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H3-H4 Histone Chaperones and Cancer

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Abstract

Histone chaperones are key regulators of chromatin structure and function. Their frequent mis-regulation in various cancers can impact tumor initiation and progression. Here, we focus on H3-H4 histone chaperones to highlight recent studies concerning their roles in several cancers thereby expanding on previous reports illustrating their functions as tumor-promoting and/or as useful biomarkers for clinical applications. In particular, we discuss how imperfect compensation between H3-H4 histone chaperones favors tumor progression by stimulating the Epithelial mesenchymal transition (EMT) or the Alternative lengthening of telomeres (ALT) pathway. Finally, we present initial studies pointing towards therapies that target H3-H4 histone chaperones for cancer treatment.

Introduction

Histone chaperones represent a class of factors that interact with histones to escort them throughout their cellular life [1,2]. They contribute to the formation of the nucleosome core, the universal repeat unit of chromatin, comprised of an octamer with two copies of the four core histones H3, H4, H2A, and H2B around which about 147 bp of DNA is wrapped [3]. In this way, the basic charges of the histones are neutralized by the phosphate backbone of the DNA in the core particle. Importantly, before their incorporation into chromatin and after eviction, when present in a soluble form, given their high basicity, the histones may engage into promiscuous interactions with any acidic partner in the cell or may form deleterious aggregates. Therefore, under most circumstances, non-nucleosomal histones are kept in check thanks to histone chaperones. The term histone chaperone was coined for nucleoplasmin, a major protein in *Xenopus* oocytes ensuring the storage of maternal histones [4,5]. Historically, histone chaperones are classified according to their selectivity for H2A-H2B or H3-H4. However, the discovery of distinct variants, notably for H3, allowed for the refinement of this selectivity for particular variants, which can be disturbed by an unbalance in either the chaperone network or the histones themselves. Histones, in particular H3 variants, have attracted attention as so called “oncohistones” after the identification of mutations in H3 encoding genes in pediatric cancers (for review on this topic see [6,7]). Despite a growing number of studies indicating histone chaperones in tumor initiation and progression, their importance remains under-appreciated. Here, we focus on recent studies in which H3-H4 histone chaperones act as tumor-promoting factors. More specifically, we highlight the discovery of an imperfect compensation between H3-H4 histone chaperones that may promote tumor development in specific cancer contexts. Finally, we point out exploratory means for cancer therapeutics by targeting H3-H4 histone chaperones.

The H3-H4 histone chaperone network

Histone chaperones function as a network to escort histones throughout their cellular life from their synthesis until their degradation. They participate in histone nuclear import, storage or buffering, degradation, folding or re-folding, deposition and recycling [1,2]. In **Figure 1**, we show nuclear H3-H4 histone chaperones and their associated H3 variants [8,9], with a focus on those that have been linked with cancer. In most eukaryotes, two types of histones exist for each histone family, the replicative and non-replicative histones [10]. The replicative histones exhibit a high peak of expression during S phase when the doubling of DNA content requires a massive provision of histones. In contrast, the expression of non-replicative histones does not increase during S phase and each variant harbors a unique temporal expression. In mammals, the replicative H3 variants are H3.1 and H3.2 and among the non-

replicative H3 variants H3.3 attracted special attention. Although closely related, with only few amino acids differences, H3.1/2 and H3.3 associate with different chaperones for their deposition onto DNA. The deposition of H3.1/2 is mediated genome wide by only one histone chaperone complex, the Chromatin assembly complex 1 (CAF-1), in a process which is dependent of DNA synthesis notably during DNA replication. The deposition of H3.3, which is independent of DNA synthesis, is mediated by two different histone chaperone complexes depending on the deposition context. The Histone regulator A (HIRA) complex deposits H3.3 mainly in transcriptionally active regions while Death domain associated protein 6 (DAXX) in association with the chromatin remodeler Alpha Thalassaemia/mental Retardation, X-linked syndrome (ATRX) deposits H3.3 at telomere and pericentric heterochromatin. These histone chaperone complexes, as described later, have been recently involved in imperfect compensatory mechanisms in cancers exhibiting a histone chaperone mis-regulation.

Tumor-promoting H3-H4 histone chaperones

For their vast majority, H3-H4 histone chaperones have been identified as tumor-promoting factors most often through their up-regulation or mutation (Reviewed in Ref. [6,11,12]) and an increasing number of studies further confirms this function in diverse cancer types. Several studies illustrate the clinical relevance of H3-H4 histone chaperone expression, for instance as novel biomarkers to guide therapeutic choices. **Table 1** compiles recent reports involving several H3-H4 histone chaperones as tumor-promoting factors and/or as potential biomarkers in various cancer types. While mis-regulation of the histone chaperone network can contribute to tumorigenesis, the underlying mechanisms are still often unknown. A promising area that could be interesting to explore is how the imbalance in the network of interactions can create situations that compromise the maintenance of cell fate and genome integrity.

Imperfect compensation between H3-H4 histone chaperones stimulates cell fate transition and a switch in telomere maintenance

The H3-H4 histone chaperones are part of a network allowing for a degree of interchangeability. If one player is deficient another can potentially step in and ensure a fail-safe mechanism. Unfortunately, this compensatory mechanism, while ensuring cell survival, reveals its imperfect function in the context of cancer. Indeed, imperfect compensation has been shown to promote tumor progression by encouraging tumor cell invasiveness and survival as shown in the following studies.

The versatility of chromatin landscape provides a plasticity [13] enabling the cellular reprogramming necessary to change cell fate and drive metastasis. However, the mechanism

underlying the normal regulation of this plasticity and its misregulation contributing to metastasis is still unclear. Processes of invasion and metastasis have been associated with a cellular transition known as the Epithelial to Mesenchymal Transition (EMT). Cells undergoing EMT were first described in embryonic development and was associated with the acquisition of migratory properties. While an absolute requirement of EMT pathways for cancer metastasis is not clear [14], it is known that the reactivation of EMT in many cancer types increases cancer cell motility and thereby favors invasion and propagation. In this context, a recent report by Gomes et al., demonstrating that EMT inducers mis-regulate histone chaperones thus leading to the acquisition of aggressive cell traits and metastatic colonization, opens the door to a new avenue of research on the implication of histone chaperones **(Figure 2, left)** [15,16]. Specifically, in a variety of epithelial and carcinoma cell lines, the authors observed that upon EMT induction chromatin accessibility reproducibly increased, accompanied by a general decrease of total histones incorporated into chromatin. This general loss of histones, reflected both at the mRNA and protein levels for histone H3.1, was correlated with the down-regulation of the H3.1 dedicated histone chaperone CAF-1. In sharp contrast, the replacement variant H3.3 increased in chromatin correlating with the up-regulation of the H3.3 histone chaperone HIRA. This finding is reminiscent of the histone loss that facilitates reprogramming and 'gap-filling' by H3.3 [17,18]. Remarkably, instead of a random H3.3 enrichment, the authors find enrichment of H3.3 at specific promoters corresponding to genes involved in EMT. The mechanism enabling HIRA and H3.3 to be targeted to these particular promoters remains to be understood. Interestingly, CAF-1 overexpression had been previously associated with proliferation and metastasis in several cancer types [19]. In this study, it is its down-regulation that favored tumor progression for the first time. Of note, in induced reprogramming [20] and in early development [21] the suppression of CAF-1 could promote cell fate transitions. In these latter contexts whether a potential histone chaperone compensation is at work would be interesting to explore. Prohibitin (PHB) has been previously described to be associated with HIRA [22]. A recent study showed that its overexpression stabilizes the chaperone complex resulting in higher enrichment of histone H3.3 at the promoters of genes associated with EMT in breast cancer cells [23]. Expression of the latter genes increased and induced EMT. Importantly, in Gomes et al., HIRA up-regulation alone without CAF-1 down-regulation is not sufficient to stimulate EMT. It would thus be important to determine whether CAF-1 down-regulation is also a prerequisite for EMT induction in the context of PHB overexpression. In another recent study, overexpression of the centromeric H3 variant, CENP-A, favored EMT when p53 was inactivated [24]. In this case, how a possible limitation in the CENP-A chaperone HJURP and possible compensation with H3.3 histone chaperones DAXX or HIRA is at work remains to be examined. These studies underline the importance of considering a balanced histone chaperone / histone variant network to maintain cell identity. They also open up

possibilities to explore further their inter-relationships with changes affecting other chromatin regulators.

Beyond cellular identity maintenance, chromosomal integrity is also at stake in cancer cells. In this respect, the maintenance of telomeres, nucleoprotein structures found at the ends of linear chromosomes, is particularly revealing. These structures, composed of repetitive sequences, are maintained by the telomerase enzyme complex in germ cells and some stem cells, but are absent in the majority of somatic cells. The lack of telomerase in normal somatic cells leads to shortening of the telomeric repeats and a limited replicative life span. By contrast, in cancer cells with an unlimited proliferative capacity, either telomerase activity remains high or alternative strategies allowing for its bypass have evolved. The latter option is observed in a subset of tumors, approximately 10-15%, which can maintain telomere length independently of telomerase and instead use a homologous-based mechanism called the Alternative lengthening of telomeres (ALT) pathway [25]. Among the genes affected in the activation of ALT, the chromatin remodeler ATRX has been recurrently found mutated. This remodeler is part of a complex with DAXX, a dedicated histone H3.3 chaperone which is key for the enrichment of H3.3 in repetitive sequences, including telomeric repeats. Hoang et al. recently described that the viability of ALT cancer cells with a deletion in ATRX gene, which are deficient therefore for the DAXX-ATRX associated function, depends on another H3.3 histone chaperone complex, HIRA [26] (**Figure 2, right**). Furthermore, pARYlation of the HIRA subunit is required for its association with ALT telomeres. This is critical specifically in G2 to ensure the deposition of H3.3 at telomeres when DAXX-ATRX cannot function. Thus, the PAR-dependent regulation of HIRA could represent a fail-safe mechanism to allow the restoration of telomeric chromatin prior to mitosis, a means for DAXX-ATRX-deficient cells to survive. However, although HIRA efficiently deposits H3.3, it is not redundant with other roles of the remodeler ATRX, in particular, its role in mitigating replicative stress imposed by DNA secondary structures (for example, G4s, single-stranded DNA gaps). These unresolved DNA secondary structures alter nucleosome density within telomeres and/or interfere with the proper binding of telomere-specific proteins. Thus, the incomplete compensation by HIRA leaves telomeres susceptible to persistent DNA damage and replicative stress which in turn would stimulate the ALT pathway.

While HIRA has been previously involved in suppression of neoplasia [27], the studies described above uncovered a new aspect of HIRA function in maintaining cancer cells in the absence of other chaperones. In both cases, the deficiency of either CAF-1 or DAXX-ATRX functions lead to a switch in the reliance on another histone chaperone, notably HIRA, to compensate for their defects, thus standing central in maintaining some form of chromatin “integrity”. However, cancer cells survive and thrive due to an imperfect compensation which in one case favors cell fate transition and metastasis

by EMT and in the other case is associated with maintenance of telomeres via the ALT pathway. While these recent studies focused mainly on the HIRA subunit, it would be interesting to determine whether the other subunits of the complex participate in promoting EMT and the ALT pathway, specifically probing the involvement of the different HIRA partners involved in either de novo deposition or recycling of H3.3 [28]. Furthermore, the HIRA subunit has also been involved in transcription independently of its role of H3.3 chaperone [29] and whether this property is also important in the above processes should be evaluated. Finally, the dependency of cancer cell survival and propagation on HIRA points to possible new therapeutics targeting this histone chaperone along two lines: (i) prevention of the EMT program and thereby metastasis in cancer where CAF-1 is affected and (ii) leveraging HIRA dependency as a Achilles's heel to kill DAXX-ATRAX-deficient ALT cancer cells.

H3-H4 histone chaperone-targeted cancer therapeutics

To date, among anti-cancer compounds known to inhibit histone chaperone activity, curaxins are the best characterized. They interfere with the histone chaperone complex FACT (Facilitates chromatin transcription) (see **Figure 1**) by intercalating into DNA to induce indirect chromatin-trapping of this histone chaperone complex [30]. However, while there is increasing emphasis on the importance of H3-H4 histone chaperones as potential oncogenes, only a few studies have explored means to inhibit their action as novel therapeutic strategies. Although the lack of enzymatic activity has made histone chaperones less attractive for drug design, the following recent studies highlight strategies for inhibiting the histone chaperone Anti-silencing function 1 (ASF1) with promising leads for cancer therapy. In a manner similar to other epidrugs [31], their use in synergy with other anti-cancer therapies could have a significant impact on ameliorating current cancer treatments and in reversing acquired therapy resistance.

ASF1 is a histone chaperone involved in handing over histone H3.1-H4 to CAF-1 and H3.3 to HIRA in distinct nucleosome assembly pathways (see **Figure 1**). The studies by Bakail et al. combined structural, computational, and biochemical approaches to design peptides that inhibit the ASF1a/b-histone interaction [32,33]. Starting from the structure of the human ASF1a/b-histone complex, they developed a rational design strategy combining epitope tethering and optimization of interface contacts to identify a potent peptide inhibitor. In cultured cells, these inhibitors impaired cell proliferation, cell-cycle progression, cell migration and invasion as a function of their affinity for ASF1. Their most potent ASF1 peptide inhibitor injected in mouse allografts reduced tumor growth. These findings thus open avenues to use ASF1 inhibitors in anti-cancer therapies. Given the cooperation of ASF1 with HIRA, it would also be interesting to test these inhibitors in the processes described above in which HIRA and

the deposition of H3.3 appear critical for tumor cell survival and progression. Finally, given the major progress in determining protein structure due to recent technological advances, one can anticipate that similar strategies could be used for other interfacial drug design.

In the context of combining epigenetic drugs with other therapies for cancer treatment [31], Li and colleagues reasoned that because epigenetic regulators can control the tumor microenvironment they may be ideal candidates for potential adjuvant therapy in combination with immunotherapy [34,35]. Indeed, in Kirsten rat sarcoma (KRAS)-mutant lung adenocarcinoma, immunotherapy has proved effective in most patients, but for a subset of patients response rates are only 10-15%. The authors conducted an in vivo CRISPR (Clustered regularly interspaced short palindromic repeats) screen for epigenetic regulators that would potentiate the effects of anti-Programmed cell death protein 1 (anti-PD-1) immunotherapy using a lung cancer mouse model. Using this approach, the authors uncovered that knockout of the histone chaperone ASF1a in the adenocarcinoma cells sensitized the tumor to checkpoint blockade. Mechanistic approaches revealed that tumor cell-intrinsic ASF1a deficiency potentiated T-cell activation in combination with anti-PD-1. Although the authors did not examine methods to inhibit ASF1a, this study provides a rationale for a possible therapy combining ASF1a inhibition and anti-PD-1 immunotherapy. This data stresses the importance of sensitizing the cancer cells and the tumor microenvironment to boost the outcomes shown with immunotherapy. In the future, it will be important to evaluate whether interfering with other histone chaperones could also boost the efficacy of immunotherapies.

Conclusions

Recent literature has emphasized the importance of H3-H4 histone chaperones in cancer with an increasing number of studies describing histone chaperones as cancer biomarkers mainly for prognosis, contributing to improve treatment of patients. However, since the initial discovery of their link with various tumorigenic processes in the early 2000s, the precise underlying mechanisms have often remained elusive. In cancer cells, the existence of a partial compensation between H3-H4 histone chaperones when one activity is deficient is particularly revealing. Indeed, a compensatory mechanism may help the tumor cells to survive, but could also make them highly dependent on the back-up histone chaperones and possibly more vulnerable. Furthermore, compensatory events may be more frequent than previously thought, not only in the context of direct chaperone deficiency but also when an imbalance occurs among histone chaperones and histone variants. Considering that imbalanced situations are likely frequent in cancer when a histone chaperone is mis-regulated, this concept deserves further exploration. Therapies that target histone chaperones for cancer treatment would be

therefore interesting to investigate. Recent data describing inhibition strategies of ASF1 offer promising avenues for expanding these methodologies to other chaperones. Finally, we also anticipate that the capacity to better analyze individual cells in complex tumors [36] will shed light on the heterogeneity of cell behavior with respect to the histone chaperone / histone variant network within the cancer ecosystem. This opens the door to a whole area of exploration with increased precision in future studies on the roles of histone chaperones in cancer.

Declaration of interest

None.

CRediT authorship contribution statement

Dominique Ray-Gallet: Conceptualization, Writing - original draft, Writing - review & editing.

Geneviève Almouzni: Conceptualization, Writing - review & editing - Funding acquisition.

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Table 1 Histone H3-H4 chaperones as tumor-promoting (recent publications)

H3-H4 histone chaperone	Histone variant selectivity	Function(s)	Mis-regulation in cancer	Type of cancer	Cancer biomarker	References
ASF1a	H3.1/2-H4 H3.3-H4	Transfer to HIRA and CAF-1, and recycling	Up-regulation	Variety of cancers	Prognostic	[37]
ASF1b			Up-regulation	Cervical cancer	Prognostic	[38]
			Up-regulation	Prostate cancer	Prognostic	[39]
			Up-regulation	Variety of cancers	Prognostic	[40]
CAF-1 Complex	H3.1/2-H4	Deposition DSC	Up-regulation	Cervical cancer, cutaneous lymphoma, oral squamous carcinoma	Prognostic	[19,41,42]
DAXX-ATRX	H3.3-H4	Deposition at telomeres and pericentromeres DSI	DAXX up-regulation	Carcinoma		[43]
DNAJC9	H3-H4	Folding	Up-regulation	Variety of cancers		[44]
FACT complex	H3-H4 H2A-H2B	Eviction and recycling	SSRP1 up-regulation	Bladder cancer		[45]
HJURP	CENP-A -H4	Deposition at centromeres DSI	Up-regulation	Colorectal and prostate cancers	Prognostic	[46–48]
MCM2	H3-H4	Recycling	Up-regulation	Cervical cancer	Prognostic	[49]

DSC, DNA synthesis coupled; DSI, DNA synthesis independent; CAF-1, Chromatin assembly factor 1; HJURP, Holliday junction recognition protein; CENP-A, Centromeric protein A; DAXX, Death domain associated protein 6; ATRX, α -thalassemia, mental retardation, X-linked syndrome; ASF1, Anti-silencing function 1; MCM2, Minichromosome maintenance complex 2; FACT, Facilitates chromatin transcription; DNAJC9, DnaJ Heat Shock Protein Family (Hsp40) Member C9.

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Annotated references

(**) Gomes et al:

The authors described for the first time that EMT induction promotes imbalanced incorporation of histone H3 variants. Decreased amount of the histone chaperone complex CAF-1 leads to less H3.1 incorporation and promotes, as a compensatory mechanism, H3.3 deposition notably at promoters of EMT promoting factors by the histone chaperone HIRA. This H3.3 incorporation stimulates the EMT program and is essential for acquisition of aggressive traits.

(**) Hoang et al :

The authors described for the first time that the histone chaperone HIRA deposits H3.3 at telomeres in absence of DAXX-ATRX activity. This fail-safe mechanism allows the restoration of telomeric chromatin allowing the DAXX-ATRX-deficient cells to survive. However, HIRA's inability to compensate for ATRX-DAXX's other roles would stimulate the ALT pathway.

(*) Bakail et al :

The authors developed a strategy for designing peptide inhibitors of the interaction histone-histone chaperone ASF1. These peptide inhibitors were proved efficient to impair cancer cell proliferation using culture cells and mouse allograft models.

(*) Huang et al :

The authors reported that the increased expression of PHB in breast cancer cells resulted in the enrichment of H3.3 at the promoters of EMT promoting factors through the stabilization of the histone chaperone HIRA. This coincided with an increased expression of these factors and induction of EMT.

(*) Li et al :

The authors showed that deletion of ASF1a sensitizes lung adenocarcinoma cancer cells to immune checkpoint blockade using anti-PD-1 therapy. This provides a rationale for future combination therapy with ASF1a inhibitors and immunotherapy.

Figure Legends

Figure 1. The histone chaperone network

Histone chaperones escort histones throughout their cellular life. They shuttle histones from their place of synthesis into various pathways for their nuclear import, storage or buffering, degradation, folding or re-folding, deposition and recycling. Here we show chaperones for histones H3-H4 working in the nucleus that are involved in cancer and discussed in the review. After their nuclear import, the main pathway for the newly synthesized histones is their deposition onto DNA to form nucleosomes. In this nucleosome assembly line, H3-H4 are escorted by different histone chaperones depending on the H3 variant. H3.1/2-H4 are deposited by the histone chaperone complex CAF-1 (that consists of CHAF1A p150, CHAF1B p60 and RBBP4 p48 subunits) during replication and repair in a process coupled to DNA synthesis (DSC). By contrast, H3.3-H4 and CENP-A-H4 are incorporated into chromatin independently of DNA synthesis (DSI). H3.3-H4 are deposited either by the histone chaperone complex HIRA that consists of UBN1/2 (that directly interacts with histones), CABIN1 and HIRA subunits, or by the histone chaperone DAXX (the subunit that directly interacts with histones) in association with ATRX. HIRA incorporates H3.3-H4 mainly at transcriptionally active regions and potentially at nucleosome free regions while DAXX-ATRX deposits H3.3-H4 at pericentric heterochromatin and telomeres. The centromeric histone H3, CENP-A, is deposited at centromeres by the histone chaperone HJURP. Upstream in this assembly line, the histone chaperone ASF1 transfers H3.1/2-H4 and H3.3-H4 to CAF-1 and HIRA, respectively. During processes such as replication and transcription, nucleosomal histones can be evicted to allow DNA-associated enzymatic machineries to play their roles such as DNA or RNA polymerases. The evicted histones re-associate with histone chaperones and can be recycled to re-form nucleosomes or can be targeted for degradation. ASF1 with MCM2 recycle H3-H4 during replication while ASF1 with the HIRA subunit recycle H3.3-H4 during transcription. The histone chaperone FACT (that consists of two subunits, SPT16 and SSRP1) evicts both the H2A-H2B dimer and (H3-H4)₂ tetramer, keeping them positioned for re-deposition after RNA or DNA polymerases passage. When the histone supply exceeds the histone demand for nucleosome assembly, a pathway of storage or buffering exists through H3-H4 interaction to histone chaperones notably ASF1 and NASP. Then, these histones can either re-enter into the assembly line or be targeted for degradation. Misfolded H3-H4 can bind the histone chaperone DNAJC9 which recruits heat shock factors to fold and release H3-H4 that can then enter or re-enter into the nucleosome assembly line. CAF-1, Chromatin assembly factor 1; HIRA, Histone regulator A; UBN1/2, Ubinuclein 1 and 2; CABIN1, Calcineurin binding protein 1; HJURP, Holliday junction recognition protein; CENP-A, Centromeric

protein A; DAXX, Death domain associated protein 6; ATRX, α -thalassemia, mental retardation, X-linked syndrome; ASF1, Anti-silencing function 1; MCM2, Minichromosome maintenance complex 2; FACT, Facilitates chromatin transcription; SPT16, Suppressor of Ty 16; SSRP1, Structure-specific recognition protein 1; DNAJC9, DnaJ Heat Shock Protein Family (Hsp40) Member C9; NASP, Nuclear autoantigenic sperm protein; DSC, DNA synthesis coupled; DSI, DNA synthesis independent.

Figure 2. Imperfect compensation between histone chaperones in cancer

In normal conditions, H3-H4 histone chaperones are known to be selective for one or several H3 variants and to be involved in a specific pathway(s). In particular tumor contexts, the provoked imbalance of histone chaperones has been described to lead to compensatory mechanisms between chaperones. However, imperfect compensation was reported to favor tumor progression. In the context of breast carcinoma (left panel), activation of EMT by established inducers decreases the amount of chromatin-bound H3.1/2 and increases the amount of chromatin-bound H3.3 [15]. The decrease of H3.1/2 is due to a transcriptional down-regulation of its dedicated chaperone complex CAF-1 as a consequence of the ERK pathway activation. This decrease of histone abundance due to CAF-1 deficiency leads to a compensatory mechanism between chaperones with an increase of HIRA. HIRA activity partially compensates for the loss of CAF-1 by depositing H3.3 potentially through its gap-filling activity. A particular enrichment of H3.3 occurs at promoters of several EMT-inducing genes which is correlated with their transcriptional activation and consequently the acquisition of invasive traits and metastatic dissemination. In the context of DAXX-ATRX-deficient ALT cancer (right panel), a deletion in the ATRX gene associated with the loss of the protein, leads to altered deposition of H3.3 at telomeres [26]. This leads to a compensatory mechanism with deposition of H3.3 at telomeres by the histone chaperone complex HIRA in place of DAXX-ATRX. The association of HIRA with telomeres to deposit H3.3 is dependent on the PARylation of HIRA. This fail-safe mechanism of telomeric chromatin is absolutely required for cell survival. However, HIRA cannot compensate ATRX's other roles, such as replicative stress imposed by DNA secondary structures, leaving telomeres susceptible to persistent DNA damage which in turn stimulates the ALT pathway. The requirement of the histone chaperone complex HIRA in both of these cancer cell contexts highlights it as a possible new target for the development of novel cancer therapeutics.

Figure 1

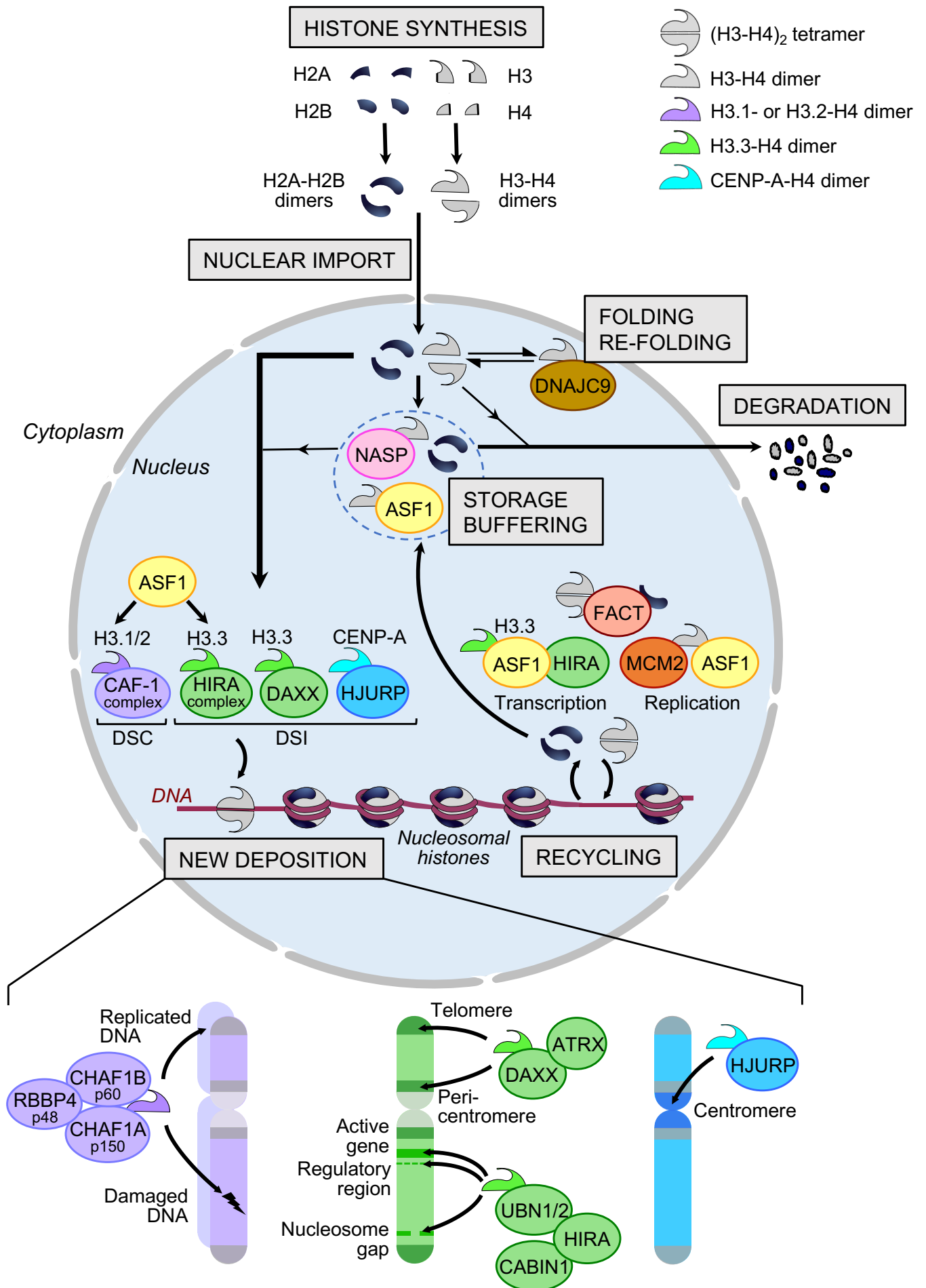


Figure 2

