Chromatin targeting drugs in cancer and immunity

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Recent advances in the enzymology of transcription and chromatin regulation have led to the discovery of proteins that play a prominent role in cell differentiation and the maintenance of specialized cell functions. Knowledge about post-synthetic DNA and histone modifications as well as information about the rules that guide the formation of multimolecular chromatin-bound complexes have helped to delineate gene-regulating pathways and describe how these pathways are altered in various pathological conditions. The present review focuses on the emerging area of therapeutic interference with chromatin function for the purpose of cancer treatment and immunomodulation.

The immune system plays a pivotal role in the control of cancer growth and metastasis (Vesely et al. 2011); the failure of the immune system to detect and eliminate cancer cells that are phenotypically different from the surrounding tissues is a major cause of cancer. Therefore, therapeutic agents that negatively affect immune cell development or activation may have a negative effect on immune surveillance of malignant cells and thereby promote cancer growth (Schreiber et al. 2011). However, most of the currently licensed anti-cancer drugs have a negative impact on hematopoiesis and hence on the immune system. Chemotherapeutic-induced immunosuppression increases susceptibility to infections and may prevent the successful usage of cell-based therapies that rely on cancer cell killing by activated lymphocytes (Mellman et al. 2011). Cancer immunotherapy is poised to become increasingly relevant due to the ascent of potent approaches that rely on rampant T-cell activation caused by suppression of the inhibitory signaling pathways in these cells (Sharma et al. 2011).

Immune cell function is regulated by a large number of specialized transcription factors, which overlap only partially with transcription factors that operate in normal and malignantly transformed cells (Busslinger 2004; Naito et al. 2011; Smale 2012). However, the basic chromatin processes that control DNA accessibility to transcription factors or support the chromatin-coupled processes such as RNA polymerase II (Pol II) pausing, elongation, or splicing as well as many others are likely to be common among every cell type in the human body. Consequently, the systemic administration of drugs that target chromatin regulators in cancer cells is likely to affect the same set of proteins in immune cells and vice versa. However, the degree of dependence of various immune cell subsets on the activity of specific transcription factors and chromatin regulators is likely to be different than that of tumor cells. For example, the dependence of rapidly dividing and actively metabolizing tumor cells on transcriptional regulators of the Myc family distinguishes malignant and nonmalignant cells (Shaughnessy 2008; Dang 2012). Distinct requirements for transcriptional circuits in immune versus tumor cells may present an opportunity for the therapeutic targeting of chromatin processes involved in tumor cell growth or pathologically activated immune cells. Ultimately, the source for the selective drug effect may lie not in the nature of the target chromatin protein, which could be common among cell types, but in the differential dependence of individual genes on a particular chromatin regulator. In this context, knowledge of chromatin-based mechanisms of immune cell regulation may serve as a blueprint for the rational design of therapies to selectively target cancer cells with little impact on immune cell function. Furthermore, information about the negative effects of anti-cancer drugs on immunity may contribute to the development of comprehensive supplementary therapies aimed at alleviating immunological side effects.

A brief overview of chromatin processes associated with immune cell responses

The ultimate aim of the immune system is to achieve a degree of diversity that mirrors the complexity of pathogens in the environment. In cells of the adaptive immune system, represented by B and T lineage cells, this diversity is achieved largely through the generation of highly selective antigen receptors, which collectively cover the complexity of environmental antigens (Rajewsky 1996; Abbas and Janeway 2000). The interaction of antigens with the corresponding receptors on B or T lineage cells results

in cell activation followed by eventual elimination of the antigen.

During antigen-driven immune responses, cells of the adaptive immune system engage in multiple intercellular interactions that involve nonimmune cells as well as cells of the innate immune system (Iwasaki and Medzhitov 2010). The latter are represented largely by the migrating or tissue-specific myeloid lineage cells (e.g., macrophages, glia cells, or neutrophils) which possess the ability to recognize pathogens or damaged tissues through the pattern recognition receptor system (Palm and Medzhitov 2009). Initially described by Medzhitov and Janeway (1997), the pattern recognition system senses chemically distinct pathogen components such as nucleic acids, membrane lipids, or, in the case of damaged host tissues, cellular proteins such as high-mobility group protein 1 (Palm and Medzhitov 2009). The specificity of pattern recognition relies on membrane-bound receptors such as Toll-like receptors (TLRs), intracellular nucleic acid sensors such as RIG-I and MDA5, or NOD-like receptors (Medzhitov 2001; Pasare and Medzhitov 2005; Meylan et al. 2006).

The diverse nature of immune cell receptor signaling is further augmented by the existence of a cytokine-driven signaling system that modulates immune and nonimmune cell responses (Bezbradica and Medzhitov 2009). This cytokine signaling is functionally intertwined with antigen and pattern receptor signaling and is essential for optimal immune responses. Cytokine involvement also allows for the generation of whole-body awareness of local inflammatory processes, whereby changes in the cytokine concentration in the blood can affect the function of the nonimmune organs such as the heart, liver, or brain (Medzhitov 2008).

Immune system diversification uses signaling-coupled and RNA transcription-coupled processes to increase cell-to-cell variability in individual gene expression within a range imposed by the immune cell lineage constraints. In turn, the efficacy of the immune response requires the existence of mechanisms that can markedly and coordinately activate a large number of genes (Zak and Aderem 2009; Smale 2012). Execution of transcription factor activity at the chromatin template largely depends on post-translational histone modifications, which define the level of DNA accessibility and contribute to the recruitment of proteins that support RNA transcription (Jenuwein and Allis 2001; Kouzarides 2007; Ruthenburg et al. 2007). Similar to other cell types, active genes in immune cells are associated with nucleosomes enriched for histone H3 trimethylated at Lys 4 (H3K4me3) and acetylated histones H3 and H4 (Wei et al. 2009; Cuddapah et al. 2010). Opposite to these "positive" histone marks, histone H3 dimethylation at Lys 9 (H3K9me2) or H3K27me3 has been implicated in gene silencing in immune cells (De Santa et al. 2007; Wei et al. 2009; Kruidenier et al. 2012), which contributes to cytokine production by activated macrophages and other cell types. Early studies by the Natoli group (Saccani and Natoli 2002) show rapid demethylation of H3K9me2 at promoters of genes activated by macrophage treatment with bacteria-derived lipopolysaccharide (LPS). An important role for H3K9me2 in the regulation of cytokine expression was confirmed by findings showing lower levels of H3K9me2 at inflammatory gene promoters in innate immune cells as compared with nonimmune cells (Fang et al. 2012).

Pathogen-derived proteins that target various arms of the immune response frequently antagonize immune cells' drive to achieve maximum diversity and efficiency. Both bacteria and viruses express proteins that can enter the nucleus and interfere with distinct processes, including transcription and chromatin regulation (Bierne et al. 2012). One of the most glaring examples is human adenovirus, which employs viral E1A protein to hijack host transcription by binding to the histone acetyltransferase CBP (Ferrari et al. 2008) or the ubiquitin ligase hBre1 (Fonseca et al. 2012). Bovine and human papilloma viruses express E2 protein that binds to the C-terminal portion of the bromodomain-containing BRD4 protein, coupling histone lysine acetylation to RNA Pol II activation and RNA elongation (You et al. 2004). Similarly, HIV Tat protein employs Brd4 for the activation of virus transcription (Bisgrove et al. 2007; Sobhian et al. 2010; Rice 2013). Pathogen interference with the host epigenome may also involve proteins that carry histone-like sequences or "histone mimics"—short amino sequences that are similar to the amino acid sequences within the N-terminal histone portions (Sampath et al. 2007). Histone mimics are present in numerous mammalian and pathogen-derived proteins (Lee et al. 2012). In some cases, such as the histone methyltransferase G9a, the histone mimic can fully recapitulate the protein-binding capacity of its histone H3 counterpart (Sampath et al. 2007). In other cases, histone mimics serve as recognition modules that enable post-translational modification of nonhistone proteins for purposes not directly linked to chromatin function (Lee et al. 2010, 2012; Donlin et al. 2012).

Pathogen-derived histone mimics can compete with host histones for common binding partners required for transcriptional activation. For example, the histone mimic within the C-terminal portion of the immunosuppressive NS1 protein of the H3N2 influenza virus binds directly to the transcriptional elongation regulator PAF1 (polymerase-associated factor 1) (Zhou et al. 2012). By binding to the Paf1, which represents an essential part of the PAF1C (PAF1 complex) elongation complex (Krogan et al. 2003; Kim et al. 2010), NS1 inhibits elongation of virus-induced genes and attenuates the antiviral response (Marazzi et al. 2012). Accordingly, siRNA-induced suppression of Paf1 also attenuates the antiviral response and increases viral replication (Marazzi et al. 2012).

The ability of pathogen-derived proteins to control gene expression by interfering with gene transcription is reminiscent of drug-induced suppression of transcription in mammalian cells. Proteins such as BRD4 (see below) have been the focus of studies aimed at suppressing tumor growth and even reversing dedifferentiation associated with malignant transformation. However, the rise of novel anti-cancer drugs targeting transcriptional circuits in tumor cells requires an assessment of the potential

effect of these drugs on similar transcriptional processes in immune cells.

Recent reviews have comprehensively described the multitude of chromatin processes that could be targeted for the purpose of cancer treatment. Here, we focus exclusively on transcription circuits that involve the histone methyltransferase Ezh2 and double-bromodomain-containing transcriptional regulators (BET [bromodomain and extraterminal]). Compounds that target these two classes of proteins display anti-cancer activity in vitro and in vivo and are considered potential candidates for cancer treatment in humans. Additionally, BET protein inhibitors have a marked impact on proinflammatory gene expression and can attenuate systemic inflammatory processes in mice (Nicodeme et al. 2010; Belkina et al. 2013).

Targeting Ezh2 for cancer treatment and its effect on immunity

The histone methyltransferase Ezh2, which catalyzes HK27me3 (Cao et al. 2002; Czermin et al. 2002), could be legitimately considered as a poster child of modern cancer "epigenetics," which largely studies the transcriptional response and has little in common with "epigenetics" in Waddington's sense of it. At the time of writing this review, a PubMed search for "Ezh2 and cancer" yielded 620 references; the initial prominence of Ezh2 as a potential target for cancer therapy has been largely driven by findings of Ezh2 overexpression in metastatic prostate cancer cells as well as in rapidly progressing cancers of other types (van Kemenade et al. 2001; Varambally et al. 2002; Kleer et al. 2003).

Ezh2 operates within the PRC2 protein complex, where the presence of other PRC2 components such as Eed, Suz12, and RbAp48 is essential for the catalysis of H3K27me3 (Cao and Zhang 2004; Margueron and Reinberg 2011). In addition to the core components of PRC2, targeting PRC2 to specific gene loci in mammalian cells involves auxiliary proteins such as Jarid2 (Peng et al. 2009; Landeira et al. 2010; Li et al. 2010; Pasini et al. 2010). Most of the studies that deal with Ezh2 overexpression in tumors, including the initial description of Ezh2 overexpression in prostate cancer cells (Varambally et al. 2002), omit a detailed analysis of Ezh2-associated PRC2 components. Therefore, it is not clear how Ezh2 overexpression itself could be sufficient to affect H3K27me3, which requires the stochiometrically assembled PRC2.

It is generally assumed that Ezh2 expression controls cell division (van Kemenade et al. 2001; Pasini et al. 2004). The expression levels of PRC2 increase in dividing cells, and suppression of the Ezh2 in vitro by siRNA or specific inhibitors frequently leads to growth arrest (Varambally et al. 2002; Martinez-Garcia and Licht 2010). However, the mechanism of this suppression as well as the nature of genes or signaling processes that mediate it remain largely elusive. Confusion about the role of H2K27me3 and Ezh2 in cancer is compounded by studies showing the potential oncogenic function of both the loss-of-function and gain-of-function Ezh2 mutant proteins (Ernst et al. 2010; Martinez-Garcia and Licht 2010; Morin et al. 2010; Guglielmelli et al. 2011; Jankowska et al. 2011; Vainchenker et al. 2011; Yap et al. 2011; Ntziachristos et al. 2012). Recent work by Allis' group (Lewis et al. 2013) raised the question about the overall role of H3K27me3 in the regulation of tumor phenotypes. In highly malignant human gliomas, interactions between Ezh2 and a mutated histone H3 variant (in which the lysine at position 27 is substituted by the methionine) inactivate Ezh2 (Lewis et al. 2013). Tumors that carry H3K2K7-M mutations display negligible levels of H3K27me3, but this does not affect either cell division or the degree of malignancy. Essentially, these studies, along with the independent observation of Ezh2 inactivation by H3K2K7-M (Chan et al. 2013), show that neither Ezh2 activity nor H3K27me3 is required to support tumor growth and maintenance of the malignant phenotype.

The tumor-suppressive effect of Ezh2 inhibitors may also reflect the growth-promoting effect of Ezh2 up-regulation of specific targets. A limited set of data suggests that PRC2 can directly stimulate gene expression. In muscle cells, the Ezh2 homolog Ezh1 positively supports transcriptional elongation (Mousavi et al. 2012). Similarly, PRC2 has been implicated in the positive regulation of actively transcribed cytokine genes (Jacob et al. 2008, 2011). Similarly, the oncogenic function of EZH2 in castration-resistant prostate cancer is independent of its role as a transcriptional repressor but involves the ability of EZH2 to act as a coactivator for critical transcription factors, including the androgen receptor (Xu et al. 2012).

Despite the lack of sufficient clarity about the mechanism of Ezh2 involvement in carcinogenesis and tumor progression, a significant effort has been put into Ezh2 inhibition for the purpose of cancer therapy (Melnick 2012). Treatment of diffuse large B-cell lymphoma (DLBCL) that harbors Ezh2-activating mutations with a potent small-molecule inhibitor of EZH2 methyltransferase activity decreased global H3K27me3 levels, reactivated silenced PRC2 target genes, and inhibited the proliferation of these EZH2 mutant DLBCL cells (McCabe et al. 2012).

Before Ezh2 inhibitors gain further support as anti-tumor drugs, the potential side effect for relatively broad immunosuppression should be considered. Ezh2 deficiency in developing B lineage cells diminishes the antibody repertoire (Su et al. 2003) due to the selective impairment of V_H gene rearrangement residing at the 5′ end of the 2.3-Mb-long immunoglobulin heavy chain (igH) gene locus (Malin et al. 2010). These so-called "distal" V_H genes comprise a large portion of the immunoglobulin repertoire in mice and humans (Ebert et al. 2011). Perturbations in distal V_H rearrangement cause partial humoral immunodeficiency associated with a paucity of certain antibody classes. In addition to V_H gene rearrangement, Ezh2 is also involved in rearrangement of immunoglobulin light chain genes via a mechanism involving IL-7 receptor signaling (Mandal et al. 2011). Ezh2 is expressed at high levels in germinal center (GC) B cells, which are involved in the generation of antibodies with high affinities to their antigen (Velichutina et al. 2010). In GC B cells, EZH2 targets a large number of GC-specific

targets, thus suggesting a key role for Ezh2 in GC B-cell function. Consequently, Ezh2 deficiency in GC B cells may reduce the efficacy of the long-lasting humoral immune response that relies on the presence of B cells expressing high-affinity antibodies.

In addition to its impact on B cells, Ezh2 deficiency also has a negative effect on T-cell immunity. Lack of Ezh2 in early hematopoietic progenitors prevents expansion of early T-cell precursors in the thymus (Su et al. 2005). Furthermore, Ezh2 deficiency reduces the T-cell antigen receptor (TCR)-driven proliferation of T cells in vitro and abrogates antigen-driven T-cell responses in vivo (He et al. 2012). Administration of the histone methylation inhibitor 3-deazaneplanocin A (DZNep) arrests ongoing T-cell-induced graft rejection in mice after allogeneic bone marrow transplantation and selective apoptosis in alloantigen-activated T cells mediating host tissue injury.

The nonnuclear function of Ezh2 in T-cell activation has been linked to the ability of cytosolic Ezh2 to control signal-driven actin polymerization in an H3K27me3-independent but methyltransferase-dependent fashion (Su et al. 2005). A cytosolic presence of PRC2 components has been reported for Eed (Witte et al. 2004) and Ezh1 (Ogawa et al. 2003) in addition to Ezh2 (Su et al. 2005; Bryant et al. 2008; Gonzalez et al. 2011). In T cells, cytosolic Ezh2 binds to the signaling protein Vav1, which plays an essential role in actin polymerization (Hobert et al. 1996a,b; Nolz et al. 2005; Su et al. 2005). Binding to Vav1 may explain the ability of overexpressed Ezh2 to activate the phosphoinositide 3-kinase (PI3K)/Akt pathway in breast cancer cells (Gonzalez et al. 2011) and control actin polymerization in the prostate cancer cells (Bryant et al. 2008). The exact nature of cytosolic Ezh2 substrates is not known, but the likelihood of these substrates' existence is highlighted by the recent identification of several nonhistone targets of Ezh2, such as RORα (Lee et al. 2012). It is tempting to speculate that Ezh2 involvement in actin polymerization—a process that plays a prominent role in tumor cell invasion (Kim et al. 2009)—may contribute more to tumor spreading than do putative changes in gene expression caused by altered Ezh2 expression or activity levels.

Ezh2 has been indirectly implicated in the regulation of the inflammatory gene expression in the innate immune cells. Activation of macrophages by LPS is associated with a selective increase in the H3K27me3-specific demethylase JMJD3 (De Santa et al. 2007). Conversely, JMJD3 deficiency or pharmacological inhibition affects macrophage gene expression (Kruidenier et al. 2012). In light of these findings, one would expect to see an increase in proinflammatory gene expression following suppression of Ezh2.

Potential effects of Ezh2 on the immune system have to be viewed differently in the context of solid tumors and blood malignancies. Unless delivered in a targeted fashion, systemically applied Ezh2 inhibitors may have a more immediate impact on the immune cells than on tumor cells. In such a case, immunodeficiency may precede a potential anti-tumor effect. In fact, in the case of blood malignancies, the immunosuppressive function of Ezh2

inhibition could be advantageous for the treatment of B- or T-cell lymphomas that rely on Ezh2-mediated cytosolic and nuclear signaling networks.

Targeting bromodomain-containing transcriptional regulators and effects on immunity

Lysine acetylation on various histone molecules as well as on nonhistone nuclear proteins is a hallmark of and prerequisite for transcription in mammalian cells (Cheung et al. 2000; Bannister and Kouzarides 2011). Acetyl-lysines bind to highly conserved bromodomains present in numerous cellular proteins and play an essential role in the assembly of protein networks that control gene expression (Zeng and Zhou 2002; Mujtaba et al. 2007). Recently, the tandem BET domain-containing BET proteins BRD2, BRD3, BRD4, and BRDT became the focus of studies on the pharmacological control of gene expression (Arrowsmith et al. 2012; Prinjha et al. 2012). Before gaining prominence as potential drug targets, BET proteins were known as regulators of gene expression in vitro and in vivo (Belkina and Denis 2012). Some of the BET proteins, such as BRD4, were found in association with the Mediator complex to play a prominent role in transcription (Jiang et al. 1998). In addition to its association with Mediator, BRD4 gained additional importance as the only ubiquitously expressed BET protein that can bind directly to p-TEFb through an extended C-terminal domain (Dey et al. 2003; Peterlin and Price 2006; Zhou et al. 2012). Connection to p-TEF-B provided a direct link between BRD4 binding to the acetyl-lysines and transcriptional elongation (Zhou et al. 2012). BRD2 and BRD3 can also participate in elongation through their association with the RNA Pol II-associated elongation complex PAF1C (Dawson et al. 2011). The PAF1C/BET interaction likely relies on bromodomain-unrelated sequences such as ET or other not yet identified motifs (Rahman et al. 2011). The interaction of the ET domain of BETs with numerous effector proteins such as NSD3 (a SET domain-containing histone methyltransferase), JMJD6 (a histone arginine demethylase), and CHD4 (a catalytic component of the NuRD nucleosome remodeling complex) points to active BET involvement in chromatin modifications that might be required for transcriptional elongation (Rahman et al. 2011). The complexity of BET-mediated regulation is further increased by the ability of BET proteins such as BRD4 or BRD2 to bind directly to acetylated lysines within transcription factors such as NF-κB or GATA1 (Huang et al. 2009; Lamonica et al. 2011). It is important to note that the nucleus may not be the only place where BET functions. Brd2 translocation from the cytoplasm to the nucleus is controlled by serum factors (Guo et al. 2000), which suggests a signal-dependent control of Brd2-mediated gene regulation. In the developing mouse neural tube and dorsal root ganglia, Brd2 localized to the nucleus during proliferation but was predominantly cytoplasmic when cells were terminally differentiated (Crowley et al. 2004).

The involvement of BET proteins in transcriptional regulation and the specificity of BET bromodomain

binding to acetyl-lysines provided a foundation for the development of synthetic compounds that control gene expression by inhibiting BET binding to acetylated lysines. The first generation of BET inhibitors was developed independently by several groups, including GlaxoSmithKline (I-BET) in collaboration with our group (Nicodeme et al. 2010) and Bradner's group (Filippakopoulos et al. 2010) (JQ1 in collaboration with the Structural Genomics Consotium (SGC). The lion's share of studies that use BET inhibitors describe the effect of the inhibitors on tumor growth (Dawson et al. 2011; Delmore et al. 2011; Zuber et al. 2011; Dawson and Kouzarides 2012; Loven et al. 2013). It appears that MYC-overexpressing tumors are especially sensitive to BET inhibitors, which suppress MYC expression followed by a dampening of the magnitude of the MYC-driven transcriptional response (Delmore et al. 2011; Ott et al. 2012; Loven et al. 2013; Puissant et al. 2013). In addition, BET inhibitors act effectively against tumors that express a rare form of an oncogenic BRD4-NUT fusion protein (Filippakopoulos et al. 2010). The ability of BET inhibitors to suppress tumor growth is not entirely unexpected in light of the earlier studies of Ozato's group (Maruyama et al. 2002; Dey et al. 2003), which demonstrated a crucial role for BRD4 during mitosis.

One of the first studies of BET inhibitors (GSK525762 compound, designated as I-BET) revealed a potent impact on inflammatory gene expression (Nicodeme et al. 2010). This finding was partly expected due to previous studies revealing an important role for BRD4 in the regulation of proinflammatory gene expression. BRD4-supported cotranscriptional mRNA splicing is important for controlling LPS-inducible inflammatory gene expression in macrophages (Hargreaves et al. 2009). In the absence of stimulation, RNA Pol II generates low levels of full-length but unspliced and untranslatable transcripts at many of the LPS-induced response genes (Hargreaves et al. 2009). Compared with BRD4, which appears to be a generic regulator of elongation, BRD2, which also binds to I-BET, could play a more selective role in the regulation of immune response genes. The positioning of the *BRD2* gene within the myosin heavy chain (MHC) class II gene cluster on human chromosome 6 or in syntenic regions of other organisms (Belkina and Denis 2012) could be seen as a sign of specialized BRD2 involvement in immune responses. In support of this model, low levels of BRD2 are associated with the reduced cytotoxic cytokine production by in vitro triggered macrophages (Belkina et al. 2013).

One of the surprising outcomes of studies on the effect of I-BET on LPS-triggered macrophages was the rather selective impact of I-BET on gene expression (Nicodeme et al. 2010). A common theme that has emerged from studies of LPS-inducible genes is a connection between the timing of gene expression and the state of the chromatin associated with the promoter and transcriptional start site of the inducible gene. Different temporal patterns of gene expression in response to LPS appear to be embedded within the CpG content of inducible gene promoters (Natoli et al. 2011; Smale 2012). In macrophages, CpG island-rich promoters are prevalent among primary and weakly induced secondary response genes, while CpG-low promoters are much more prevalent among more highly induced secondary response genes (Bhatt et al. 2012). BET proteins are associated with both primary and secondary response genes at relatively similar levels before LPS induction of macrophages (Nicodeme et al. 2010). However, treatment of macrophages in vitro with I-BET resulted in the strong and selective attenuation of secondary response gene expression while leaving the expression of primary response genes largely unaffected (Nicodeme et al. 2010). Most significantly, the selective effect of I-BET on secondary response genes holds true for macrophage as well as fibroblast responses to not only LPS, but secondary mediators of the inflammatory responses such as TNF or type I interferon (IFN).

The ability of I-BET to profoundly suppress numerous proinflammatory genes in cells of the innate as well as adaptive immune system (Bandukwala et al. 2012) should be considered, as it might affect the host response to pathogens. The negative impact of I-BET on immunity is particularly relevant in cancer patients who may additionally suffer from the effects of tumor- and/or chemotherapy-induced immunosuppression.

Summary

Rapidly emerging information about the transcriptional control of tumor growth and activated immune cells is likely to continue to fuel excitement about the therapeutic promise of drugs that target catalytic activity of the chromatin-modifying enzymes as well as protein–protein interactions within chromatin-bound regulatory complexes. Additional data on the aberrant structure of tumor-expressed chromatin regulators may further the rational design of therapeutics to achieve a therapeutic effect in tumor cells but spare healthy tissues. The effort to affect tumor growth by interfering with overexpressed—but structurally unaltered—chromatin regulators may cause potential side effects, including immunosuppression. However, the likely differences in gene regulation in tumor cells and cells of the immune system may provide an opportunity for the selective targeting of gene circuits involved in a particular type of tumor cell. Ultimately, however, using chromatin targeting drugs to control systemic immune disorders without causing broad immunosuppression or persistent damage to nonimmune cells will require a better understanding of the transcriptional pathways that govern pathological functions of immune cell subsets that drive the disease.

Acknowledgments

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