Sperm Protein (NASP) (Groth et al., 2005). NASP protects soluble H3-H4 from degradation (Cook et al., 2011), hence making it a good candidate for chaperoning evicted histones in response to DNA damage. Importantly, the replicative helicase MiniChromosome Maintenance (MCM) associates with several histone chaperones in addition to ASF1. The human histone chaperone Tonsoku Like-MMS22 Like (TONSL-MMS22L) bound to MCM5 is thought to have a role in replication-coupled histone eviction (Campos et al., 2015). Since TONSL localizes to UV damage sites in human cells (Hill et al., 2014) and promotes HR of replication-associated DSBs (Duro et al., 2010; O'Connell et al., 2010; O'Donnell et al., 2010), it is tempting to speculate that this chaperone could stimulate histone dynamics in damaged chromatin. The histone chaperone FACT also forms a complex with MCM and histones in yeast and human cells (Foltman et al., 2013; Tan et al., 2006). Considering that FACT disrupts nucleosome structure by competing with DNA for binding H2A-H2B (Hondele et al., 2013; Kemble et al., 2015), this chaperone could initiate

nucleosome disassembly at the replication fork. Notably, even though the literature does not report a direct role for FACT in nucleosome disassembly at repair sites, FACT promotes chromatin exchange of the damage-responsive histone variant H2AX (Heo et al., 2008) and H2A turnover at sites of UVC irradiation human cells (Dinant et al., 2013).

Inheritance of histone marks

Beyond histone dynamics promoted by histone chaperones, the inheritance of histone marks at the replication fork is another critical aspect of epigenome maintenance that has stimulated intense research. Differential labeling of old and new histones combined with immunodetection or quantitative proteomics of histone PTMs has been instrumental for monitoring epigenome inheritance at the replication fork (reviewed in Annunziato, 2015; Huang et al., 2013). A recent study in human cells thus demonstrates that parental histones are recycled with their PTMs at replication forks and that all parental PTMs are restored within one cell cycle (Alabert et al., 2015). This is achieved by the modification of new histones with parental marks, except for H3K9 and K27 trimethylation marks, which require continuous modification of both parental and new histones. It contrasts with the situation in *Drosophila* embryos where parental histone methylation marks are erased during replication and re-established through the stable association of histone methyltransferases with replicating chromatin (Petruk et al., 2012). While these studies shed light on how histone PTMs are propagated during replication, further work is needed to characterize the inheritance of histone marks after DNA damage repair. Isolation of nascent chromatin at repair sites, employing similar experimental strategies as those developed for replication forks (Alabert et al., 2014) or pulling down specifically UVC-damaged chromatin (Zavala et al., 2014) could be useful tools to explore this issue. Likewise, the induction of transient site-specific DSBs combined with histone mark profiling (Aymard et al., 2014; Massip et al., 2010) appears to be a powerful technique to follow changes in histone modifications during DNA damage repair. To approach this issue, it could also be interesting to focus on chromatin domains characterized by a specific set of histone marks like heterochromatin (Saksouk et al., 2015).

Duplication of higher-order chromatin structures

How heterochromatin affects DNA damage repair has been the focus of intense research in recent years (detailed below). Reciprocally, it will be important to investigate how higher-order chromatin structures are altered during the DDR and re-established after repair. It is reasonable to assume that similar mechanisms could support higher-order chromatin dynamics during repair and replication. In this respect, the interaction of the histone chaperone CAF-1 with the heterochromatin protein HP1 is critical for the duplication of pericentric heterochromatin domains in mouse cells (Quivy et al., 2008; Quivy et al., 2004). The HP1-CAF-1 tandem also associates with the histone methyltransferase SET Domain, Bifurcated 1 (SETDB1), which imposes H3K9me1 for subsequent trimethylation in mouse pericentric regions (Loyola et al., 2009), and with Methyl-CpG Binding Domain Protein 1 (MBD1), which couples replication of methylated DNA with maintenance of the H3K9me3 heterochromatic mark in human cells (Sarraf and Stancheva, 2004). Given that HP1, SETDB1 and CAF-1 are involved in chromatin dynamics in response to DNA damage, it will be worthwhile investigating how they contribute to maintain heterochromatin integrity.

Future work will determine if the mechanisms and molecular players highlighted in the above studies focused on DNA replication also underlie epigenome maintenance during DNA damage repair.

Coordinated maintenance of genome and epigenome integrity in response to DNA damage

Safeguarding both genetic and epigenetic information after damage entails orchestrating chromatin dynamics with the DDR to ensure timely and efficient repair. Recent studies indeed put forward genome and epigenome maintenance as an integrated process, supported by direct molecular interactions of DDR factors with chromatin modifiers and histone modifications (Figure 2).

In particular, histone modifications resulting from the activity of DNA damage checkpoint proteins are integral components of the DNA damage signaling cascade (reviewed in Smeenk and van Attikum, 2013). Another critical step, early on in the DDR, is the coordination between DNA damage detection and chromatin dynamics, which is thought to facilitate access to downstream repair factors. This is exemplified with the histone chaperone Nucleolin that is rapidly recruited to DSBs via its interaction with the RAD50 subunit of the DSB recognition complex MRE11-RAD50-NBS1 (MRN), thereby mediating nucleosome disruption and the recruitment of downstream repair factors at I-PpoI cut sites in mammalian cells (Goldstein et al., 2013). Nucleosome destabilization at DSBs is also promoted by the ATPase p400 and the acetyltransferase Tip60 (Xu et al., 2012; 2010). Notably, Tip60 is targeted to DSBs by the MRN complex (Sun et al., 2009) and p400 recruitment requires the checkpoint protein Mediator of DNA damage Checkpoint 1 (MDC1) (Xu et al., 2010), thus providing additional molecular bases for coordinating damage detection and signaling with histone dynamics.

Similarly, during the UVC damage response, new histone deposition by HIRA is linked to damage detection by the human UV-Damaged DNA Binding complex (UV-DDB) (Adam et al., 2013). Later on during repair synthesis, the polymerase sliding clamp PCNA acts as a molecular anchor for the CAF-1 histone chaperone (Moggs et al., 2000; Polo et al., 2006). PCNA is also thought to coordinate completion of mismatch repair with CAF-1-mediated nucleosome assembly (Schöpf et al., 2012). Contrary to CAF-1 and HIRA, the recruitment of the histone chaperone FACT to damaged chromatin has not been directly connected to DNA damage repair, and the mechanisms underlying FACT recruitment to UVC damage sites and IR-induced foci remain to be elucidated (Dinant et al., 2013; Oliveira et al., 2014). Like histone chaperones, chromatin remodelers also have direct connections to damage signaling and repair machineries, as exemplified by the human SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 5 (SMARCA5), which interacts with the damage signaling factor Ring Finger protein 168 (RNF168) in a PARP-dependent manner, stimulating RNF168 accumulation at DSBs and downstream signaling events (Smeenk et al., 2013). The SMARCA5-associated subunit ATP-utilizing chromatin assembly and remodeling factor 1 (ACF1) directly interacts with the NHEJ factor Ku70 and promotes Ku accumulation at DSBs (Lan et al., 2010). SMARCA5 also associates

- directly or indirectly - with the early repair factor Cockayne Syndrome B protein (CSB) and stimulates CSB recruitment to UVC-damaged chromatin (Aydin et al., 2014a).

Similar to damage-induced histone dynamics and chromatin remodeling, the maintenance of DNA methylation is likely to be directly coupled to DNA damage signaling and repair. Indeed, recent studies in human cells report that the maintenance DNA methyltransferase DNMT1 is recruited to DSBs via PCNA and the checkpoint factors Chk1 and 9-1-1 (Ha et al., 2011), and via mismatch repair proteins to sites of oxidative damage (Ding et al., 2015).

Interestingly, the coupling between chromatin dynamics and the DDR also provides a means to coordinate damaged chromatin disruption and reassembly, as both are connected to repair. To validate this hypothesis, it will be useful to examine the possible crosstalks between parental and newly synthesized histone dynamics at damage sites.

Furthermore, the coupling between genome and epigenome maintenance after damage actually goes both ways, with chromatin restoration having a feedback effect on DNA damage repair and genome stability in some instances. Although new H3.1 and H3.3 deposition in UVC-damaged chromatin are dispensable for UVC damage repair in human cells (Adam et al., 2013; Polo et al., 2006), H3.3 is important for maintaining genome stability in mouse embryonic fibroblasts (Jang et al., 2015) and for replication fork progression in response to UV damage in chicken cells (Frey et al., 2014). Furthermore, HIRA-mediated histone replacement contributes to protect DNA from damage during mouse oogenesis (Nashun et al., 2015), arguing that histone dynamics can also be crucial for the maintenance of genome integrity.

In addition to the direct coupling between chromatin dynamics and the DDR, which takes place during DNA damage repair, epigenome maintenance may also rely on chromatin maturation events after completion of DNA repair, similar to those that occur after DNA replication (Figure 1). It will be of major interest to further investigate the stepwise restoration of chromatin after damage to determine when and by which mechanisms the original epigenetic information is fully re-established (in terms of histone modification, histone variant and DNA methylation patterns, nucleosome spacing). In particular, how repair completion and termination of checkpoint signaling are coordinated with the erasure of DNA damage-induced histone modifications remains to be elucidated. Ultimately, understanding the coordination between DNA damage repair and the re-establishment of higher-order chromatin structures and nuclear domains would complete our view of epigenome maintenance in response to DNA damage.

Impact of nuclear organization on genome maintenance in response to DNA damage

One of the most fundamental properties of the eukaryotic cell nucleus is the non-random organization of the genome within the tridimensional space of the nucleus, where chromosomes occupy discrete territories and which determines long-range chromatin interactions (Dekker and Misteli, 2015; Sexton and Cavalli, 2015). Nuclear organization

plays a critical role not only in the regulation of gene expression, but also in the maintenance of genome stability (Misteli and Soutoglou, 2009).

Role of chromosome territories in the biogenesis of chromosomal translocations

The spatial proximity of genomic regions located in neighboring chromosome territories is a major determinant in the frequency of chromosomal translocations (Figure 3A). Indeed, genomic regions whose nuclear territories are proximal or overlapping recombine more efficiently than spatially distant sequences both in yeast and mammals (Agmon et al., 2013; Roukos et al., 2013; Soutoglou et al., 2007). In mammalian cells, this can be explained by the relative positional stability of broken chromosomes (Soutoglou et al., 2007), although the mobility of broken ends, observed mostly in other systems, can contribute to homology search (Dion and Gasser, 2013). The idea that spatial proximity can guide illegitimate joining of DSBs genome-wide is supported by several studies focusing on the genesis of recurrent translocations that drive tumor development in mouse lymphoid cells (Chiarle et al., 2011; Hakim et al., 2012; Klein et al., 2011; Rocha et al., 2012; Zhang et al., 2012). It is also in lymphoid cells that the molecular features defining recurrent chromosome breakpoints were originally unraveled: chromatin loops and H3K4me3 focus and stimulate the V(D)J endonuclease, and also potentially the class-switch recombinase, leading to the programmed recombination of antigen receptor genes (Hu et al., 2015; Shimazaki et al., 2009; Stanlie et al., 2010). Chromosomal translocations arise from defects during these programmed genome rearrangements. A recent study in human hematopoietic cells further strengthens the prominent role of the local chromatin environment and of histone modifications - H3K4 methylation in particular - in predisposing chromosome regions to breakage and translocations (Burman et al., 2015). Interestingly, H3K4me3 also specifies meiotic recombination hotspots in yeast and mammals by promoting the recruitment of the meiotic nuclease complex (reviewed in Baudat et al., 2013). Altogether, these studies put forward chromosome positioning and epigenetic marks as key determinants in shaping chromosomal recombination and translocation patterns.

Nuclear compartmentalization governs DSB repair pathway choice

In addition to chromosome territories, the eukaryotic cell nucleus contains a variety of functionally distinct compartments and chromatin domains, which can direct DNA repair, particularly DSB repair pathway choice (Figure 3B). Targeting DSBs to distinct nuclear compartments in human cells was instrumental for demonstrating the effect of the subnuclear localization of the damage on favoring different repair mechanisms (Lemaître et al., 2014). While DSBs located in the nuclear interior and at nuclear pores can be repaired both by HR and NHEJ, the presence of compact heterochromatin associated with the lamina at the inner nuclear membrane delays DNA damage signaling and impairs HR (Lemaître et al., 2014). Furthermore, DSBs within lamina-associated domains do not migrate to HR-permissive compartments but are repaired *in situ* by NHEJ or Alternative End Joining (A-EJ). By contrast, heterochromatic breaks in *Drosophila* move to the nuclear periphery to complete HR (Ryu et al., 2015). Interestingly, DSB repair compartmentalization at the nuclear periphery is conserved in yeast: persistent breaks migrate to the nuclear periphery where their anchoring with nuclear pores or with the nuclear envelope determines different repair outcomes, error-prone repair or error-free HR, respectively (Horigome et al., 2014).

Furthermore, in a given chromatin domain, pre-existing histone modifications also contribute to dictate DSB repair pathway choice, as demonstrated for H3K36me₃ that, in mammalian cells, enhances repair by HR, while the dimethylation of the same residue stimulates NHEJ (reviewed in Clouaire and Legube, 2015). Noteworthy, H3K36me₃ also positively influences mismatch repair in human cells (Li et al., 2013). Thus, DNA damage repair is tightly integrated within nuclear architecture as it operates in response to a specific nuclear localization in a defined chromatin environment.

Heterochromatin domains: barriers to repair

Among chromatin domains in the eukaryotic cell nucleus, highly condensed and poorly transcribed heterochromatin (Saksouk et al., 2015) has a major impact on genome stability. Indeed, heterochromatin high compaction levels present a barrier to DNA damage repair (Figure 3C), suggesting that cells need to use specific mechanisms for accessing damage within heterochromatin. Slower repair kinetics have been observed for IR-induced damage associated with pericentromeric heterochromatin in mouse cells (Goodarzi et al., 2008) and for UVC damage in H3K9me₃-enriched chromatin in human fibroblasts (Han et al., 2015). Other studies, both in yeast and mammalian systems, found that heterochromatin damaged by IR, radiomimetic drugs or endonuclease cut was devoid of γ H2AX (Cowell et al., 2007; Kim et al., 2007), thus suggesting that heterochromatin domains are refractory to DNA damage signaling and repair. Indeed, the DDR is impaired in human perinuclear heterochromatin as described above (Lemaître et al., 2014). In line with this, higher point mutation rates have been observed in heterochromatin in human cancers (Schuster-Böckler and Lehner, 2012). Interestingly, heterochromatin constraints on the DDR are relieved by replication (Cowell et al., 2007) and also by transcription, as shown in the context of Nucleotide Excision Repair (NER) of UV damage (Zheng et al., 2014). Strikingly, even though compact heterochromatin appears refractory to the DDR, it has been shown that dynamic compaction of chromatin is required for the activation of DNA damage signaling (Burgess et al., 2014). In fact, early DDR steps efficiently operate in heterochromatin and only late steps are inhibited, as observed in *Drosophila* cells exposed to IR (Chiolo et al., 2011). Late steps of DNA damage signaling and repair occur at the periphery of heterochromatin domains, after heterochromatin expansion and extrusion of repair foci. The dynamic relocation of repair centers to the periphery of heterochromatin domains, observed both in *Drosophila* and mammalian cells (Chiolo et al., 2011; Jakob et al., 2011), is thought to play a critical role in preventing ectopic recombination between heterochromatic repeats. Importantly, there are substantial differences in heterochromatin organization between model organisms, which may underlie mechanistic discrepancies in the repair of heterochromatic damage. As observed for late repair steps, DNA replication is also confined to the periphery of pericentric heterochromatin domains in mouse cells (Quivy et al., 2004), suggesting a common mechanism for repair and replication of these heterochromatin regions. Similarly, in nucleoli, DSBs are relocated from the nucleolar interior to anchoring points at the periphery, where ribosomal DNA becomes accessible to repair factors, as reported both in yeast and mammalian cells (Harding et al., 2015; Torres-Rosell et al., 2007; van Sluis and McStay, 2015) (Figure 3B). These data illustrate how different chromatin contexts, characterized by the presence of repeated sequences, impose similar constraints limiting unscheduled DNA repair.

While nuclear organization, through chromosome territories, chromatin domains and nuclear compartments, has a major impact on genome stability, how it affects epigenome maintenance after damage is still elusive. Targeting DNA damage to specific chromatin domains and nuclear territories, via site-specific endonucleases or laser micro-irradiation techniques, will be critical for addressing this question. Further studies will also be needed to assess whether nuclear organization, and in particular the presence of compact heterochromatin domains, poses boundaries to chromatin restoration after damage.

Epigenome integrity vs. plasticity after DNA damage

As described in the previous sections, we have increasing knowledge of the epigenetic alterations that take place in damaged chromatin and of the molecular players involved in these chromatin rearrangements. However, whether the epigenome is faithfully restored after DNA damage repair is still a matter of debate. A repaired state strictly identical to the original one would ensure the maintenance of epigenome integrity; alternatively the epigenetic landscape could be reshaped in response to DNA damage, owing to the inherent plasticity of epigenetic information, which is reversible in nature. A damage scar with altered epigenetic marks could then persist on chromatin. As such, chromatin repair can be seen as a window of opportunity for modulating epigenetic information and shaping gene expression in response to genotoxic stress (Figure 4).

Damage scar on chromatin

Changes in DNA methylation, histone variants, histone PTMs and even histone density at damage sites can all contribute to leave a mark of DNA damage repair on chromatin. Indeed, the base excision repair machinery is involved in erasing DNA methylation in several eukaryotic systems (Wu and Zhang, 2014), while DSB repair by HR stably alters the DNA methylation pattern and gene expression at recombination sites in HeLa cells (Morano et al., 2014). In addition to DNA methylation, modification of histone patterns can also participate in marking sites of DNA damage. The *de novo* histone deposition taking place at UV damage sites in human cells (Adam et al., 2013; Dinant et al., 2013; Polo et al., 2006) raised the question of whether it changes the histone variant and PTM landscape. Since new histone marks differ from the parental ones (Loyola et al., 2006), it is likely that new histone deposition at least transiently affects histone PTMs at damage sites. Importantly, PTM changes associated with genome instability can have a profound and long-lasting impact on transcription profiles as shown in chicken cells, where replication defects generate epigenetic instability by uncoupling DNA synthesis from parental histone recycling. The failure to recycle pre-existing histone marks results in alterations in gene expression (Papadopoulou et al., 2015; Sarkies et al., 2012; Sarkies et al., 2010). Finally, the local accumulation of histones observed after repair at laser micro-irradiation sites in human U2OS cells (Strickfaden et al., 2015) suggests that changes in histone density could also be part of the damage scar on chromatin.

In contrast to the different types of DNA lesions that form in response to various sources of genotoxic stress, such chromatin scar could constitute a common epigenetic signature of DNA damage. Future challenges will include determining whether the observed epigenetic

changes are transient or long-term, if they occur in a pathological context - contributing to aging or tumorigenesis - or in a programmed manner, and how relevant they are to the cellular response to DNA damage.

Functional relevance of epigenome plasticity after DNA damage

Regarding the significance of epigenome plasticity after DNA damage, several hypotheses could be raised, based on recent studies. On one hand, the persistence of a damage scar on chromatin could potentially serve as a 'damage memory' mark, facilitating the response to a second genotoxic stress insult, analogous to immune memory. Note that the persistence of the damage scar may depend on the repair pathway engaged, the transcriptional activity of the damaged region and/or the cell type affected. On the other hand, recent work in *Drosophila* highlights the importance of new histone deposition for the maintenance of stem cell identity. Indeed, during asymmetric division of *Drosophila* male germline stem cells, chromatin containing newly synthesized histones is segregated to differentiating cells, while parental histones are retained in the stem cells (Tran et al., 2012). This relies on differential phosphorylation of parental and new H3 (Xie et al., 2015). One could hypothesize that a similar mechanism may operate upon DNA damage in mammalian cells. New histone deposition coupled to repair would ensure that only undamaged information is kept in stem cells, thus preserving stem cell molecular properties. Another possible function of a persistent damage scar on chromatin could relate to cell reprogramming. Indeed, efficient reprogramming relies on chromatin alterations (Apostolou and Hochedlinger, 2013) and also requires DNA damage repair activities in mammalian cells, such as the HR pathway (González et al., 2013) and the NER complex containing Xeroderma Pigmentosum, complementation group C (XPC) (Fong et al., 2011). In line with this, histone variants and chaperones involved in chromatin dynamics in response to DNA damage also play a major role in development, reprogramming and in regulating cell pluripotency (Filipescu et al., 2013; Skene and Henikoff, 2013). In particular, the histone chaperone HIRA and the H3.3 histone variant have been implicated both in cell reprogramming and transcription plasticity in *Xenopus*, mouse and human systems (Banaszynski et al., 2013; Jullien et al., 2012; Lin et al., 2014; Maze et al., 2015; Ng and Gurdon, 2008; Wen et al., 2014). The histone chaperone ASF1 is also required for the maintenance of pluripotency and human cell reprogramming (Gonzalez-Muñoz et al., 2014). In contrast, the histone chaperone CAF-1 has been characterized as a negative regulator of reprogramming in mouse cells (Cheloufi et al., 2015; Ishiuchi et al., 2015; Nakano et al., 2011) and was shown to promote cell differentiation during neurodevelopment in the nematode (Nakano et al., 2011). Future work will determine if a persistent damage scar on chromatin indeed contributes to local or global reprogramming of transcription in response to genotoxic stress, with possible consequences on cell identity.

Conclusions & Future challenges

In recent years, it has become increasingly clear that safeguarding genome function entails reshaping chromatin. The coordinated maintenance of genome and epigenome integrity in response to DNA damage is supported by direct molecular interactions between DDR factors and chromatin modifiers. Recent studies also emphasize a critical interplay between

genome maintenance pathways and the topological organization of the genome in the cell nucleus. Studying the maintenance of chromatin integrity after DNA damage thus appears as a multifaceted research field, at the crossroads of epigenetics, genome stability and nuclear organization.

Nevertheless, much remains to be learned about how the epigenetic landscape is altered and in which form it is ultimately re-established during the course of DNA damage repair. Furthermore, while the impact of nuclear organization on genome maintenance is clearly established, it will be important to understand how DNA damage repair affects chromatin nuclear domains and genome topology. Combining genotoxic stress with Hi-C techniques for genome-wide analysis of chromatin interactions, now applicable at the single-cell level (Nagano et al., 2013; Risca and Greenleaf, 2015), could be extremely valuable to address this issue. In addition, the cross-talks between damaged chromatin dynamics and transcriptional activity (Adam and Polo, 2014), but also with post-transcriptional events such as splicing regulation (Tresini et al., 2015) and the importance of non-coding RNAs in the DDR (d'Adda di Fagagna and d'Adda di Fagagna, 2014) are emerging topics that will surely shape future research in the field. Another remarkable feature that has become increasingly recognized is the strong influence of cell metabolism on both epigenetic marks and the DDR (Janke et al., 2015; Shimizu et al., 2014), which could provide mechanistic insights into how damaged chromatin plasticity is regulated. *In fine*, in depth understanding of the cellular mechanisms underlying epigenome maintenance in response to genotoxic stress could open up new strategies for modulating damaged chromatin dynamics and driving phenotypic changes with therapeutic benefit.

Acknowledgements

We are grateful to Salomé Adam, Constance Alabert and Evi Soutoglou for critical reading of the manuscript. Research in S.E.P. group is supported by the European Research Council (ERC-2013-StG-336427 “Epln”), the French National Research Agency (ANR-12-JSV6-0002-01), and the “Who am I?” laboratory of excellence (ANR-11-LABX-0071) funded by the French Government through its “Investments for the Future” program (ANR-11-IDEX-0005-01). J.D. is the recipient of a PhD fellowship from Paris Diderot University and A.F. is funded by an international PhD fellowship from Sorbonne Paris Cité University.

References

- Adam S, Polo SE. Blurring the line between the DNA damage response and transcription: the importance of chromatin dynamics. *Exp Cell Res*. 2014; 329:148–153. [PubMed: 25062983]
- Adam S, Dabin J, Polo SE. Chromatin plasticity in response to DNA damage: The shape of things to come. *DNA Repair (Amst.)*. 2015a; 32:120–126. [PubMed: 25957486]
- Adam S, Dabin J, Bai S-K, Polo SE. Imaging Local Deposition of Newly Synthesized Histones in UVC-Damaged Chromatin. *Methods Mol Biol*. 2015b; 1288:337–347. [PubMed: 25827889]
- Adam S, Polo SE, Almouzni G. Transcription Recovery after DNA Damage Requires Chromatin Priming by the H3.3 Histone Chaperone HIRA. *Cell*. 2013; 155:94–106. [PubMed: 24074863]
- Agmon N, Liefshitz B, Zimmer C, Fabre E, Kupiec M. Effect of nuclear architecture on the efficiency of double-strand break repair. *Nat Cell Biol*. 2013; 15:694–699. [PubMed: 23644470]
- Alabert C, Groth A. Chromatin replication and epigenome maintenance. *Nat Rev Mol Cell Biol*. 2012; 13:153–167. [PubMed: 22358331]
- Alabert C, Barth TK, Reverón-Gómez N, Sidoli S, Schmidt A, Jensen ON, Imhof A, Groth A. Two distinct modes for propagation of histone PTMs across the cell cycle. *Genes Dev*. 2015; 29:585–590. [PubMed: 25792596]

- Alabert C, Bukowski-Wills J-C, Lee S-B, Kustatscher G, Nakamura K, de Lima Alves F, Menard P, Mejlvang J, Rappsilber J, Groth A. Nascent chromatin capture proteomics determines chromatin dynamics during DNA replication and identifies unknown fork components. *Nat Cell Biol.* 2014; 16:281–293. [PubMed: 24561620]
- Alagoz M, Katsuki Y, Ogiwara H, Ogi T, Shibata A, Kakarougkas A, Jeggo P. SETDB1, HP1 and SUV39 promote repositioning of 53BP1 to extend resection during homologous recombination in G2 cells. *Nucleic Acids Res.* 2015; 43:7931–7944. [PubMed: 26206670]
- Alatwi HE, Downs JA. Removal of H2A.Z by INO80 promotes homologous recombination. *EMBO Rep.* 2015; 16:986–994. [PubMed: 26142279]
- Annuziato AT. The Fork in the Road: Histone Partitioning During DNA Replication. *Genes (Basel).* 2015; 6:353–371. [PubMed: 26110314]
- Apostolou E, Hochedlinger K. Chromatin dynamics during cellular reprogramming. *Nature.* 2013; 502:462–471. [PubMed: 24153299]
- Aydin OZ, Marteiijn JA, Ribeiro-Silva C, Rodríguez López A, Wijgers N, Smeenk G, van Attikum H, Poot RA, Vermeulen W, Lans H. Human ISWI complexes are targeted by SMARCA5 ATPase and SLIDE domains to help resolve lesion-stalled transcription. *Nucleic Acids Res.* 2014a; 42:8473–8485. [PubMed: 24990377]
- Aydin OZ, Vermeulen W, Lans H. ISWI chromatin remodeling complexes in the DNA damage response. *Cell Cycle.* 2014b; 13:3016–3025. [PubMed: 25486562]
- Aymard F, Bugler B, Schmidt CK, Guillou E, Caron P, Briois S, Iacovoni JS, Daburon V, Miller KM, Jackson SP, et al. Transcriptionally active chromatin recruits homologous recombination at DNA double-strand breaks. *Nat Struct Mol Biol.* 2014; 21:366–374. [PubMed: 24658350]
- Ayrapetov MK, Gursoy-Yuzugullu O, Xu C, Xu Y, Price BD. DNA double-strand breaks promote methylation of histone H3 on lysine 9 and transient formation of repressive chromatin. *Proc Natl Acad Sci USA.* 2014; 111:9169–9174. [PubMed: 24927542]
- Badeaux AI, Shi Y. Emerging roles for chromatin as a signal integration and storage platform. *Nat Rev Mol Cell Biol.* 2013; 14:211–224.
- Bakkenist CJ, Kastan MB. Chromatin perturbations during the DNA damage response in higher eukaryotes. *DNA Repair (Amst.).* 2015; 36:8–12. [PubMed: 26391293]
- Banaszynski LA, Wen D, Dewell S, Whitcomb SJ, Lin M, Diaz N, Elsässer SJ, Chapgier A, Goldberg AD, Canaani E, et al. Hira-dependent histone H3.3 deposition facilitates PRC2 recruitment at developmental loci in ES cells. *Cell.* 2013; 155:107–120. [PubMed: 24074864]
- Bannister AJ, Kouzarides T. Regulation of chromatin by histone modifications. *Cell Res.* 2011; 21:381–395. [PubMed: 21321607]
- Bartholomew B. Regulating the Chromatin Landscape: Structural and Mechanistic Perspectives. *Annu Rev Biochem.* 2014; 83:671–696. [PubMed: 24606138]
- Baudat F, Imai Y, de Massy B. Meiotic recombination in mammals: localization and regulation. *Nat Rev Genet.* 2013; 14:794–806. [PubMed: 24136506]
- Brachet E, Béneut C, Serrentino M-E, Borde V. The CAF-1 and Hir Histone Chaperones Associate with Sites of Meiotic Double-Strand Breaks in Budding Yeast. *PLoS ONE.* 2015; 10:e0125965. [PubMed: 25938567]
- Burgess RC, Burman B, Kruhlak MJ, Misteli T. Activation of DNA damage response signaling by condensed chromatin. *Cell Rep.* 2014; 9:1703–1717. [PubMed: 25464843]
- Burman B, Zhang ZZ, Pegoraro G, Lieb JD, Misteli T. Histone modifications predispose genome regions to breakage and translocation. *Genes Dev.* 2015; 29:1393–1402. [PubMed: 26104467]
- Campos EI, Smits AH, Kang Y-H, Landry S, Escobar TM, Nayak S, Ueberheide BM, Durocher D, Vermeulen M, Hurwitz J, et al. Analysis of the Histone H3.1 Interactome: A Suitable Chaperone for the Right Event. *Mol Cell.* 2015; 60:697–709. [PubMed: 26527279]
- Ceccaldi R, Rondinelli B, D'Andrea AD. Repair Pathway Choices and Consequences at the Double-Strand Break. *Trends Cell Biol.* 2016; 26:52–64. [PubMed: 26437586]
- Cheloufi S, Elling U, Hopfgartner B, Jung YL, Murn J, Ninova M, Hubmann M, Badeaux AI, Euong Ang C, Tenen D, et al. The histone chaperone CAF-1 safeguards somatic cell identity. *Nature.* 2015; 528:218–224. [PubMed: 26659182]

- Chen B, Gilbert LA, Cimini BA, Schnitzbauer J, Zhang W, Li G-W, Park J, Blackburn EH, Weissman JS, Qi LS, et al. Dynamic imaging of genomic loci in living human cells by an optimized CRISPR/Cas system. *Cell*. 2013; 155:1479–1491. [PubMed: 24360272]
- Chiarle R, Zhang Y, Frock RL, Lewis SM, Molinie B, Ho Y-J, Myers DR, Choi VW, Compagno M, Malkin DJ, et al. Genome-wide Translocation Sequencing Reveals Mechanisms of Chromosome Breaks and Rearrangements in B Cells. *Cell*. 2011; 147:107–119. [PubMed: 21962511]
- Chiolo I, Minoda A, Colmenares SU, Polyzos A, Costes SV, Karpen GH. Double-strand breaks in heterochromatin move outside of a dynamic HP1a domain to complete recombinational repair. *Cell*. 2011; 144:732–744. [PubMed: 21353298]
- Cho NW, Dilley RL, Lampson MA, Greenberg RA. Interchromosomal homology searches drive directional ALT telomere movement and synapsis. *Cell*. 2014; 159:108–121. [PubMed: 25259924]
- Chou DM, Adamson B, Dephoure NE, Tan X, Nottke AC, Hurov KE, Gygi SP, Colaiácovo MP, Elledge SJ. A chromatin localization screen reveals poly (ADP ribose)-regulated recruitment of the repressive polycomb and NuRD complexes to sites of DNA damage. *Proc Natl Acad Sci USA*. 2010; 107:18475–18480. [PubMed: 20937877]
- Ciccio A, Elledge SJ. The DNA damage response: making it safe to play with knives. *Mol Cell*. 2010; 40:179–204. [PubMed: 20965415]
- Clouaire T, Legube G. DNA Double Strand Break repair pathway choice: A chromatin based decision? *Nucleus*. 2015; 6:107–113. [PubMed: 25675367]
- Cook AJL, Gurard-Levin ZA, Vassias I, Almouzni G. A Specific Function for the Histone Chaperone NASP to Fine-Tune a Reservoir of Soluble H3-H4 in the Histone Supply Chain. *Mol Cell*. 2011; 44:918–927. [PubMed: 22195965]
- Cowell IG, Sunter NJ, Singh PB, Austin CA, Durkacz BW, Tilby MJ. gammaH2AX foci form preferentially in euchromatin after ionising-radiation. *PLoS ONE*. 2007; 2:e1057. [PubMed: 17957241]
- d'Adda di Fagagna F, d'Adda di Fagagna F. A direct role for small non-coding RNAs in DNA damage response. *Trends Cell Biol*. 2014; 24:171–178. [PubMed: 24156824]
- Dantuma NP, van Attikum H. Spatiotemporal regulation of posttranslational modifications in the DNA damage response. *The EMBO Journal*. 2015; 35:6–23. [PubMed: 26628622]
- Dekker J, Misteli T. Long-Range Chromatin Interactions. *Cold Spring Harb Perspect Biol*. 2015; 7:a019356. [PubMed: 26430217]
- Dimitrova N, Chen Y-CM, Spector DL, de Lange T. 53BP1 promotes non-homologous end joining of telomeres by increasing chromatin mobility. *Nature*. 2008; 456:524–528. [PubMed: 18931659]
- Dinant C, Luijsterburg MS. The emerging role of HP1 in the DNA damage response. *Mol Cell Biol*. 2009; 29:6335–6340. [PubMed: 19805510]
- Dinant C, Ampatzidis-Michailidis G, Lans H, Tresini M, Lagarou A, Grosbart M, Theil AF, van Cappellen WA, Kimura H, Bartek J, et al. Enhanced Chromatin Dynamics by FACT Promotes Transcriptional Restart after UV-Induced DNA Damage. *Mol Cell*. 2013; 51:469–479. [PubMed: 23973375]
- Ding N, Bonham EM, Hannon BE, Amick TR, Baylin SB, O'Hagan HM. Mismatch repair proteins recruit DNA methyltransferase 1 to sites of oxidative DNA damage. *J Mol Cell Biol*. 2015 mjev050.
- Dion V, Gasser SM. Chromatin movement in the maintenance of genome stability. *Cell*. 2013; 152:1355–1364. [PubMed: 23498942]
- Duro E, Lundin C, Ask K, Sanchez-Pulido L, MacArtney TJ, Toth R, Ponting CP, Groth A, Helleday T, Rouse J. Identification of the MMS22L-TONSL complex that promotes homologous recombination. *Mol Cell*. 2010; 40:632–644. [PubMed: 21055984]
- Elia AEH, Boardman AP, Wang DC, Huttlin EL, Everley RA, Dephoure N, Zhou C, Koren I, Gygi SP, Elledge SJ. Quantitative Proteomic Atlas of Ubiquitination and Acetylation in the DNA Damage Response. *Mol Cell*. 2015; 59:867–881. [PubMed: 26051181]
- Filipescu D, Szenker E, Almouzni G. Developmental roles of histone H3 variants and their chaperones. *Trends Genet*. 2013; 29:630–640. [PubMed: 23830582]
- Foltman M, Evrin C, De Piccoli G, Jones RC, Edmondson RD, Katou Y, Nakato R, Shirahige K, Labib K. Eukaryotic replisome components cooperate to process histones during chromosome replication. *Cell Rep*. 2013; 3:892–904. [PubMed: 23499444]

- Fong YW, Inouye C, Yamaguchi T, Cattoglio C, Grubisic I, Tjian R. A DNA repair complex functions as an Oct4/Sox2 coactivator in embryonic stem cells. *Cell*. 2011; 147:120–131. [PubMed: 21962512]
- Frey A, Listovsky T, Guilbaud G, Sarkies P, Sale JE. Histone H3.3 Is Required to Maintain Replication Fork Progression after UV Damage. *Curr Biol*. 2014; 24:2195–2201. [PubMed: 25201682]
- Gallo M, Coutinho FJ, Vanner RJ, Gayden T, Mack SC, Murison A, Remke M, Li R, Takayama N, Desai K, et al. MLL5 Orchestrates a Cancer Self-Renewal State by Repressing the Histone Variant H3.3 and Globally Reorganizing Chromatin. *Cancer Cell*. 2015; 28:715–729. [PubMed: 26626085]
- Goldstein M, Derheimer FA, Tait-Mulder J, Kastan MB. Nucleolin mediates nucleosome disruption critical for DNA double-strand break repair. *Proc Natl Acad Sci USA*. 2013; 110:16874–16879. [PubMed: 24082117]
- Gong F, Miller KM. Mammalian DNA repair: HATs and HDACs make their mark through histone acetylation. *Mutat Res*. 2013; 750:23–30. [PubMed: 23927873]
- Gong F, Chiu L-Y, Cox B, Aymard F, Clouaire T, Leung JW, Cammarata M, Perez M, Agarwal P, Brodbelt JS, et al. Screen identifies bromodomain protein ZMYND8 in chromatin recognition of transcription-associated DNA damage that promotes homologous recombination. *Genes Dev*. 2015; 29:197–211. [PubMed: 25593309]
- Gonzalez-Muñoz E, Arboleda-Estudillo Y, Otu HH, Cibelli JB. Cell reprogramming. Histone chaperone ASF1A is required for maintenance of pluripotency and cellular reprogramming. *Science*. 2014; 345:822–825. [PubMed: 25035411]
- González F, Georgieva D, Vanoli F, Shi Z-D, Stadtfeld M, Ludwig T, Jasin M, Huangfu D. Homologous recombination DNA repair genes play a critical role in reprogramming to a pluripotent state. *Cell Rep*. 2013; 3:651–660. [PubMed: 23478019]
- Goodarzi AA, Noon AT, Deckbar D, Ziv Y, Shiloh Y, Löbrich M, Jeggo PA. ATM signaling facilitates repair of DNA double-strand breaks associated with heterochromatin. *Mol Cell*. 2008; 31:167–177. [PubMed: 18657500]
- Groth A, Corpet A, Cook AJL, Roche D, Bartek J, Lukas J, Almouzni G. Regulation of replication fork progression through histone supply and demand. *Science*. 2007; 318:1928–1931. [PubMed: 18096807]
- Groth A, Ray-Gallet D, Quivy J-P, Lukas J, Bartek J, Almouzni G. Human Asf1 regulates the flow of S phase histones during replicational stress. *Mol Cell*. 2005; 17:301–311. [PubMed: 15664198]
- Gurard-Levin ZA, Quivy J-P, Almouzni G. Histone chaperones: assisting histone traffic and nucleosome dynamics. *Annu Rev Biochem*. 2014; 83:487–517. [PubMed: 24905786]
- Gursoy-Yuzugullu O, Ayrapetov MK, Price BD. Histone chaperone Anp32e removes H2A.Z from DNA double-strand breaks and promotes nucleosome reorganization and DNA repair. *Proc Natl Acad Sci USA*. 2015a; 112:7507–7512. [PubMed: 26034280]
- Gursoy-Yuzugullu O, House N, Price BD. Patching broken DNA: Nucleosome dynamics and the repair of DNA breaks. *J Mol Biol*. 2015b
- Ha K, Lee GE, Pali SS, Brown KD, Takeda Y, Liu K, Bhalla KN, Robertson KD. Rapid and transient recruitment of DNMT1 to DNA double-strand breaks is mediated by its interaction with multiple components of the DNA damage response machinery. *Hum Mol Genet*. 2011; 20:126–140. [PubMed: 20940144]
- Hakim O, Resch W, Yamane A, Klein I, Kieffer-Kwon K-R, Jankovic M, Oliveira T, Bothmer A, Voss TC, Ansarah-Sobrinho C, et al. DNA damage defines sites of recurrent chromosomal translocations in B lymphocytes. *Nature*. 2012; 484:69–74. [PubMed: 22314321]
- Han C, Srivastava AK, Cui T, Wang Q-E, Wani AA. Differential DNA lesion formation and repair in heterochromatin and euchromatin. *Carcinogenesis*. 2015; 37:129–138. [PubMed: 26717995]
- Harada A, Okada S, Konno D, Odawara J, Yoshimi T, Yoshimura S, Kumamaru H, Saiwai H, Tsubota T, Kurumizaka H, et al. Chd2 interacts with H3.3 to determine myogenic cell fate. *The EMBO Journal*. 2012; 31:2994–3007. [PubMed: 22569126]
- Harding SM, Boiarsky JA, Greenberg RA. ATM Dependent Silencing Links Nucleolar Chromatin Reorganization to DNA Damage Recognition. *Cell Rep*. 2015; 13:251–259. [PubMed: 26440899]

- Heo K, Kim H, Choi SH, Choi J, Kim K, Gu J, Lieber MR, Yang AS, An W. FACT-mediated exchange of histone variant H2AX regulated by phosphorylation of H2AX and ADP-ribosylation of Spt16. *Mol Cell*. 2008; 30:86–97. [PubMed: 18406329]
- Hill SJ, Rolland T, Adelmant G, Xia X, Owen MS, Dricot A, Zack TI, Sahni N, Jacob Y, Hao T, et al. Systematic screening reveals a role for BRCA1 in the response to transcription-associated DNA damage. *Genes Dev*. 2014; 28:1957–1975. [PubMed: 25184681]
- Hinde E, Kong X, Yokomori K, Gratton E. Chromatin dynamics during DNA repair revealed by pair correlation analysis of molecular flow in the nucleus. *Biophys J*. 2014; 107:55–65. [PubMed: 24988341]
- Hoeijmakers JHJ. DNA Damage, Aging, and Cancer. *N Engl J Med*. 2009; 361:1475–1485. [PubMed: 19812404]
- Hondele M, Stuwe T, Hassler M, Halbach F, Bowman A, Zhang ET, Nijmeijer B, Kotthoff C, Rybin V, Amlacher S, et al. Structural basis of histone H2A-H2B recognition by the essential chaperone FACT. *Nature*. 2013; 499:111–114. [PubMed: 23698368]
- Horigome C, Oma Y, Konishi T, Schmid R, Marcomini I, Hauer MH, Dion V, Harata M, Gasser SM. SWR1 and INO80 chromatin remodelers contribute to DNA double-strand break perinuclear anchorage site choice. *Mol Cell*. 2014; 55:626–639. [PubMed: 25066231]
- Hu J, Zhang Y, Zhao L, Frock RL, Du Z, Meyers RM, Meng F-L, Schatz DG, Alt FW. Chromosomal Loop Domains Direct the Recombination of Antigen Receptor Genes. *Cell*. 2015; 163:947–959. [PubMed: 26593423]
- Huang C, Xu M, Zhu B. Epigenetic inheritance mediated by histone lysine methylation: maintaining transcriptional states without the precise restoration of marks? *Philos Trans R Soc Lond B Biol Sci*. 2013; 368:20110332. [PubMed: 23166395]
- Huang H, Strømme CB, Saredi G, Hödl M, Strandsby A, González-Aguilera C, Chen S, Groth A, Patel DJ. A unique binding mode enables MCM2 to chaperone histones H3-H4 at replication forks. *Nat Struct Mol Biol*. 2015; 22:618–626. [PubMed: 26167883]
- Ishiuchi T, Enriquez-Gasca R, Mizutani E, Bošković A, Ziegler-Birling C, Rodríguez-Terrones D, Wakayama T, Vaquerizas JM, Torres-Padilla M-E. Early embryonic-like cells are induced by downregulating replication-dependent chromatin assembly. *Nat Struct Mol Biol*. 2015; 22:662–671. [PubMed: 26237512]
- Jackson SP, Bartek J. The DNA-damage response in human biology and disease. *Nature*. 2009; 461:1071–1078. [PubMed: 19847258]
- Jakob B, Splinter J, Conrad S, Voss K-O, Zink D, Durante M, Löbrich M, Taucher-Scholz G. DNA double-strand breaks in heterochromatin elicit fast repair protein recruitment, histone H2AX phosphorylation and relocation to euchromatin. *Nucleic Acids Res*. 2011; 39:6489–6499. [PubMed: 21511815]
- Jang C-W, Shibata Y, Starmer J, Yee D, Magnuson T. Histone H3.3 maintains genome integrity during mammalian development. *Genes Dev*. 2015; 29:1377–1392. [PubMed: 26159997]
- Janke R, Dodson AE, Rine J. Metabolism and Epigenetics. *Annu Rev Cell Dev Biol*. 2015; 31:473–496. [PubMed: 26359776]
- Jullien J, Astrand C, Szenker E, Garrett N, Almouzni G, Gurdon JB. HIRA dependent H3.3 deposition is required for transcriptional reprogramming following nuclear transfer to *Xenopus* oocytes. *Epigenetics Chromatin*. 2012; 5:17. [PubMed: 23102146]
- Jungmichel S, Rosenthal F, Altmeyer M, Lukas J, Hottiger MO, Nielsen ML. Proteome-wide identification of poly(ADP-Ribosyl)ation targets in different genotoxic stress responses. *Mol Cell*. 2013; 52:272–285. [PubMed: 24055347]
- Kakarougkas A, Ismail A, Chambers AL, Riballo E, Herbert AD, Künzel J, Löbrich M, Jeggo PA, Downs JA. Requirement for PBAF in transcriptional repression and repair at DNA breaks in actively transcribed regions of chromatin. *Mol Cell*. 2014; 55:723–732. [PubMed: 25066234]
- Kallappagoudar S, Yadav RK, Lowe BR, Partridge JF. Histone H3 mutations—a special role for H3.3 in tumorigenesis? *Chromosoma*. 2015; 124:177–189. [PubMed: 25773741]
- Kalouisi A, Hoffbeck A-S, Selemenakis PN, Pinder J, Savage KI, Khanna KK, Brino L, Delleire G, Gorgoulis VG, Soutoglou E. The nuclear oncogene SET controls DNA repair by KAP1 and HP1 retention to chromatin. *Cell Rep*. 2015; 11:149–163. [PubMed: 25818296]

- Kemble DJ, McCullough LL, Whitby FG, Formosa T, Hill CP. FACT Disrupts Nucleosome Structure by Binding H2A-H2B with Conserved Peptide Motifs. *Mol Cell*. 2015; 60:294–306. [PubMed: 26455391]
- Khurana S, Kruhlak MJ, Kim J, Tran AD, Liu J, Nyswaner K, Shi L, Jailwala P, Sung M-H, Hakim O, et al. A macrohistone variant links dynamic chromatin compaction to BRCA1-dependent genome maintenance. *Cell Rep*. 2014; 8:1049–1062. [PubMed: 25131201]
- Kim J-A, Kruhlak M, Dotiwala F, Nussenzweig A, Haber JE. Heterochromatin is refractory to gamma-H2AX modification in yeast and mammals. *J Cell Biol*. 2007; 178:209–218. [PubMed: 17635934]
- Klein IA, Resch W, Jankovic M, Oliveira T, Yamane A, Nakahashi H, Di Virgilio M, Bothmer A, Nussenzweig A, Robbiani DF, et al. Translocation-Capture Sequencing Reveals the Extent and Nature of Chromosomal Rearrangements in B Lymphocytes. *Cell*. 2011; 147:95–106. [PubMed: 21962510]
- Klement K, Luijsterburg MS, Pinder JB, Cena CS, Del Nero V, Wintersinger CM, Dellaire G, van Attikum H, Goodarzi AA. Opposing ISWI- and CHD-class chromatin remodeling activities orchestrate heterochromatic DNA repair. *J Cell Biol*. 2014; 207:717–733. [PubMed: 25533843]
- Kornberg RD. Structure of Chromatin. *Annu Rev Biochem*. 1977; 46:931–954. [PubMed: 332067]
- Kruhlak MJ, Celeste A, Dellaire G, Fernandez-Capetillo O, Müller WG, McNally JG, Bazett-Jones DP, Nussenzweig A. Changes in chromatin structure and mobility in living cells at sites of DNA double-strand breaks. *J Cell Biol*. 2006; 172:823–834. [PubMed: 16520385]
- Lan L, Ui A, Nakajima S, Hatakeyama K, Hoshi M, Watanabe R, Janicki SM, Ogiwara H, Kohno T, Kanno S-I, et al. The ACF1 complex is required for DNA double-strand break repair in human cells. *Mol Cell*. 2010; 40:976–987. [PubMed: 21172662]
- Lans H, Marteijs JA, Vermeulen W. ATP-dependent chromatin remodeling in the DNA-damage response. *Epigenetics Chromatin*. 2012; 5:4. [PubMed: 22289628]
- Latreille D, Bluy L, Benkirane M, Kiernan RE. Identification of histone 3 variant 2 interacting factors. *Nucleic Acids Res*. 2014; 42:3542–3550. [PubMed: 24393775]
- Lemaître C, Grabarz A, Tsouroula K, Andronov L, Furst A, Pankotai T, Heyer V, Rogier M, Attwood KM, Kessler P, et al. Nuclear position dictates DNA repair pathway choice. *Genes Dev*. 2014; 28:2450–2463. [PubMed: 25366693]
- Li F, Mao G, Tong D, Huang J, Gu L, Yang W, Li G-M. The histone mark H3K36me3 regulates human DNA mismatch repair through its interaction with MutSa. *Cell*. 2013; 153:590–600. [PubMed: 23622243]
- Li G, Reinberg D. Chromatin higher-order structures and gene regulation. The Emerging Role of Polycomb Repressors in the Response to DNA Damage. 2011; 21:175–186.
- Liang C-C, Zhan B, Yoshikawa Y, Haas W, Gygi SP, Cohn MA. UHRF1 is a sensor for DNA interstrand crosslinks and recruits FANCD2 to initiate the Fanconi anemia pathway. *Cell Rep*. 2015; 10:1947–1956. [PubMed: 25801034]
- Lin C-J, Koh FM, Wong P, Conti M, Ramalho-Santos M. Hira-mediated H3.3 incorporation is required for DNA replication and ribosomal RNA transcription in the mouse zygote. *Developmental Cell*. 2014; 30:268–279. [PubMed: 25087892]
- Lottersberger F, Karssemeijer RA, Dimitrova N, de Lange T. 53BP1 and the LINC Complex Promote Microtubule-Dependent DSB Mobility and DNA Repair. *Cell*. 2015; 163:880–893. [PubMed: 26544937]
- Loyola A, Bonaldi T, Roche D, Imhof A, Almouzni G. PTMs on H3 variants before chromatin assembly potentiate their final epigenetic state. *Mol Cell*. 2006; 24:309–316. [PubMed: 17052464]
- Loyola A, Tagami H, Bonaldi T, Roche D, Quivy J-P, Imhof A, Nakatani Y, Dent SYR, Almouzni G. The HP1alpha-CAF1-SetDB1-containing complex provides H3K9me1 for Suv39-mediated K9me3 in pericentric heterochromatin. *EMBO Rep*. 2009; 10:769–775. [PubMed: 19498464]
- Luger K, Mäder AW, Richmond RK, Sargent DF, Richmond TJ. Crystal structure of the nucleosome core particle at 2.8 Å resolution. *Nature*. 1997; 389:251–260. [PubMed: 9305837]
- Luijsterburg MS, de Krijger I, Wiegant WW, Shah RG, Smeenk G, de Groot AJL, Pines A, Vertegaal ACO, Jacobs JLL, Shah GM, et al. PARP1 Links CHD2-Mediated Chromatin Expansion and

- H3.3 Deposition to DNA Repair by Non-homologous End-Joining. *Mol Cell*. 2016; 61:547–562. [PubMed: 26895424]
- Luijsterburg MS, Lindh M, Acs K, Vrouwe MG, Pines A, van Attikum H, Mullenders LH, Dantuma NP. DDB2 promotes chromatin decondensation at UV-induced DNA damage. *J Cell Biol*. 2012; 197:267–281. [PubMed: 22492724]
- Marzluff WF, Wagner EJ, Duronio RJ. Metabolism and regulation of canonical histone mRNAs: life without a poly(A) tail. *Nat Rev Genet*. 2008; 9:843–854. [PubMed: 18927579]
- Massip L, Caron P, Iacovoni JS, Trouche D, Legube G. Deciphering the chromatin landscape induced around DNA double strand breaks. *Cell Cycle*. 2010; 9:2963–2972. [PubMed: 20714222]
- Matsuoka S, Ballif BA, Smogorzewska A, McDonald ER, Hurov KE, Luo J, Bakalarski CE, Zhao Z, Solimini N, Lerenthal Y, et al. ATM and ATR substrate analysis reveals extensive protein networks responsive to DNA damage. *Science*. 2007; 316:1160–1166. [PubMed: 17525332]
- Maze I, Noh K-M, Soshnev AA, Allis CD. Every amino acid matters: essential contributions of histone variants to mammalian development and disease. *Nat Rev Genet*. 2014; 15:259–271. [PubMed: 24614311]
- Maze I, Wenderski W, Noh K-M, Bagot RC, Tzavaras N, Purushothaman I, Elsässer SJ, Guo Y, Ionete C, Hurd YL, et al. Critical Role of Histone Turnover in Neuronal Transcription and Plasticity. *Neuron*. 2015; 87:77–94. [PubMed: 26139371]
- Mello JA, Silljé HHW, Roche DMJ, Kirschner DB, Nigg EA, Almouzni G. Human Asf1 and CAF-1 interact and synergize in a repair-coupled nucleosome assembly pathway. *EMBO Rep*. 2002; 3:329–334. [PubMed: 11897662]
- Miné-Hattab J, Rothstein R. DNA in motion during double-strand break repair. *Trends Cell Biol*. 2013; 23:529–536. [PubMed: 23867212]
- Misteli T, Soutoglou E. The emerging role of nuclear architecture in DNA repair and genome maintenance. *Nat Rev Mol Cell Biol*. 2009; 10:243–254. [PubMed: 19277046]
- Moggs JG, Grandi P, Quivy J-P, Jónsson ZO, Hübscher U, Becker PB, Almouzni G. A CAF-1-PCNA-mediated chromatin assembly pathway triggered by sensing DNA damage. *Mol Cell Biol*. 2000; 20:1206–1218. [PubMed: 10648606]
- Morano A, Angrisano T, Russo G, Landi R, Pezone A, Bartollino S, Zuchegna C, Babbio F, Bonapace IM, Allen B, et al. Targeted DNA methylation by homology-directed repair in mammalian cells. Transcription reshapes methylation on the repaired gene. *Nucleic Acids Res*. 2014; 42:804–821. [PubMed: 24137009]
- Mortusewicz O, Schermelleh L, Walter J, Cardoso MC, Leonhardt H. Recruitment of DNA methyltransferase I to DNA repair sites. *Proc Natl Acad Sci USA*. 2005; 102:8905–8909. [PubMed: 15956212]
- Nagano T, Lubling Y, Stevens TJ, Schoenfelder S, Yaffe E, Dean W, Laue ED, Tanay A, Fraser P. Single-cell Hi-C reveals cell-to-cell variability in chromosome structure. *Nature*. 2013; 502:59–64. [PubMed: 24067610]
- Nakano S, Stillman B, Horvitz HR. Replication-coupled chromatin assembly generates a neuronal bilateral asymmetry in *C. elegans*. *Cell*. 2011; 147:1525–1536. [PubMed: 22177093]
- Nashun B, Hill PWS, Smallwood SA, Dharmalingam G, Amouroux R, Clark SJ, Sharma V, Ndjetehe E, Pelczar P, Festenstein RJ, et al. Continuous Histone Replacement by Hira Is Essential for Normal Transcriptional Regulation and De Novo DNA Methylation during Mouse Oogenesis. *Mol Cell*. 2015; 60:611–625. [PubMed: 26549683]
- Ng RK, Gurdon JB. Epigenetic memory of an active gene state depends on histone H3.3 incorporation into chromatin in the absence of transcription. *Nat Cell Biol*. 2008; 10:102–109. [PubMed: 18066050]
- O'Connell BC, Adamson B, Lydeard JR, Sowa ME, Ciccio A, Bredemeyer AL, Schlabach M, Gygi SP, Elledge SJ, Harper JW. A genome-wide camptothecin sensitivity screen identifies a mammalian MMS22L-NFKBIL2 complex required for genomic stability. *Mol Cell*. 2010; 40:645–657. [PubMed: 21055985]
- O'Donnell L, Panier S, Wildenhain J, Tkach JM, Al-Hakim A, Landry M-C, Escribano-Diaz C, Szilard RK, Young JTF, Munro M, et al. The MMS22L-TONSL complex mediates recovery from

- replication stress and homologous recombination. *Mol Cell*. 2010; 40:619–631. [PubMed: 21055983]
- O'Hagan HM. Chromatin modifications during repair of environmental exposure-induced DNA damage: a potential mechanism for stable epigenetic alterations. *Environ Mol Mutagen*. 2014; 55:278–291. [PubMed: 24259318]
- O'Hagan HM, Mohammad HP, Baylin SB. Double Strand Breaks Can Initiate Gene Silencing and SIRT1-Dependent Onset of DNA Methylation in an Exogenous Promoter CpG Island. *PLoS Genet*. 2008; 4:e1000155. [PubMed: 18704159]
- O'Hagan HM, Wang W, Sen S, Destefano Shields C, Lee SS, Zhang YW, Clements EG, Cai Y, Van Neste L, Easwaran H, et al. Oxidative damage targets complexes containing DNA methyltransferases, SIRT1, and polycomb members to promoter CpG Islands. *Cancer Cell*. 2011; 20:606–619. [PubMed: 22094255]
- Oksenyshyn V, Zhovmer A, Ziani S, Mari P-O, Eberova J, Nardo T, Stefanini M, Giglia-Mari G, Egly J-M, Coin F. Histone methyltransferase DOT1L drives recovery of gene expression after a genotoxic attack. *PLoS Genet*. 2013; 9:e1003611. [PubMed: 23861670]
- Oliveira DV, Kato A, Nakamura K, Ikura T, Okada M, Kobayashi J, Yanagihara H, Saito Y, Tauchi H, Komatsu K. Histone chaperone FACT regulates homologous recombination by chromatin remodeling through interaction with RNF20. *J Cell Sci*. 2014; 127:763–772. [PubMed: 24357716]
- Papadopoulou C, Guilbaud G, Schiavone D, Sale JE. Nucleotide Pool Depletion Induces G-Quadruplex-Dependent Perturbation of Gene Expression. *Cell Rep*. 2015; 13:2491–2503. [PubMed: 26686635]
- Petruk S, Sedkov Y, Johnston DM, Hodgson JW, Black KL, Kovermann SK, Beck S, Canaani E, Brock HW, Mazo A. TrxG and PcG proteins but not methylated histones remain associated with DNA through replication. *Cell*. 2012; 150:922–933. [PubMed: 22921915]
- Polo SE, Almouzni G. Chromatin dynamics after DNA damage: The legacy of the access-repair-restore model. *DNA Repair (Amst.)*. 2015; 36:114–121. [PubMed: 26429064]
- Polo SE, Roche D, Almouzni G. New histone incorporation marks sites of UV repair in human cells. *Cell*. 2006; 127:481–493. [PubMed: 17081972]
- Povlsen LK, Beli P, Wagner SA, Poulsen SL, Sylvestersen KB, Poulsen JW, Nielsen ML, Bekker-Jensen S, Mailand N, Choudhary C. Systems-wide analysis of ubiquitylation dynamics reveals a key role for PAF15 ubiquitylation in DNA-damage bypass. *Nat Cell Biol*. 2012; 14:1089–1098. [PubMed: 23000965]
- Pradhan SK, Su T, Yen L, Jacquet K, Huang C, Côté J, Kurdistani SK, Carey MF. EP400 Deposits H3.3 into Promoters and Enhancers during Gene Activation. *Mol Cell*. 2016; 61:27–38. [PubMed: 26669263]
- Qian M-X, Pang Y, Liu CH, Haratake K, Du B-Y, Ji D-Y, Wang G-F, Zhu Q-Q, Song W, Yu Y, et al. Acetylation-Mediated Proteasomal Degradation of Core Histones during DNA Repair and Spermatogenesis. *Cell*. 2013; 153:1012–1024. [PubMed: 23706739]
- Quivy J-P, Gérard A, Cook AJL, Roche D, Almouzni G. The HP1-p150/CAF-1 interaction is required for pericentric heterochromatin replication and S-phase progression in mouse cells. *Nat Struct Mol Biol*. 2008; 15:972–979. [PubMed: 19172751]
- Quivy J-P, Roche D, Kirschner D, Tagami H, Nakatani Y, Almouzni G. A CAF-1 dependent pool of HP1 during heterochromatin duplication. *The EMBO Journal*. 2004; 23:3516–3526. [PubMed: 15306854]
- Ramachandran S, Henikoff S. Replicating Nucleosomes. *Sci Adv*. 2015; 1
- Ray-Gallet D, Woolfe A, Vassias I, Pellentz C, Lacoste N, Puri A, Schultz DC, Pchelintsev NA, Adams PD, Jansen LET, et al. Dynamics of histone H3 deposition in vivo reveal a nucleosome gap-filling mechanism for H3.3 to maintain chromatin integrity. *Mol Cell*. 2011; 44:928–941. [PubMed: 22195966]
- Richet N, Liu D, Legrand P, Velours C, Corpet A, Gaubert A, Bakail M, Moal-Raisin G, Guerois R, Compper C, et al. Structural insight into how the human helicase subunit MCM2 may act as a histone chaperone together with ASF1 at the replication fork. *Nucleic Acids Res*. 2015; 43:1905–1917. [PubMed: 25618846]

- Risca VI, Greenleaf WJ. Unraveling the 3D genome: genomics tools for multiscale exploration. *Trends Genet.* 2015; 31:357–372. [PubMed: 25887733]
- Rocha PP, Micsinai M, Kim JR, Hewitt SL, Souza PP, Trimarchi T, Strino F, Parisi F, Kluger Y, Skok JA. Close proximity to Igh is a contributing factor to AID-mediated translocations. *Mol Cell.* 2012; 47:873–885. [PubMed: 22864115]
- Rodriguez Y, Hinz JM, Smerdon MJ. Accessing DNA damage in chromatin: Preparing the chromatin landscape for base excision repair. *DNA Repair (Amst.).* 2015; 32:113–119. [PubMed: 25957487]
- Roukos V, Voss TC, Schmidt CK, Lee S, Wangsa D, Misteli T. Spatial dynamics of chromosome translocations in living cells. *Science.* 2013; 341:660–664. [PubMed: 23929981]
- Ryu T, Spatola B, Delabaere L, Bowlin K, Hopp H, Kunitake R, Karpen GH, Chiolo I. Heterochromatic breaks move to the nuclear periphery to continue recombinational repair. *Nat Cell Biol.* 2015; 17:1401–1411. [PubMed: 26502056]
- Saksouk N, Simboeck E, Déjardin J. Constitutive heterochromatin formation and transcription in mammals. *Epigenetics Chromatin.* 2015; 8:3. [PubMed: 25788984]
- Sarkies P, Murat P, Phillips LG, Patel KJ, Balasubramanian S, Sale JE. FANCD1 coordinates two pathways that maintain epigenetic stability at G-quadruplex DNA. *Nucleic Acids Res.* 2012; 40:1485–1498. [PubMed: 22021381]
- Sarkies P, Reams C, Simpson LJ, Sale JE. Epigenetic Instability due to Defective Replication of Structured DNA. *Mol Cell.* 2010; 40:703–713. [PubMed: 21145480]
- Sarraf SA, Stancheva I. Methyl-CpG binding protein MBD1 couples histone H3 methylation at lysine 9 by SETDB1 to DNA replication and chromatin assembly. *Mol Cell.* 2004; 15:595–605. [PubMed: 15327775]
- Schick S, Fournier D, Thakurela S, Sahu SK, Garding A, Tiwari VK. Dynamics of chromatin accessibility and epigenetic state in response to UV damage. *J Cell Sci.* 2015; 128:4380–4394. [PubMed: 26446258]
- Schöpf B, Bregenhorn S, Quivy J-P, Kadyrov FA, Almouzni G, Jiricny J. Interplay between mismatch repair and chromatin assembly. *Proc Natl Acad Sci USA.* 2012; 109:1895–1900. [PubMed: 22232658]
- Schuster-Böckler B, Lehner B. Chromatin organization is a major influence on regional mutation rates in human cancer cells. *Nature.* 2012; 488:504–507. [PubMed: 22820252]
- Schübeler D. Function and information content of DNA methylation. *Nature.* 2015; 517:321–326. [PubMed: 25592537]
- Scully R, Xie A. Double strand break repair functions of histone H2AX. *Mutat Res.* 2013; 750:5–14. [PubMed: 23916969]
- Seeber A, Hauer M, Gasser SM. Nucleosome remodelers in double-strand break repair. *Curr Opin Genet Dev.* 2013; 23:174–184. [PubMed: 23352131]
- Semrau S, van Oudenaarden A. Studying Lineage Decision-Making In Vitro: Emerging Concepts and Novel Tools. *Annu Rev Cell Dev Biol.* 2015; 31:317–345. [PubMed: 26566114]
- Sexton T, Cavalli G. The role of chromosome domains in shaping the functional genome. *Cell.* 2015; 160:1049–1059. [PubMed: 25768903]
- Shibahara K, Stillman B. Replication-dependent marking of DNA by PCNA facilitates CAF-1-coupled inheritance of chromatin. *Cell.* 1999; 96:575–585. [PubMed: 10052459]
- Shimazaki N, Tsai AG, Lieber MR. H3K4me3 stimulates the V(D)J RAG complex for both nicking and hairpinning in trans in addition to tethering in cis: implications for translocations. *Mol Cell.* 2009; 34:535–544. [PubMed: 19524534]
- Shimizu I, Yoshida Y, Suda M, Minamino T. DNA Damage Response and Metabolic Disease. *Cell Metabolism.* 2014; 20:967–977. [PubMed: 25456739]
- Siggens L, Cordeddu L, Rönnertblad M, Lennartsson A, Ekwall K. Transcription-coupled recruitment of human CHD1 and CHD2 influences chromatin accessibility and histone H3 and H3.3 occupancy at active chromatin regions. *Epigenetics Chromatin.* 2015; 8:4. [PubMed: 25621013]
- Skene PJ, Henikoff S. Histone variants in pluripotency and disease. *Development.* 2013; 140:2513–2524. [PubMed: 23715545]

- Smeenk G, van Attikum H. The chromatin response to DNA breaks: leaving a mark on genome integrity. *Annu Rev Biochem.* 2013; 82:55–80. [PubMed: 23414304]
- Smeenk G, Wiegant WW, Martejn JA, Luijsterburg MS, Sroczyński N, Costelloe T, Romeijn RJ, Pastink A, Mailand N, Vermeulen W, et al. Poly(ADP-ribosyl)ation links the chromatin remodeler SMARCA5/SNF2H to RNF168-dependent DNA damage signaling. *J Cell Sci.* 2013; 126:889–903. [PubMed: 23264744]
- Smerdon MJ. DNA repair and the role of chromatin structure. *Curr Opin Cell Biol.* 1991; 3:422–428. [PubMed: 1892653]
- Smith DJ, Whitehouse I. Intrinsic coupling of lagging-strand synthesis to chromatin assembly. *Nature.* 2012; 483:434–438. [PubMed: 22419157]
- Smith S, Stillman B. Stepwise assembly of chromatin during DNA replication in vitro. *The EMBO Journal.* 1991; 10:971–980. [PubMed: 1849080]
- Soria G, Polo SE, Almouzni G. Prime, repair, restore: the active role of chromatin in the DNA damage response. *Mol Cell.* 2012; 46:722–734. [PubMed: 22749398]
- Soutoglou E, Dorn JF, Sengupta K, Jasin M, Nussenzweig A, Ried T, Danuser G, Misteli T. Positional stability of single double-strand breaks in mammalian cells. *Nat Cell Biol.* 2007; 9:675–682. [PubMed: 17486118]
- Stanlie A, Aida M, Muramatsu M, Honjo T, Begum NA. Histone3 lysine4 trimethylation regulated by the facilitates chromatin transcription complex is critical for DNA cleavage in class switch recombination. *Proc Natl Acad Sci USA.* 2010; 107:22190–22195. [PubMed: 21139053]
- Strickfaden H, McDonald D, Kruhlak MJ, Haince J-F, Th'ng JPH, Rouleau M, Ishibashi T, Corry GN, Ausio J, Underhill DA, et al. Poly(ADP-ribosyl)ation-dependent transient chromatin decondensation and histone displacement following laser micro-irradiation. *J Biol Chem.* 2015; 291:1789–1802. [PubMed: 26559976]
- Su C, Gao G, Schneider S, Helt C, Weiss C, O'Reilly MA, Bohmann D, Zhao J. DNA damage induces downregulation of histone gene expression through the G1 checkpoint pathway. *The EMBO Journal.* 2004; 23:1133–1143. [PubMed: 14976556]
- Sun Y, Jiang X, Xu Y, Ayrapetov MK, Moreau LA, Whetstone JR, Price BD. Histone H3 methylation links DNA damage detection to activation of the tumour suppressor Tip60. *Nat Cell Biol.* 2009; 11:1376–1382. [PubMed: 19783983]
- Tagami H, Ray-Gallet D, Almouzni G, Nakatani Y. Histone H3.1 and H3.3 complexes mediate nucleosome assembly pathways dependent or independent of DNA synthesis. *Cell.* 2004; 116:51–61. [PubMed: 14718166]
- Tan BC-M, Chien C-T, Hirose S, Lee S-C. Functional cooperation between FACT and MCM helicase facilitates initiation of chromatin DNA replication. *The EMBO Journal.* 2006; 25:3975–3985. [PubMed: 16902406]
- Thorslund T, Ripplinger A, Hoffmann S, Wild T, Uckelmann M, Villumsen B, Narita T, Sixma TK, Choudhary C, Bekker-Jensen S, et al. Histone H1 couples initiation and amplification of ubiquitin signalling after DNA damage. *Nature.* 2015; 527:389–393. [PubMed: 26503038]
- Tian Y, Paramasivam M, Ghosal G, Chen D, Shen X, Huang Y, Akhter S, Legerski R, Chen J, Seidman MM, et al. UHRF1 contributes to DNA damage repair as a lesion recognition factor and nuclease scaffold. *Cell Rep.* 2015; 10:1957–1966. [PubMed: 25818288]
- Torres-Rosell J, Sunjevaric I, De Piccoli G, Sacher M, Eckert-Boulet N, Reid R, Jentsch S, Rothstein R, Aragón L, Lisby M. The Smc5–Smc6 complex and SUMO modification of Rad52 regulates recombinational repair at the ribosomal gene locus. *Nat Cell Biol.* 2007; 9:923–931. [PubMed: 17643116]
- Tran V, Lim C, Xie J, Chen X. Asymmetric division of *Drosophila* male germline stem cell shows asymmetric histone distribution. *Science.* 2012; 338:679–682. [PubMed: 23118191]
- Tresini M, Warmerdam DO, Kolovos P, Snijder L, Vrouwe MG, Demmers JAA, van Ijcken WFJ, Grosveld FG, Medema RH, Hoeijmakers JHJ, et al. The core spliceosome as target and effector of non-canonical ATM signalling. *Nature.* 2015; 523:53–58. [PubMed: 26106861]
- Ui A, Nagaura Y, Yasui A. Transcriptional Elongation Factor ENL Phosphorylated by ATM Recruits Polycomb and Switches Off Transcription for DSB Repair. *Mol Cell.* 2015; 58:468–482. [PubMed: 25921070]

- van Sluis M, McStay B. A localized nucleolar DNA damage response facilitates recruitment of the homology-directed repair machinery independent of cell cycle stage. *Genes Dev.* 2015; 29:1151–1163. [PubMed: 26019174]
- Vissers JHA, van Lohuizen M, Citterio E. The emerging role of Polycomb repressors in the response to DNA damage. *J Cell Sci.* 2012; 125:3939–3948. [PubMed: 23104738]
- Wang H, Wang M, Yang N, Xu R-M. Structure of the quaternary complex of histone H3-H4 heterodimer with chaperone ASF1 and the replicative helicase subunit MCM2. *Protein Cell.* 2015; 6:693–697. [PubMed: 26186914]
- Wen D, Banaszynski LA, Liu Y, Geng F, Noh K-M, Xiang J, Elemento O, Rosenwaks Z, Allis CD, Rafii S. Histone variant H3.3 is an essential maternal factor for oocyte reprogramming. *Proc Natl Acad Sci USA.* 2014; 111:7325–7330. [PubMed: 24799717]
- Wu H, Zhang Y. Reversing DNA methylation: mechanisms, genomics, and biological functions. *Cell.* 2014; 156:45–68. [PubMed: 24439369]
- Xie J, Wooten M, Tran V, Chen B-C, Pozmanter C, Simbolon C, Betzig E, Chen X. Histone H3 Threonine Phosphorylation Regulates Asymmetric Histone Inheritance in the *Drosophila* Male Germline. *Cell.* 2015; 163:920–933. [PubMed: 26522592]
- Xu Y, Ayrapetov MK, Xu C, Gursoy-Yuzugullu O, Hu Y, Price BD. Histone H2A.Z controls a critical chromatin remodeling step required for DNA double-strand break repair. *Mol Cell.* 2012; 48:723–733. [PubMed: 23122415]
- Xu Y, Sun Y, Jiang X, Ayrapetov MK, Moskwa P, Yang S, Weinstock DM, Price BD. The p400 ATPase regulates nucleosome stability and chromatin ubiquitination during DNA repair. *J Cell Biol.* 2010; 191:31–43. [PubMed: 20876283]
- Yang X, Li L, Liang J, Shi L, Yang J, Yi X, Zhang D, Han X, Yu N, Shang Y. Histone acetyltransferase 1 promotes homologous recombination in DNA repair by facilitating histone turnover. *J Biol Chem.* 2013; 288:18271–18282. [PubMed: 23653357]
- Yu Y, Teng Y, Liu H, Reed SH, Waters R. UV irradiation stimulates histone acetylation and chromatin remodeling at a repressed yeast locus. *Proc Natl Acad Sci USA.* 2005; 102:8650–8655. [PubMed: 15939881]
- Zane L, Sharma V, Misteli T. Common features of chromatin in aging and cancer: cause or coincidence? *Trends Cell Biol.* 2014; 24:686–694. [PubMed: 25103681]
- Zavala AG, Morris RT, Wyrick JJ, Smerdon MJ. High-resolution characterization of CPD hotspot formation in human fibroblasts. *Nucleic Acids Res.* 2014; 42:893–905. [PubMed: 24137003]
- Zhang H, Liu H, Chen Y, Yang X, Wang P, Liu T, Deng M, Qin B, Correia C, Lee S, et al. A cell cycle-dependent BRCA1-UHRF1 cascade regulates DNA double-strand break repair pathway choice. *Nat Commun.* 2016; 7:10201. [PubMed: 26727879]
- Zhang Y, McCord RP, Ho Y-J, Lajoie BR, Hildebrand DG, Simon AC, Becker MS, Alt FW, Dekker J. Spatial organization of the mouse genome and its role in recurrent chromosomal translocations. *Cell.* 2012; 148:908–921. [PubMed: 22341456]
- Zheng CL, Wang NJ, Chung J, Moslehi H, Sanborn JZ, Hur JS, Collisson EA, Vemula SS, Naujokas A, Chiotti KE, et al. Transcription restores DNA repair to heterochromatin, determining regional mutation rates in cancer genomes. *Cell Rep.* 2014; 9:1228–1234. [PubMed: 25456125]

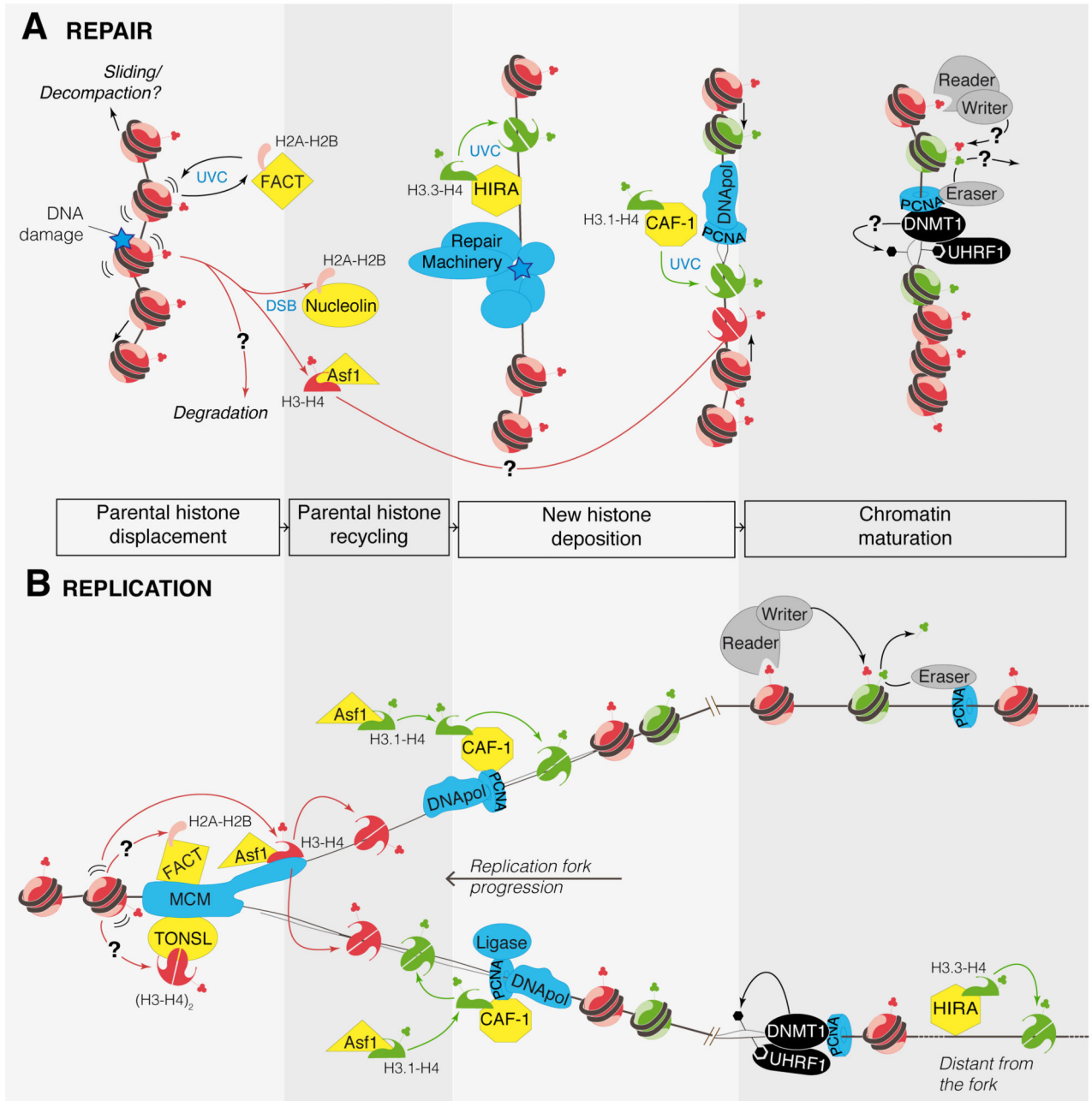


Figure 1. Epigenome maintenance in mammalian cells: parallel between replication and repair. DNA repair (**A**) and replication (**B**) involve similar chromatin dynamics with shared histone chaperones (yellow) promoting the mobilization of parental histones (red) and the deposition of newly synthesized histones (green). For simplicity, shared chromatin remodeling complexes are not represented. Both at the replication fork and at UV damage repair sites, new H3.1 deposition by CAF-1 is coupled to DNA synthesis while new H3.3 histones are deposited by HIRA independently of DNA synthesis. The histone chaperone FACT also promotes histone dynamics in response to UVC damage while ASF1 and Nucleolin are

involved in the response to DSBs. Subsequent chromatin maturation involves erasure of naive histone marks (green), transmission of parental histone marks (red) to newly synthesized histones, and maintenance of DNA methylation (black). Although such processes have been described at the replication fork, related mechanisms at repair sites are still to be characterized. Repair and replication factors are represented in blue.

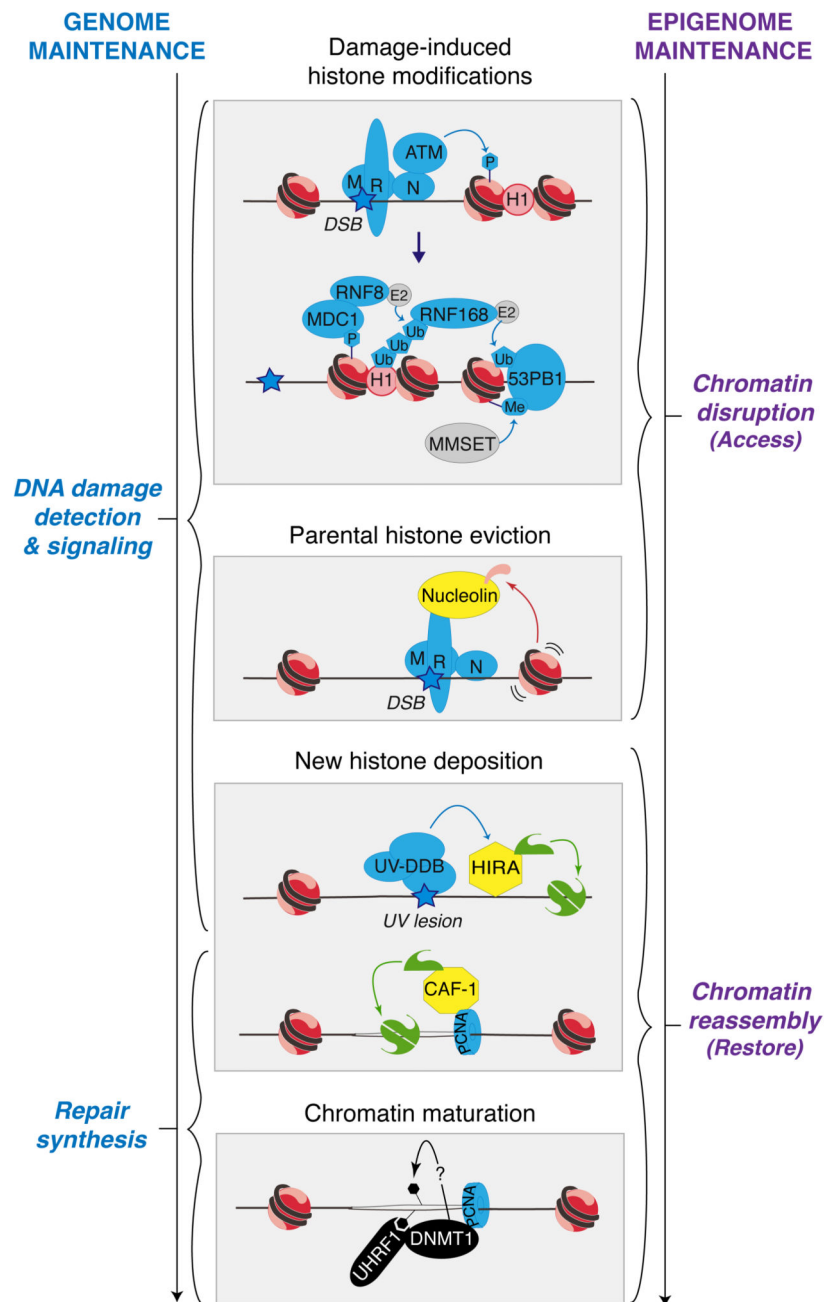


Figure 2. Coordination between genome and epigenome maintenance in response to DNA damage.

The coordinated maintenance of genome integrity and epigenome stability along the repair process in mammalian cells is supported by direct molecular interactions of DDR factors (blue) with histone modifications (P: phosphorylation; Ub: ubiquitination; Me: methylation), histone chaperones (yellow) and the DNA methylation machinery (black). DNA damage signaling factors: ATM: Ataxia Telangiectasia Mutated; MDC1: Mediator of DNA damage Checkpoint 1; RNF: RING Finger protein; MMSET: Multiple Myeloma SET domain; 53BP1: TP53 Binding Protein 1.

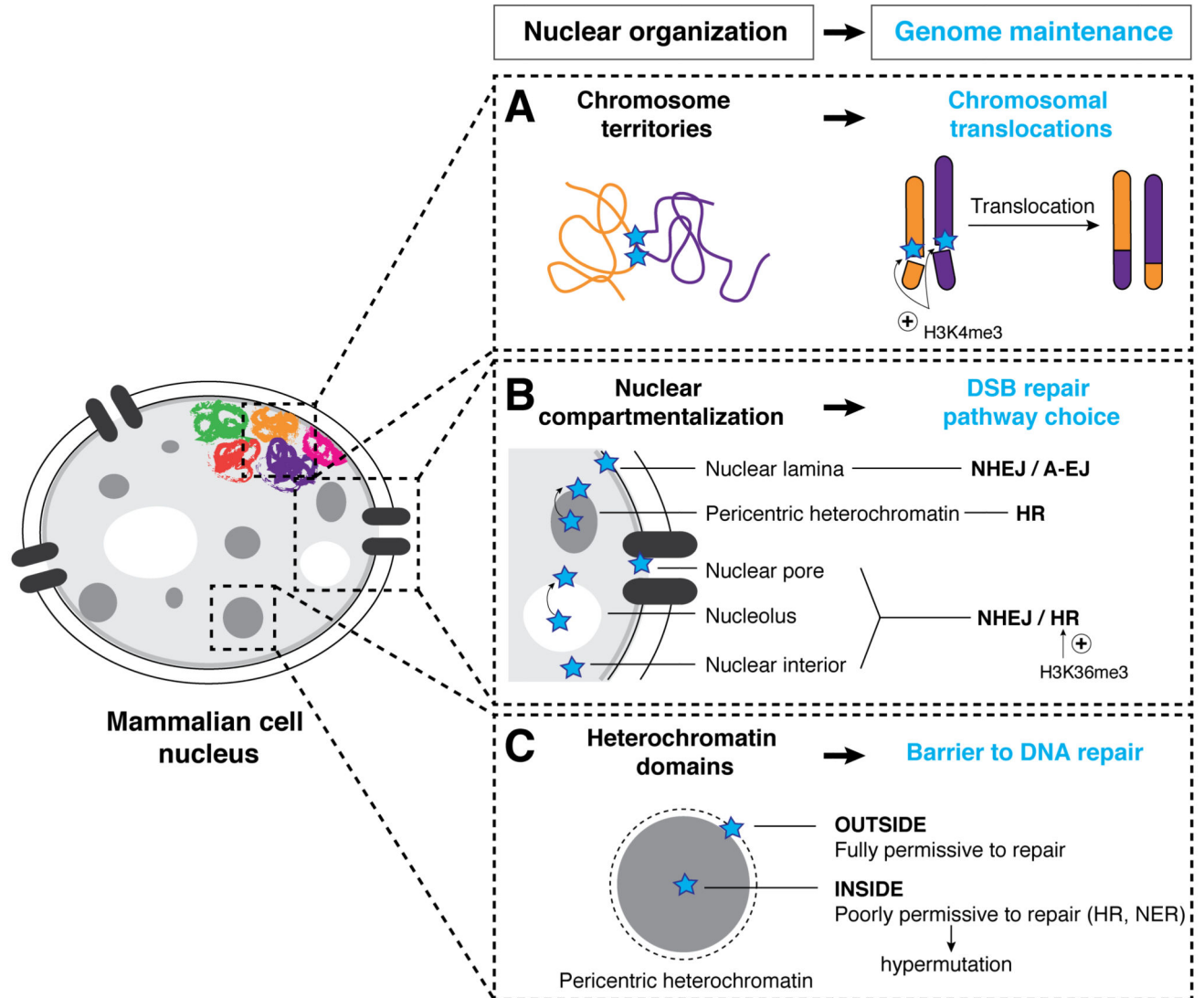


Figure 3. Impact of nuclear organization on genome maintenance in response to DNA damage in mammalian cells

(A) The spatial proximity of chromosome territories in the mammalian cell nucleus determines partner selection in chromosome translocations. Chromosome breakpoints (blue stars) are characterized by an enrichment in the transcription-associated histone mark H3K4me3, which facilitates DSB formation.

(B) Nuclear position of DSBs (blue stars) dictates repair pathway choice. NHEJ: non-homologous end-joining, A-EJ: alternative end joining, HR: homologous recombination. DSBs located in actively transcribed genes are targeted to HR repair via the transcription elongation-associated histone mark H3K36me3.

(C) Highly compact heterochromatin domains pose a barrier to repair of DNA damage (blue star). HR: homologous recombination, NER: nucleotide excision repair.

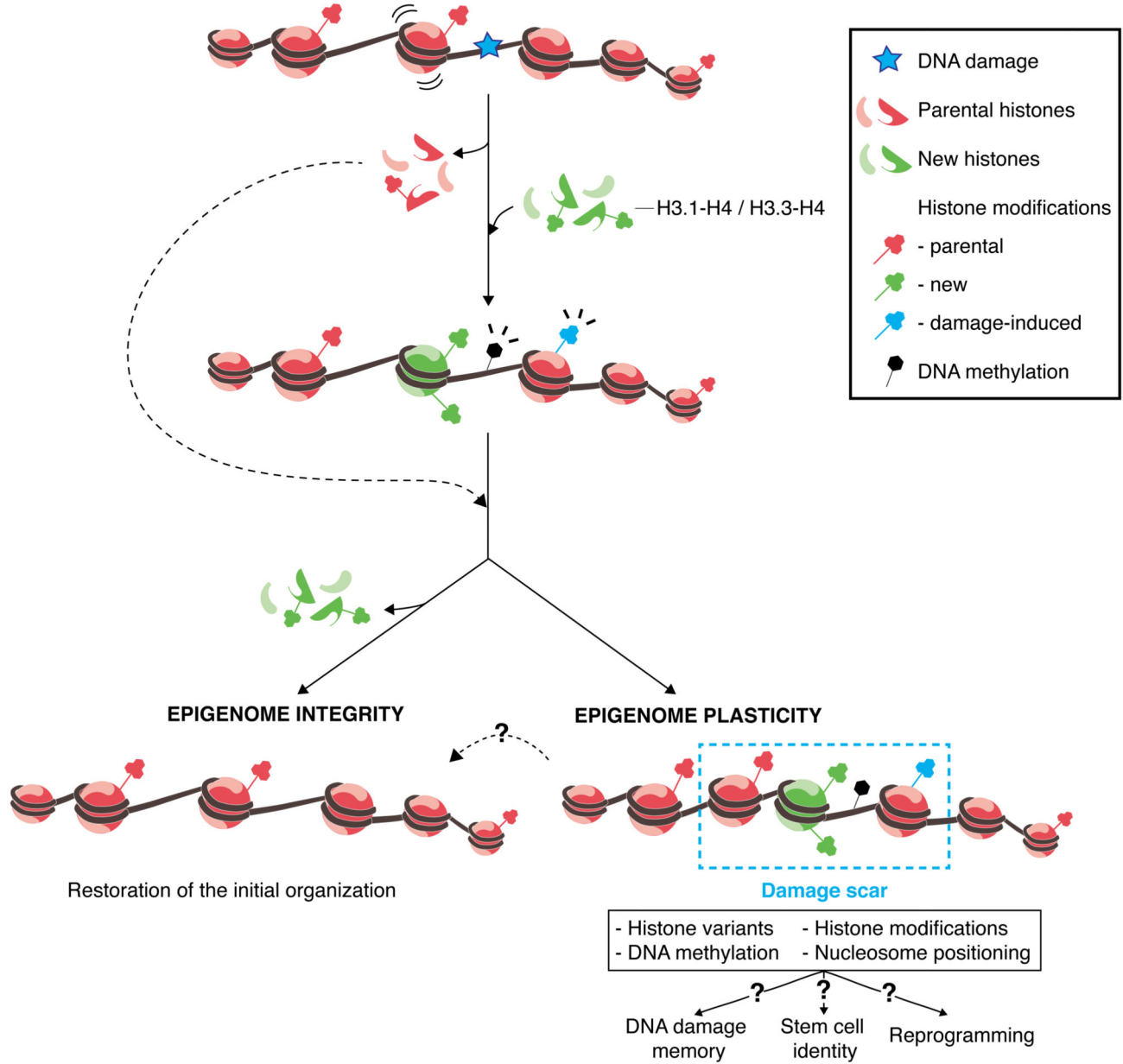


Figure 4. Epigenome integrity vs. plasticity in response to DNA damage in mammalian cells
 DNA damage (blue star) elicits substantial chromatin rearrangements, with a loss of parental information (red) due to the mobilization of pre-existing histones, and the incorporation of new information with histone variant exchange and deposition of newly synthesized histones (green), DNA damage-responsive PTMs (blue) and DNA methylation (black). For simplicity, factors escorting and mobilizing histones and modifying enzymes for histones and DNA are not represented. Future challenges in the field will be to determine whether or not the pre-existing chromatin landscape is ultimately faithfully restored after genotoxic stress, thus allowing the maintenance of epigenome integrity. Alternatively, the persistence

of a damage scar on chromatin (dotted line box) could contribute to damage memory, maintenance of stem cell identity or reprogramming.