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Mutat Res. Author manuscript; available in PMC 2020 April 01.

Published in final edited form as:
Mutat Res. 2019 ; 780: 55–60. doi:10.1016/j.mrrev.2017.11.002.

Histone Variants in Environmental-stress-induced DNA Damage Repair

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Abstract

Environmental stress such as genotoxic agents can cause DNA damage either indirectly through the generation of reactive oxygen species or directly by interactions with the DNA molecule. Damage to the genetic material may cause mutations and ultimately cancer. Genotoxic mutation can be prevented either by apoptosis or DNA repair. In response to DNA damage, cells have evolved DNA damage responses (DDR) to detect, signal, and repair DNA lesions. Epigenetic mechanisms play critically important roles in DDR, which requires changes in chromatin structure and dynamics to modulate DNA accessibility. Incorporation of histone variants into chromatin is considered as an epigenetic mechanism. Canonical histones can be replaced with variant histones that change chromatin structure, stability, and dynamics. Recent studies have demonstrated involvement of nearly all histone variants in environmental-stress-induced DNA damage repair through various mechanisms, including affecting nucleosome dynamics, carrying variant-specific modification, promoting transcriptional competence or silencing, mediating rearrangement of chromosomes, attracting specific repair proteins, among others. In this review, we will focus on the role of histone variants in DNA damage repair after exposure to environmental genotoxic agents. Understanding the mechanisms regulating environmental exposure-induced epigenetic changes, including replacement of canonical histones with histone variants, will promote the development of strategies to prevent or reverse these changes.

Keywords

Histone variant; DNA repair; Environmental exposure; Chromatin; Epigenetic change

Introduction

Epigenetics is the study of mitotically and/or meiotically heritable changes in gene expression that are not due to the alterations in the DNA sequence [1]. Epigenetic mechanisms include DNA methylation, post translational histone modifications, non-coding

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RNA expression, and incorporation of variant histones [2, 3].Epigenetic changes are critical for almost all DNA-templated processes such as transcription, DNA repair, replication and recombination [4]. Epigenetic changes can be induced by environmental factors at different times in life and are potentially reversible. Exposure-induced epigenetic alterations may play a direct or indirect role in disease occurrence and/or progression [5, 6]. For example, exposures to genotoxic agents can cause DNA damage either indirectly through the generations of reactive oxygen species (ROS) or directly by interactions with the DNA molecule [3, 7], which could cause disease through inducing mutation that leads to gain of function or loss of function of key genes associated with the disease. Recent studies have shown that epigenetic changes may contribute to environmental diseases through their roles in repair processes of DNA damage induced by environmental stress.

In this review, we will focus on the roles of histone variants in DNA damage repair after exposure to environmental genotoxic agents. Histones are small, basic, and highly conserved proteins that serve as structural scaffolds for DNA packaging. The nucleosome core particle is the first level of compaction, which consists of 147 base pairs of DNA wrapped around a histone octamer composed of two H2A–H2B dimers and a H3–H4 tetramer [8]. The linker histone H1 binds to the nucleosome core particle to form the chromatosome that are organized into a higher-order chromatin structure. Canonical histones in a nucleosome can be replaced with histone variants. Histone variants are different from canonical histones not only by their amino acid sequences, but also by the way they are deposited into chromatin. While canonical histones are assembled in a replication-coupled manner, variant histones are incorporated into chromatin in a replication-independent way. The replacement of their canonical counterparts with histone variants leads to changes in nucleosomes properties, i.e., structure, stability, dynamics, and ultimately DNA accessibility [9]. DNA accessibility in regions of DNA damage is a key factor for efficient DNA repair. In fact, numerous studies have implicated possible roles of histone variants in DNA damage repair. Among these studies, the roles of H3 variants in environmental exposure-induced chromatin dynamics and DNA damage responses are most well studied. Thus, in this review, we will mainly focus on the histone H3 family. The various histones and their variants are discussed below in numerical order.

1. Histone H1 Family

Until now, about 126 different members of the histone H1 family have been found in diverse species, which vary from 194 to 346 amino acids in their length (http://www.actrec.gov.in/histome/). In humans, histone H1 has eleven variants, coded by a single gene that exhibits either replication-dependent or replication-independent expression. The distribution of these eleven histone genes is highly conserved between the human, mouse and rat genomes. Three of the H1 variants are testis-specific (e.g. HIST1H1T, H1FNT, and H1LS1), one of them is oocyte-specific (H1oo), and the others are somatic variants [10]. HIST1H1T is expressed in spermatocytes [11], and both H1FNT and H1LS1 are expressed in spermatids [12, 13]. Linker histone H1 is involved in chromatin compaction and plays a role in the formation of higher-order chromatin structure and gene regulation [14, 15].

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Among mutations in H1 variants in chicken cells, only H1.R mutants have increased sensitivity to the DNA damage agent methyl methanesulfonate (MMS) [16]. H1.R mutants exhibit reduced gene targeting, impaired sister chromatid exchange and an accumulation of ionizing radiation-induced chromosomal aberrations at the G2 phase, indicating H1.R plays a role in Rad54-mediated homologous recombination (HR) pathway [16]. However, the precise role of histone H1 variants in DNA repair in other species is still far from clear and is the least well studied. Studying the genomic distribution of H1 variants is also challenging due to the lack of H1 variant-specific antibodies [10].

2. Histone H2A Family

Histone H2A proteins are composed of ~130 amino acid residues. The H2A family is one of the most sequence-divergent families, including macroH2A, H2A.X, H2A.Z and H2A-Bbd. At least 265 different members of histone H2A have been discovered in various species (http://www.actrec.gov.in/histome/). In humans, nineteen variants of histone H2A encoded by 16 genes have been reported. Sequence diversity comes mainly from divergent C-terminal tails, but to date the biological relevance of this diversity remains unclear [17]. The H2A C-terminus is located at the DNA entry/exit site, making variations at this domain a powerful tool for differentiating nucleosomes by changing their stability and dynamics, binding to DNA and /or other interacting factors [18]. Canonical H2A proteins can differ in many more positions, especially in the C-terminal six amino acids [19]. However, no functional specialization of these canonical H2A isoforms has been demonstrated.

2.1 The Role of H2A.X at Double-Strand DNA Breaks—Variant H2A.X is most similar in sequence to the canonical H2A but has a divergent C-terminal tail [20]. Unlike canonical genes, the mRNA of H2A.X has either a polyA tail or the stem-loop structure in its 3’ end, suggesting that it undergoes both replication-dependent and independent transcription [21]. H2A.X can be ubiquitinated, acetylated or phosphorylated. In response to DNA double-strand breaks (DSBs), H2A.X in the vicinity of the DNA break is rapidly phosphorylated at serine 139, helping to recruit the DNA damage response proteins [22, 23]. Acetylation and ubiquitination of H2A.X also function in this process with acetylation at lysine 5 as a prerequisite for ubiquitination and subsequent release of H2A.X from the DNA damage sites [23].

When DSBs are detected, 53BP1 is rapidly recruited to the chromatin around the DSBs sites. This is regulated by a cascade signaling pathway, which is initiated by the ATM-mediated phosphorylation of H2AX (γH2A.X), followed by the accumulation of mediator of DNA damage checkpoint protein 1 (MDC1) and activation of RNF8-RNF168-dependent chromatin ubiquitylation at the DSBs sites [24]. The Mre11-Rad50-Nbs1 (MRN) complex binds to ends of the DSB and recruits auto-phosphorylated ATM monomers at the damaged chromatin sites to generate γH2A.X through ATM-dependent phosphorylation at Ser139 of H2A.X [25]. γH2A.X is then recognized by MDC1; phosphorylation of MDC1 leads to activation of a positive feedback loop by recruiting more MRN complexes and activated ATM around the damaged chromatin and the ATM phosphorylating proximal H2A.X. By these events, γH2A.X complexes can extend megabase pair distances from sites of DSBs on both sides of a break. Phosphorylated MDC1 recruits an RNF8-UBC13 complex to regulate

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ubiquitylation of H2A and H2A.X. Recent studies have demonstrated that RNF168 binds to ubiquitylated histones and facilitates the formation of polyubiquitilated histones, which further promotes recruitment of the BRCA1 complex and 53BP1 to DNA damage sites, leading to DSB repair and checkpoint arrest.

2.2 The Role of H2A.Z at Double-Strand DNA Breaks—Histone H2A.Z is highly conserved and is essential for development in higher eukaryotes [26]. Barski *et al.* have shown that H2A.Z localizes mainly in gene promoter regions, and in mammals it localizes to transcription start sites correlating with gene activation, heterochromatic silencing, and transcriptional memory [27]. Acetylation of H2A.Z has been shown to be related to its role in gene activation.

H2A.Z has been found to be enriched at sites of DNA DSBs [28], but this enrichment could be detectable only at late time points after damage and in poorly transcribed chromatin regions, which originally display low H2A.Z content [28, 29]. The accumulation of H2A.Z at DSBs sites occurs by exchanging p400 motor ATPase into chromatin. p400 is a component of the Tip60 (Tat-interacting protein of 60kDa) chromatin-remodeling complex. Tip60 complex acetylates H2A.Z and H4 to create a more open chromatin structure. H2A.Z exchange is important for ubiquitylation of the chromatin through RNF8 (RING finger protein 8, acts as an ubiquitin ligase (E3) in the ubiquitination of certain nuclear proteins), and also for recruiting downstream components of both NHEJ and HR repair pathways, such as 53BP1 and RIF1 [28, 30].

2.3 The Role of macroH2A at Double-Strand DNA Breaks—The histone H2A variant macroH2A is characterized by a large 'macro domain' at the C-terminal [31]. MacroH2A is generally considered as transcriptionally repressive because of its association with condensed chromatin, such as the inactive X chromosome [32, 33]. There are two paralogous genes encoding macroH2A1 and macroH2A2, and macroH2A1 has two splicing variants, macroH2A1.1 and macroH2A1.2 [34].

One of the early events in DSBs repair is the activation of Poly (ADP-ribose) polymerase 1 (PARP1) binding to the DNA DSB ends. PARP1 is an enzyme, that adds ADP-ribose moieties (ADPR) from NAD^+ to form PAR [35]. The accumulation of macroH2A1.1 on damaged chromatin contributes to DSB repair by HR and local chromatin compaction [36, 37]. In particular, the macrodomain-containing form of macroH2A—macroH2A1.1 but not macroH2A1.2 and macroH2A2—associates with damaged chromatin in a PAR-dependent manner [37, 38]. Unlike other variants behaving as a *bona fide* histone protein, macroH2A1.1 acts as a chromatin-associated factor. Moreover, macroH2A1 can accumulate at DSBs sites after being transiently depleted from damaged chromatin [36].

2.4 The Role of H2A.Bbd in DNA Damage Response—Histone H2A.Bdb (Barr body deficient) was first identified about one decade ago [39]. H2A.Bbd is encoded by a polyadenylated mRNA. On the protein level, H2A.Bbd lacks the C-terminal tail and part of the docking domain. H2A.Bbd is not present in all tissues, but it is strongly expressed in testis and brain [40].

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H2A.Bbd has been found to be enriched at sites of UVA laser damage repair [41]. In mouse embryonic fibroblasts, GFP-tagged H2A.Bbd, which wraps less DNA than canonical H2A, was transiently localized to sites of DNA synthesis during S-phase and during DNA repair [41]. However, the general functional relevance to cells of this ectopic expression is uncertain, because it needs the ectopic expression of H2A.Bbd in mouse embryonic fibroblasts, which is normally expressed only in testis and brain cells [36].

3. Histone H2B Family

The histone H2B family contains 214 different members described from diverse species (http://www.actrec.gov.in/histome/). Histone H2B forms a dimer with histone H2A in nucleosome cores. Histone H2B has 17 isoforms encoded by 25 genes in humans, the majority of which are assembled in cluster 1 [19]. Compared with other core histones, there are not many posttranslational modifications (PTMs) identified to date among the amino acid resides of histone H2B [42]. Some studies have shown that H2B ubiquitination can contribute to DSB damage responses in mammals [43]. After IR exposure, RNF20, which can ubiquitinate H2B at K119, formed nuclear foci that accumulated at the DSB sites [44].

4. Histone H3 Family

Histone H3 consists of ~136 amino acids. The histone H3 family contains 216 different members from various species (http://www.actrec.gov.in/histome/). In humans, 20 genes encode 8 variants of histone H3, most of which are located on chromosome 6 [19]. Histone H3 is the most extensively post-translationally modified among the five histones. Three main variants of H3 are surprisingly similar in sequence: H3.2 only differs from H3.1 in Cysteine 96 to Serine 96, and H3.3 differs from H3.1 by only 5 residues [20]. However, these variants have great differences in their expression, localization in chromatin and modification state. The canonical variants (H3.1 and H3.2) are only expressed during S phase, while H3.3 is expressed in a replication-independent manner [45]. H3.3 is usually localized to active promoters and gene bodies, regulatory regions, and pericentric and telomere regions. H3.3 is enriched for histone modifications that are associated with gene activation. In contrast, H3.1 and H3.2 do not show specific regions of localization in the genome [46, 47]. Different histone chaperones recognize and assemble H3.1 and H3.3 into nucleosomes in a replication-dependent and independent manner, respectively [48].

4.1 UV Radiation and Histone H3 Variants—UV radiation exposure through sunlight and artificial sources is a primary risk factor for the development of melanoma. Chronic exposure of the skin of mice to UVB radiation or of human keratinocytes in culture to UVA radiation induces changes in chromatin and DNA methylation at specific gene promoters [49, 50]. Exposure of skin to UV radiation induces oxidative stress, inflammation, and DNA damage in the form of DNA photoproducts such as cyclobutane pyrimidine dimers [51].

The role of histone H3 variants in DNA damage responses has been investigated mainly in human cells exposed to ultraviolet (UVC) irradiation or laser micro-irradiation, which results in nucleotide excision repair [52]. The first evidence for *de novo* histone incorporation at DNA damage sites was found for H3.1. With the development of the SNAP-tag technology, tracking newly synthesized histones *in vivo* was instrumental for visualizing

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the *de novo* deposition of more histone variants at UV sites [53, 54]. A number of studies have demonstrated that the deposition of newly synthesized H3.1 in UVC damaged chromatin is promoted by histone chaperone Chromatin Assembly Factor 1 (CAF-1), which recruits both the H3.1 and H3.2 coupled to late repair steps [52, 55]. In contrast, after UVC irradiation, newly synthesized H3.3 variants deposited by the histone chaperone HIRA (histone regulator A) to sites of UVC irradiation upon detection of damage prior to repair that primes damaged chromatin for later reactivation of transcription [56, 57]. Beyond restoring nucleosome structure, newly synthesized histone deposition at DNA damage sites also has critical functional consequences. Although neither H3.1 nor H3.3 deposition seems to affect UVC damage repair in human cells [52, 56], H3.3 plays a critical role in replication fork progression after DNA damage in chicken cells [58]. Moreover, histone chaperone HIRA specific for H3.3 deposition is required for transcription recovery upon repair completion in human cells [56, 59].

4.2 Arsenic Exposure and Histone H3 Variants—Chromatin structure and dynamics regulates DNA accessibility and DNA repair process. Environmental toxins may modulate chromatin organization in regions of DNA damage and repair by interfering with deposition of histone variants. Arsenic is a well-established human carcinogen. Even today, hundreds of millions of people are exposed to dangerous levels of naturally occurring arsenic in drinking water throughout the world [60]. While the ROS produced by arsenic exposure are considered as a key factors in arsenic carcinogenicity [61], it has been demonstrated that arsenic can alter histone modifications and DNA methylation at gene promoters, leading to abnormal gene expression [62–64].

The histone H3 genes can be classified into three distinct groups. One group contains replication-dependent genes encoding the canonical histones, whose expression is largely limited to the S phase of the cell cycle (e.g., H3.1). Another group contains replication-independent genes encoding replacement histones that are expressed throughout the cell cycle (H3.3). A third group of H3 genes encodes tissue-specific isotopes (H3t genes)[65]. Canonical histone H3 mRNAs are unique–they do not have poly(A) tail in their 3' ends, but instead possess a stem-loop structure. Stem-loop binding protein (SLBP) binds to this stem-loop structure and regulates histone pre-mRNA processing. We found that arsenic exposure induces polyadenylation of the canonical histone H3.1 mRNA, which was accompanied by a depletion of SLBP mRNA and protein [57]. In addition, the expression of other genes that are known to play a role in canonical histone mRNA processing (i.e. LSM10, CPSF2, CPSF3, etc.) was not altered by arsenic [66], suggesting that depletion of SLBP is likely the main reason for arsenic-induced polyadenylation of H3.1 mRNA. We further demonstrated that the observed increase in canonical histone gene expression was at least in part due to the aberrant polyadenylation of canonical histone mRNAs in a number of human cell lines, including epithelial lung cells (BEAS2B and A549), lymphoma B cell line (BL41), as well as in As-transformed clones (BEAS2B) that no longer had any arsenic exposure [66]. Interestingly, polyadenylation of canonical histone H3.1 mRNA stabilized the transcripts, which in turn greatly increased the level of H3.1 in the M cell cycle phase [67]. In normal condition, only H3.3 should exists during M phase. The significant increase of H3.1 in M phase following arsenic exposure might compete with H3.3 for incorporation into the

chromatin that could change the chromatin structure and dynamics (Fig. 1). This is currently under investigation.

4.3 The Role of CENP-A in DNA Repair—CENP-A is the centromere-specific histone H3 variant. Vertebrate cenH3 (CENP-A) has been shown to be recruited transiently to some DNA damage sites, such as DSBs [68]. Expression of GFP-tagged CENP-A resulted in a rapid localization of CENP-A to sites of the DSBs in human and mouse cells, while in a study using SNAP-tag technology, new CENP-A was not observed at DNA damage sites [56]. In another study, endogenous CENP-A was not detected at laser damage sites, whereas GFP-CENP-A was only weakly recruited in a limited number of cells [69]. Perpelescu M. *et al.* also failed to detect CENP-A by immunofluorescence at IR damage sites, although an interaction between CENP-A and ATM, which is dependent on IR and remodeling and spacing factor 1 (RSF1), could be detected after crosslinking. RSF1 has an IR-dependent association with ATM, which is required for DSBs repair [69, 70]. RSF1 also affects the establishment of CENP-A at centromeres [71] and its interaction with CENP-A is independent of IR [70], suggesting that some CENP-A deposition might be depend on other histone chaperones such as HJURP (Holliday junction recognition protein). HJURP is a CENP-A chaperone originally reported to be involved in DSBs repair through interaction with the MRN complex [72].

5. Histone H4 Family

Histone H4 contains only 103 amino acids and constitutes a heterodimer (H3–H4) or heterotetramer $(H3–H4)_2$ with histone H3. The histone H4 family has 116 members discovered in a variety of organisms. Surprisingly, in humans the histone H4 protein is encoded by 14 distinct H4 genes, and most of them are clustered on chromosome 6 [19]. Interestingly, no H4 variants have been found in higher eukaryotes [73]. Yet, histone H4 may have impacts on DNA repair process by changing the dynamics of other histone variants.

The acetylation of lysines 5 and 12 on histone H4 plays an important role in chromatin assembly regulation [74]. H4K5&K12ac, a diacetylation catalyzed by histone acetyltransferase 1 (HAT1), is detectable on newly synthesized histone H4 from yeast to humans as an early modification occurring on H3–H4 [74–78]. The H4K5&K12 double mutants are imported into the nucleus less efficiently than wild-type histones [75, 79]. Moreover, HAT1 and H4K5&K12 regulate the association of H3–H4 with the histone translocator protein importin 4 and the histone chaperone ASF1, indicating that H4K5&K12 might regulate chromatin assembly pathways by regulating H3–H4 nuclear import and assembly [75, 78–80]. We have demonstrated that the potential carcinogen acrolein, which is abundant in cigarette smoke and cooking fumes, reacts with lysines 5 and 12 on cytosolic histone H4 *in vitro* and in cells, preventing these sites from being physiologically acetylated by histone acetyltransferases including HAT1 [71, 72]. Reduction of H4K5&12ac and/or other histone modifications following acrolein exposure disrupted the association of H3–H4 with importin 4 as well as Asf1, leading to inhibition of histone nuclear import and assembly into chromatin [81, 82]. To examine if this could be a common characteristic of other type of aldehydes, we further investigated how established carcinogen formaldehyde, a simplest aldehyde, regulates histone modifications and chromatin assembly. We found that

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formaldehyde exposure is also able to reduce the level of cytosolic H4K5&12ac add the global level of nucleosomal histone H4 as compared with the untreated controls, a suggestive of inhibition of chromatin assembly [83]. The outcome of defective chromatin assembly is the lack of histone supplies. Since histone variant H3.3 localizes primarily to active regions of the genome with high rates of histone turnover, the impact of lack of histone supplies should be greatest in these H3.3 regions. In addition, while the assembly of canonical H3.1 and H3.2 is replication-coupled, the assembly of H3.3 is not dependent on DNA replication. Therefore, we made use of chromatin immunoprecipitation assays (CHIP) to test the level of H3.3 at several genomic loci, since the assembly of H3.3 should be affected first by lack of histone supplies. Indeed, ChIP results showed that incorporation of histone variant H3.3 was decreased following formaldehyde exposure in the majority of sites we tested [83]. As mentioned above, H3.3 seems to be important for DNA repair process. Thus, it is possible that environmental toxins such as aldehydes may affect DNA repair processed by perturbing chromatin (e.g., H3.3) dynamics, at least in part through changing the modification status of histone H4 (Fig. 1).

Concluding remarks and future directions

The revolutionary developments of new molecular chromatin analysis technologies have allowed us to make high-resolution genomic maps of histone variants and modified nucleosomes. These maps have disclosed where, and to what extent, different histone variants are enriched on DNA damage sites. Nearly all histone variants seem to be involved in environmental-stress-induced DNA damage repair through various mechanisms. Further work still needs to be carried out to reveal detailed mechanisms by which environmental exposures induce changes in histone variant deposition and dynamics. Understanding these mechanisms will promote the development of new biomarkers for identifying environmental exposure, and will perhaps also contribute to mitigated damage via enhanced DNA repair, in order to protect the human health.

Acknowledgments

Funding

This work was supported by the National Institutes of Health [1R01ES026138-01 to C.J.]; NIEHS Center of Excellence Pilot Project Program and Career Development [5P30ES000260 to C.J.].

We thank Cathy Klein for critical review.

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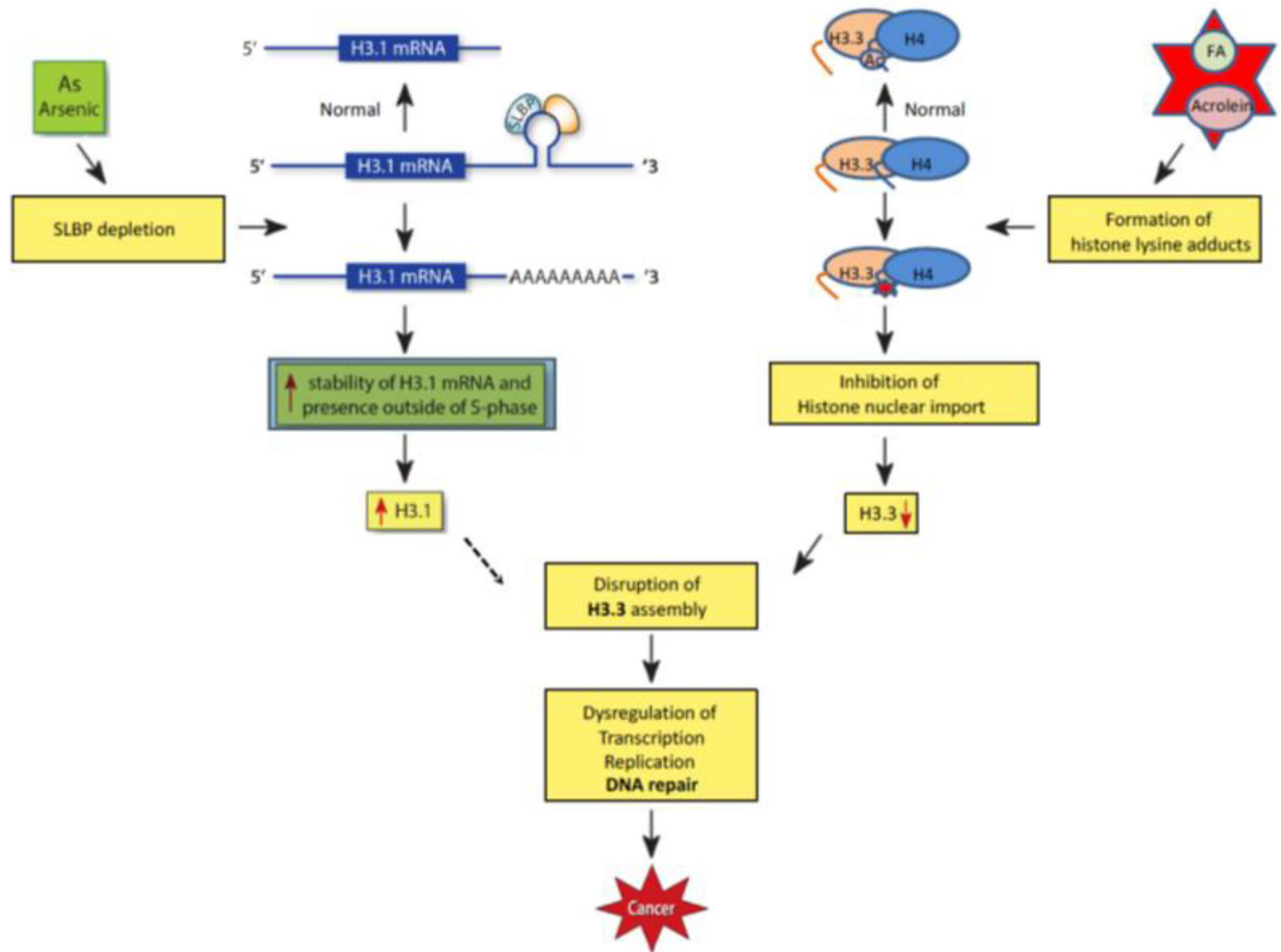

Figure 1. Disruption of chromatin structure by environmental exposures

In normal condition, the stem-loop binding protein (SLBP) binds to the stem-loop structure on 3’ end of canonical histone H3.1 mRNA, generating the histone mRNA without poly(A) tail by cleaving downstream of the stem-loop. SLBP is depleted following arsenic exposure. The loss of SLBP results in binding of less SLBP to the stem-loop structure, adding a poly(A) tail via a downstream poly(A) signal sequence. The polyadenylation increases stability of H3.1 mRNA and subsequently H3.1 protein levels outside of S-phase, which may interfere with assembly of histone variant H3.3. On the other hand, aldehyde chemicals such as acrolein and formaldehyde (FA) form adducts with lysine residues on newly synthesized histones, including H3.3 and H4, inhibiting their acetylation and subsequently compromising histone nuclear import and assembly into chromatin. Defective chromatin assembly due to H3.3 reduction may dysregulate gene expression, DNA replication and repair thereby facilitating carcinogenesis.