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Chromatin plasticity in response to DNA damage: the shape of things to come

Salomé Adam[#a,b], **Juliette Dabin**[#a], and **Sophie E. Polo**[a,*]

[a]Epigenome Integrity group, UMR 7216 CNRS/Paris Diderot University, 35 rue Helene Brion, 75013 Paris, France

[b]Chromatin Dynamics group, UMR 3664 CNRS/Institut Curie Research Center, 26 rue d'Ulm, 75005 Paris, France

[#] These authors contributed equally to this work.

Abstract

DNA damage poses a major threat to cell function and viability by compromising both genome and epigenome integrity. The DNA damage response indeed operates in the context of chromatin and relies on dynamic changes in chromatin organization. Here, we review the molecular bases of chromatin alterations in response to DNA damage, focusing on core histone mobilization in mammalian cells. Building on our current view of nucleosome dynamics in response to DNA damage, we highlight open challenges and avenues for future development. In particular, we discuss the different levels of regulation of chromatin plasticity during the DNA damage response and their potential impact on cell function and epigenome maintenance.

Keywords

Chromatin dynamics; Chromatin remodelers; DNA damage repair; Epigenome maintenance; Histone chaperones; Histone variants

1 Introduction

While the sequential molecular events of the DNA damage response (DDR) have been extensively characterized [1,2], how DNA damage signaling and repair machineries operate on a chromatin substrate is less well understood [3–6]. DNA packaging with histone proteins into nucleosomes and higher-order chromatin structures restricts DNA damage accessibility. This issue is central to the Access-Repair-Restore (ARR) model, which integrates nucleosome dynamics in the repair process [7–9] and constitutes a foundation for studying DDR-related chromatin changes. This model postulates that chromatin is disorganized prior to binding of repair factors on damaged DNA, and then rearranged after repair completion. Restoring chromatin organization and the original information that it conveys – the so-called epigenome – is key for maintaining cell identity.

[*]Corresponding author. Tel: +33 1 57 27 89 81; fax: +33 1 57 27 89 12. sophie.polo@univ-paris-diderot.fr (S.Polo).

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Histone proteins are major components of the epigenome, because they exist as sequence variants [10,11] and display multiple post-translational modifications (PTMs) [12], the combination of which regulates gene expression and cellular functions. Histone modifications as well as histone dynamics, promoted by histone chaperones [13] and remodeling factors [14], play important regulatory roles in response to DNA damage (reviewed in [15]). Much effort has been invested in exploring the molecular mechanisms of chromatin dynamics in response to genotoxic stress and how they impact on chromatin structure and function. In this review, we discuss the main features and functional consequences of chromatin dynamics at sites of DNA damage, focusing on core histone mobilization in response to DNA breaks and UV damage in mammalian cells, and we highlight open challenges in this rapidly growing field.

2 Main features of histone dynamics at sites of DNA damage

Here, we present our current knowledge of damaged chromatin dynamics at the level of the nucleosome core particle. Both inner and outer core histones display enhanced dynamics at sites of DNA damage induced by site-specific endonucleases, UVA laser micro-irradiation or local UVC irradiation (Table 1). Consistent with the ARR model [7–9], there is increasing evidence for nucleosome destabilization at damage sites, followed by a restoration of nucleosomal organization (Fig. 1).

2.1 Nucleosome destabilization and histone loss from damage sites

Genotoxic stress weakens the interactions between histones and the DNA, as shown by an increase in core histone extractability from chromatin - with some extent of histone solubilization - in response to ionizing radiations, radiomimetic drug treatment and UVC irradiation [16–18].

Beyond nucleosome destabilization, chromatin immunoprecipitation analyzes have revealed a transient loss of core histones in the vicinity of double-strand breaks (DSBs) induced by the I-PpoI endonuclease [19,20]. It needs to be clarified whether such histone loss strictly reflects nucleosome disruption rather than sliding away from DSBs, as we discuss below. Nevertheless, these dynamics involve two histone chaperones: ASF1, which removes the inner core histones H3-H4, and nucleolin, responsible for H2A-H2B mobilization. Nucleolin accumulates at DSBs and plays a crucial role in their repair by stimulating the recruitment of DSB repair factors, suggesting that nucleolin-dependent histone dynamics could be instrumental for proper DSB repair [20].

Besides histone chaperones, chromatin remodelers also contribute to DSB repair and histone mobilization from DSBs, as shown for the p400 remodeler that promotes histone H3 loss from AsiSI-induced DNA breaks and homologous recombination (HR)-mediated repair [21].

Furthermore, histone mobilization is not restricted to the DSB response as it is also observed in UVC-damaged chromatin areas. UVC exposure indeed causes an Adenosine triphosphate (ATP)-dependent reorganization of chromatin, mediated by the UV lesion sensor DNA Damage Binding protein 2 (DDB2), resulting in reduced density of core and linker histones at sites of UVC irradiation. Whether this reorganization actually corresponds to nucleosome

disruption is not known but it correlates with efficient UV damage repair [22]. The ATP-dependency of the process suggests the involvement of DDB2-associated chromatin remodeler(s), yet to be identified.

Altogether these studies support the idea that remodeling chromatin at the nucleosome level, by destabilizing or disrupting nucleosomal organization around DNA damage sites, would facilitate access to repair factors.

2.2 Enhanced histone mobility/turnover at damage sites

Alterations in nucleosomal organization in response to DNA damage also occur through increased mobility and turnover of histone proteins, which may as well answer the need for more accessible chromatin. Fluorescence recovery after photobleaching (FRAP) analyses have shown that the histone variants H2A.X and H2A.Z.2 display enhanced mobility at sites of UVA laser micro-irradiation within minutes after damage induction [23,24]. Both the histone chaperone Facilitates Chromatin Transcription (FACT) and the acetyltransferase complex Tat Interacting Protein 60 (TIP60) are involved in damage-induced H2A.X dynamics, which is regulated by H2A.X post-translational modifications [23,25,26].

The mobility of core histones has also been studied in response to UVC irradiation by imaging GFP-tagged histones [27]. This recent work shows accelerated turnover of H2A-H2B at UVC damage sites, which is not observed for inner core histones H3.1 and H4. Accelerated turnover of H2A-H2B occurs within minutes after UVC damage and independently of damage repair, suggesting that it may be important for subsequent DDR steps. Once again, the enhanced dynamics of H2A depends on the histone chaperone FACT [27]. Remarkably, this chaperone also promotes transcription recovery after UVC damage repair [27]. Whether this activity results from FACT controlling transcription-coupled repair needs to be clarified but it suggests that histone turnover at early stages of the damage response might have broader consequences than just regulating DNA repair.

2.3 Local enrichment of histone variants at damage sites

Histone turnover can also result in the accumulation of specific histone variants at damage sites, as demonstrated by ChIP at site-specific DSBs or by imaging after local irradiation. This could have a significant impact on the chromatin landscape by changing the histone variant content in damaged nucleosomes, as further discussed below. However, in most cases, we do not have yet a clear view of histone variant accumulation at damage sites because of conflicting reports and evidence is still lacking to fully support the functional relevance of this accumulation.

2.3.1 H2A variants—The H2A histone variant H2A.Z has been found enriched at DNA DSBs [28], although this does not appear to be a widespread chromatin response because it could not be reproduced by another group [29]. H2A.Z enrichment at DSBs might be detectable only at late time points after damage and in poorly transcribed chromatin regions, which originally display low H2A.Z content. The contribution of the H2A.Z variant to DSB repair is also disputed [28,29].

The accumulation of macroH2A1 variants in damaged chromatin regions has been studied in response to DBSs [30,31] and UVA laser micro-irradiation [32]. In particular, the macrodomain-containing form macroH2A1.1 associates with damaged chromatin in a Poly(ADP-ribose) (PAR)-dependent manner [32,33], but intriguingly without a proper incorporation into nucleosomes as its enrichment at DSBs cannot be detected by ChIP without prior cross-linking [30]. Thus, this variant does not behave like a *bona fide* histone protein in this context but rather like a chromatin-associated factor. Furthermore, macroH2A1 accumulates at DSBs after being transiently depleted from damaged chromatin [31]. The accumulation of this histone variant on damaged chromatin contributes to DSB repair by HR and local chromatin compaction [31,32]. The effect of macroH2A on repair by compacting rather than opening chromatin is in apparent contrast with the ARR model. We will discuss in the following sections how to reconcile these observations.

Another H2A variant that has been found enriched at sites of UVA laser damage repair is H2A.Bbd [34], but the physiological relevance of this observation is unclear because it relies on the ectopic expression of H2A.Bbd in mouse embryonic fibroblasts while it is normally expressed only in testis and brain cells [31].

2.3.2 H3 variants—Among H3 variants, H3.3 displays increased incorporation around I-SceI-induced DSBs, which is mediated by the histone chaperone Histone Regulator A (HIRA) [35]. This mechanism may be similar to the deposition of newly synthesized H3.3 histones at UVC damage sites (described below).

Although initially reported in human cells, the accumulation of the centromeric H3 variant Centromere Protein A (CENPA) at DSBs has not been confirmed in recent studies [36,37]. Actually, mis-targeting of CENPA to damage sites may be prevented under normal conditions, as shown in drosophila, to avoid the formation of ectopic kinetochores and genome instability [38].

It remains to be determined if the local enrichment of specific histone variants in damaged chromatin ensures efficient repair by regulating chromatin accessibility/compaction, and/or contributes to restoring chromatin structure and function after repair.

2.4 New histone deposition at damage sites

Damaged chromatin also incorporates new information - at least transiently - via the deposition of newly synthesized histones. The first evidence for *de novo* histone incorporation at DNA damage sites came from analyzing the dynamics of the H3.1 variant short-term after transient transfection in human cells exposed to UVC irradiation or laser micro-irradiation [39]. Using a similar approach, it was also shown that new H2A histones are deposited in UVC-damaged chromatin regions, likely mediated by the histone chaperone FACT [27]. The deposition of newly synthesized H3.1 in UVC-damaged chromatin is promoted by the histone chaperone Chromatin Assembly Factor 1 (CAF-1) [39]. Given that CAF-1 escorts both the H3.1 and H3.2 variants [40], it is likely that a similar mechanism operates for H3.2.

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The analysis of new histone dynamics in response to DNA damage has been greatly improved by the development of the SNAP-tag technology [41], which allows specific tracking of newly synthesized histones *in vivo*. Using this approach, it was established that newly synthesized H3.3 variants are deposited by the chaperone HIRA at sites of UVC damage in a manner dependent on DNA damage detection [42], which contrasts with CAF-1-mediated deposition of H3.1 that is coupled to late repair steps [39]. The recent discovery of recurrent point mutations in H3 variants in human cancers (reviewed in [43]) raises questions about the consequences of such mutations on DNA damage-associated histone dynamics, which could contribute to tumor development by compromising epigenome stability.

Beyond restoring nucleosomal structure, new histone deposition at sites of DNA damage also has important functional consequences. While neither H3.1 nor H3.3 deposition seems to impact UVC damage repair [39,42] in human cells, H3.3 plays a substantial role in replication fork progression after DNA damage in chicken cells [44], and the histone chaperone HIRA is required for transcription recovery upon repair completion in human cells [27,42].

The deposition of new histones at DNA damage sites is consistent with the concept of restoring chromatin structure developed in the ARR model [7–9] and completes our current view of histone dynamics at sites of DNA damage. However, it also raises several issues regarding how DNA damage-induced histone dynamics can be compatible with epigenome maintenance and and how they cross-talk with cellular functions. These exciting questions are still open and constitute upcoming challenges in the field, which we discuss in the following sections.

3 Exploring the mechanisms underlying histone dynamics at sites of DNA damage

As described above, there is increasing evidence that, in the early stages of the DDR, histones are mobilized away from damaged chromatin regions. However, it is still unclear whether this occurs as part of chromatin decondensation or if it reflects more profound alterations of chromatin structure affecting nucleosomal integrity. Future work should closely examine whether histones slide away from DNA damage sites as a result of nucleosome remodeling and/or if they are evicted from chromatin due to the disruption – either complete or partial – of damaged nucleosomes. Biochemical approaches, including cell fractionation experiments, should help clarify this issue by determining whether the mobilized histones become soluble or remain chromatin-bound in the vicinity of the damaged area. Note that the extent of nucleosomal alterations may be dependent on the type of DNA damage and repair pathway at work (discussed below). It will also be of major interest to develop imaging tools for tracking displaced histones and determine where they move to after DNA damage. In addition, in-depth analyses of the dynamics of outer and inner core histones will be instrumental for revealing whether they are displaced in a coordinated manner and in which form they are mobilized: single histone, dimer, tetramer or nucleosome core particle.

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Deciphering the molecular bases of nucleosome alterations in response to DNA damage is key for understanding the process of damaged chromatin disorganization and should also provide interesting insights into how chromatin is restored after repair.

4 Impact of DNA damage induced-histone dynamics on epigenome maintenance

DNA damage repair is accompanied by post-translational modification of histones and deposition of new histone species in damaged chromatin regions. The resulting pattern of histone variants and associated PTMs thus likely differs substantially from the chromatin landscape before damage infliction and provides new information, which contributes to signaling and repair of DNA lesions but may also be detrimental for the maintenance of chromatin identity (Fig. 1). Indeed, a memory of the original information should be kept and in this respect, the fate of both parental and newly deposited histones is critical. Are parental histones damaged at sites of DNA lesions and then targeted to degradation, in which case the corresponding information would be lost? Or are they mobilized away from damaged chromatin regions? The latter mechanism would secure the original information by preventing these histones from being targeted by histone modifiers at sites of DNA lesions. Recycling of these parental histones upon DNA repair completion could thus contribute to restoring faithfully the initial chromatin organization. In addition to old histone recycling, re-establishing the original chromatin landscape would require active erasure of the DNA damage-induced histone PTMs and transmission of parental marks to the newly synthesized naive histones deposited at damage sites. Furthermore, it is not yet clear if all the new information deposited in damaged chromatin ultimately gets erased or if it is – at least in part – conserved, leaving an imprint on chromatin, which may serve as a DNA damage memory and facilitate repair in case of a subsequent exposure to DNA damage. Thus, it will be critical to assess the relative contributions of new vs. parental information in repaired nucleosomes. To address this important issue, novel tools such as the SNAP-tag technology [41], which discriminates between new and old histones *in vivo,* should provide experimental means to monitor the fate of newly synthesized histones deposited at damage sites and of parental histones mobilized away from damaged regions. Another powerful technology that could shed light on chromatin composition associated with repaired DNA is nascent chromatin capture, a high-throughput proteomic approach recently developed for investigating the dynamic changes in chromatin-bound proteins and histone PTMs during DNA replication [45]. However, to properly assess the chromatin changes induced by DNA damage, it will be important to have a clear picture of the original chromatin composition before damage infliction, which is not necessarily straightforward with existing technologies. Thus, we are only beginning to appreciate the full complexity of the mechanisms underlying chromatin integrity in response to DNA damage. Deciphering these mechanisms will be key for understanding how DNA damage impacts on epigenome maintenance and plasticity.

5 Impact of DNA damage induced-chromatin plasticity on the DDR

Despite considerable efforts to elucidate the functional relevance of DNA damage-induced histone dynamics, we are still far from fully understanding the impact of this chromatin plasticity on the DDR. Indeed, studies conducted so far to evaluate the effect of depleting histone variants or their escorting factors on DNA repair have often led to conflicting results (Table 1). Some of these apparent discrepancies may be explained by differences in the cellular models [42,44] or in the strategies used to deplete the protein of interest [28,29]. Furthermore, it is always questionable whether the resulting phenotype is a direct or indirect consequence of altered histone dynamics.

When analyzing the influence of DNA damage-induced histone dynamics on the DDR, we generally assume that early events facilitate access of repair machineries to damaged DNA, while events coupled to late repair steps contribute to restoring chromatin structure and function without any implication in the DNA repair process. However, this model may be too simplistic because some factors recruited early to damage sites like the histone chaperones FACT and HIRA facilitate transcription recovery after DNA repair completion without substantial effects on DNA damage repair [27,42].

Another matter of debate is how to reconcile the ARR model with reports of chromatin compaction upon genotoxic stress [31,32]. Recent data indicate that DNA damage-induced chromatin relaxation and compaction may represent sequential events in the repair process. First, chromatin would be rapidly relaxed to allow efficient detection of DNA lesions [31,32,46], which is fully consistent with our current view of the ARR model. Then, chromatin would be transiently condensed to promote DNA damage signaling, as shown after DSB induction [46,47]. In addition to this tight temporal control, the compaction status of damaged chromatin may be spatially regulated. Indeed, high resolution profiling of chromatin compaction in live cells by measuring EGFP molecular flow recently revealed that chromatin structure becomes transiently more accessible at laser damage sites and more compact in adjacent regions [48]. It will be important to integrate these spatio-temporal changes in chromatin organization to refine our current model of DNA damage-induced chromatin plasticity.

6 Regulation of DNA damage-associated histone dynamics

Given the strong potential impact of DNA damage-induced histone dynamics on cellular functions, they should be tightly regulated. Multiple parameters, summarized below, are likely to control the level of chromatin re-organization in response to DNA damage (Fig.2).

First, efficient signaling and repair of DNA lesions may not require the same extent of chromatin reorganization depending on the type and location of DNA damage. Indeed, repair machineries would more easily detect DNA damage that highly distorts the DNA, while DNA lesions buried inside nucleosomes would require either opening or disruption of the chromatin core particle in order to be readily sensed. In addition, the extent of chromatin disorganization can vary a lot depending on the repair pathway at work to process the lesion. For example, DSB repair by HR involves extensive DNA end resection and is associated

with loss of both inner and outer core histones at DSB sites, while only outer core histones are mobilized away from damaged regions when DSBs are repaired by Non-Homologous End-Joining (NHEJ), which directly ligates the two broken ends [20]. Furthermore, it is tempting to speculate that chromatin reorganization during HR is not restricted to the damaged area, but could also affect the homologous template to favor strand invasion [21]. Extensive analyses of chromatin alterations in response to a variety of well-characterized genotoxic agents are necessary to determine the impact of DNA damage type on the extent of chromatin disorganization. Aside from the response to genotoxic stress, it will be important to better dissect chromatin plasticity associated with programmed DNA damage that occurs in meiosis or during the establishment of the immune repertoire in lymphocytes [49–51].

The cell cycle stage may also regulate DNA damage-induced histone dynamics. Indeed, not only does the cell cycle govern DNA repair pathway choice, in particular in the context of DSB repair, but it has also a profound impact on the abundance/availability of histone components and their associated factors. For example, it is conceivable that distinct chromatin alterations occur in rapidly cycling cells vs. post-replicative cells, in which the production of replicative histone variants is drastically reduced [10]. Moreover, is damaged chromatin similarly disorganized in mitotic cells, characterized by massive compaction when compared to interphase cells? Are there distinctive features of DNA damage-associated histone dynamics due to ongoing replication in S-phase cells? Synchronizing cells at specific stages in the cell cycle and considering also post-replicative cells will be required for appreciating to which extent cell cycle progression impacts on DNA damage-associated histone dynamics.

The initial chromatin organization/dynamics and transcriptional state are additional key factors influencing how DNA damage challenges chromatin organization. We will not extensively comment on these as they have already been the focus of recent reviews [52,53]. In particular, highly compact and poorly transcribed heterochromatin is generally viewed as a barrier to signaling and repair of DNA lesions, which is relieved in part by chromatin decondensation.

Chromatin dynamics are also substantially different depending on cell type, as illustrated by a higher chromatin mobility in cells that are not committed yet to differentiation [54], which might govern a specific chromatin response to DNA damage. Thus, it will be interesting to consider reshaping of damaged chromatin not only at the single cell level but also throughout the organism and during development.

7 Conclusions

Over the past decades, deciphering how both genome and epigenome integrity are preserved when challenged by DNA damage has been the focus of intense research. This contributed to build our current view of chromatin dynamics in response to genotoxic stress, where histone proteins are integral players of the DNA damage response that coordinate efficient signaling and repair of DNA lesions with the maintenance of cell identity. However, despite considerable efforts, many key issues remain unaddressed, as summarized in this review. It

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will be particularly important to further explore the molecular bases of histone dynamics in damaged chromatin and their cross-talks with cellular functions to understand their impact on cell fate. This should shed light on the potentially deleterious consequences of altered chromatin dynamics, which are widely acknowledged as hallmarks of ageing and cancer.

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Abbreviation List

ARR	Access-Repair-Restore
ASF1	Anti-Silencing Factor 1
ATP	Adenosine Triphosphate
CAF-1	Chromatin Assembly Factor-1
CENPA	Centromeric Protein A
ChIP	Chromatin Immuno-Precipitation
DDB2	DNA Damage Binding protein 2
DDR	DNA Damage Response
DSB	Double-Strand Break
FACT	Facilitate Chromatin Transcription
HIRA	Histone Regulator A
HR	Homologous Recombination
NHEJ	Non-Homologous End Joining
PAR	Poly(ADP-Ribose)
PTM	Post-Translational Modification
TIP60	Tat-Interacting Protein 60
UV (A or C)	UltraViolet (A or C)

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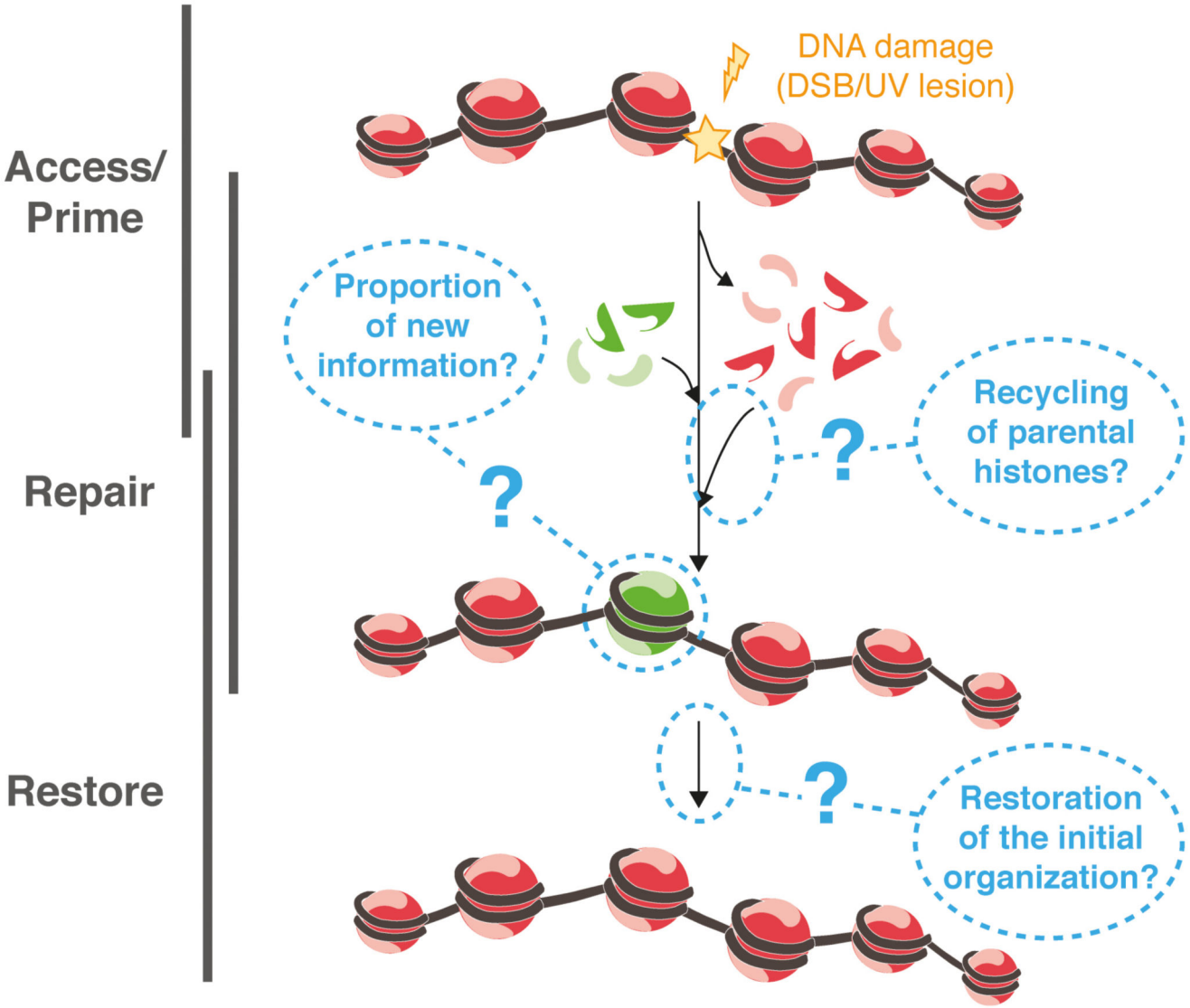

Fig.1. Histone dynamics in response to DNA damage: the issue of epigenome maintenance.

DNA damage (yellow star) elicits important chromatin rearrangements, including a loss of parental information (red) at the damage site due to the mobilization of pre-existing histones, and the incorporation of new information (green) with DNA damage-responsive PTMs, histone variant exchange and deposition of newly synthesized histones. The resulting pattern of histone variants and associated PTMs is likely to differ substantially from the original one. Future challenges in the field (open issues in blue) will be to determine to which extent the original information is diluted and whether or not the pre-existing chromatin landscape is ultimately faithfully restored after genotoxic stress, by parental histone recycling, histone variant exchange, active erasure of DNA damage-associated PTMs, and/or transmission of parental marks to newly deposited histones.

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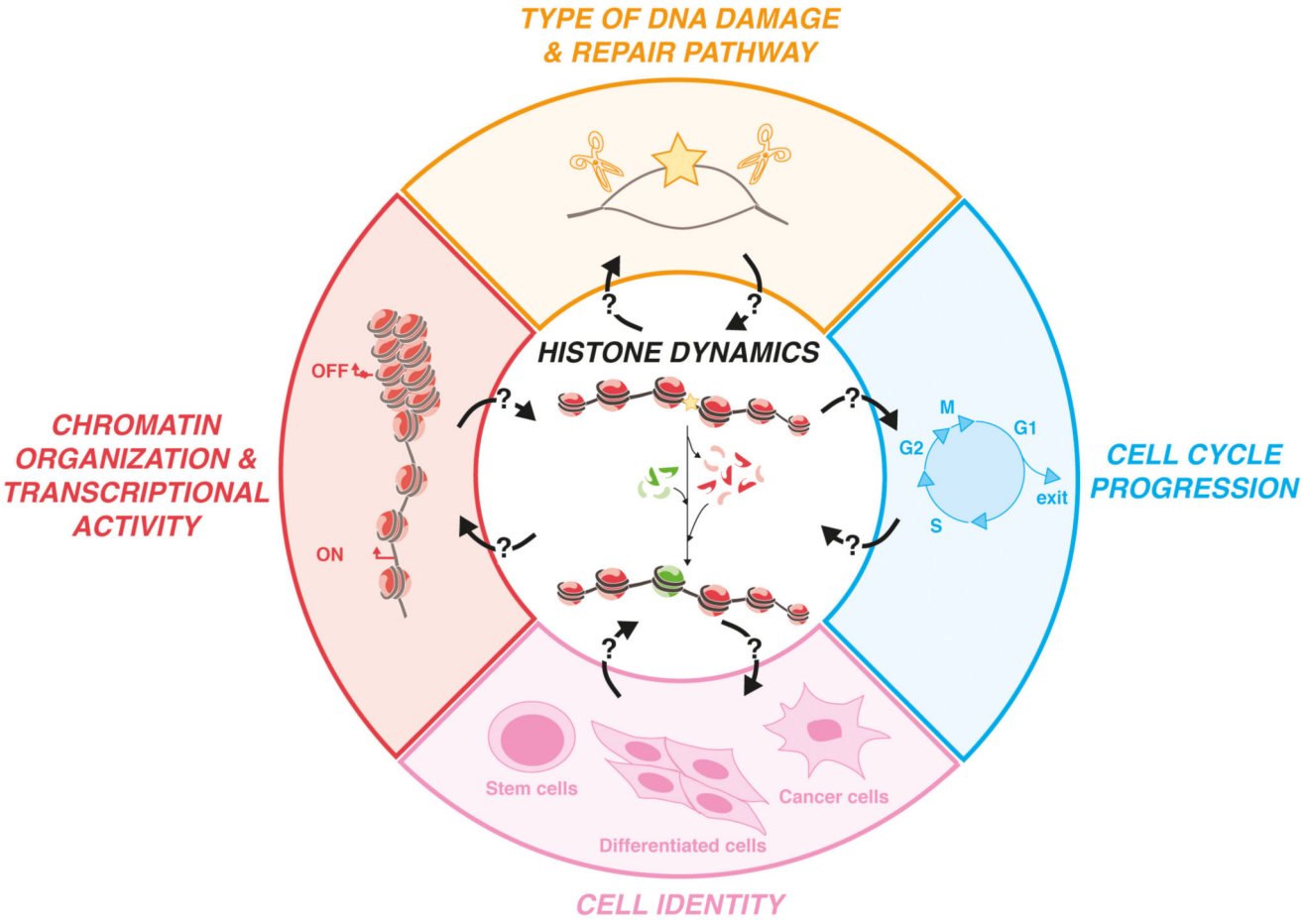

Fig.2. Cross-talks between histone dynamics in damaged chromatin and cellular functions.

The exchange of parental histones (red) with histones carrying new information (green) in response to DNA damage will impose - at least transient - changes in chromatin structure and function. Future work should closely examine to which extent these dynamics impact DNA metabolic activities (such as DNA repair and transcription) and cellular functions (proliferation and differentiation), and assess their consequences on cell identity. Conversely, it needs to be further explored how the initial chromatin organization, DNA damage type, cell cycle stage and cell state may regulate DNA damage-induced histone dynamics.

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Table 1

Core histone dynamics in response to DNA damage (as known in mammalian cells, unless stated otherwise).

53BP1: Tumor suppressor p53-binding protein 1; APLF: Aprataxin-PNK-like factor; ASF1: Anti-Silencing Factor 1; ATM: Ataxia telangiectasia mutated; ATR: Ataxia telangiectasia and Rad3-related protein; BRCA1: breast cancer early onset 1; CHRAC14: Chromatin Accessibility Complex 14; DNA-PKcs: DNA-dependent protein kinase catalytic subunit; HAT1: Histone AcetylTransferase 1; IR: Ionizing Radiation; MEF: Mouse Embryonic Fibroblasts; PARP: Poly(ADP-Ribose) Polymerase; UBC13: Ubiquitin-conjugating protein 13; XPC: Xeroderma Pigmentosum, complementation group C; XRCC4 : X-ray cross-complementing group 4.

Core histones	Dynamics at damaged sites	Regulatory factors	Impact on the DNA damage response	References
H2A/H2B (outer core histones)				
H2A-H2B	Loss of H2A-H2B density around DSBs	Nucleolin chaperone	Nucleolin promotes XRCC4 recruitment to DSBs	[19,20]
	Loss of H2A density at UVC damage sites	DDB2, ATP, PARP	DDB2, ATP and PARP promote UVC damage recognition by XPC	[22]
	Enhanced turnover at sites of UVC irradiation	FACT chaperone (SPT16 subunit)	FACT promotes transcription restart after UVC damage	[27]
	De novo incorporation of H2A at UVC damaged sites	FACT chaperone?	?	[27]
H2A.X	Phosphorylated at S139 in the vicinity of DNA damage	ATM, ATR, DNA-PKcs kinases	Docking site for the recruitment of DNA repair and checkpoint proteins	[55]; reviewed in [6]
	Nucleosomal dissociation increased upon H2A.X S139 phosphorylation	FACT chaperone TIP60 acetyltransferase & p400 remodeler (*Drosophila*)	FACT promotes DSB repair by HR	[25,26,56]
	Increased mobility in damaged chromatin (sites of UVA laser micro-irradiation)	TIP60 acetyltransferase & UBC13 ubiquitin-conjugating enzyme	TIP60 promotes RAD51 recruitment to DSBs	[23,57]
	Increased extractability from bleomycin-damaged chromatin	TIP60 acetyltransferase & p400 remodeler	p400 promotes ubiquitin-dependent DSB signaling and DSB repair by HR	[17,21]
H2A.Z	Accumulation at DSBs at late time points after damage (restricted to silent chromatin?)	p400 remodeler	Role in DSB repair by HR and NHEJ by controlling resection? (conflicting results)	[28,29]
	H2A.Z.2 (not H2A.Z.1) shows increased mobility at sites of UVA laser micro-irradiation	?	H2A.Z.2 promotes DSB repair by HR & survival to IR? (conflicting results)	[24,29]
macroH2A	mH2A1.1 macrodomain is recruited to sites of UVA laser micro-irradiation through PAR binding	PARP1 & APLF chaperone	Local chromatin compaction?	[32,33]
	mH2A1.1 associates with PARylated chromatin at DSBs (not incorporated into nucleosomes)	PARP1	Promotes 53BP1 accumulation, restrains NHEJ?	[30]
	mH2A1.2 accumulates at DSBs after transient depletion	ATM	Promotes chromatin compaction, BRCA1 recruitment and HR	[31]

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Core histones	Dynamics at damaged sites	Regulatory factors	Impact on the DNA damage response	References
H2A.Bbd	Accumulates at UVA laser-induced repair foci upon ectopic expression in MEFs	?	?	[34]
H3/H4 (inner core histones)				
H3-H4	Loss of H3-H4 density around DSBs (not in G1)	p400 remodeler, ASF1 chaperone	p400 promotes RAD51 recruitment and DSB repair by HR	[20,21]
	Loss of H4 density at UVC damage sites	DDB2, ATP, PARP	DDB2, ATP and PARP promote UVC damage recognition by XPC	[22]
	No enhanced turnover at sites of UVC irradiation			[27]
H3.1	*De novo* incorporation at UVC damage sites and at sites of UVA laser damage	CAF-1 chaperone	Coupled to repair synthesis but not required for UVC damage signaling and repair	[39]
H3.2	?	CAF-1 chaperone	?	[40]
H3.3	Accumulation at DSBs	HIRA chaperone & HAT1 (H4 acetyltransferase)	HAT1 facilitates RAD51 recruitment and DSB repair by HR	[35]35]
	De novo incorporation at UVC damage sites	HIRA chaperone	HIRA promotes transcription restart after UVC damage H3.3 promotes replication fork progression after UVC damage (*Chicken cells*)	[42] [44]
CENPA	Accumulation at DSBs? (conflicting results)			[36,37]
	Mistargeted to DSBs in the absence of CHRAC14 (*Drosophila*)	CHRAC14 (remodeling complex subunit)	Ectopic kinetochore formation & genome instability	[38]
	Not incorporated *de novo* at UVC damage sites			[42]

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