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Chromatin remodeling in Cancer: A Gateway to regulate gene Transcription

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ABSTRACT

Cancer cells are remarkably adaptive to diverse survival strategies, probably due to its ability to interpret signaling cues differently than the normal cells. It appears as if cancer cells are constantly sampling, selecting and adapting signaling pathways to favor its proliferation. This process of successful adaptive evolution eventually renders a retractile nature to therapeutic regimens, fueling to the process of cancer progression. Based on plethora of available information, it is now evident that multiple signaling pathways eventually converge, perhaps, in a tempo-spatial manner, onto DNA template-dependent dynamic processes. Considering the complexity and packaging of eukaryotic genome, this process involves energy-dependent sub-events mediated by chromatin remodelers. Chromatin remodeler proteins function as gatekeepers and constitute a major determinant of accessibility of accessory factors to nucleosome DNA, allowing a wide repertoire of biological functions. And thus, aberrant expression or epigenetic modulation of remodeler proteins confers a unique ability to cancer cells to reprogram its genome for the maintenance of oncogenic phenotypes. Cancer cells can uniquely select a multi-subunit remodeler proteome for oncogenic advantage. This review summarizes our current understanding and importance of remodeler and chromatin proteins in cancer biology and also highlights the paradoxical role of proteins with or without dual-regulator functions. It is our hope that an in-depth understanding of these events is likely to provide a next set of opportunities for novel strategies for targeted cancer therapeutics.

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1. Introduction

Cancerous cells are empowered with advantageous traits that are favored by natural selection (Merlo et al., 2006). Targeting cancer has had limited success due to the diverse nature of cell lineages with adaptive advantages that can collectively over-ride cellular checkpoints, leading to uncontrolled growth and proliferation (Krebs and Peterson, 2000). Modulation of chromatin is critical for cellular proliferation and it is not surprising that alteration of chromatin structure is often observed in cancer cells. Since the initial description of "chromatin" in the 1880's by William Flemming, our understanding of the regulatory role exerted by chromatin structure for cellular processes has undergone a complete metamorphosis (Olins and Olins, 2003). Based on the plethora of current information over two decades, it is evident that deregulation of chromatin structure is often associated with cancers.

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In a eukaryotic cell, genes are coordinately activated or repressed to ensure cellular homeostasis. In addition to a constant need to modulate the levels of expression of a large number of genes, mammalian cells are also faced with a topological challenge of packaging genetic information (about 2 m DNA) into the nucleus (Clapier and Cairns, 2009). An evolutionary solution to this problem is the unique ability of the mammalian cells to package the DNA into higher order structures, commonly referred to as chromatin. The basic building blocks of chromatin are nucleosomes that are composed of 146 base pairs of DNA wrapped around an octamer containing two each of four core DNA packaging proteins-histones H2A, H2B, H3, and H4. The nucleosomes are further folded with the aid of linker histone H1 and non-histone proteins into an ordered, compact nucleoprotein complex (Saha et al., 2006; Thomas and Kornberg, 1975). Chromatin can be functionally divided into two subtypes, euchromatin and heterochromatin. Only about 1.5% of the human genome encodes for genes and very little of this coding sequence is present in heterochromatin (Babu and Verma, 1987).

To fulfill cellular needs, genes that reside in euchromatin are continually undergoing regulated structural changes to allow for template-dependent processes like gene activation or repression. These functionally opposite events require dynamic packaging and unpacking of DNA elements, such as promoters and enhancers that control these events need to be exposed to provide access to regulatory factors and complexes. Hence, expression of genes must not only involve the general transcription machinery and specific transcription factors, but also largely depend on proteins capable of modifying the chromatin architecture. These unique proteins are called chromatin remodeling proteins or remodelers (Cairns, 2001, 2007).

The last decade has witnessed an unprecedented explosion of knowledge in the areas of chromatin remodeling complexes and epigenetic control of gene regulation (Jiang et al., 2004; Stein et al., 2010). Remodeler proteins actively seek collaboration with other cellular proteins to exert a master control of reversible DNA packing and unpacking, and thus, providing packaging solutions to regulatory machineries. Since transcriptional control is essential for living processes, it is not surprising that genetic alterations in chromatin remodeling components are intimately linked with cancer (Jones and Baylin, 2007; Shain et al., 2012).

Chromatin is an important and dynamic central regulator of transcription. A large number of genomic loci that are repressed in the physiologic state are activated by an aberrant expression and/or activity of remodelers in cancerous cells in response to deregulated oncogenic signals (Ellis et al., 2009). Therefore, deregulation of chromatin leads to altered gene activation and/or inappropriate gene silencing. Recent studies suggest that gene-translocations leading to fusions of transcription factors promote oncogenesis by altering chromatin structures (Di Croce, 2005; Donehower et al., 1992; Martens and Stunnenberg, 2010; Mitelman et al., 2007; Uribesalgo and Di Croce, 2011; Cairns 2001, 2007). In addition, several tumor suppressors such as retinoblastoma (pRb), p53 and Ini1/hSNF5 which utilize chromatin remodeling as part of its normal functions are also misregulated in certain cancers (Gregory and Shiekhattar, 2004; Hickman et al., 2002). Furthermore, changes in the epigenetic landscape are under a constant dynamic regulation in cancer. This chapter captures some of the groundbreaking research that has connected chromatin misregulation to cancer and presents selected key findings and major challenges that lie ahead.

2. Chromatin remodelers from past to present

The discovery of chromatin sparked a surge of interest in the scientific community to understand the impact of the condensed structure of DNA-histones on gene regulation. One landmark discovery that propelled this research came from the pioneering work of Weintraub and Goudine, who proposed that active and inactive chromatin can be distinguished by measuring sensitivity of chromatin to nucleases (Weintraub and Groudine, 1976). Active chromatin within eukaryotic cells was easily accessible to nucleases like DNase1 and was described as hypersensitive sites (Gross and Garrard, 1988; Krebs and Peterson, 2000; Yu et al., 1994). The work also demonstrated that generation of hypersensitive and resulting sensitivity to nucleases is the outcome of conformational change within the condensed chromatin (Carruthers and Hansen, 2000; Hansen, 2002; Horn and Peterson, 2002). Therefore, complex eukaryotic genome could be visualized as nuclease-sensitive or -insensitive zones. Many laboratories have utilized high resolution chromatin mapping to explain nuclease sensitivity of chromatin (Song and Crawford, 2010). Genetic screens carried out by Stern and colleagues in 1984 provided the first glimpse of these complex events during the course of discovery of the SWI/SNF complex, which turned out to be an essential regulator of mating-type switching in the yeast (Stern et al., 1984). Biochemical purification of the SWI/SNF complex was independently carried out in several laboratories, leading to the presence of an ATPase enzymatic activity in the complex (Peterson et al., 1994; Peterson and Tamkun, 1995). Further analysis of the higher order of histone octamer structures provided a new generation of biochemical tools for understanding the chromatin structure (Schwarz and Hansen, 1994). This was followed by the demonstration of the ability of the purified SWI/SNF complex to exhibit an increased nucleosomal accessibility using a reconstituted DNA template in an ATP dependent manner (Cote et al., 1994). This ground breaking research provided the first documentation of the long sought remodeling activity by a protein complex with enzymatic activity. The work led to the purification of several other ATP-dependent macromolecular machineries, or remodelers, like the nucleosome remodeling and histone deacetylase complex (NuRD), Nucleosome remodeling factor (NURF), chromatin assembly complex (CHRAC) (Tsukiyama and Wu, 1995; Varga-Weisz et al., 1997; Xue et al., 1998). Similarly, using reconstituted nucleosome array on the *Drosophila* heat shock promoter, Wu and colleagues demonstrated that the generation of hypersensitive sites requires a concerted interaction between the DNA binding GAGA transcription factor and an ATP-dependent NURF remodeling complex (Tsukiyama et al., 1994). These elegant experiments described a fundamental role of remodeler protein machineries as accessory factors for DNA template-dependent processes like transcription, replication, splicing

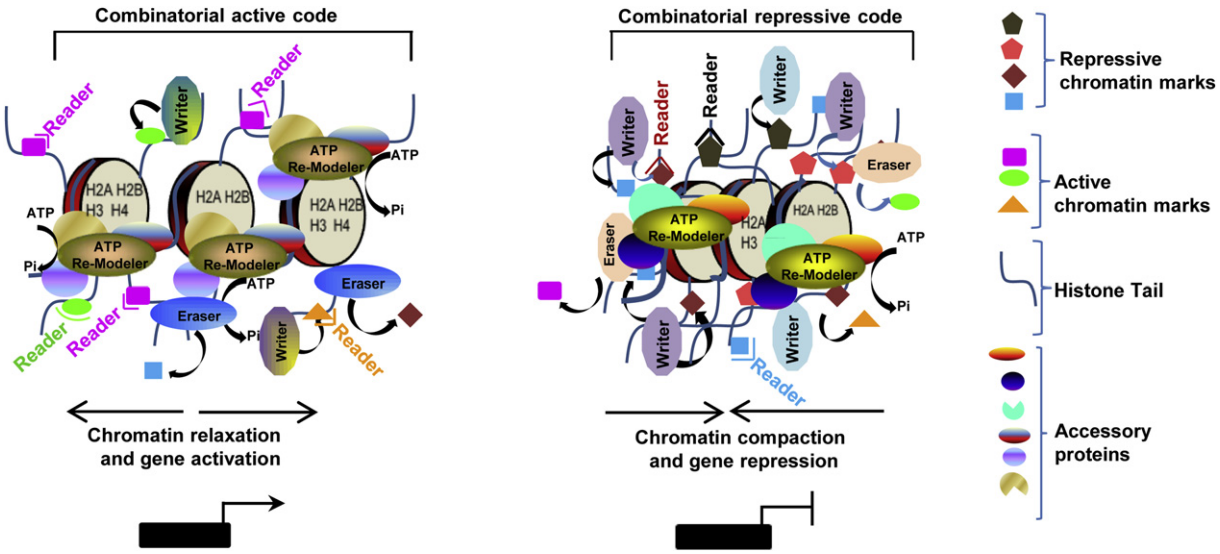

Figure 1 – Chromatin remodeler as core orchestrator of transcriptional response. ATP dependent chromatin remodelers function as gate-keepers to gatekeepers to alter accessibility accessibility of histone modifying enzymes (writers) and accessory proteins (readers) for DNA-template dependent processes. Combinatorial active code triggers gene transcription while a combinatorial repressive code results in gene repression.

etc. It is generally believed that chromatin remodeling factors dictate the nature interactions of the cellular factors with the target DNA and thus, any perturbation or misregulation of these unique machineries is expected to change the transcriptomic status in a cancerous state.

3. Biological specialization of the chromatin remodelers

Remodelers impart dynamic character to the chromatin for optimal biological response (Figure 1). These unique proteins can displace, engage, and alter the nucleosomal structure. To date, four remodeler families have been well characterized they include: SWI/SNF, ISWI, INO80 and NuRD/Mi-2. The four remodeler proteins share unifying properties and include (a) Ability to interact with nucleosome core, (b) Affinity for post-translationally modified nucleosomal histone-tail residues, (c) Core ATPase activity that utilizes energy from ATP hydrolysis to fuel remodeler functions, (d) Regulatory domains that are subject to various biochemical and epigenetic alterations, and (e) Specific protein domains and motifs that accommodate protein–protein interactions. Even though the remodeler proteins share five basic properties they have evolved mechanistically to perform non-overlapping functions (Clapier and Cairns, 2009). Thus remodeler families are functionally specialized and have a unique role in regulating distinct transcriptional programs in response to cellular cues.

3.1. *The SWI/SNF Family*

The SWI/SNF (switching defective/sucrose non-fermenting) family of remodelers were initially purified from *Saccharomyces cerevisiae* and represent an evolutionarily conserved multi-subunit family of chromatin remodelers. This bromodomain family is made of at-least, 8-14 distinct subunit proteins that contribute to the wide repertoire of biological activities of this multisubunit complex observed *in-vivo*(Armstrong and Emerson, 1998). Analysis of subunit composition of this conserved family revealed an important subunits that form part of the catalytic ATPase core. In yeast, the DNA-dependent ATPase activity is derived from SWI/SNF and RSC complexes (Cairns et al., 1996; Laurent et al., 1991) while in Drosophila the BRM-based BAP and -PBAP complexes function as the core-ATPase. In human, the conserved hBRM or hBRG-based BAF and PBAF complexes constitute the catalytic core of this remodeler family. While the core-subunits are important for ATPase activity of the multi-subunit complex, the other conserved subunits bear additional domains such as SANT and SWIRM domains in human BAF155/170 and SwiB domain in hBAF60, for wide range of chromatin remodeling functions observed *in vivo* (Cairns et al., 1998; Szerlong et al., 2008). Chromatin remodeling functions of SWI/SNF family is ATP-dependent and can slide and eject nucleosomes *in vivo* for multitude of biological processes. Interestingly, this family of remodelers do not participate in chromatin assembly.

3.2. *The ISWI Family*

The ISWI (imitation switch) family of remodelers was initially purified from *Drosophila* embryos. A characteristic feature of this multisubunit family of ATPases is presence of C-terminal SANT domain adjacent to SLIDE domain (subunits found in yeast include SWI3, ADA2 and NCoR, TFIIIB in humans) (Elfring et al., 1994). The SANT-SLIDE domain forms a nucleosome recognition module that has been demonstrated to bind unmodified histone tail. In addition to core-subunits this remodeler family also contains accessory proteins that provide additional domains for biological activities. Some of the well characterized domains studied so far include the

histone-fold motif found in hCHRAC, plant homeodomain (PHD) and bromodomain found in bromodomain PHD finger transcription factor (hBPTF). The ATP-utilizing chromatin assembly and remodeling factor (hACF) and hCHRAC represent the core ATPase of ISWI family of remodelers and function to control chromatin assembly by regulating nucleosome spacing and thereby regulate transcription. However one other member of the ISWI family the nucelosome remodeling factor (NuRF) promotes transcription by randomizing nucleosome organization thus creating a permissive environment for gene transcription (Clapier and Cairns, 2009).

3.3. *The CHD/NuRD Family*

The characteristic feature of this family is the presence of CHD (chromodomain) protein with core-ATPase, DNA binding and helicase activity. The initial studies of CHD/NuRD family of chromatin remodelers from *Xenous laevis* revealed a multisubunit protein complex with 5–10 subunits (Marfella and Imbalzano, 2007). In addition to the core CHD domain, chromatin remodeler function is tightly regulated due to presence of additional chromatin interaction domains (SANT, PHD) from interacting proteins. CHD proteins promote transcription by ejecting or sliding nucleosomes. Interestingly, the well characterized Mi-2/NuRD (nucleosome remodeling and deacetylase) complex which contains histone deacetylases (HDAC1/2), metastasis associated (MTA1/2) proteins and methyl CpG-binding domain (MBD) proteins function as global repressors. (Denslow and Wade, 2007; Lai and Wade, 2011). Metastatic tumor antigen 1 (MTA1), a core-subunit of the NuRD complex is upregulated in variety of cancers (Manavathi and Kumar, 2007). Intriguingly, MTA1 is the only dual coregulator that can accommodate both co-repressor function and (Li et al., 2010; Marzook et al., 2012) co-activator functions on target gene promoters (Sankaran et al., 2012; Pakala et al., 2011). In an attempt to explain this paradoxical role of MTA1, work from our laboratory has successfully identified several upstream epigenetic players that regulate MTA1 functions in a physiological context (Figure 2).

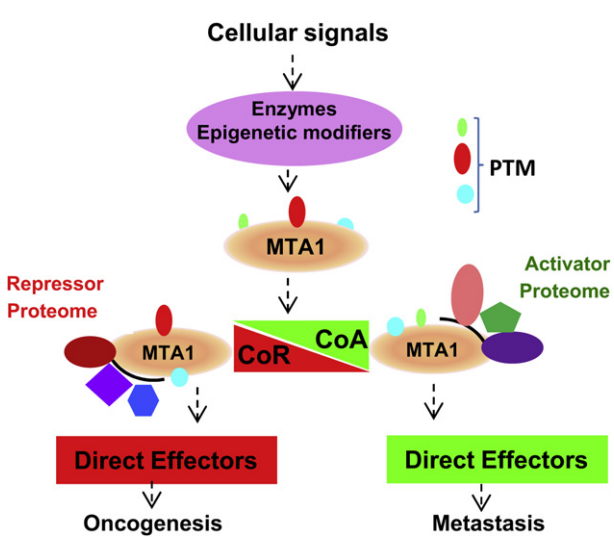

Figure 2 – Dual-coregulator role by master coregulator MTA1. Post-translational modification (PTM) of MTA1 nucleates activator or repressor proteome at target gene promoters.

3.4. *The INO80 Family*

Initially purified from *S. cerevisiae* the INO80 (inositol requiring 80) family of chromatin remodelers constitutes a multisubunit family with more than 10 subunits (Shen et al., 2000). Domain organization studies have shown that a "split" ATPase domain is the characteristic feature of this family of remodelers. Several orthologs identified in higher eukaryotes include human INO80, SRCAP (SNF2-related CREB-activator protein) and p400 proteins (Bao and Shen, 2007; Morrison and Shen, 2009). The INO80 family of chromatin remodelers perform multitude of functions, including transcriptional regulation and recent studies have demonstrated a critical role for these proteins in orchestrating cellular response to DNA damage (Morrison and Shen, 2009). Mammalian Swi/Snf2-related adenosine triphosphate complex (SWRI) is a nucleosome dependent ATPase closely related to INO80 however functionally diverse due to its unique ability to exchange nucleosomal histones. SWRI facilitates DNA repair by removing canonical H2A-H2B dimers from damaged nucleosome and replacing with variant histone H2A.Z-H2B dimers. Thus SWRI has unique property to restructure chromatin (van Attikum et al., 2007).

4. Chromatin remodeling by nucleosomal histones

Transcriptional control of genome, a complex process that sums up cellular responses to environment is dictated by a balance between gene repression and activation. This process is maintained by sequence specific transcription factors that bind DNA, as well as by coregulatory proteins. However, the packaging of eukaryotic genome as chromatin provides an obvious obstruction and occludes DNA from transcription factors. Hence, interaction of genome with cellular components for optimal DNA-template driven processes is achieved by chromatin remodeling. In addition to ATP-dependent chromatin remodelers, the core nucleosome histone structures have a unique role in determining chromatin architecture. Interaction of histone proteins H2A, H2B, H3 and H4 with nucleosomal DNA has a special relevance in chromatin biology as these interactions regulate an overall affinity of nucleosome histones with DNA, leading to a relaxed or condensed chromatin.

The four core histones are subject to a plethora of post-translational modifications that are inscribed by histone-modifying enzymes and multiple modifications, such as phosphorylation, acetylation, methylation, ubiquitination, and citrulation (Peterson and Laniel, 2004). While it is believed that post-translational modifications of histone-tails and residues within globular histone can alter nucleosome mobility, recent studies have demonstrated that a combinatorial pattern of histone modification may constitute an epigenetic code to be recognized, interpreted or modified by other chromatin binding proteins with specialized histone binding domains. Binding of effector proteins to modified histone modules are important for full transcriptional outcomes. Recent studies have

demonstrated that the epigenetic language, or "histone code", acts as a molecular beacon and might offer a bird's eye view of the chromatin landscape for transcription factors and coregulatory proteins with roles in gene expression or repression (Strahl and Allis, 2000).

Modifications of histone tail in the steady- or dynamic-state of chromatin is tightly controlled by histone modifying enzymes and perturbations in such components that are often associated in cancer. Histones function as cellular sensors and modifications thereof plays a major role in epigenetic regulation of biologic responses which could be categorized into two separate categories viz "*cis*" and "*trans*" (Wang, 2007a,b). Post-translational modifications of histones within a nucleosome (intra-nucleosomal) or between nucleosomes (inter-nucleosomal) constitute the *cis*-mechanism of epigenetic regulation. Modulation of nucleosomal histones is dictated by histone modifying enzymes that add a specific modification (also referred to as "*writers*") or that remove a specific modification (also referred to as "*eraser*"). Specific histone modifications trigger a *trans*-mechanism of epigenetic regulation wherein these modifications are recognized by modules within non-histone proteins, also known as "*readers*", for complete functional outcome (Strahl and Allis, 2000). Readers function as scaffolding proteins and influence protein–protein interactions that are essential for ensuring interaction between multiple complexes and with various enzymatic activities. Therefore, histone's post-translational modifications increase capacity of genome to store and/or transmit biologic information. Since alterations in histone-modifications have often associated with cancer, these changes are viewed as an adaptive strategy employed by tumor cells to modulate cellular checkpoints. Following are few examples of cancers resulting from deregulation of histone modifications.

5. Histone acetylation – Cancer perspective

Acetylation of histone tail is associated with transcription activation. This process is carried out by special class of enzymes called histone acetyl-transferases (HATs) (Grunstein, 1997; Loidl, 1994). Activities of HATs are counteracted by another class of enzymes called histone deacetylases (HDACs) (Cress and Seto, 2000). Mammalian HATs can be classified into three distinct families, the Gcn5-related-N-acetyltransferase (GNAT) family, which includes the Gcn5 and p300/CBP-associated factor (PCAF), the MYST family of HATs that includes monocytic leukemia zinc finger (MOZ) and TAT-interactive protein (Tip60), and the p300/CBP family of HATs that consist of CREB-binding protein and p300. Recent studies have demonstrated that a subset of nuclear receptor coregulator of steroid receptor coactivator family of proteins (SRC1 and SRC3) have intrinsic HAT activity and enhance transactivation of nuclear hormone receptors in ligand-dependent manner (Kimura et al., 2005).

Acetylation of nucleosome histone-tail increases nucleosome mobility and in-turn, access to transcription factors. Mounting evidence supports a direct connection between the deregulation of HATs and oncogenesis. For example, oncogenic mutations of p300 and CBP have been observed in hepatocellular, breast, colorectal, and gastric cancers (Iyer et al., 2004). Gross chromosomal reorganizations including, oncogenic fusions of MLL-p300 and MLL-CBP, have been observed in a variety of hematologic malignancies. Acetylated state of histones is reversible and deacetylation is carried out by HDACs. In contrast to histone acetylation that results in transcriptional activation, deacetylation of histones has been shown to create a repressive chromatin state in general (Tyler and Kadonaga, 1999). However, there are also examples of HDAC recruitment to transcriptionally active genomic loci and HDAC2 recruitment was shown to determine poising of RNA polymerase II for future activation of target genes. HDACs are classified into four classes: class 1 (HDAC1-3 and -8), class II (HDAC4-7 and -9 and 10), class III (Sirtuin proteins 1-7), and class IV (HDAC11). HDACs are involved in a variety of cellular functions and aberrant expression of one or more classes of HDAC proteins (HDAC 1-3) results in constitutive repression of tumor suppressor genes, which could lead to in oncogenesis (Glozak and Seto, 2007).

Both HATs and HDACs contribute to cancer by targeting non-histone proteins such as Retinoblastoma (Rb), E2F, p53 and TFIIF etc. Acetylation and deacetylation of non-histone proteins affect the stability of proteins and resulting functions (Glozak et al., 2005). While the specificity of HDACs for specific acetyl group in target proteins is not well defined, HDACs are known to function as part of large multisubunit complexes that recruit HDACs to target gene promoters. HDACs are integral components of macromolecular machineries like NuRD and REST corepressor complexes that control multitude of cellular functions.

The Sin3A-HDAC complex is ubiquitously expressed and operational in almost all cell types. This complex functions as an accessory factor for repressor machineries. The Sin3A-HDAC is a good example of complexes that ties chromatin remodeling with cancer. Most of the tumor suppressor functions of Retinoblastoma (Rb) protein are modulated by the Sin3A-HDAC complex (Tokitou et al., 1999) Rb-E2F recruits deacetylase functions of the Sin3A-HDAC complex at E2F target genes with roles in G1-S transition. The nucleosome remodeling activity directed by SWI-SNF ATP-remodeler complex provides accessibility to HDACs leading to deacetylation and repression of target chromatin (Vignali et al., 2000). Therefore, a functional integration of nucleosome-remodeling and -modifying complexes directs chromatin accessibility to accessory factors to DNA. In brief, cancer determining activity targets both chromatin remodeler machineries and histone modifying complexes, and it will be important to better understand the cancer causing perturbations within chromatin-remodeling and/or histone modifying complexes.

6. Histone lysine methylation, chromatin remodeling and Cancer

Since changes in histone methylation patterns have been linked with cancer (Jones, 2002; Rice and Allis, 2001), covalent methyl modifications of lysine residues in nucleosome histones are viewed as a powerful example of epigenetic regulation. The significance of histone methylation gained recognition of a core player in epigenetic regulation after the

discovery of first demethylase LSD1/KDM1 (Shi et al., 2004). It is generally accepted that the early state of cancer development is associated with the loss of trimethylation at lysine 4 of histone H4 (H4K20Me3) (Shi et al., 2004). Likewise, deregulation of H3K4 and H3K27 methylation patterns are also commonly observed in multiple cancers. Eukaryotic genome displays a remarkable pattern of methyl modifications that define chromosomal boundaries. For example, heterochromatin regions enriched in Histone H3-K9Me3, -K27Me3 and histone H4K20Me3 marks contribute to a repressed chromatin state (Richards and Elgin, 2002). In contrast, histone H3-K4Me3, -K36me3, -K79Me3 modifications in Euchromatic regions of genome recruit ATP-dependent remodeler complexes to remodel nucleosomes for the steady state transcription.

7. Polycomb group (PcG) and H3K4 methyltransferases in Cancer

The polycomb (PcG) group of proteins were initially identified in *Drosophila melanogaster* (Kennison, 1995). The polycomb (PcG) families of proteins are responsible for most, if not all the levels of H3K27Me3 repressive marks in the promoters of eukaryotic genome (Campos and Reinberg, 2009; Min et al., 2003). The PRC1 (BMI-1, Ring-1 and HPC) complex contains a histone "reader" BMI that recognizes nucleosomes enriched in H3K27Me3 and facilitates in the maintenance of a repressed state (Fischle et al., 2003). The PRC2 (EZH2, SUV12 and EED) complex is responsible for inscribing H3K27Me3 marks and contains a SET domain, methyltransferase enhancer of zeste homologue 2 (EZH2), a histone "writer" protein (Hernandez-Munoz et al., 2005). Components of the PRC2 complex are over-expressed in cancer, including lymphoma, melanoma, breast, and prostate. One of the mechanisms of EZH2-mediated oncogenesis has been linked to nucleosome-remodeling activity of EZH2-HDAC repressor complex on tumor-suppressor genes. Tumor-suppressor loci are maintained in a repressor state during cancer progression by coordinated interaction between the EZH2-HDAC and DNA methyltransferase DNMT1 complexes (Hernandez-Munoz et al., 2005).

The repressive state serves as an epigenetic memory for the survival of cancer cells and transmitted to the progeny cells during successive cell divisions, thus leading to propagation of oncogenic signal. In addition, epigenetic regulation of cancer cell survival activity is counteracted by cellular machineries involved in the restoration of nucleosome H3K27Me3 levels to the normal status (Katoh and Katoh, 2004) Such a function is performed by the Jumonji family of histone trimethyl "eraser" proteins and examples include, UTX and JMJD3 which demethylate repressive H3K27Me3/2 marks (Bracken et al., 2007; Kotake et al., 2007). Likewise, over-expression of JMJD3 in fibroblast cells has been demonstrated to restore normal level of H3K27 levels and re-expression of the *Ink4b–A rf–Ink4a* pathway (Agger et al., 2009; Barradas et al., 2009). Intriguingly, the levels of both UTX and JMJD3 are deregulated in cancer by inactivating mutations in the UTX gene and transcriptional downregulation of JMJD3, respectively (Nigro et al., 1989; van Haaften et al., 2009). These observations suggest a distinct role of histone modifiers in cancer cell survival.

Similar to the status of H3K27, the level of H3K4 methylation are also altered during cancer .For example, MLL1 core complex (ASH2L WDR5 and RBBP5) inscribes the histone H3K4Me3 mark at core promoters of genes, leading to transcriptional activation of oncogenes in neoplastic cells (Dou et al., 2006; Krivtsov and Armstrong, 2007). Genomic rearrangements leading to translocation and/or fusions of MLL have been also reported in early oncogenic events contributing to infant leukemia, adult myeloid (AML) and lymphoid leukemia (Krivtsov and Armstrong, 2007). Aberrant expression of MLL proteins and chromatin remodeling are believed to disrupt regulatory effects on the HoxA gene clusters (Ferrando et al., 2003). For example, HoxA9 gene is expressed in hematopoietic precursors while its expression is significantly downregulated in the differentiated blood cells (Pineault et al., 2002; Sauvageau et al., 1994). The fused MLL1 results in the re-expression of Hoxa9 in the blood cells and contributes to leukemia. Deregulation of the Jumonji family of demethylases also contributes to an aberrant expression of oncogenes (Cloos et al., 2008) and correlates with the progression of cancer (Pedersen and Helin, 2011). For example, JAR1DIA, JAR1D1B and JAR1D1C have been shown to be associated with myeloid leukemia, prostate and breast, and renal cell carcinomas, respectively.

8. Targeting remodelers for Cancer therapy

Chromatin remodeling is a dynamic process dependent on synergic interactions between ATP-dependent remodelers and nucleosome histone modifying complexes. Even though the significance of ATP-dependent remodelers in oncogenesis has been established, therapeutic targeting of chromatin remodeling components is just beginning to be realized in the face of obvious challenges that lie ahead. One plausible explanation for this would be potential unbeneficial effects of targeting ATPase as such macromolecular machineries are likely to target other cellular ATPase's. Due to the reversible nature of histone modifications, drugs targeting histone modifying enzymes have received a wider recognition as such agents could effectively restore the epigenetic state of genome back to normalcy. Inhibitors targeting histone acetyltransferases, histone methyltransferases, histone demethylases, ADP-ribosyl transferases and E3-ubiquitin ligases are also rapidly moving into the clinical arena. Clinical efficacy of garcinol small molecule inhibitor of PCAF, anachardic acid small molecule inhibitors of p300 have been tested *in-vitro* with promising results. However, *invivo* these therapeutic compounds have poor cell permeability, low potency and metabolism and non-specific effects which remain a major drawback to develop these molecules for an effective targeted therapy (Keppler and Archer, 2008a,b). One strategy to overcome these drawbacks is to develop synthetic analogs following structural optimization of structural features that could be used to enhance target specificity. In this context, newer synthetic modifications of anarchardic acid have been successfully developed as potent HAT inhibitor with significant antitumor activity (Balasubramanyam et al., 2003, Mai et al., 2006, Sun et al., 2006).

9. Conclusions

Chromatin remodelers provide accessibility to cellular factors for template-mediated processes. In addition, chromatin remodeling machinery cross-talks with the histone modifying enzymes to coordinately regulate epigenetic processes. Chromatin remodelers can be viewed as gate-keepers that integrate cellular signals to the genome for maintaining cellular homeostasis. The chromatin remodeling complexes have provided a unique platform to cancer cell biologists and biochemists to understand the mechanisms by which cancer-causing factors influence chromatin remodeling to develop adaptive strategies for the progression of cancer. With advent of next-generation sequencing methodologies and genome-wide recruitment profiles using ChIP-seq studies combined with the murine models, the field is expected to make a quantum leap to our understanding of genes and loci targeted by chromatin remodeler proteins. It is clear that epigenetic regulation holds a great promise to revert the cancer-state to a normal-like state in the coming years and offer newer avenues for targeted cancer therapeutics.

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