

# Altered primary chromatin structures and their implications in cancer development

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## Abstract

**Background** Cancer development is a complex process involving both genetic and epigenetic changes. Genetic changes in oncogenes and tumor-suppressor genes are generally considered as primary causes, since these genes may directly regulate cellular growth. In addition, it has been found that changes in epigenetic factors, through mutation or altered gene expression, may contribute to cancer development. In the nucleus of eukaryotic cells DNA and histone proteins form a structure called chromatin which consists of nucleosomes that, like beads on a string, are aligned along the DNA strand. Modifications in chromatin structure are essential for cell type-specific activation or repression of gene transcription, as well as other processes such as DNA repair, DNA replication and chromosome segregation. Alterations in epigenetic factors involved in chromatin dynamics may accelerate cell cycle progression and, ultimately, result in malignant transformation. Abnormal expression of remodeler and modifier enzymes, as well as histone variants, may confer to cancer cells the ability to reprogram their genomes and to yield, maintain or exacerbate malignant hallmarks. At the end, genetic and epigenetic alterations that are encountered in cancer cells may culminate in chromatin changes that may, by altering

the quantity and quality of gene expression, promote cancer development.

**Methods** During the last decade a vast number of studies has uncovered epigenetic abnormalities that are associated with the (anomalous) packaging and remodeling of chromatin in cancer genomes. In this review I will focus on recently published work dealing with alterations in the primary structure of chromatin resulting from imprecise arrangements of nucleosomes along DNA, and its functional implications for cancer development.

**Conclusions** The primary chromatin structure is regulated by a variety of epigenetic mechanisms that may be deregulated through gene mutations and/or gene expression alterations. In recent years, it has become evident that changes in chromatin structure may coincide with the occurrence of cancer hallmarks. The functional interrelationships between such epigenetic alterations and cancer development are just becoming manifest and, therefore, the oncology community should continue to explore the molecular mechanisms governing the primary chromatin structure, both in normal and in cancer cells, in order to improve future approaches for cancer detection, prevention and therapy, as also for circumventing drug resistance.

**Keywords** Nucleosomes · Epigenetics · Chromatin remodeling · Histone modifications · Histone variants · Cancer

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## 1 Introduction

In order to control genome plasticity in a spatiotemporal manner, eukaryotic cells have developed epigenetic mechanisms such as DNA methylation, covalent post-translational histone modification and nucleosome repositioning, which act in concert to regulate gene expression by modifying, among others, the primary structure of chromatin [1, 2]. Critical alterations in

cancer cells, such as silencing of tumor-suppressor genes [3], activation of oncogenes [4] and deficiencies in DNA repair, can be caused not only by genetic but also by epigenetic changes that affect nucleosome distribution along the genome. Here, I will review the most recent literature focusing on deregulation of nucleosome positioning in pathological conditions such as cancer due to mutations or alterations in the expression of multimeric complexes implicated in the biology of chromatin. The role of DNA methylation and non-coding RNAs [5] will not be discussed here.

Chromatin is a complex of DNA and histone proteins. The basic units of this complex are nucleosomes. A single nucleosome is formed by ~147 base-pairs (bp) of DNA wrapped around an octamer of histone proteins (two copies of histone H2A, H2B, H3 and H4). Neighbouring nucleosomes, and the adjacent H1 histones, are separated by ~10–100 base-pairs of linker DNA. Nucleosomes are not randomly distributed and it is known that they occupy favoured positions throughout, but not all of, the genome [6]. The position of nucleosomes is determined and influenced by a number of factors, including DNA sequence, DNA methylation, histone modification, chromatin remodeling and transcription factor (TF) binding [7]. In processes involving DNA as a substrate, such as transcription, replication, recombination, repair and chromosome segregation, the primary structure of chromatin presents inherent barriers that restrict the access of DNA to processing enzymes. Therefore, it is not surprising that imprecise chromatin dynamics due to incorrect deposition, removal, modification and configuration of nucleosomes has been found to have significant implications for cancer development.

Both the local and global chromatin architecture depend on the position and density of nucleosomes, as well as on the presence of histone variants and modifications. Specialized remodeling complexes and histone modifier enzymes are able to bind nucleosomes and, by doing so, to regulate chromatin architecture. In general, remodeling complexes include subunits that use energy from the hydrolysis of ATP to restructure nucleosome-DNA interactions. Modifier enzymes can modify histone proteins at multiple sites and, similar to remodelers, are able to change the non-covalent links between DNA and histone octamers. Chromatin remodeling ATPases and modifiers are found in all eukaryotic organisms and typically work together as multimeric complexes. During cancer development, chromatin assembly and remodeling, which mediate the inter-nucleosomal spacing of chromatin, are key components involved in the epigenetic control of the DNA-related processes mentioned above. Although high-resolution maps as well as detailed primary chromatin architectures are not yet available for all cancer (sub) types, in-depth analysis of the organization of chromatin in tumor cells has been initiated in recent years. As a result, ample data have been gathered to support the idea that changes in chromatin lead to the initiation and progression of cancer, equally well as the accumulation of

DNA mutations. While single aspects of chromatin architecture are reported daily, as yet no comprehensive review has been published that summarizes mechanisms such as chromatin remodelling, histone modification, histone variant and nucleosome positioning in cancer.

## 2 Chromatin remodeling complexes

During cellular proliferation and differentiation chromatin undergoes a series of coordinated biological changes that result in either loosening or condensing its structure, which in turn allows DNA replication and repair, as well as the transcription of cell type-specific genes, to occur. This phenomenon is known as chromatin remodeling and, as mentioned above, is performed by a class of enzymes called chromatin remodelers. Chromatin remodelers govern DNA accessibility and, by affecting the nature of interactions between cellular factors and target DNA, they dictate the dynamics of chromatin [8]. Misplaced nucleosomes, for example, may affect the accessibility of TFs to promoter and/or enhancer sites and, by doing so, may result in altered expression of cancer-related genes. Chromatin remodelers belong to the helicase superfamily 2 (SF2). This superfamily includes several families of helicase-related proteins, among which the sucrose non-fermenting-type ATPase (Snf2) family. All remodelers act through a Snf2-type ATPase. A further subdivision of the Snf2 family results in two groups of chromatin remodeling complexes, i.e., Snf2-like and Ino80-like [9, 10]. Although so far four Snf2 subfamilies have been reported: (1) SWI/SNF (switching defective/sucrose non-fermenting), (2) ISWI (imitation SWI), (3) CHD (chromodomain helicase DNA binding) and (4) INO80 (inositol requiring 80) [11–13], at least two other Snf2-related ATPase remodelers must be considered: (5) HELLS (lymphoid-specific helicase in yeast; LSH) and (6) SMARCAD1 (Function unknown 30 in yeast; Fun30) [14–16].

### 2.1 SWI/SNF alterations in cancer

It has been hypothesized by Gonzalez-Perez et al. that alterations in chromatin organization and gene expression programs may be driven by mutation and/or aberrant expression of chromatin remodeling factors. This hypothesis was based on the observation that ~20 % of all human tumors analyzed in their study harbored mutations in at least one member of the SWI/SNF complex [17]. Subsequent studies have reported a high prevalence of SWI/SNF mutations in ovarian carcinoma (75 %), renal cell carcinoma (57 %), hepatocellular carcinoma (40 %), gastric cancer (36 %), melanoma (34 %) and pancreatic cancer (26 %) [18, 19]. One mechanism by which mutations in one or more subunits of chromatin remodeling complexes may induce malignant transformation was reported by

Wilson et al. in 2010. They showed that cancer cells harboring an inactive SWI/SNF complex, due to absence of the SNF5 subunit, were unable to remove polycomb complexes and their repressive histone modification mark, i.e., lysine 27 trimethylation of the H3 tail (H3K27me<sub>3</sub>), from the *p16<sup>INK4a</sup>* locus. This inability results in silencing of the *p16<sup>INK4A</sup>* gene, which normally acts as a tumor-suppressor that controls cancer cell proliferation [20].

The most frequently mutated subunits of the SWI/SNF complex in cancer are those with enzymatic functions (BRM/SMARCA2 and BRG1/SMARCA4) and those with DNA-binding properties (BAF250a/ARID1A, BAF250b/ARID1B, BAF200/ARID2 and BAF180/PBRM1). Even though the pattern of mutations varies from one tumor type to another, it is noteworthy that ARID1A ranks at the 4th position of Davoli's list of tumor-suppressor genes, turning it into one of the most important tumor-related genes [21]. Furthermore, a t(X,18) translocation, involving the SS18 subunit of the SWI/SNF complex, has been reported in ~100 % of human synovial sarcomas. This translocation creates an in-frame fusion between the *SS18* gene on chromosome 18 and either the *SSX1*, *SSX2* or *SSX4* gene on the X chromosome. These in-frame fusions impair the function of the SWI/SNF complex [22]. Since synovial sarcoma is uniquely characterized by the t(X,18) translocation [23], impairment of the SWI/SNF function is considered a central driver of this type of cancer. Other mechanisms that highlight the role of the SWI/SNF complex in cancer have been identified in human malignant rhabdoid tumors (MRT). Jagani et al. showed that activation of the Hedgehog (Hh) pathway in these tumors is due to absence of the SNF5 protein, which counteracts activation of the Hh pathway through the glioma-associated zinc finger-1 gene (*GLI1*) [24]. SNF5 dysfunction and its associated chromatin alterations are also known to be involved in various aspects of cancer biology, including cancer cell migration. Caramel et al. found e.g., that the high migratory properties of MRT cells are dramatically reduced upon SNF5 expression. SNF5 has been found to activate the expression of ARHGAP5, which in turn reduces the activity of the well-known pro-migratory small GTPase RhoA [25].

## 2.2 ISWI alterations in cancer

Chromatin remodeling ISWI complexes were initially purified from *Drosophila* embryos. ISWI complexes possess the ability to directly bind to core histones and, by regulating nucleosome spacing, affect gene transcription [26]. Like other ATP-dependent chromatin remodeling complexes, ISWI remodelers contain a conserved catalytic DEXD ATPase domain and a helicase domain. The ISWI family members are characterized by a combination of three C-terminally located domains, known as HAND, SANT and SLIDE. The SANT domain binds unmodified histone tails, the SLIDE domain

binds nucleosomal DNA near the histone octamer core, and the HAND domain is implicated in both histone and DNA binding/recognition [11, 27]. Mammalian cells express two orthologs of the *Drosophila* ISWI gene, i.e., SNF2L (SMARCA1) and SNF2H (SMARCA5). Combination of one of these two members with other subunits may give rise to at least eight different ISWI remodeling complexes (i.e., ACF1, CHRAC, RSF, CERF, NoRC, WICH, WCRF and NURF). Since almost all ISWI members are able to bind DNA and to mobilize nucleosomes, alterations in their functions may have profound effects on the primary chromatin structures, which in turn may have significant implications for cancer development. In fact, although it has been found that certain human cancer-derived cells may express SNF2L at levels similar to those in normal cells, inhibition of SNF2L expression has been found to dramatically effect cell viability, DNA damage response (DDR) and apoptosis in cancer-derived cells but not in normal cells [28]. Accordingly, over-expression of SMARCA5 (SNF2H) was found to positively correlate with TNM stage, tumor size, high proliferation index and poor overall survival in breast cancer [29]. Furthermore, over-expression of the RSF-1 subunit (which together with SNF2H is part of the RSF complex) has been observed in almost all oral squamous cell carcinomas (OSCC) and found to significantly correlate with the presence of abnormal mitoses, angio-lymphatic invasion, metastasis, tumor recurrence and advanced stage disease. Again, inhibition of RSF-1 was found to remarkably decrease cellular proliferation and to induce apoptosis in OSCC-derived cell lines [30]. Over-expression of RSF-1 has also been shown to promote chromosomal instability, to enhance tumor progression and to contribute to the aggressiveness of ovarian tumors [31–33]. Collectively, these findings indicate that ISWI chromatin remodeling factors may play crucial roles in cancer development, possibly in an oncogene-like fashion. Of note, Eckey et al. reported an opposite effect for SNF2L ablation in HeLa cells. They found that silencing of SNF2L enhanced the proliferation and up-regulated the expression of several oncogenes in these cells. Additionally, it was found that in normal melanocytes SNF2L is abundantly expressed, whereas in malignant melanoma cells it does not seem to be expressed at all [34]. The latter studies seem to contradict previous reports in which SNF2L activation was found to underlie cancer development. It should be stressed here that epigenetic mechanisms are likely to work together to bring about functional chromatin states and that local chromatin landscapes may be cell type-specific. This notion appears to be particularly true for the *ISWI* family because, even though their ability to order nucleosomes is altered in cancer, their deficiency may not be sufficient for malignant cell transformation. Additional alterations of remodelers/modifiers that regulate gene expression may be necessary to obtain full-blown transformation. In the end, it may not be surprising to find that specific proteins may have a

dual role, i.e., in certain cells or tissues they may act as tumor-enhancers whereas in others they may act as tumor-suppressors.

### 2.3 CHD alterations in cancer

The CHD family members differ from other remodeler proteins in that they possess two tandemly arranged chromodomains in the N-terminus of their catalytic subunit. Certain CHD remodeler complexes have the ability to slide or eject nucleosomes from DNA to promote transcription. Members of this family of complexes are CHD1 to CHD9, NuRD and dMec. The best studied CHD family member in cancer is NuRD. More than a decade ago the expression of the Metastasis-Associated Protein 1 (*MAT1*) gene, a component of the NuRD complex, was found to closely correlate with the aggressiveness of several cancer types [35]. In addition, it was found that exogenous over-expression of *MAT1* increased *in vitro* anchorage-independent growth and *in vivo* proliferation of breast and pancreatic cancer cell-derived xenografts [36, 37]. *MAT1* is able to activate the expression of Breast Cancer Amplified Sequence 3 (*BCAS3*), a gene that is located in chromosomal region 17q23, which contains several oncogenes and is amplified in ~20 % of primary breast tumors. It is associated with breast cancer progression and a poor prognosis [38, 39]. Next to these reports, a number of studies (reviewed by Basta et al. [40]) revealed that the NuRD complex plays an important role in regulating gene transcription, genome integrity and cell cycle progression, and that alterations in the activity of this multimeric complex can lead to cancer formation. The mechanisms proposed for this capacity are mainly based on the ability of the NurD complex to interact directly with DNA and histones and, by doing so, to (de)regulate gene expression and genome integrity.

As a result of improvements in whole genome sequencing technologies in recent years, allowing routine analysis of e.g., numerous tumor biopsies, also in other members of the CHD family DNA mutations have been detected. These observations have reinforced the idea of Gonzalez-Perez et al. [17] that alterations in chromatin remodeling complexes may act as cancer drivers. Indeed, somatic mutations affecting the chromatin remodeler CHD2 have been detected in chronic lymphocytic leukemia (5.3 %) and in monoclonal B lymphocytosis (7 %). Mutant forms of CHD2 were found to show altered nuclear distributions and defective associations with active chromatin [41]. Furthermore, it is worth noting that, with the exception of CHD5, mutations have been identified in all CHD family members in bladder, gastric and colon cancers. These studies have provided further evidence for the notion that the CHD proteins may play a broad role in cancer development, including an involvement in pathways related to DNA damage repair and nucleosome deposition/reposition [42–45].

A CHD family member that has only recently been linked to cancer is CHD4, i.e., high levels of CHD4 have been observed in a particular sub-population of EpCAM-positive cells in hepatocellular carcinoma (HCC) patients. Based on this observation, and since a role in chemoresistance and the maintenance of stemness of liver cancer stem cells has been proposed for CHD4 [46], it appears that chromatin and nucleosome (re) organization may play a role not only in cancer development but also in anti-cancer drug responses. Interestingly, not only CHD4 over-expression but also its absence seems to play a role in anti-cancer drug responses. Indeed, recent work has shown that loss of CHD4 expression confers cisplatin resistance to ovarian cancer-derived cell lines and that its re-expression is crucial for restoring drug sensitivity [47]. In addition, CHD4/Mi-2b has been found to be deleted in a considerable fraction (17 %) of endometrial cancers [48]. It has also been found that CHD8 mRNA expression levels are significantly down-regulated in gastric cancer tissues compared to normal gastric tissues, and that knockdown of CHD8 expression in gastric cancer-derived cell lines promotes proliferation [49]. Wang et al. made similar observations for another CHD family member, CHD5. They found that decreased CHD5 expression in gliomas was significantly associated with their pathological grade and that the overall survival of patients with a low CHD5 protein expression was shorter compared to those with a high expression [50].

### 2.4 INO80 alterations in cancer

INO80 complexes have been linked to DNA repair, DNA replication and H2A variant deposition/eviction. The INO80 family of proteins is characterized by the presence of a long insertion in its ATPase domain that directs complex assembly [51–55]. In mammals these complexes encompass three members, INO80, SRCAP and EP400 [56]. A comprehensive meta-analysis of whole-exome and whole-genome sequencing data has revealed that only a small sub-group of human tumors exhibits mutations in INO80 family members. This observation raises the possibility that the involvement of INO80 in cancer development may not be due to DNA mutations, but rather to altered gene expression levels [57]. Accordingly, Raymond et al. reported that a component of the INO80 complex, Reptin (also known as RUVBL2), which is frequently over-expressed in hepatocellular carcinomas, is able to sustain cancer cell growth. After Reptin inhibition, hepatocellular carcinoma cells were found to become more sensitive to etoposide and  $\gamma$ -irradiation, and a concomitant reduction in cellular growth and colony forming capacity was observed [58].

The SRCAP complex, as INO80, is involved in DNA repair and is able to incorporate the H2A.Z variant in mononucleosomes in order to act as a co-activator of transcription [59–61]. Through its ability to control transcription, SRCAP

is e.g., able to regulate the expression of the prostate specific antigen (PSA) in patients with prostate cancer. Indeed, knock-down of SRCAP has been found to result in decreased H2A.Z binding to the enhancer region of the PSA promoter, as also to a significant inhibition of androgen-dependent prostate cancer cell growth [62]. Furthermore, up-regulation of SRCAP expression has been found in primary prostate tumors with a biochemical recurrence (i.e., increased PSA level) compared to primary prostate tumors without a biochemical recurrence [63]. Next to altered SCARP expression levels, recently published whole-genome sequencing data revealed recurrent SRCAP mutations in glioblastomas, bladder cancers and colon cancers [43, 64, 65]. A direct involvement of these mutations in cancer initiation and/or progression, however, remains to be established.

### 2.5 HELLS alterations in cancer

Helicase, lymphoid-specific (HELLS) belongs to the Snf2-like group of ATP-dependent helicases [9]. It acts in DNA double-strand break repair and is required for phosphorylation of H2A.X [66]. Its function is also required for the modulation of genome-wide cytosine methylation patterns at repeat and non-repeat sequences and for maintaining nucleosome density [67, 68]. An involvement of HELLS in cancer has been reported since 2000. HELLS (also denoted as PASG) mRNA e.g., exhibits a high frequency of in-frame 75-nucleotide deletions in acute myelogenous leukemia and acute lymphoblastic leukemia samples [69]. Yano et al. found a particular splicing variant of HELLS, i.e., a 44-nucleotide insertion between exons 3 and 4, exclusively in tumor tissues of non-small cell lung cancer patients [70]. Whereas the latter two studies do not provide direct experimental proof of an involvement of aberrant HELLS mRNA in cancer development, recent work has shown that an abnormal chromatin remodeling activity of HELLS may contribute to it. In these studies it was shown that HELLS can interact with the cancer-related TF E2F, thereby enhancing E2F target gene induction and subsequent cell cycle re-entry. The authors also found that HELLS, as well as E2F3, is over-expressed in several human tumors. Importantly, silencing of HELLS by short hairpin RNA (shRNA) was found to be sufficient to impair the activation of E2F target genes and to mitigate cell proliferation, even in E2F over-expressing cells [71, 72].

### 2.6 SMARCAD1 alterations in cancer

The SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A containing DEAD/H box 1 (SMARCAD1) belongs to the Ino80-like subfamily of chromatin remodelers [9]. It ensures that chromatin remains silenced in critical regions, such as the peri-centromeric heterochromatin region, in dividing cells [73]. An early study mapped *SMARCAD1* (also denoted as Hhhl1) to the q22–

q23 region of human chromosome 4 and reported that this region bears breakpoints and deletions of genes involved in neoplastic disorders such as leiomyosarcomas, hepatocellular carcinomas and several hematologic malignancies. The author of this early study hypothesized that alterations of the SMARCAD1 locus may play a role in genetic instability and, consequently, cancer development [74]. Recent work has shown that changes in the SMARCAD1 locus are frequently encountered in cancer. The SMARCAD1 locus has for example found to be frequently deleted in tumor tissues of colorectal cancer patients [75] and a meta-analysis revealed that changes in the SMARCAD1 locus are associated with testicular germ cell cancer [76]. Furthermore, Cetin et al. found that loss of heterozygosity for the *SMARCAD1* gene frequently occurs in head and neck squamous cell carcinomas [77]. Even though more studies are required to substantiate these findings, the data gathered up till now suggest a potential tumor-suppressor role of SMARCAD1 to silence chromatin domains and to maintain genome stability. This notion is supported by very recently published work in which SMARCAD1 expression was found to be associated with an increase in overall survival of bladder cancer patients [78].

## 3 Covalent post-translation histone modifications

Histones, as mentioned above, represent the subunits that form nucleosomes. They constitute highly basic nuclear proteins and are among the best evolutionary conserved proteins in eukaryotes. Their N-terminal domain represents a characteristic sequence of amino acids (tail) that protrudes from the core histone. Both histone tails and core domains undergo covalent post-translational modifications. These modifications are not permanent and can be tuned in order to modify interactions between nucleosomes and DNA, which serve to change the primary structure of chromatin [79–81]. Indeed, structural changes resulting from histone modifications may render the chromatin permissive or non-permissive to processes that use DNA as a template, including transcription, DNA replication and repair, and chromosome segregation. To date there are at least eight different classes of histone modifications, including lysine (K) (1) acetylation, lysine mono-, di-, and tri- (2) methylation and arginine (R) methylation, serine (S) and threonine (T) (3) phosphorylation, lysine (4) ubiquitination, glutamate (E) (5) poly-ADP ribosylation, lysine (6) sumoylation, arginine (7) deimination and proline (P) (8) isomerization [82]. Histone modifications are executed by enzymes that can be grouped into two families: (1) “writers”, enzymes that deposit the modification and (2) “erasers”, enzymes that remove the modification. Furthermore, histone marks can be “read” by functional proteins that bind to specific histone modifications, thereby leading to its corresponding functional consequences. Prominent examples of such

marks are H3K4 methylation, H3K9 methylation and H3K27 methylation, which are recognized (“read”) by inhibitor of growth (ING) proteins, heterochromatin protein 1 (HP1) and polycomb proteins [79]. Besides methylation, also acetylation of lysine residues can be “read” by evolutionarily conserved proteins involved in the regulation of chromatin dynamics and gene expression. The recognition of acetyl-lysine residues primarily occurs by proteins containing a functional domain, named bromodomain, which exhibits a high affinity for regions harboring multiple lysine acetylation sites [83]. Within the human proteome 61 proteins containing bromodomains have been identified. These bromodomain-containing proteins are found both in the nuclear and cytoplasmic compartments of the cell and include members of modifier enzymes, SWI/SNF-related helicases (such as SMARCA5) and chromatin remodeling complexes, transcriptional co-activators and mediators, nuclear scaffolding proteins and proteins belonging to the bromodomain and extra-terminal (BET) family [84]. The fact that many enzymatic complexes related to chromatin remodeling bear the ability to “read” acetylation patterns at regulatory domains indicates how deep and complex the interplay between alterations in histone modification patterns and transcription regulation programs linked to phenotypic changes can be. Like most biological processes, covalent histone post-translational modifications can be deregulated, resulting in disease. Since histone modification patterns are mitotically heritable, they can play the same roles and undergo the same selective processes as genetic alterations in the development of cancer. Nevertheless, unlike genetic alterations, abnormal histone modifications can be recovered by blocking the aberrant enzymatic activities that sustain them. Previous epigenetic studies have e.g., revealed altered acetylation patterns of histone tail residues in cancer genomes [85]. Shortly thereafter clinical trials were started to test histone deacetylase inhibitors (HDACIs) in cancer patients with promising results [86]. HDACIs constitute a class of anti-cancer drugs that belong to a broader category, named “chromatin modifying agents”. Indeed, by modifying the activity of epigenetic factors and thus by altering gene expression, HDACIs may bring about a multitude of effects in downstream pathways of cells, culminating in cytotoxicity [87, 88]. Although it is known that all histone proteins can undergo post-translational modifications, until recently the cancer community focused mainly on those affecting histones H3 and H4, i.e., H3K4me3, H3K4me1, H3K27ac, H4K8ac and H4K16ac, that by recruiting on-site remodeling complexes, promote nucleosome sliding or eviction to create nucleosome-free regions. These nucleosome-free regions are accessible to TFs leading to gene activation. In this regard, it is important to realize that only a few TFs, named “pioneer TFs”, are able to bind DNA wrapped around nucleosomes, whereas all others require nucleosome-free DNA to bind to specific regulatory elements [89].

Conversely, regulatory regions, gene loci or even entire chromosomes can be inactivated or silenced by histone modifications (e.g., H4K20me3, H3K27me3 or H4K20me3), leading to chromatin compaction. Also in these cases remodeling complexes are recruited and nucleosomes are remodeled. In addition, it has recently been found that besides modifications in histone-tail residues, also modifications (e.g., phosphorylation) in histone-core residues may result in chromatin conformation changes and, subsequently, DNA template-based processes (81, 82). Finally, particular chromatin domains may undergo both activating and repressing histone modifications. These domains are active mainly during cell differentiation and development and are called bivalent domains [90].

### 3.1 Deregulation of post-translation histone modifications in cancer

Although the classical function of histone proteins is DNA packaging, chromatin structures are highly dynamic and can undergo local or global conformational changes. Histone acetylation and phosphorylation reduce the positive charge of histones, whereby electrostatic interactions between histones and DNA are disrupted. Such conformational changes facilitate DNA access to proteins such as those involved in transcription. Acetylation may occur on various histone tail lysine residues, including H3K9, H3K14, H3K18, H4K5, H4K8 and H4K12 [77]. Methylation of histone tail lysine residues (e.g., H3K4, H3K9, H3K27 and H4K20) also plays a pivotal role in transcription regulation. In contrast to lysine acetylation, mono-, di-, or tri-methylation of lysine residues does not reduce the positive charge of histones, and thus studies have long focused on identifying domains and proteins that recognize (“read”) these marks, rather than on the concomitant changes in chromatin structure itself [91].

Histone modifications can occur at virtually all functional residues at both the local and the global level. Global loss of tri-methylation of H4K20 (H4K20me3) and loss of acetylation of H4K16 (H4K16Ac) have been observed, along with DNA hypo-methylation, at repetitive DNA sequences in various primary tumors [92]. Further evidence for the role of lysine methylation in cancer comes from direct comparisons of chromatin changes in normal and malignant tissues. In a recent study it has been shown that in distinct groups of promoters loss of H3K27me3 (repressive mark) was associated with an accumulation or retention of H3K4me3 (active mark) in human colorectal cancers. These promoters, with bivalent properties, were able to control the transcription of many cancer-promoting genes such as *SNAI2*, *CCND1*, *RRM2*, *MKI67*, *CLDN1*, *EPCAM*, *COX2/PTGS2* and *MET* [93]. Alterations in modification patterns affecting histones H2A and H2B, which affect gene expression, have also been found in cancer cells. For example, a highly mono-ubiquitinated

histone H2A (a chromatin modification associated with transcription repression) due to up-regulation of the H2A-specific ubiquitin ligase TRIM37, has been found in breast cancer [94], whereas loss of H2B mono-ubiquitination (a chromatin modification associated with transcription activation) has been found in several other human cancers [95]. In the first case, the authors showed that the TRIM37 ligase targets and ubiquitinates H2A at regulatory domains of more than 7600 genes, 469 of which have been recorded as putative tumor-suppressor genes [94]. In the second case, loss of mono-ubiquitination of H2B results in impairment of the tumor-suppressor gene cell division cycle 73 (*CDC73*). Indeed, in many cancers *CDC73* is mutated or down-regulated. *CDC73* binds the E3 ubiquitin-ligase RNF20–RNF40 complex and is indispensable for H2B-K120 mono-ubiquitination, both *in vivo* and *in vitro* [96].

As stated above, histone mark patterns are mitotically heritable and may contribute to evolutionary processes that culminate in selection of the most aggressive tumor cell phenotypes. Global histone mark analyses of human cancers including prostate, lung, gastric, breast and esophagus cancer, as well as acute myeloid leukemia, revealed highly significant correlations between histone modifications, biomarker phenotypes and clinical outcomes [97–102]. Silencing of crucial genes, e.g., those that maintain genome stability, may trigger tumor progression through alterations in cellular homeostasis. In mammals, two main protein groups, named Polycomb Repressive Complex 1 and 2 (PRC1 and PRC2), control chromatin compaction through the addition of methyl groups to H3K27. In cancer cells, components of PRC1 and PRC2 such as EZH2 and EZH1 have been found to be up-regulated, mutated or down-regulated [103–106]. Although PRC1/2-dependent methylation normally targets repressive domains that must remain silenced after differentiation, some loci may exhibit bivalency and be targeted by PRC1/2 even after terminal differentiation [107]. These latter domains are in general found in DNA segments near cancer-related genes that act as promoters or enhancers. An example of a mechanism through which abnormal chromatin compaction at bivalent domains may cause cancer is the PRC2-dependent silencing of the *Ink4/Arf* locus (also known as the *Cdkn2a* locus). This locus encodes the tumor-suppressors  $p16^{\text{Ink4a}}$ ,  $p19^{\text{Arf}}$  and  $p15^{\text{Ink4}}$  that are silenced in many cancer types due to enhanced PRC2 activity [108, 109]. However, not only enhanced activity of polycomb proteins may cause cancer. Indeed, though in many tumor types PRC2 components are over-expressed, it has been found that in breast cancer [105] and in malignant peripheral nerve sheath tumors [106] loss of PRC2 activity promotes tumorigenesis and genome instability. As such, this loss may potentially be used as a biomarker. Furthermore, EZH2 change-of-function mutations have been reported as putative cancer-causing, mainly in lymphomas [104]. Also interesting is the observation that transcriptional changes due to

EZH2 loss are predominantly irreversible [105]. Accordingly, it is now clear that the balance between activating and repressing marks plus nucleosome distribution dictate chromatin dynamics and gene expression that, in turn, lead to permanent phenotypical changes. Indeed, new insights are gradually changing the concept of “histone code” in that gene repression is tightly correlated to the state of chromatin compaction and not necessarily to H3K27me3 levels in cancer cells [110].

## 4 Histone variants

Histone variants represent a small percentage of the total cellular histone pool and they most frequently occur in the H2A, H3 and H1 families [111]. These variants may exhibit temporal and tissue-specific expression patterns and require histone chaperones and remodeling complexes in order to be incorporated [112]. Based on their tissue-specificity they may confer novel structural and functional properties to nucleosomes, which are brought about by specific chromatin remodeling and histone modifying factors. Since histone variants possess unique abilities to regulate key cellular processes, their deregulation is anticipated to contribute to cancer initiation and/or progression. In recent years various variants have been identified in the three histone families mentioned above. For H2A the following five variants are currently known: H2A.X, H2A.Z, macroH2A1/2 (mH2A1/2), H2A.B (Barr body-deficient) and H2A.J [113]. For H3 so far eight variants have been reported: H3.1, H3.2, H3.3, H3t (H3.4), H3.5, H3.X, H3.Y and CENP-A [114], whereas for histone H1 the variants identified so far are: H1.0 to H1.5, H1t, H1T2, H1x and H1oo [115].

### 4.1 H2A variants and cancer

Dardenne et al. reported that mH2A1 splicing isoforms are differentially expressed in primary breast cancers that either give rise to metastases or not, and that these isoforms differentially regulate breast cancer cell invasiveness through transcriptional regulation of genes involved in redox metabolism, including the *SOD3* gene [116]. Another H2A variant that has been found to be over-expressed in metastatic melanoma and to be associated with a poor prognosis is H2A.Z. For this variant it has been reported that it is associated with highly expressed cell cycle regulatory factors that acquire a unique H2A.Z occupancy signature in melanoma cells, i.e., enriched in the promoter region and depleted in the gene body [117]. The same researchers also uncovered tumor suppressor roles for histone mH2A variants. Generally, loss of mH2A variants is associated with chromatin condensation and altered gene expression. The authors reported that knockdown of mH2A variants in melanoma cells increased their proliferation and migration *in vitro*, as well as their metastatic growth *in vivo*

through up-regulation of the *CDK8* gene [118]. Subsequently, the potential tumor suppressor role of mH2A variants was confirmed in another study. Novikov et al. found that alternative splicing of the mH2A1 pre-mRNA, which leads to a decrease in mH2A1.1 expression, occurs in a variety of cancers, including testicular, lung, bladder, cervical, breast, colon, ovarian and endometrial cancer [119]. Since it has been shown that mH2A acts as a predominant barrier to cell-reprogramming [120] and since many analogies exist between cancer development and cellular reprogramming, the tumor suppressor effects may be related to the ability of mH2A to keep chromatin in an unfavorable silenced state, especially at sites where growth promoting genes (oncogenes) are located.

#### 4.2 H3 variants and cancer

CENP-A is a histone variant that has several functions. It is e.g., required for centromere formation and maintenance [121] and it forms a platform for kinetochore assembly, thereby allowing proper chromosome segregation [122]. It is, therefore, not surprising that incorrect deposition, expression or mutation of CENP-A may have severe consequences for the stability of the genome. It has in recent years amply been shown that CENP-A may be over-expressed in different human cancers including colorectal, lung, testicular, breast and hepatocellular cancers and osteosarcomas, and that its expression level may be associated with tumor grade [123–129]. However, the exact mechanisms underlying cancer development due to CENP-A over-expression are still poorly understood. Some answers may be deduced from recent work performed in human colorectal cancers and its derived cell lines. Athwal et al. for example found that when CENP-A is over-expressed, it localizes not only to centromeres but also to non-centromeric regions such as DNase I hypersensitive sites, TF binding sites and gene promoters across the human genome. Among these domains, the authors found that CENP-A nucleosomes clustered at a sub-telomeric site (8q24) where the well-known and often amplified oncogene *c-MYC* is located, thereby suggesting a possible involvement in chromosome instability and cancer development [130]. Additional evidence supporting a putative cancer-inducing role for CENP-A over-expression came from a study performed on prostate cancer cells. By inhibiting the cyclooxygenase-2 (*COX-2*) gene, which encodes an enzyme involved in the prostaglandin pathway, a dramatic down-regulation of CENP-A and other key proteins involved in kinetochore/centromere assembly was observed. Following this down-regulation, prostate cancer cell proliferation was found to be arrested, thereby underscoring a pivotal role of centromere assembly deregulation in cancer initiation and/or progression [131].

As mentioned above, not only alterations in histone variant expression may underlie human cancer development, but also

histone variant mutations may act as such by altering its interactions with DNA or chaperone proteins. Indeed, recent exome sequencing studies have uncovered frequent H3.3 mutations in pediatric glioblastomas multiforme (31 %) and diffuse intrinsic pontine gliomas (78 %) [132, 133]. In both cases the mutation hot spots identified led to amino acid substitutions at two critical positions within the N-terminal tail of histone H3, which are associated with either transcription repression (K27) or activation (K36). Of note, it is known that this highly conserved N-terminal tail influences the dynamic regulation of chromatin structure and accessibility.

Finally, a recent high throughput study performed on follicular lymphomas has uncovered several mutations in H1 variants. Overall, mutations affecting at least one of the H1 variants were observed in 28 % of the samples tested, with the HIST1H1C (H1.2) and HIST1H1E (H1.4) variants being most frequently mutated. Most of the histone H1 mutations represented missense variants and were found to be clustered in the highly conserved globular domain affecting residues directly involved in DNA binding. To substantiate the impact of these mutations on the stability of the primary chromatin structure, mouse embryonic stem cells (mESCs) harboring multiple mutated H1 variants were generated. These mESCs showed impaired associations of the mutant H1 variants with chromatin compared to the respective wild-type proteins, which is indicative of a loss-of-function scenario affecting chromatin compaction and gene regulation [134].

#### 5 Nucleosome dynamics and cancer

As indicated above, nucleosomes can inhibit the access of a wide range of DNA-binding proteins to DNA. At the transcription start sites (TSS) of genes nucleosomes are e.g., known to be located at the tightest positions designated as  $-1$  (upstream the TSS) and  $+1$  (downstream the TSS) [135]. The TATA-binding protein, a basic component of the RNA polymerase II transcription machinery, is known to be unable to bind nucleosomal DNA and to require nucleosome-free regions to bind core promoters and to initiate transcription [136]. Moreover, only a few TFs called “pioneers” (e.g., FoxA and GATA) can bind their target sites in the context of nucleosomal DNA, all others require nucleosome-free DNA [89].

High-resolution genome-wide analyses in model organisms and healthy human donors have revealed a common pattern of nucleosome distribution, i.e., they are mostly depleted at enhancer, promoter and terminator regions, and typically occupy preferred positions in coding and non-coding regions [137–139]. Furthermore, nucleosome distributions around TSSs are highly organized. Indeed, the 5' end of the  $+1$  nucleosome in active promoters peaks at  $+40$  bp relative to the TSS, whereas the 5' end of the  $+1$  nucleosome in inactive



promoters peaks at +10 bp relative to the TSS. A similar distribution was observed for the 3' end [140]. Interestingly, the RNA polymerase II binding sites at promoter regions of active genes peak around +10 bp relative to TSSs, thus overlapping with the nucleosome peak in inactive promoters.

In addition, the positions of nucleosomes along the DNA as well as the chromatin architecture have been linked to the functionality of the splicing machinery. It has been suggested that in eukaryotic genomes marking of exons by nucleosomes may play a role in defining the exon-intron design of genes [141]. Surprisingly, Schwartz et al. found that the length distribution of exons among all analyzed metazoans peaks between 125 and 165 bp, which is in marked conformity with the 147 bp of DNA that is wrapped around a mono-nucleosome. Taken together, it may be concluded that the nucleosomal context may be critical for several activities that involve DNA. As such, factors involving its (de) regulation are under intense investigation by the oncology community.

### 5.1 Nucleosome positioning, DNA mutation and repair

Mutations arise because cellular genomes are continuously exposed to DNA damage induced by either external sources such as irradiation and carcinogens, or endogenous sources such as the generation of oxidative products. To guarantee cellular homeostasis and to avoid genomic instability, several mechanisms have evolved to both detect and repair DNA damages [142]. Mutations are, however, not always recognized and corrected and, as such, they can be transmitted to daughter cells to generate cellular clones that will permanently bear these mutations. Since nucleosomes affect DNA accessibility, they are able to alter the susceptibility of DNA to mutate or to be repaired at specific sites. In fact, correlations between chromatin structures, DNA variations, single nucleotide polymorphisms (SNPs) and mutations around TSSs have been investigated in detail [143, 144], as well as at selected nucleotide positions in the vicinity of intron-exon boundaries [145] and, very recently, at the whole-genome level [146]. This work has provided ample indications that DNA mutations are not randomly distributed along a given genome. Similar to normal genomes, the mutation rate of cancer genomes seems to be influenced by the primary chromatin structure. In a recent study, Polak et al. analysed the distribution of cancer-associated genetic mutations in a total of 173 genomes from 8 different cancer types [147]. They found that chromatin accessibility, together with modification and replication timing, could explain up to 86 % of the variance in mutation rates among cancer genomes. Interestingly, this study also showed that, since chromatin primary structure and nucleosome distribution are cell type-specific, the susceptibility of DNA to mutate at specific sites (“hotspots”) is also cell type-specific. It is important to note here that cell type-specific mutations have important implications for cancer biology. In

fact, according to the COSMIC data base (Catalogue of Somatic Mutation in Cancer, <http://cancer.sanger.ac.uk/cosmic>), the *KRAS* gene is e.g., commonly mutated in human pancreatic cancer (>57 %), but rarely in human breast cancer (<2 %). A possible explanation for such a tissue-specificity could be that in normal breast tissue the *KRAS* chromatin structure has a different conformation (i.e., nucleosome distribution and density) than in normal pancreatic tissue. Other noteworthy findings reported by Polak et al. are that: (i) active chromatin and transcriptional activity are associated with a low mutation density, whereas repressive chromatin features are associated with regions of high mutation density and (ii) the local density of somatic mutations is highly reduced specifically in accessible regulatory DNA domains, since the DNA repair machinery has an easy access to these domains [147, 148]. The same variation has also been observed in another study aimed at assessing diverse genetic and epigenetic features and their interplay with DNA mutations. Schuster-Bockler and Lehner found, through bioinformatic analyses of genomic data, that a single feature such as the level of H3K9me3 could account for more than 40 % of the mutation rate variation and that, by using more features, it was possible to explain over 55 % of this variation. They also found that heterochromatin and euchromatin domains are critical for regional mutation rate variations in somatic cells [149]. Hodgkinson et al. assessed the genomic distribution of mutations taking into account, among others, the nucleosome occupancy in two different cancer types, i.e., skin and lung cancer. They found that the density of mutations correlated with the nucleosome occupancy score, but that the two tumor types showed different associations, i.e., positive in skin cancer and negative in lung cancer, although nucleosome occupancy scores were highly correlated between the different tissues [150]. Again, it can be hypothesized that the cell-type specific variation may depend both on global and local chromatin landscapes. Moreover, it may be postulated that local rotational DNA changes may affect the rate of mutation, since mutated nucleotides facing inward or outward of the nucleosome core may be repaired at different rates. This notion is relevant since the orientation of DNA sequences on the nucleosome surface, as mentioned previously, determines its accessibility and the activity of nuclear factors. A rotational change may be caused for example by a small (2–3 nucleotides) insertion or deletion (“indel”) or even a SNP in DNA surrounding a nucleosome. Interestingly, a statistically significant association between SNPs in the *TP53* gene and somatically acquired *TP53* mutations has been found in liver and lung cancers, but in these studies the nucleosome distribution at the *TP53* locus was not investigated [151, 152]. Moreover, it has been found that in cancer SNPs and indels are enriched within nucleosomal DNA, suggesting that the nucleosomal architecture may have a substantial impact on cancer through increased mutation rates within the core particles [146].

Chromatin structure is also emerging as a feature for the activation of DNA repair pathways, not only as a barrier as discussed above. Indeed, the presence of heterochromatin has been found to delay DNA damage responses and to impair homologous recombination [153], whereas DNA damage responses are activated at double strand breaks located within actively transcribed genes residing in euchromatin [154, 155]. Additional evidence on nucleosome density and DNA repair rate in cancer genomes has been reported by Zheng et al. [156]. These authors analyzed tumors from patients with xeroderma pigmentosum (XP), which is associated with defects in nucleotide excision repair, and concluded that transcription may reduce the mutation prevalence specifically by relieving the constraints imposed by chromatin structure on DNA repair. It seems that the action of some oncogenes may also directly be related to chromatin condensation. Kalousi et al. found that the nuclear oncoprotein SET is able to retain KAP1 and HP1, two transcriptional mediators, to chromatin. This retention translates into a more compact chromatin, which impairs DNA damage responses and homologous recombination-mediated DNA repair [157]. Changes in chromatin structure and DNA repair rate also seem to be linked to cancer progression. This latter conclusion was drawn by Gkatzamanidou et al., who studied chromatin architecture associated with three loci (NRAS, p53, D-globin) in multiple myelomas. The authors reported a progressive increase in the loosening of the local chromatin structure, the gene expression level and the DNA repair efficiency as the disease evolved from a benign to a full-blown phenotype [158].

## 5.2 Nucleosome positioning and gene expression

A distinctive characteristic of cancer cells is the aberrant expression of oncogenes and tumor suppressor genes, which allows uncontrolled growth. The position of nucleosomes marks the TSSs of these genes [7, 135]. Hesson et al. reported that altered nucleosome distribution at these TSSs, and thus alterations in their primary chromatin structure, may represent an early event in cancer development [159]. The same group also reported an involvement of nucleosome distribution in acquired drug resistance. In a colorectal cancer-derived cell line subjected to decitabine treatment (a DNA hypomethylating agent), they found that the *MLH1* gene was re-silenced because of a rapid reassembly of nucleosomes at the TSS of this gene [160].

Aberrant chromatin acetylation has been linked to pathological genomic rearrangements in NUT midline carcinomas (NMC), a subtype of squamous cell carcinomas that is one of the most aggressive human solid malignancies known. Alekseyenko et al. found that the chromatin regulator BRD4-NUT tends to accumulate at regions enriched in H3K27ac and to form large nuclear foci called megadomains. Although the locations of these megadomain are typically cell

type-specific, the authors showed that the *c-MYC* and *TP63* regions were targeted in all NMCs tested and played functional roles in tumor growth [161]. Finally, nucleosome occupancy has been proven to be extremely important for activation of the cancer-testis antigen and androgen receptor co-activator MAGEA11, which is commonly over-expressed in prostate and other cancer types. It has been shown that nucleosome occupancy specifically at the  $-1$  position of the TSS of *MAGEA11* was altered in cancer-derived cell lines compared to control cell lines and that depletion of nucleosome  $-1$  enhanced the binding of transcription factors and RNAase polymerase II which, in turn, led to *MAGEA11* over-expression [162].

## 6 Conclusions and perspectives

Although chromatin remodeling, histone modification and nucleosome (re) positioning have been discussed here separately, it should be stressed that the ultimate epigenetic control over eukaryotic genomes results from a concerted action of these different processes. Indeed, a synchronized execution of histone modifications and nucleosome deposition/removal allows a correct realization of the genetic information present within the DNA. Despite the fact that the molecular mechanisms underlying chromatin remodeling have been elucidated in detail in several model organisms, the involvement of similar networks and factors has yet to be defined in detail in various human diseases, including cancer. For example, questions such as the distribution of nucleosomes along the entire human cancer genome, the role of nucleosomes at non-regulatory and non-coding domains, as well as potential interactions with non-coding RNAs need to be answered in order to fully understand the interplay between the primary chromatin structure and cancer development. In addition, although it is known that the chromatin structure affects the susceptibility of DNA to be repaired and/or to mutate, up till now only few studies have addressed the question whether the most frequently mutated hotspots in cancer are located in nucleosomal or in nucleosome-free DNA regions. Gaining such detailed knowledge may be highly relevant for the prediction of tumor cell behavior and, ultimately, cancer prevention. Recently, whole genome sequencing has revealed mutations in a multitude of epigenetic regulators in various cancers. These novel data should be investigated in further detail in order to establish direct relationships between such epigenetic alterations and cancer development, and to uncover new ways to specifically target these alterations. Since epigenetic deregulation, unlike genetic mutation, may be reverted by restoring or blocking specific enzymes, drugs that re-establish the epigenetic balance may represent exciting new therapeutic options. Finally, the involvement of chromatin alterations in acquiring drug resistance is becoming clear now. As we continue to

explore the molecular (de) regulation of chromatin in cancer, effective preventive strategies could be based on new epigenetic biomarkers able to predict acquired resistance in response to specific anti-cancer treatments.

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#### Compliance with ethical standards

**Conflict of interest** Nothing to declare.

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