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Histone Variants: The Unsung Guardians of the Genome

Ernest O. N. Phillips[1], **Akash Gunjan**[1,*]

[1]Department of Biomedical Sciences, College of Medicine, Florida State University, 1115 West Call Street, Tallahassee, FL 32306-4300, USA

Abstract

Histones H2A, H2B, H3, H4 and H1 are highly conserved, positively charged proteins which form a disc-shaped protein core around which genomic DNA is wrapped to form a nucleosome. Immediately following DNA synthesis, replication-dependent canonical histones help package the DNA into nucleosomes to form compact chromatin fibers that can fit within the confines of the cell nucleus. Histone variants, which vary from the canonical histones in their primary amino acid sequence and expression patterns, replace their canonical counterparts throughout the cell cycle in important biological processes such as transcription, replication, DNA repair and heterochromatin formation. DNA damage is a continual threat to genomic stability and cell survival. Unrepaired DNA lesions are either lethal or can promote mutations if the damaged cells escape programmed cell death due to apoptosis. In order to repair DNA damage, cells use multiple DNA repair pathways, all of which require the recruitment of a multiple DNA damage signaling and repair factors. In order for these repair factors to be recruited efficiently and function properly at sites of DNA damage, the local chromatin environment surrounding the DNA lesion is often altered. Cells are able to regulate chromatin structure in the vicinity of DNA lesions through the addition of posttranslational modifications on histones and DNA, as well as through histone variant incorporation or removal. Recruitment or removal of histone variants at sites of DNA damage can alter the local chromatin structure by destabilizing it and making it more accessible to repair factors. Alternatively, some histone variants and their modifications may also provide specific binding sites for the recruitment of various DNA repair factors, thereby influencing repair pathway choice or repair efficiency, or both. This review seeks to provide an overview of our current understanding of the roles played by histone variants in DNA repair, especially in mammalian cells.

Keywords

DNA repair; DNA damage; genome stability; histone variant; chromatin; cancer

INTRODUCTION

Cells experience an estimated one hundred thousand DNA lesions per cell per day [1]. Such damage can result from the exposure to various external chemical, physical and biological agents, as well as due to by-products of normal internal cellular metabolism [2]. Left

[*]**Corresponding Author:** akash.gunjan@med.fsu.edu.

unresolved, these DNA lesions are detrimental to cell survival, as even a single unrepaired DNA double strand break (DSB) could result in cell death [3,4], or in mutations that could potentially drive genomic instability, which in turn is known to contribute strongly to cancer formation [5]. It is therefore crucial that cells have both highly efficient and effective methods to repair the DNA damage they incur daily.

The cell accomplishes efficient DNA repair through the use of multiple repair pathways which require the recruitment of a plethora of DNA repair factors to the lesion. The choice of the DNA repair pathway is determined based on the nature and location of the DNA damage, which directs the recruitment of specific DNA repair factors. Defects in a single DNA base pair (bp), such as a chemical alteration of the base via addition of a bulky alkyl group is repaired through the Base Excision Repair (BER) pathway; while the presence of a mismatched nucleotide is resolved by the Mismatch Repair (MMR) pathway (Figure 1) [6,7]. More extensive or complex damage, such as the formation of pyrimidine-pyrimidine dimers or intra-strand crosslinks, is repaired through the Nucleotide Excision Repair (NER) pathway (Figure 1) [8]. Additionally, Single-Strand Breaks (SSB) in DNA are repaired by the Single-Strand Break Repair (SSBR) pathway, while DSBs are repaired either by the Homologous Recombination (HR) or Nonhomologous End Joining (NHEJ) pathways (Figure 2). The HR pathway involves the copying of the missing DNA sequence in the vicinity of the DSB from the sister chromatid as an accurate method of DNA repair, while the NHEJ pathway uses the simple re-ligation of the two broken DNA ends to repair the damage, irrespective of whether any sequence information was altered or lost at the site of the break [9,10]. Throughout these DNA repair pathways, multiple chromatin components are removed and (re)deposited at the sites of the damage to both alter the chromosome architecture, as well as provide potential binding sites for the recruitment of DNA repair factors [2,11].

Histones are small positively charged proteins that help package the negatively charged DNA inside the nuclei of cells to form compact nucleoprotein filaments called chromatin in all eukaryotes. During DNA synthesis in S-phase, 147 base pairs of DNA wrap around an octameric structure known as the nucleosome core particle which is composed of 2 copies of each of the canonical core histone proteins H2A, H2B, H3 and H4 [12,13]. In most eukaryotes, a single linker histone or histone H1 molecule binds asymmetrically near the entry/exit site of the DNA around the octamer to complete the nucleosome [14,15]. The nucleosome forms the fundamental building blocks of chromatin and is repeated to package all the genomic DNA, thereby contributing to the first level of DNA compaction. Histone variants differ from their canonical counterparts in their primary amino acid sequence (Figure 3), and often in their timing/patterns of expression as well. Multiple histone variants have been shown to replace their canonical counterparts under specific circumstances and at certain genomic locations. Often, just a few amino acid alterations in their sequence allow for at least some of the variants to function in new ways that are distinct from their canonical counterparts. These histone variants play a role in various processes involving the DNA, such as replication, transcription, chromatin protection, chromatin compaction and DNA repair. Not surprisingly, histone mutations aberrant expression of histones have been increasingly linked to modulating carcinogenesis [16], leading to them being referred to as oncohistones [17]. Although in recent years a significant amount of research has been

focused on the role that histone variants play in DNA repair, our knowledge of the specific functions of individual histone variants are still evolving and is far from being complete [18]. The aim of this review is to provide a broad overview of our current state of knowledge on the role of histone variants in DNA repair, especially in mammalian cells, with particular focus on resolving some of the controversies regarding the reported roles of specific histone variants in DNA repair.

HISTONE H1 FAMILY

Unlike the four core histones, members of the H1 family are not incorporated inside the core of the nucleosome, but rather sit asymmetrically on the outside of the nucleosome core particle [19–21]. Also known as the linker histone, H1 functions to asymmetrically protect the free linker DNA (~20bp) at either the entrance or the exit site of the DNA in the nucleosome. H1 is essential for the maintenance of proper chromatin structure [22], especially during higher order chromatin folding [23], and has been shown to play important roles in transcriptional regulation [24–26].

In comparison to other histone families, members of the H1 histone family are the most internally dissimilar and are consist of 11 members in mammals. The greatest variations in amino acid sequences are found in the C- and N-termini of these proteins, while most of the similarities occur within their central globular domains (Figure 3A) [27–29]. There are seven somatic H1 histones, including five (H1.1 through H1.5) that are replication-dependent and are upregulated during during DNA replication, plus the replacement variant H1.0 that accumulates in non-dividing cells and the ubiquituously expressed H1.10 [30]. Additionally, there are tissue specific variants comprising of the three testis specific H1.6, H1.7 and H1.9 variants, while H1.8 is an oocyte specific variant. Although significant progress over the past two and a half decades has shown H1 variant specific effects on gene expression [31,32], much of the research on the role of H1 in other chromatin activities such as DNA repair has been performed without distinguishing the specific variants involved in the process being studied [27]. Furthermore, compared to the core histones, currently relatively little is known about the specific physiological functions that H1 variants play in DNA repair, particularly in mammals [33]. Below, we discuss the H1 variants that have been implicated in aspects of DNA repair and/or cancer.

Somatic H1 Variants

H1.0—H1.0 behaves as a replacement variant as it accumulates in non-dividing and terminally differentiated cells [34]. It has been previously shown to be enriched within repetitive DNA elements in the nucleoli where it serves to stabilize these regions and may help prevent unregulated DNA synthesis [35,36]. H1.0 has also been found to be downregulated in various cancers [36,37] indicating a potential role as a tumor suppressor, though this needs to be investigated further. Given the known connections between tumorigenesis and DNA repair defects [5], it is possible that H1.0 may influence DNA repair, but this requires confirmation.

H1.10 (formerly known as H1.X)—H1.10 is found within euchromatic regions of the genome such as hypomethylated CpG islands and active genes, which suggests a role in

transcriptional regulation for this variant [35]. Additionally, H1.10 has been shown to be upregulated in neuroendocrine tumors [38], suggesting a potential role as an oncogene as well. Along with several other linker histones (see below), H1.10 has also been reported to be polyubiquitylated via K63 ubiquitin chains at sites of DSBs, in a RNF8 (Ring Finger Protein 8), UBC13 (Ubiquitin conjugating E2 enzyme 13), and HUWE1 (HECT, UBA and WWE Domain Containing E3 Ubiquitin Protein Ligase 1) dependent manner. This modification provides a binding site crucial for the proper recruitment of RNF168 as well as p53-Binding Protein 1 (53BP1) protein that is a major DSB repair pathway choice factor and stimulates canonical or classic-NHEJ (c-NHEJ) [39,40].

H1.1-H1.5 histones—The bulk of the studies involving histone H1 use one or more of the relatively abundant replication dependent H1 histones, H1.1 through H1.5, often without distinguishing the exact subtype involved in the biological process being studied, with a few notable exceptions [31,32]. Previous research has found that the ligation step of c-NHEJ repair pathway is inhibited *in vitro* by the presence of histone H1 [41]. This inhibition is relieved by phosphorylation of H1 by the DNA-Dependent Protein Kinase (DNA-PK), a c-NHEJ factor (Figure 2A). Although this *in vitro* study presents a very plausible scenario, it utilized a mixture of bulk purified H1 histones rather than individual variants and needs further *in vivo* studies to determine any variant specific contributions.

Initial *in vivo* studies have found that cells deficient in the expression of replication dependent H1 histones exhibit resistance to DNA damage in both yeast [42] and mammalian cells [43]. In yeast cells, canonical H1 was postulated to play an inhibitory role within the HR repair pathway [42], while in mammalian cells the canonical H1 was postulated to restrict accessibility of DNA repair factors at DNA lesions, thereby preventing unregulated DNA repair specifically in the telomeric regions [43]. More importantly, mutations in the globular domain of a number of replication dependent H1 isoforms, especially H1.4 and H1.2, have been shown to be among the top driver mutations in B-cell lymphoma development, supporting their role as tumor suppressors. These mutations alter chromatin compaction and patterns of histone posttranslational modifications (PTMs) such as an increase in the activating methylation mark H3K36me2, and/or a loss of the repressive H3K27me3 mark, which result in chromatin decompaction and the upregulation of various stem cell renewal genes [44]. Although these results suggest important roles of the canonical H1 histones in DNA repair, they too do not clearly distinguish between the contributions of different H1 isoforms. Much of the available research on histone H1 in the context of DNA repair has been performed on the more abundant isoforms H1.2 and H1.4, which are discussed individually below.

H1.2—Linker histone variant H1.2 has been uniquely shown to play multiple roles in the context of DNA repair. H1.2 and H1.1 have a fairly dynamic binding affinity to nucleosomes when compared to H1.3-H1.5 [45]. H1.2 has been implicated in gene silencing by binding to the H3K27me3 repressive posttranslational methylation marks to increase chromatin compaction [46], as well as play an important role in proper cell cycle progression [47].

The condensation of chromatin by H1.2 has been shown to inhibit HR by preventing (Ataxia-Telangiectasia Mutated) ATM activity and proper localization of MRE11-RAD50-

NBS1 (MRN), both of which are DSBR and HR factors [48]. H1.2 is believed to be displaced from DSB sites following ADP-ribosylation and subsequently degraded in a proteasome dependent manner to allow repair to continue. Furthermore, K63-linked polyubiquitin chains deposited on H1.2 through the action of the E3 ligase HUWE1 along with UBC13 and RNF8 help amplify the ubiquitylation cascade at the DSB site, while also providing a binding site for the c-NHEJ factor 53BP1 to regulate DSB repair (Figure 2A) [39,40]. In contrast to the inhibition of c-NHEJ by H1 [41], H1.2 has been shown to promote DSB repair via the alternative NHEJ (alt-NHEJ) pathway, although these results were obtained using cell extracts [49]. In addition to the reported roles of H1.2 in DNA repair, in the event of persistent unrepaired DSBs, H1.2 has been shown to be transported from the nucleus to the cytoplasm, where it stimulates the mitochondria to release cytochrome C, which in turn induces apoptosis (programed cell death) [50]. The involvement of any histone H1 chaperone in this transport (or in other DNA repair related activities of H1) is unclear, although H1 chaperones such as the proto oncoprotein SET (aka TAF1) that impact DNA damage sensitivity of mammalian cells have been reported to actively evict H1.2 in response to DNA damage [15,51].

H1.4—H1.4 has been shown to play a role in facilitating the condensation of chromatin by recruiting Heterochromatin Protein 1 (HP1) following the acetylation of its lysine 85 residue by P300/CBP-associated factor (PCAF) under normal conditions [52]. However, upon DNA damage, this lysine is rapidly deacetylated by Histone Deacetylase 1 (HDAC1), which is believed to result in the loss of HP1, leading to chromatin decondensation to allow efficient DNA repair. Since this lysine is highly conserved in all somatic H1 histones (Figure 3A), it is possible that other H1 proteins contribute to this regulation in a very similar way as well. As pointed out earlier, driver H1.4 mutations were found in 42.6% of Diffuse Large B-cell Lymphomas (DLBCL) [44] highlighting its importance in tumor suppression.

HISTONE H2A FAMILY

Histone H2A forms a dimer with H2B and, together with H3 and H4, makes up the nucleosome core particle (Figure 4). In comparison to the other core histones, H2A has the largest number of reported histone variants. Unlike other core histones that only have N-terminal tails, H2A also has a C-terminal tail which varies in length between variants and serves to regulate nucleosome formation and stability by directly binding to linker DNA. The majority of the differences found between the canonical H2A histone and its variants occurs on the C-terminus of the histone (Figure 3B) [53,54]. Additionally, fewer but structurally important differences also occur in the L1 loop between the first and second alpha helices of the histone fold domain in H2A variants (Figure 4), although how exactly these differences may be contributing to the functions of these variants in DNA repair is not fully understood [55–57]. Importantly, canonical histone H2A and several of its variants undergo many PTMs, including extensive ubiquitylation on multiple lysine residues to modulate important events in DSB repair [58]. Below, we review the known roles of H2A variants in the context of DNA repair.

H2A.X

The best studied histone variant in the context of DNA repair is H2A.X [59,60]. This variant shares a ~90% homology with the canonical H2A and only varies at a few amino acids (Figure 3B). H2A.X is estimated to make up 2-10% of all H2A in mammalian cells and is ubiquitously incorporated throughout the genome. However, if not already present, H2A.X is quickly recruited to sites of DNA damage in a Facilitates Chromatin Transcription (FACT) dependent manner [61,62]. The presence of H2A.X within the nucleosome increases the efficiency of recruitment of the DNA repair factor poly-ADP Ribose Polymerase 1 (PARP1) to sites of DNA damage [63].

In addition to the passive role of H2A.X in PARP1 recruitment during DNA repair, the H2A.X variant provides crucial PTM sites to initiate, amplify and regulate a cascade of DNA repair factor recruitment around DSB sites. Although H2A.X has many sites for potential PTMs, the most significant among these is the phosphorylation of S139 within it slightly extended C-terminal tail region, upon which it is referred to as γH2A.X (Figure 3B and Figure 4) [57]. γH2A.X is detected around DSBs immediately after their formation and can spread over a couple of megabases of chromatin [64,65]. Interestingly, recent evidence suggests that this spreading of γH2A.X from DSB sites is regulated by chromatin contacts in the context of topologically associating domains (TADs) and spreads bidirectionally within the TAD when the DSB is internal to the TAD, but asymmetrically into adjacent TADs when the DSB is located at the TAD border [66]. There are a number of kinases such as the phosphoinositide (PI) family of DNA Damage Response (DDR) kinases Ataxia Telangiectasia Mutated (ATM), ATM and Rad3-related (ATR) and DNA-PK that are responsible for this phosphorylation of H2A.X at sites of DSBs [67–69]. This modification assists both in the recruitment and retention of various DNA repair factors that not only help in the repair of the damage, but also stabilize the chromatin surrounding the break [70,71]. Specifically, γH2A.X foci formation provides a binding site for Mediator of DNA damage Checkpoint 1 protein (MDC1) [72] which then facilitates additional MRN complex recruitment [73] to prepare the DSB for repair as well as assist in the recruitment of a cascade of E3 ubiquitin ligases (RNF8, RNF168), that subsequently promote the recruitment of 53BP1 and Breast Cancer type 1 susceptibility protein (BRCA1), which are NHEJ and HR promoting factors respectively [74–77]. Almost immediately after the DSB is resolved, γH2A.X is removed either through histone exchange or through dephosphorylation [78]. Mice lacking H2A.X exhibit genomic instability and enhanced rates of cancer in the absence of p53 [79]. The importance of this H2A.X phosphorylation in the DDR can be further gauged by the fact that apart from mammals, other eukaryotic species also undergo this phosphorylation. In the budding yeast, the canonical H2A protein undergoes an analogous phosphorylation on S129 upon DNA damage and appears to perform similar functions [80]. In fruit flies, the histone variant H2Av, which appears to perform the functions of both H2A.X and H2A.Z variants (see below) in mammals, is phosphorylated on S137 upon DNA damage [81]. In contrast to the phosphorylation on S139, H2A.X can also be phosphorylated on Y142 in unstressed cells, apparently by the William-Beuren Syndrome Transcription Factor (WSTF) kinase. However, upon DNA damage, Y142 is dephosphorylated by EYA1 or EYA3 phosphatases which allows for the proper localization of DNA repair factors such as MDC1. If the phosphorylation of Y142 is not appropriately reversed upon DNA damage,

it can result in the recruitment of factors to promote apoptosis [82,83]. A vast amount of literature is available on the role of H2A.X in DNA repair and cancer prevention, which cas been covered extensively in a number of excellent reviews and papers by the Bonner, Nussenzweig and other labs and we would like to point the readers to these [59,84–89]. Here, we will focus on the roles of other histone variants that have not be reviewed recently or in detail elsewhere.

H2A.Z

Histone H2A.Z is a highly conserved H2A variant and shares a near 60% homology (Figure 3B) with its canonical counterpart [90]. In vertebrates, H2A.Z is made up of 2 major isoforms (H2A.Z.1 and H2A.Z.2), which only differ by 3 amino acids [91,92]. Compared to the canonical H2A, the H2A.Z variant has an extended acidic patch as well as alterations in the L1 loop at the dimer interface within the nucleosome core particle (Figure 4), that can significantly alter the stability of the H2A.Z containing nucleosomes and hence their properties [55,90]. H2A.Z is found in actively transcribing genes as well as within chromosome centromeres [93]. Incorporation of H2A.Z into nucleosomes may render it less stable relative to nucleosomes containing canonical H2A [94]. H2A.Z is deposited into nucleosomes by p400 or Snf2 Related CREBBP Activator Protein (SRCAP) enzyme in human cells, or its homolog Swr1 in yeast cells, while it is evicted by the INO80 chromatin remodeling complex [95–97].

In the budding yeast, H2A.Z is evicted along with other core histones from DSBs in a Ino80 dependent manner [98], and cells lacking Ino80 show enhanced incorporation of H2A.Z at DSBs which blocks them from undergoing checkpoint adaptation in the presence of a persistent DSB [97]. Furthermore, the presence of Swr1, but not H2A.Z at DSBs appeared to promote the binding of Ku proteins and repair via c-NHEJ [98]. On the other hand, the Ino80 mediated eviction of H2A.Z promotes Mre11 recruitment and end-resection, as well as checkpoint signaling, although no effect on HR mediated repair was observed. It should be noted that these studies in yeast were performed using the galactose regulated *HO* endonuclease to generate a DSB at either the native *MAT* locus or ectopic sites, followed by Chromatin Immuno-Precipitation (ChIP) to detect the presence of specific proteins at the DSBs one or more hours after the induction of DSBs, which precludes the study of H2A.Z dynamics immediately after DSB formation.

In contrast to the general agreement on the role of H2A.Z in the context of DNA repair in yeast cells, results in mammalian cells were quite contradictory initially. In human cells, H2A.Z was shown to be recruited to sites of DSBs [99]. This study showed that H2A.Z functions to assist in the recruitment of a number of DNA repair factors for the HR pathway (MRE11, BRCA1 and RAD51), as well as in the c-NHEJ pathway (KU70/80 complex) [97–99]. However, subsequent findings directly contradict these early data and showed that H2A.Z did not recruit to sites of DNA damage and depletion of H2A.Z did not cause any alterations in the efficiency HR or NHEJ pathways [100]. One possible explanation for these discrepancies is that important differences in the reagents and methodologies used by the two groups could have affected their results [99,100]. A major difference was the method used for decreasing H2A.Z levels, with the Price lab using stable transfections of small

hairpin RNA (shRNA) for H2A.Z knockdown [99], while the Canitrot lab used transient transfections of small interfering RNA (siRNA) [100]. Additionally, lasers of different wavelengths were used to induce DNA damage to observe H2A.Z recruitment, with the Price lab using 405 nm laser on cells that were pre-sensitized with Hoechst dye 33258 [99], while the Canitrot lab used a 532 nm laser to induce damage [100]. It should be noted that many such pre-sensitization drugs bind to or intercalate within DNA, thus potentially altering chromatin structure [101,102]. Although these differences may have potentially led to the different results obtained in these studies, they remained quite perplexing until it was shown more recently that H2A.Z is only temporarily needed at DSBs [103,104]. After being recruited to DSBs immediately after their formation, H2A.Z is then rapidly evicted within 10 minutes of incorporation from sites of DSBs in an Acidic Nuclear Phosphoprotein 32 Family Member E (ANP32E) dependent manner. This temporal specificity of H2A.Z was essential for proper C-terminal binding protein 1 interacting protein (CtIP) endonuclease function, as well as RAD51 localization to DSB sites for repair by the HR pathway [103–105]. Interestingly, additional research suggests that the DNA repair function of H2A.Z may be primarily due to the H2A.Z.2 isoform [105]. Hence, it is possible that some of the initial inconsistencies regarding the role of H2A.Z in DNA repair in the published data may also be the result of different isoforms being followed in the earlier studies.

So, what might be the function of the rapid deposition of H2A.Z initially at DSBs, followed by their subsequent removal a short time later? Evidence from yeast [98] and mammalian cells [99] both suggest that H2A.Z may contribute to NHEJ mediated repair and so one possibility is that this process may be facilitated by the initial deposition of H2A.Z at DSBs. Consistent with this, Swr1 mediated H2A.Z deposition has been suggested to facilitate the activity of Exonuclease 1 (Exo1) during MMR in yeast [106] and it is known that this nuclease also plays a role in end processing during DSB repair in yeast [107]. However, if NHEJ mediated repair does not fix the DSB quickly, then H2A.Z removal from the DSBs may be necessary to subsequently facilitate repair via the HR pathway. This two-step scenario would be consistent with much of the data on the role of H2A.Z in DNA repair available so far, as well as the reported sequential assembly of NHEJ factors prior to HR factors in both yeast [108] and mammalian cells [109].

In addition to its proposed role in HR repair pathways, H2A.Z has also been suggested to play a role in other DNA repair pathways. Nucleosomes with H2A.Z were shown to enhance BER activity *in vitro* in comparison to those composed of the canonical H2A [110]. Furthermore, H2A.Z incorporation has been shown to promote both MMR and NER pathways as well, although these results have only been demonstrated in yeast so far [106,111]. Overall, the information available so far suggests the possibility for H2A.Z to play roles in BER, MMR and NER pathways, in addition to its significant contributions to DSB repair.

mH2A (formerly known as macroH2A)

The histone variant mH2A shares a nearly 60% homology with the canonical H2A, but with an additional ~200 amino acid domain on the C-terminus of the protein (Figure 3B). Despite the addition of such a large domain, nucleosomes with mH2A retain the basic

nucleosome core particle structure (Figure 4), although the mH2A nucleosomes appear to be more stable with the DNA more tightly bound than those with canonical H2A [57,112,113]. mH2A is specifically enriched within the inactive X-chromosome (Barr-body) in female cells. Not only does mH2A play an essential role in the maintenance and development of heterochromatin, but it is also involved in multiple molecular processes such as transcriptional repression and DNA repair [114]. mH2A has multiple isoforms (mH2A.1.1, mH2A.1.2 and mH2A.2) (Figure 3B), which adds further complexity to its potential roles [115,116].

The enzyme PARP1 is involved in sensing DNA damage, SSBR, recruiting multiple DNA repair factors, as well as stabilizing DNA replication forks [117]. PARP1 is the main enzyme which posttranslationally attaches poly(ADP-ribose) (PAR) chains to various protein targets. The attachment of PAR chains creates a binding site for various proteins that carry a conserved globular domain known as a macrodomain to trigger a veriety of downstream cellular signaling events.

Although the mH2A.1.1 and mH2A.1.2 isoforms share a nearly 70% homology (Figure 3B) with each other, a crucial difference is the presence of a macrodomain only in mH2A.1.1 [118,119]. Not surprisingly, mH2A.1.1, rather than mH2A.1.2, has been shown to be recruited to sites of DSB repair by binding to PAR chains on PARP1 after the latter localizes to DSBs, rather than being directly recruited to DSB sites as part of nucleosomes [120,121]. Once recruited, mH2A.1.1 assists in proper Checkpoint Kinase 2 (CHEK2) activation, as well as the recruitment of various DNA repair factors such as KU70/80 and 53BP1, both of which are NHEJ factors [120].

A reduction in the expression of mH2A.1.1 has been shown to increase the endogenous levels of 8-oxo-7,8-dihydroguanine (8-oxoG), a major type of oxidative DNA damage, as well as an enhanced vulnerability to alkylation damage by methyl methane sulfonate (MMS) that is repaired by BER [122]. Moreover, research also suggests the that the mH2A containing nucleosomes enhance the activity of BER in comparison to nucleosomes containing the canonical H2A [110,120]. These data suggest that mH2A.1.1 plays a role in BER repair. Further investigation suggested that the role of mH2A.1.1 in BER is fairly upstream and is mediated through its regulation of both PARP1 activity and degradation of PAR chains[110,122], but its precise role is not fully understood.

Despite mH2A.1.2 not having a macrodomain, it still appears to play an important role in DNA repair. This isoform has been shown to be enriched within chromosomal fragile sites and telomeres that have an increased incidence of DSBs as a result of replication stress [123]. mH2A.1.2 is also actively recruited to such DSBs in a FACT dependent manner [124,125]. At these sites, mH2A.1.2 enhances BRCA1 recruitment and retention to ensure that these DSBs are repaired through the HR and not the NHEJ pathway [126]. In contrast, as pointed out above, the mH2A.1.1 isoform promotes DSB repair via NHEJ [120,125].

The mH2A.2 isoform shares a 67% homology with mH2A.1 and also has a conserved globular domain. Despite these similarities, the macrodomain of mH2A.2 is unable to bind PAR chains, limiting its interaction with PARP1 [127]. mH2A.2 has been previously shown

to play a prominent role in inhibiting somatic cell reprograming, as well as suppressing melanoma progression [128,129]. Additionally, a very recent study has shown that proper mH2A incorporation is crucial for RAD51 loading as well as regulating the balance of BRCA1 and 53BP1 binding, particularly at stalled replication forks, although this research did not distinguish between mH2A isoforms [130].

Based on the published data so far, mH2A undoubtedly plays important roles in DSB repair by both NHEJ and HR, as well as in the BER repair pathway. Due to the close connections between mH2A and PARP1, it is quite possible that mH2A isoforms may play additional roles in other DNA repair pathways, such as SSBR pathway. Further research is needed to determine the specific roles that mH2A isoforms may play within these pathways. However, it would be important to distinguish the roles of each isoform of mH2A in such studies, since they have been already shown to play significantly different roles in DNA repair pathways [120,125,126].

H2A.B (formerly known as H2A.Bbd)

H2A.B (H2A Barr-body deficient) is a rapidly evolving placental-mammal specific variant which only shares approximately 50% amino acid homology with its canonical H2A counterpart (Figure 3B). H2A.B has been found to be distributed throughout the genome, except for the inactive Barr body in human cells [131,132]. Interestingly, H2A.B containing nucleosomes only protect 118bp of DNA unlike the 147bp of DNA protected by canonical nucleosomes [132]. H2A.B incorporation has been shown to result in an open conformation of chromatin and is specifically enriched in the body of actively transcribed genes [133,134]. H2A.B is encoded by 3 genes and it was recently shown that loss of all three genes in mice results in aberrant post-meiotic male germ cell chromatin, but only very mild defects in fertility, whereas more significant effects were observed on post-implantation embryonic development in a pattern that is suggestive of H2A.B genes being strong parental-effect genes [135]. Recently, it has also been suggested that short H2A (sH2A) variants such as H2A.B may have oncogenic features and their aberrant expression may allow them to serve as oncohistones during carcinogenesis [17].

Generally, H2A.B is found to be transiently deposited at sites of DNA replication where it co-localizes with Proliferating Cell Nuclear Antigen (PCNA), a DNA synthesis factor, during early and late stages of replication [136,137]. H2A.B has also been shown to be recruited to sites of DNA damage, although this recruitment does not appear to play a direct role in any particular DNA repair pathway [136]. Instead, this study found that the exogenous expression of H2A.B enhances the sensitivity of cells to UV damage, suggesting a potential inhibitory effect of H2A.B on NER. Similarly, there is some indication that the presence of H2A.B in nucleosomes negatively affects the chromatin remodeling activity of SWI/SNF (SWItch/Sucrose Non-Fermentable) in facilitating the recruitment of various factors to properly remove 8-oxoG by the BER pathway, suggesting that H2A.B may need to be removed for efficient BER [138]. Interestingly, unlike most other histone variants, H2A.B has been shown to be able to replace its canonical counterpart without the use of a chaperone [134].

Currently, a specific role of H2A.B at sites of DNA damage remains unclear. However, based on the lack of the need of a chaperone for H2A.B and its ability to relax chromatin conformation, it is conceivable that H2A.B simply acts as a place holder for other H2A variants at DNA damage sites. Additionally, the transient incorporation of H2A.B at DNA damage sites could be enough to increase the accessibility of DNA to allow for the efficient recruitment for DNA repair factors. Although no significant defects in the repair of meiotic DSBs were observed in H2A.B knockout mice [135,139], it will be interesting to test the DNA damage sensitivity and the DDR of the H2A.B knockout mice, or somatic cells derived from them, to get a better insight into any role played by H2A.B in DNA repair.

H2A.J

H2A.J is a mammalian specific H2A variant which shares a near 94% homology to the canonical H2A and differs from it at just 5 residues [140]. Not surprisingly, due to this near identical amino acid sequence (Figure 3B), no significant structural differences were observed between nucleosome core particles containing H2A.J compared to those with canonical H2A (Figure 4) [141]. H2A.J has been shown to accumulate in senescent cells carrying DNA damage where it appears to promote the expression of inflammatory genes [141,142]. However, a specific role for H2A.J at DNA damage sites is currently not known.

HISTONE H2B

Of all the histone variants, H2B variants are the least studied, although well over a dozen H2B variant proteins have been identified and four variants (subH2B, H2B.E, H2B.W and hTSH2B) have been studied to some extent in mammalian cells [143–147]. To date, none of the H2B histone variants have been found a play a role in any of the known DNA repair pathways. However, the canonical H2B itself has been shown to serve as a major binding site for various DNA repair factors, especially after the deposition of specific PTMs. Under normal conditions the Copper Metabolism gene MURR1 Domain Containing 4 (COMMD4) protein has been shown to directly bind to unmodified H2B to protect it from unregulated PTMs, especially monoubiquitylation. However, soon after DSB occurrence, ATM phosphorylates H2BS14, stimulating the release of COMMD4 from H2B [148,149]. The removal of COMMD4 allows for the proper recruitment of RNF20-RNF40, which ubiquitylates H2BK120 within an hour of DSB formation. Furthermore, this ubiquitylated site serves as a binding site for, and promotes the recruitment of prominent HR repair factors, namely BRCA1, CtIP and NBS1 to assist in proper end resection [150,151]. Since these studies did not attempt to distinguish the H2B variants involved in these processes (which would be difficult, especially in the absence of reagents such as good H2B variant specific antibodies), it is formally possible that one or more H2B variants are involved in these processes, rather than the canonical H2B itself. Much more research is needed to understand the role of H2B variants in cell physiology and DNA repair, which is still in its infancy.

HISTONE H3 FAMILY

Histone H3 partners with H4 and is incorporated into nucleosomes immediately after DNA synthesis [152]. Histone H3 also has the largest number of known PTMs which can serve to

modulate chromatin structure and function in a variety of ways [153]. Additionally, unlike the variants in other histone families, most H3 variants are nearly identical to the canonical H3, varying at just a few residues (Figure 3C).

cenH3 (CENPA)

cenH3 is a centromeric H3 variant that localizes specifically within the centromeres of chromosomes. cenH3 serves as an epigenetic marker for centromeres and has also been found to be essential for centromeric interactions within the kinetochore protein complex [154]. cenH3 shares only a ~45% homology with the canonical H3, which is the least among H3 variants by far (Figure 3C). cenH3 nucleosome core particle structure resembles its canonical counterpart, however, the DNA on either end of the nucleosome core particle is more flexible, with only 121bp of DNA wrapped around the core structure, presumably due to its longer unstructured N-terminal tail with a short α-helix (Figure 5) [155,156].

cenH3 has been shown to reliably recruit to sites of DSBs [157]. Despite this observed recruitment, little is known about its role in the DSB repair pathway. Though not fully understood, evidence suggests that cenH3 may play a role in the proper recruitment or retention of ATM, which phosphorylates H2A.X immediately after DNA damage [154,157,158]. The Holliday Junction Recognition Protein (HJURP, a downstream Holliday junction binding factor in the HR pathway) has been shown to act as a primary chaperone for cenH3, incorporating it into new centromeric nucleosomes [159], suggesting that HJURP maybe depositing cenH3 at DSBs. A trivial possibility is that the enhanced expression of HJURP that is observed following DSBs, along with its interactions with proteins such as NBS1 [160], simply results in the deposition of cenH3 at DSBs due to the chaperone function of HJURP. However, this study demonstrated clear HJURP foci formation in response to radiation, in addition to a HR repair defect as well as genomic instability upon HJURP knockdown. Hence, it is formally possible that some of these phenotypes associated with HJURP knockdown may actually be associated with a defect in cenH3 deposition at the DNA damage sites.

Apart from its recruitment to DSBs [157], cenH3 has also been shown to undergo disassembly from centromeric repeats following their transcriptional activation in an ATM and p53 dependent manner upon DNA damage with the topoisomerase poison etoposide which causes DSBs [161]. This response may be important in initiating and/or maintaining a senescent state in cells that exhibit persistent DNA damage signaling. Overall, these data suggest that the normal homeostasis between cenH3 deposition and eviction from chromatin may be altered following DNA damage, raising the possibility that some of the cenH3 lost from centromeric regions under these conditions may then be redeposited at DSBs [157], perhaps in an attempt to form neocentromeres to avoid the potential loss of genetic material if DSB repair fails [162].

Interestingly, cenH3 and HJURP stabilize each other and both are overexpressed in cells lacking functional p53, which normally serves to repress these two genes [163,164]. p53 deficient tumor cells were also found to be dependent (or “addicted”) to high levels of HJURP and cenH3 for survival. Additionally, HJURP depletion in cells with wild type p53 resulted in activation of p53 and cell cycle arrest without concomitant DNA damage. On the

other hand, cenH3 overexpression in cells with wild type p53 resulted in radiosensitivity, growth inhibition and senescence, although this was related to the suppression of several cell cycle related genes. Furthermore, in cells lacking p53, cenH3 overexpression resulted in epithelial to mesenchymal transition, which could contribute to carcinogenesis. Together, these data suggest a very significant and complex role of cenH3 in regulating aspects of DDR, cell cycle and carcinogenesis in a p53 dependent manner. However, more research is needed to explore any potential cross talk between these roles of cenH3 and its putative role in DNA repair.

In addition to its recruitment to DSB, cenH3 has also been shown to interact with a number of DNA repair factors such as Damage Specific DNA Binding Protein 1 (DDB1, a recognition protein in both NER and BER pathways) [165] and PARP1 [166]. However, these interactions are likely related to cenH3's role in the centromere due to its simultaneous interaction with multiple proteins in the CEN complex. Finally, proper cenH3 assembly was also found to be dependent on Uracil-DNA glycosylase 2 (UNG2, a BER factor) activity in *Xenopus* [167,168]. These interactions suggest potential roles for cenH3 in HR and BER pathways, although the molecular details are yet to be investigated.

H3.3

H3.3 is nearly identical (96% homology) in amino acid sequence to the canonical H3 (H3.1 and H3.2) (Figure 3C) [169]. Previous research has shown that H3.3 is enriched in both the loosely packaged euchromatin, such as the promoters of actively transcribed genes, as well as the highly compact regions of genomes, such as the heterochromatin found at telomeres, pericentromeric regions, and rDNA. The deposition of H3.3 into these varying chromatin structures is dependent on two H3.3 specific chaperones, Histone Regulator (HIRA) and Alpha-Thallassemia Mental Retardation X-linked protein/Death domain Associated protein (ATRX/DAXX), which are responsible for its incorporation in euchromatin and heterochromatin respectively [170–172]. Interestingly, despite the near identical amino acid sequences of the major non-centromeric H3 variants (Figure 3C), nucleosomes with H3.3 have been found to be less stable than those containing canonical H3 (Figure 5), especially if the same nucleosomes also contain the H2A.Z variant (Figure 4) [173,174].

Specific point mutations in H3.3 have been shown to drive Diffuse Intrinsic Pontine Gliomas (DIPG, caused by the H3.3K27M mutation), high grade pediatric glioblastomas (H3.3G34R/V), giant cell tumors of the bone (H3.3G34W) and chondroblastomas (H3.3K36M) primarily in children [175–177]. Tumors associated with mutant H3.3 seem to have a generally early onset during development [177–179]. Pediatric high-grade gliomas (both H3.3K27M and H3.3G34R/V) make up about 11% of all reported pediatric central nervous system tumors, with approximately 400 new diagnosed cases in the United States of America every year [180]. Additionally, wild type H3.3 has been shown to be overexpressed in certain lung cancers where it promotes cancer metathesis and migration [181].

Defects in DNA repair are intimately linked to cancer formation [5]. Consistent with its putative role in cancer prevention, multiple studies, including our own unpublished studies, have found that H3.3 is recruited to sites of DNA damage, especially DSBs. Initially, H3.3 was shown to be recruited to sites of UV damage where it is required for replication fork

progression in a HIRA dependent manner in mammalian [182] and chicken [183] cells. These findings suggest that H3.3 may play a role in the NER pathway.

The exact role of H3.3 in DNA repair is far from clear, in part due to the inconsistencies between the published studies [182–186]. H3.3 has been reported to be required for the efficient repair of DSBs via both NHEJ and HR pathways [184,185]. These studies suggested that H3.3 is deposited at DSBs in a Chromodomain Helicase DNA Binding Protein 2 (CHD2) and PARP1 dependent manner. Once deposited, H3.3 is believed to assist in the proper recruitment of X-Ray Repair Cross Complementing 4 (XRCC4) in a KU70/80 dependent manner to perform repair via the c-NHEJ pathway. However, data from these studies should be interpreted with caution since the U2OS cells used therein lack functional ATRX chaperone or p53, and relied on transient knockdown of H3.3 for assays that take weeks to complete [185]. Furthermore, these cancer cells also exhibit the Alternative Lengthening of Telomeres (ALT) phenotype and show highly aberrant H3.3S31 phosphorylation patterns [187]. Another study reported the deposition of H3.3 at sites of DSBs in a HIRA dependent manner, following which H3.3 was acetylated on lysine 12 by Histone Acetyltransferase 1 (HAT1) to facilitate proper RAD51 recruitment to Replication Protein A (RPA) coated single stranded DNA in the HR pathway [186]. Interestingly, subsequent research also suggests that H3.3 plays a crucial role in the recruitment of MUS81 and other downstream HR factors to assist in the proper formation of double Holliday junctions. Furthermore, even in this context, the recruitment the HR factors occurred in an ATRX/DAXX dependent manner [184,188].

So far, studies indicate that H3.3 does play important roles in DNA repair, specifically within pathways involved in DSB repair (HR & NHEJ), as well as possibly in the NER pathway. However, the data is still unclear on its specific functions within each pathway. Since nucleosomes containing H3.3 are less stable than those containing canonical H3 [173], it is possible that H3.3 incorporation may assist DNA repair by increasing the accessibility of the damage site to repair factors by opening up the chromatin. This would be particularly important for DSB repair via the HR pathway which involves long stretches of chromatin. H3.3 could also facilitate the proper recruitment of various DNA repair factors via direct interactions with them, or indirectly via interactions with its PTMs, including through its unique S31 residue in the N-terminus that can be reversibly phosphorylated. The S31 residue has been shown to be particularly important for the role of H3.3 in the NER pathway and for proper DNA synthesis after DNA repair [167]. Additionally, incorporation of H3.3 in chromatin has been shown to inhibit H1 binding in those regions [189]. Since histone H1 has been shown to promote DSB repair via NHEJ [41,49], it is possible that the presence of H3.3 in the vicinity of the DSBs serves as a novel repair pathway choice factor by destabilizing H1 binding, which in turn would suppress NHEJ, upon which HR may become the preferred pathway for DSB repair. Additional studies are needed to verify this possibility experimentally. Overall, although H3.3 appears to play a major role in multiple DNA repair pathways, further research is needed to clarify these roles at the molecular level. This would be particularly crucial for the development of therapeutics for cancers driven by H3.3 mutations.

Other H3 Variants

Apart from cenH3 and H3.3, additional H3 variants such as H3.4 (aka H3t), H3.5, H3.Y (aka H3.Y.1) and H3.Y.2 (aka H3.X) are known. However, it is currently unknown if they play a specific role in any DNA repair pathway. H3.4 is a testis specific H3 variant which shares 97% homology (Figure 3C) with the canonical H3 [190]. H3.4 incorporation results in nucleosomes with significantly less stability and is predicted to lead to more open chromatin [191]. H3.4 has also been be shown to play an essential role in spermatogenesis [192]. H3.5 is a primate specific variant of H3 which shares a ~93% homology with the canonical H3 and a ~96% homology with H3.3 (Figure 3C). Although H3.3 and H3.5 containing nucleosome core particles have nearly identical structures, the latter has been shown to have a decreased interaction with the neighboring H4 histone resulting in less stable nucleosomes [193]. H3.5 is specifically expressed in the seminiferous tubules of human testis and has been found to be deposited in the euchromatic regions of the genome. As a result of its similarity to H3.3 in amino acid sequence, H3.5 has been shown to compensate for the loss of H3.3 in cell culture [194,195]. This may endow H3.5 with a similar function to H3.3 in DNA repair within specific contexts, such as in HR during crossing-over in meiosis while forming gametes. However, further research needs to be done to verify this possibility. Finally, the primate specific H3 variants H3.Y.1 and H3.Y.2, both share a near 72% homology with the canonical H3 and have nearly identical amino acid sequence relative to each other (Figure 3C). Little is known about H3.Y.2, but H3.Y.1 has been shown to be incorporated around the transcriptional start sites of genes and affects the expression of genes involved in cell cycle progression. Nucleosomes with H3.Y.1 have also been found to form more relaxed and less tightly packaged chromatin than those containing either canonical H3 or H3.3 [196]. Additionally, just like H3.3 has been shown to counteract H1 deposition in chromatin [189], H3.Y.1 has also been shown to decrease the efficiency of linker histone H1 binding, and its incorporation would be predicted to further open up chromatin [195,196].

HISTONE H4

Until recently, there were no known H4 variants in mammalian cells [197–199]. However, two H4 variants H4.G and H4.I have been identified recently [200,201]. The H4G variant exhibits 85% identity to canonical human histone H4 and is missing the last 5 residues. It has been shown to be involved in regulating rDNA transcription and is overexpressed in breast cancer [200]. Currently, these newly identified histone H4 variants have not been studied in the context of DNA repair.

The relative lack of prominent histone H4 variants is more than compensated by the multiple PTMs on canonical histone H4 that have been shown to be important for DDR, specifically for regulating repair pathway choice between HR and NHEJ for repairing DSBs [202,203]. These PTMs have been shown to alter chromatin structure [204] to facilitate access to DNA damage sites, as well as provide a binding site for DNA repair factors [205]. For example, H4K20 has been shown to be methylated through much of the cell cycle [206]. Although this modification is fairly ubiquitous and found throughout the genome, both SET Domain Containing Lysine Methyltransferase 8 (SETD8) and Multiple Myeloma SET

domain / Wold-Hirschhorn Syndrome Candidate 1 (MMSET/WHSC1) have been shown to sequentially methylate H4K20 at sites of DSBs [207–209]. This modification provides a binding site for the tandem Tudor domain of 53BP1, which in turn promotes c-NHEJ [205]. Paradoxically, the Nucleosome Acetyltransferase of histone H4 / Tat-Interactive Protein 60 (NuA4/TIP60) acetyltransferase complex has also been shown to bind to mono/di-methylated forms of H4K20 at sites of DSB, where it can potentially acetylate lysines at positions 5, 8, 12 and 16 on histone H4 to promote HR repair [210,211]. In addition to the competition between the NuA4/TIP60 complex and 53BP1 for binding to H4K20, recent research has found that the acetylation of H4K16 prevents 53BP1 binding at sites of DSBs [212]. Finally, the acetyltransferase HAT1 has been shown to facilitate the assembly of H3.1-H4 nucleosomes by preferentially acetylating H4K 5 and H4K12 in this complex over the analogous variant H3.3-H4 containing complexes [213].

CONCLUSIONS

Our knowledge of the roles that histone variants play in DNA repair is still evolving. While some histone variants have been studied to a considerable extent, much remains to be learned about the molecular roles that these variants play within specific DNA repair pathways, especially in mammals. In general, histone variants seem to play two specific roles within the DNA repair pathways. First, histone variants are actively recruited to sites of DNA damage to either assist/repel the binding of various DNA repair factors. This in turn could regulate the kinetics of DNA repair or influence the choice of the pathway used to repair the particular damage. Secondly, histone variants may also play of the role of a “place holder” for canonical nucleosomes during DNA repair, whereby variants are incorporated in nucleosomes to potentially stabilize chromatin, therefore preventing additional damage, while repair proceeds. This place holding function may be particularly important in repair pathways that require DNA synthesis (HR, BER, alt-NHEJ, NER), especially for repair that occurs outside of the S-phase of the cell cycle where the supply of the canonical histones is limited. Though we acknowledge the trivial possibility that some histone variants may simply be recruited to DNA damage sites in an opportunistic and non-consequential manner, it is very likely that several of the histone variants play very important roles in DNA repair under specific circumstances, as exemplified by the specific DNA repair defects observed in cells deficient in certain variants.

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Abbreviations:

53BP1	p53 Binding Protein 1
8-oxoG	8-oxo-7,8-dihydroguanine

alt-NHEJ	Alternative (or microhomology mediated) Nonhomologous End Joining
ANP32E	Acidic Nuclear Phosphoprotein 32 Family Member E
APLF	Aprataxin and PNK-like factor
ALT	Alternative Lengthening of Telomeres
ATM	Ataxia-Telangiectasia Mutated
ATR	ATM and Rad3-related
ATRX	Alpha-Thallassemia Mental Retardation X-linked protein
BARD1	BRCA1 Associated RING Domain 1
BER	Base Excision Repair
bp	base pair
BRCA1	Breast Cancer type 1
BRCA2	Breast Cancer type 2
c-NHEJ	Classic (or Canonical) Nonhomologous End Joining
CHD2	Chromodomain Helicase DNA Binding Protein 2
CHEK2	Checkpoint Kinase 2
ChIP	Chromatin Immuno-Precipitation
COMMD4	Copper Metabolism gene MURR1 Domain Containing 4
CtIP	C-terminal binding protein 1 interacting protein
DAXX	Death domain Associated
DDB1	Damage Specific DNA Binding Protein 1
DDR	DNA Damage Response
DIPG	Diffuse Intrinsic Pontine Glioma
DLBCL	Diffuse Large B-cell Lymphoma
DNA-PK	DNA-Dependent Protein Kinase
DSB	Double Strand Break
DSBR	Double Strand Break Repair
Exo1	Exonuclease 1
FACT	Facilitates Chromatin Transcription

HAT1	Histone Acetyltransferase 1
HDAC1	Histone Deacetylase 1
HIRA	Histone Regulator
HJURP	Holliday Junction Recognition Protein
HP1	Heterochromatin Protein 1
HR	Homologous Recombination
HUWE1	HECT, UBA And WWE Domain Containing E3 Ubiquitin Protein Ligase 1
LSH	Lymphoid Specific Helicase
MDC1	Mediator of DNA damage Checkpoint 1
MMR	Mismatch Repair
MMS	Methyl Methane Sulfonate
MMSET	Multiple Myeloma SET domain
MRN	MRE11-RAD50-NBS1 complex
NER	Nucleotide Excision Repair
NuA4	Nucleosome Acetyltransferase of histone H4
PAR	poly(ADP-ribose)
PARP1	poly-ADP Ribose Polymerase 1
PCAF	P300/CBP-associated factor
PCNA	Proliferating Cell Nuclear Antigen
PTM	Posttranslational Modifications
RPA	Replication Protein A
RNF8	Ring Finger Protein 8
RNF20	Ring Finger Protein 20
RNF40	Ring Finger Protein 40
RNF168	Ring Finger Protein 168
SETD8	SET Domain Containing Lysine Methyltransferase 8
shRNA	small hairpin RNA
siRNA	small interfering RNA

SRCAP	Snf2 Related CREBBP Activator Protein
SSB	Single-Strand Break
SSBR	Single-Strand Break Repair
SWI/SNF	SWItch/Sucrose Non-Fermentable
TAD	Topologically associating domain
TAF1	Template Activating Factor 1
TIP60	Tat-Interactive Protein 60
UBC13	Ubiquitin-conjugating E2 enzyme 13
UNG2	Uracil-DNA glycosylase 2
WHSC1	Wold-Hirschhorn Syndrome Candidate 1
WSTF	William-Beuren Syndrome Transcription Factor
XRCC1	X-Ray Repair Cross Complementing 1
XRCC4	X-Ray Repair Cross Complementing 4

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Highlights:

- Specific histone variants play important roles in DNA repair following their recruitment to sites of DNA damage.
- Histone variants regulate chromatin structure at sites of DNA damage to facilitate the recruitment and/or retention of specific DNA repair factors, often following posttranslational modifications.
- In doing so, they affect the efficiency of DNA repair, or influence DNA repair pathway choice, or both.

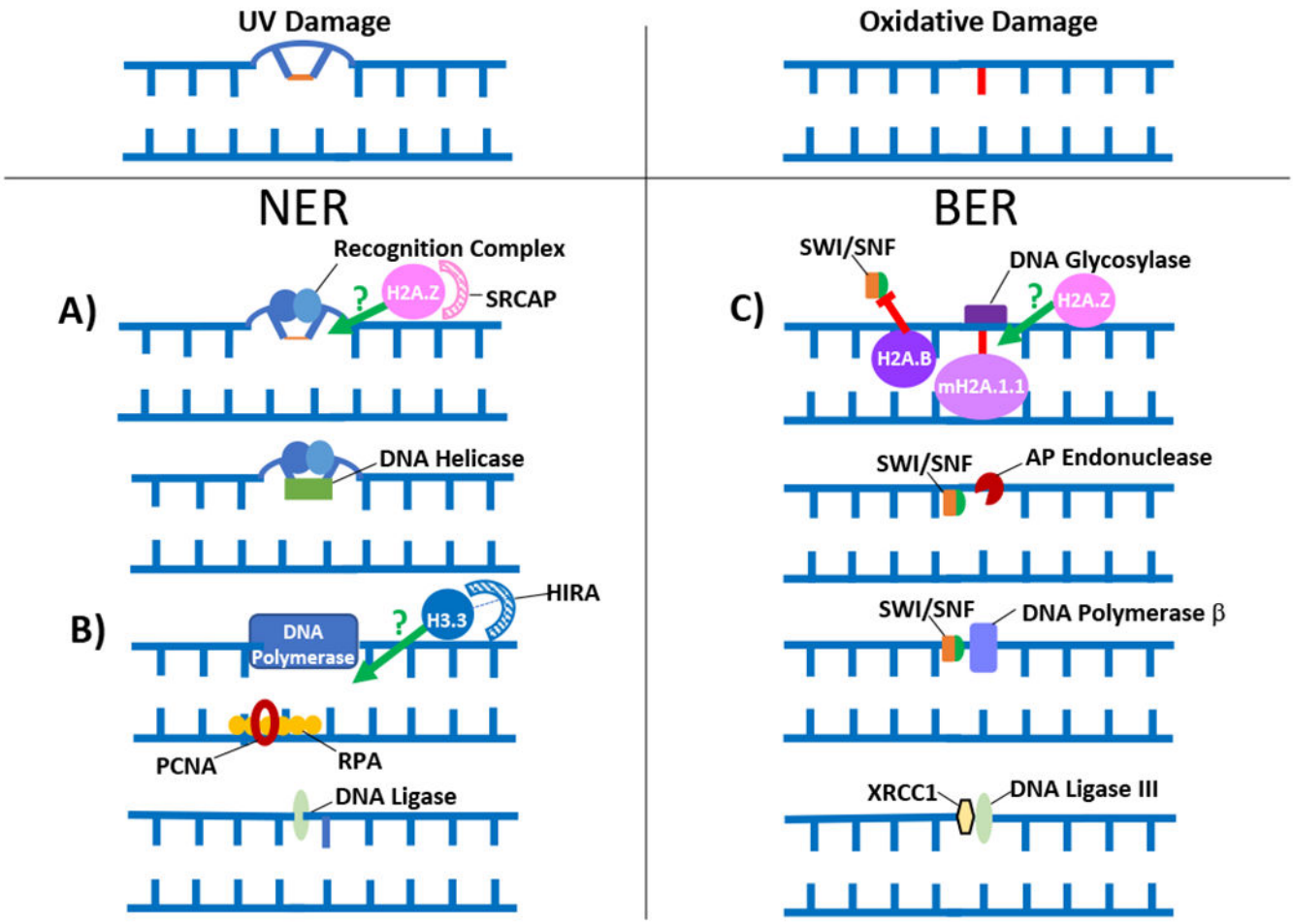

Figure 1. The role of histone variants in Nucleotide Excision Repair (NER) and Base Excision Repair (BER).

Red symbols (inhibitory) and green arrows (stimulatory) indicate where a histone variant may be potentially playing a role in the DNA repair pathway. Stripped arcs represent the most likely chaperones for the corresponding histones in the biological process under consideration. **(A)** H2A.Z (chaperoned by SRCAP) may assist the NER recognition complex to properly localize to the damage sites [111]. **(B)** H3.3 (with help from its chaperone HIRA) is potentially recruited to sites of UV damage where it may be required for replication fork progression [182,183]. **(C)** H2A.Z (along with its chaperone SRCAP) and mH2A.1.1 (chaperoned by LSH) have been shown to assist in promoting DNA glycosylase activity [110]. Additionally, nucleosomes containing the H2A.B are poorly remodeled by the SWI/SNF complex *in vitro*, suggesting that this variant either negatively affects the SWI/SNF remodeling function which appears to facilitate multiple steps of the BER pathway, or that H2A.B containing nucleosomes are inherently unstable and hence may not need to be remodeled, especially *in vivo* [138]. See text for more details. P = phosphorylation. Note: The shape, size and structure of the factors depicted are not drawn to scale.

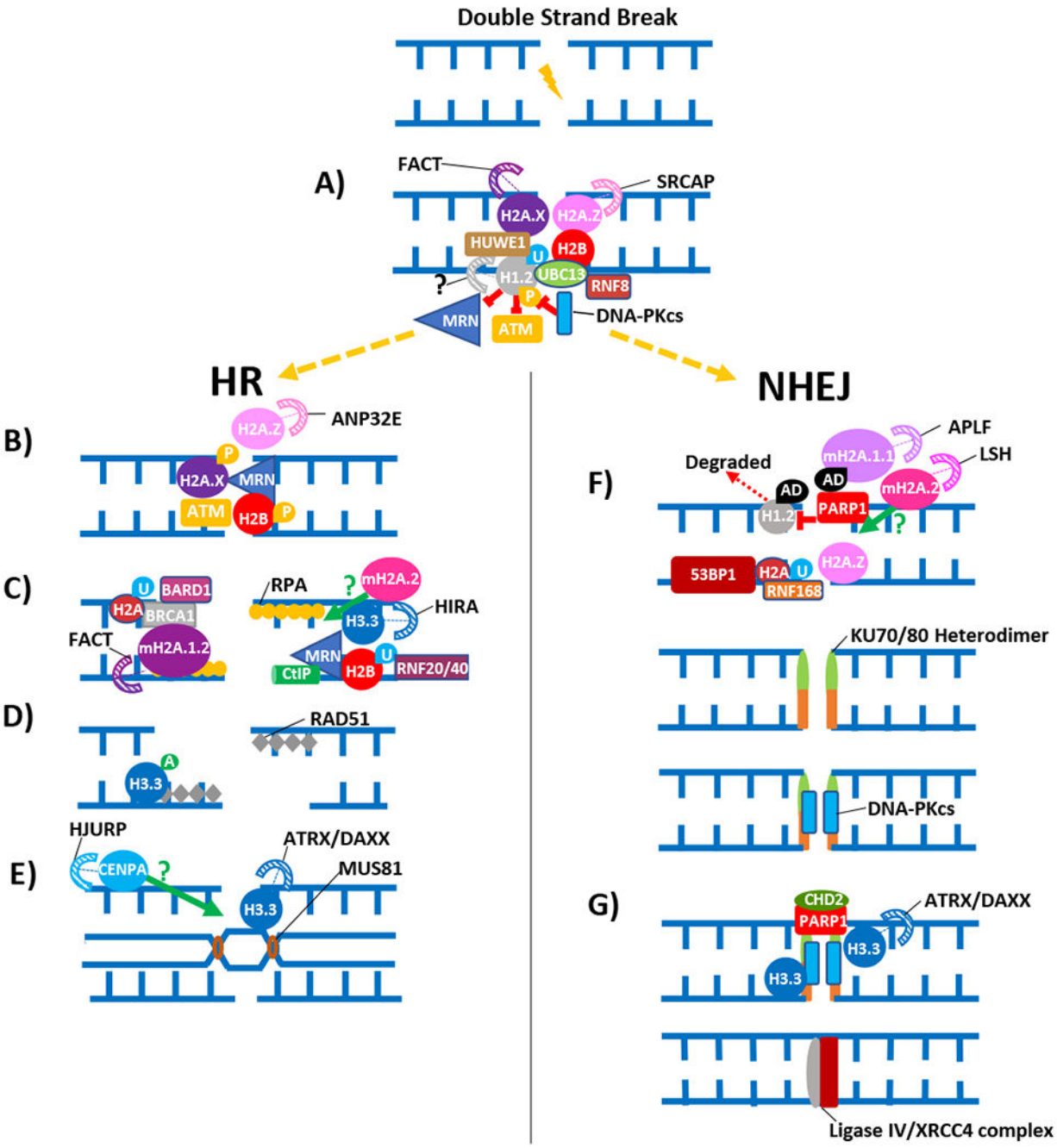

Figure 2. The role of histone variants in HR and NHEJ pathways for repairing DSBs.

Red symbols and green arrows show the steps where the indicated histone variants may be potentially playing a negative or positive role respectively in the indicated DNA repair pathways. Stripped arcs represent the most likely chaperones for the corresponding histone variants. **(A)** At the DSB, histone H1 generally appears to inhibit the activities of the MRN complex and ATM in HR, as well as in c-NHEJ, although DNA-PK mediated phosphorylation H1 has been suggested to overcome this inhibition during c-NHEJ [41]. Histone variants H2A.X (chaperoned by FACT) and H2A.Z (chaperoned by SRCAP) are

either already at the DSB sites, or are quickly recruited to these sites. The DSB can be repaired either by the HR pathway, or by the NHEJ pathways. **(B)** The DSB triggers a phosphorylation cascade, whereby H2A.X is phosphorylated at S139 almost as soon as a DSB occurs [60] by the ATM, ATR or DNA-PK kinases [67–69] and serves as a binding site for downstream DDR factors. Additionally, ATM also phosphorylates H2B at serine 14 which stimulates COMMD4 release [148,149]. H2A.Z may assist in the recruitment of various HR factors [97,98]. **(C)** Next, a ubiquitylation cascade follows, whereby H2BK120 is ubiquitylated by RNF20/RNF40 at DSBs, while H2A K125, K127 and K129 are ubiquitylated by the BRCA1/BARD1 complex to assist in proper end resection [58,150,151]. H3.3 may promote the coating of ssDNA by RPA at DSBs [186], while mH2A.1.2 (chaperoned by FACT) is recruited to DSBs to assist in BRCA1 localization [124–126]. Incorporation mH2A.2 (chaperoned by LSH) is crucial for proper Rad51 recruitment [130]. **(D)** H3.3 is acetylated by HAT1 to facilitate Rad51 recruitment [186]. **(E)** H3.3 (chaperoned by ATRX/DAXX) is believed to facilitate the recruitment of MUS81 to assist in double Holliday junction resolution [184,188]. cenH3 (deposited by HJURP) can also potentially assist in double Holliday junction formation or removal [160]. **(F)** Histone H1 is believed to dissociate from DSBs following poly-ADP ribosylation by PARP1 and is subsequently degraded to facilitate alt-NHEJ [49]. H2AK15 is ubiquitylated by RNF168 and promotes 53BP1 binding and c-NHEJ [58]. H2A.Z assists in Ku70/80 recruitment during repair by c-NHEJ [98]. mH2A.1.1 (chaperoned by APLF) binds to PAR chains on PARP1 at DSBs to promote the recruitment of KU70/80 and p53BP1 [120], while mH2A.2 (chaperoned by LSH) may also assist in proper p53BP1 localization [130]. **(G)** H3.3 (chaperoned by ATRX/DAXX) localizes to DSBs and may facilitate XRCC4 recruitment at the ligation step [185]. See text for more details. A = acetylation; AD = poly-ADP ribosylation (PARylation); P = phosphorylation; U = ubiquitylation. Note: The shape, size and structure of the factors depicted are not drawn to scale.

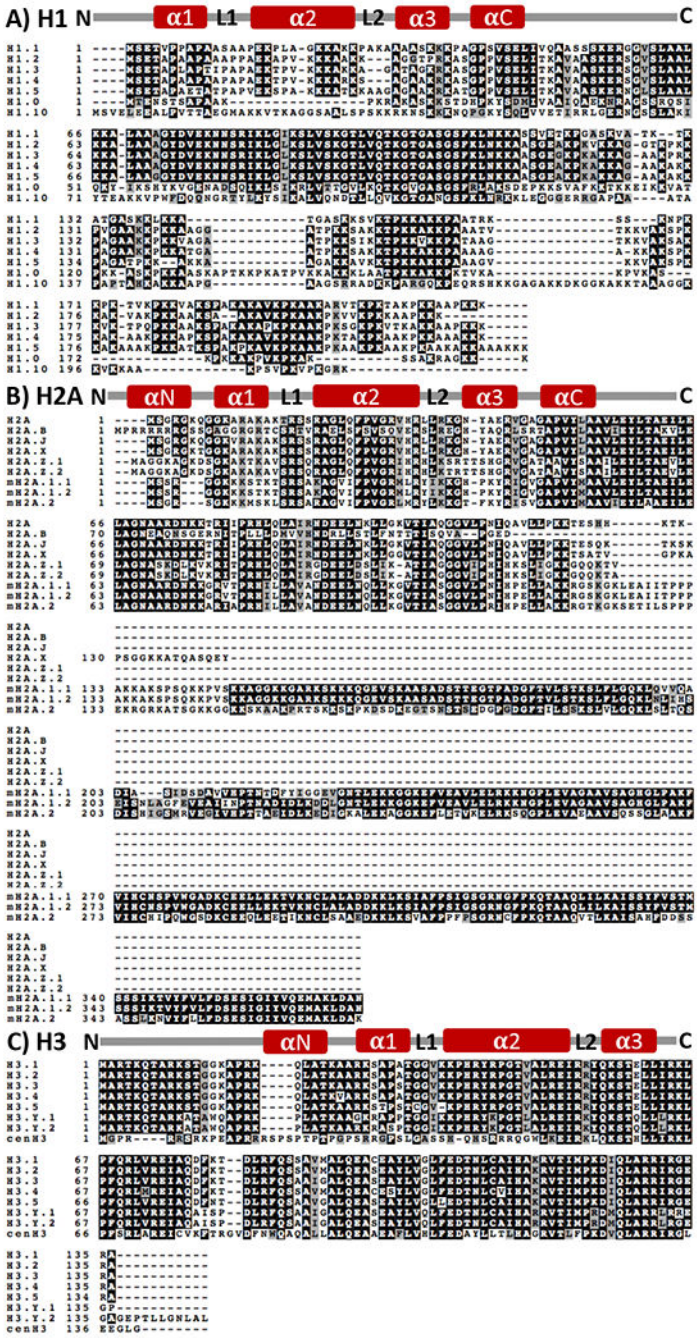

Figure 3. Domain structure and sequence alignment of histone H1, H2A and H3 families.

Specific members of these histone families have been implicated in different aspects of DNA repair. Amino acids highlighted in black represent identical residues in the protein sequences between the different histone variants, while those highlighted in grey represent conservative changes in amino acids that have similar characteristics/properties. Unshaded residues represent major non-conservative amino acid changes between the variants. Dashes represent amino acid residues that are absent in that particular histone variant. **(A)** Amino acid sequence alignment of the histone H1 family. **(B)** Amino acid sequence alignment of

the histone H2A family. **(C)** Amino acid sequence alignment of the histone H3 family. Alignment was carried out with T-Coffee web [29]. The general domain structure of each family of histone variants is shown above the alignments and is not drawn to scale with the protein sequence.

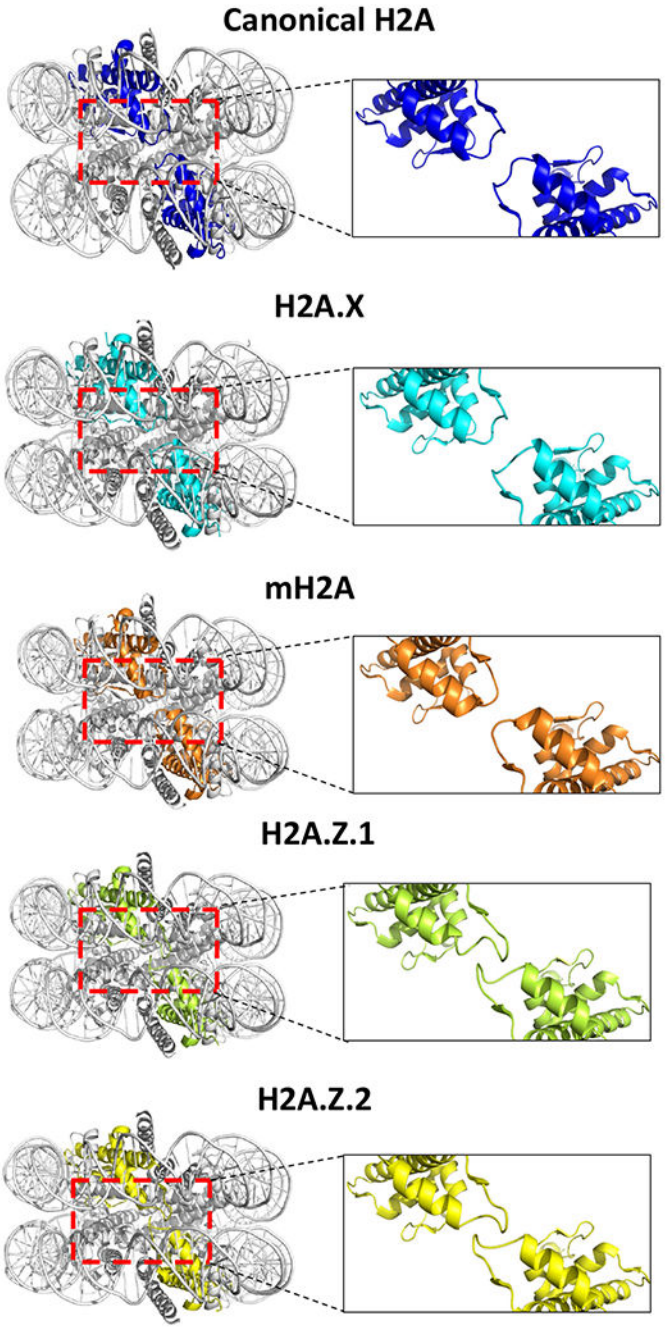

Figure 4. Structural diversity of histone H2A variants within the nucleosome core particle.
The side view of the crystal structures of human nucleosome core particles with either canonical or H2A variants is shown to highlight the location of the L1 loops of the H2A variants. A close-up view of the L1 loop region of the canonical and of each H2A variant is shown. Canonical H2A (PDB ID: 5Y0C) [16], H2A.X (PDB ID:6K1J) [63], mH2A (PDB ID:1U35) [57], H2A.Z.1 (PDB ID: 3WA9) [55] and H2A.Z.2 (PDB ID:3WAA)[55]. Nucleosome core particle figures were made using PyMol software.

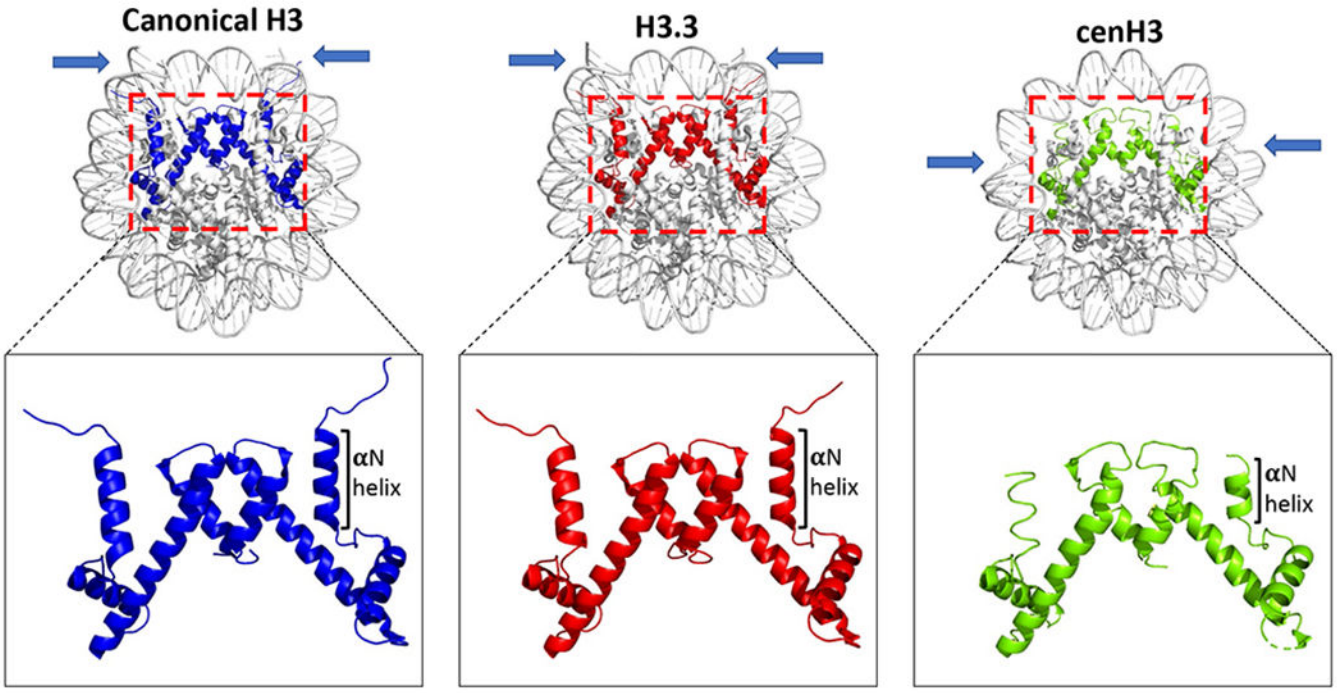

Figure 5. Structural diversity of histone H3 variants within the nucleosome core particle.

Crystal structures of human nucleosome core particles containing either canonical histone H3.1 (PDB ID: 5Y0C) [16], histone variant H3.3 (PDB ID:3AV2) [174] or histone variant cenH3 (PDB ID: 3AN2) [156] are shown. A close-up view of the histone H3 variants highlighting the α-N helix in cenH3 is shown. Note the shorter α-N helix in cenH3 compared to H3.1 and H3.3. The blue arrows point to the DNA ends visible in the crystal structures of the nucleosome core particles corresponding to the different H3 variants. Note the shorter tract of DNA associated with the histone octamer within the cenH3 nucleosome core particle. Nucleosome core particle figures were made using PyMol software.

Table 1.

Histone variants with known or suspected roles in the DNA damage response or in specific DNA repair pathways. Percent homology indicates the percent similarity in the amino acid sequence of the variants compared to the primary amino acid sequence of canonical histones H2A type 1 for the H2A variants and H3.1 for the H3 variants.

Variant Name	Histone Family	Percent Homology to canonical histone	Endogenous Localization	Involvement in DDR or DNA Repair Pathways	References
H1.2	H1	N/A	Enriched at silenced genes	HR, c-NHEJ, alt-NHEJ, apoptosis	[39,41,48–51]
H1.4	H1	N/A	Enriched at silenced genes	HR, c-NHEJ, alt-NHEJ	[52]
H1.0	H1	N/A	Repetitive DNA elements within the nucleoli; accumulates on silenced genes in non-dividing cells	N/A	[35–37]
H1.10	H1	N/A	Hypomethylated CpG islands and active genes	c-NHEJ	[35,39,51]
H2A.X	H2A	90%	Ubiquitously throughout the genome	HR, c-NHEJ	[59,61,62,65,84–89].
H2A.Z	H2A	60%	Actively transcribing genes and centromeres	BER, HR, c-NHEJ	[90,93,96,98,99]
mH2A	H2A	60%	Barr-body heterochromatin	BER, NER, HR	[110,122,123,125,126]
H2A.B	H2A	50%	Ubiquitously (except in the Barr-body)	N/A	[131,132]
H2A.J	H2A	94%	Enriched in senescent cells with DNA damage	N/A	[140,142]
cenH3	H3	45%	Centromeres	BER, HR	[154,157,159,163,164,167,168]
H3.3	H3	96%	Promoters of transcribing genes, telomeres, pericentromeric, rDNA heterochromatin	NER, HR, c-NHEJ	[169,182–186]
H3.4	H3	97%	N/A	N/A	[190]
H3.5	H3	93%	Euchromatic regions (seminiferous tubules)	N/A	[194,195]
H3.Y.1	H3	72%	Transcription start sites	N/A	[195,196]

N/A = Not applicable.