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Review

An emerging role for bromodomain-containing proteins in chromatin regulation and transcriptional control of adipogenesis

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ABSTRACT

Transcriptional co-activators, co-repressors and chromatin remodeling machines are essential elements in the transcriptional programs directed by the master adipogenic transcription factor PPARγ. Many of these components have orthologs in other organisms, where they play roles in development and pattern formation, suggesting new links between cell fate decision-making and adipogenesis. This review focuses on bromodomain-containing protein complexes recently shown to play a critical role in adipogenesis. Deeper understanding of these pathways is likely to have major impact on treatment of obesity-associated diseases, including metabolic syndrome, cardiovascular disease and Type 2 diabetes. The research effort is urgent because the obesity epidemic is serious; the medical community is ill prepared to cope with the anticipated excess morbidity and mortality associated with diet-induced obesity.

1. A newly described gene that influences obesity

Worldwide, 1.7 billion people are classified as overweight [1]. Excess consumption of calories leads to human obesity, which is one of the major health crises of this century. The World Health Organization estimates that 171 million people worldwide have diabetes, due primarily to obesity. This figure is expected to at least double by 2030. The US Centers for Disease Control reports that six US states currently have a prevalence of obesity of ⩾30% and only one state (Colorado) has a prevalence of obesity of <20%. Obesity is characterized by dysregulated metabolism, dyslipidemia, insulin resistance, metabolic syndrome, non-alcoholic fatty liver disease, hyperglycemia, hypertension, some forms of cancer and increased risk for development of Type 2 diabetes (T2D) and its co-morbidities, the most serious of which is cardiovascular disease (CVD). About 90% of T2D is attributable to excess weight [2]. Unless reversed, the deepening problem of obesity predicts an epidemic of these co-morbidities that will strain or break many health care delivery systems. Thus, obesity poses a formidable challenge of overarching importance for public health. However, the obesogenic genes, transcriptional processes and chromatin regulation that control weight gain remain incompletely understood.

The in vivo mechanisms that regulate adipogenic transcription are crucial for cell fate decisions, the formation of adipose tissue from progenitors and the response of adipocytes to over-nutrition. Recent work showing that mice with reduced whole-body expression of the ubiquitously expressed, dual bromodomain protein Brd2 ('Bromodomain-containing 2') have dramatically expanded adipose tissue [3], has refocused attention on the role of bromodomain-containing transcriptional co-activators/co-repressors in adipogenesis. Specifically, Brd2 hypomorphic mice, which harbor a *lacZ* disruption of the gene that encodes this transcriptional co-activator/co-repressor, showed severe adipogenesis and obesity. These '*brd2 lo*' animals gained fat on an ad libitum diet of regular rodent chow to weights approaching 100 g by 12 months of age. At all ages, *brd2 lo* mice accumulate about twice the fat of matched

Abbreviations: BAF, BRM/BRG1-associated factors; BAT, brown adipose tissue; BET, bromodomain and extraterminal domain; BMP, bone morphogenetic proteins; BRG1, brahma-related gene 1; BRM, brahma; CBP, CREB (cyclic AMP-responsive element binding) binding protein; C/EBP, CCAAT/enhancer binding protein; ChIP, chromatin immunoprecipitation; co-IP, co-immunoprecipitation; CVD, cardiovascular disease; HAT, histone acetyltransferase; HDAC, histone deacetylase; MHO, metabolically healthy obese; P/CAF, p300/CBP-associated factor; PPARγ, peroxisome proliferator-activated receptor γ; PPRE, PPAR-responsive element; RB, retinoblastoma protein; RXR, retinoid X receptor; SMRT, silencing mediator of retinoid and thyroid hormone receptors; SWI/SNF, switch mating type/sucrose non-fermenting; TAF, TBP (TATA box binding protein)-associated factors; TRAP, thyroid hormone receptor-associated protein; TZD, thiazolidinedione; T2D, Type 2 diabetes; WAT, white adipose tissue.

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control mice. For example, epididymal adipocytes of male *brd2 lo* mice on chow diet were significantly larger than age-matched wild-type controls on chow diet: 62.9% of *brd2 lo* adipocytes were larger than 10 000 μm^2, compared to only 1.1% of wild-type adipocytes ($P < 0.001$) [3]. Interestingly, all adipose depots were healthy; severe obesity was observed without concomitant insulin resistance. Until this report, Brd2 function had not been linked to obesity or glucose homeostasis.

Significantly, shRNA knockdown of Brd2 in 3T3-L1 pre-adipocytes strongly promotes adipogenic differentiation. Pre-adipocytes with Brd2 stably knocked down show about 50% more Oil Red O staining upon insulin/dexamethasone/isobutylmethylxanthine differentiation than control adipocytes. Brd2 and PPARγ are each detectable by co-immunoprecipitation of the other, and shRNA knockdown in vitro of Brd2 in 3T3-L1 cells approximately doubles the signal from a PPAR-responsive element (PPRE)-regulated transcriptional reporter. Taken together, these results suggest a mechanism that works through alleviated Brd2 co-repression of PPARγ-directed transcription of adipogenic genes [3]. Previous work has identified histone modification enzymes and nucleosome remodeling proteins associated with Brd2-containing multiprotein complexes [4,5]. These new results offer an opportunity to revisit what is known about the role of chromatin in adipogenic transcription and to develop hypotheses that will channel effort into a deeper excavation of the relevant mechanisms.

2. The bromodomain and extraterminal domain (BET) family of regulators

The metazoic members of the Brd2 family, the best known subgroup of BET proteins, possess dual, mutually-related bromodomains in the amino-terminal region of the protein that bind to acetylated chromatin, and protein–protein interaction domains for association with transcription machinery in the carboxyl-terminal region. The bromodomains account for the reported co-localization with chromosomes of this protein family (Fig. 1). Specifically, the bromodomains bind to acetylated lysine 12 of histone H4 in nucleosomal promoters [6], a chromatin-binding function first illustrated for the single-bromodomain histone acetyltransferase (HAT) Gcn5 [7] and P/CAF (a p300/CREB binding protein-associated factor) [8]. Structural requirements for chromatin interaction have been established in detail for Brd2 [5,6,9,10]. Similar interactions have been reported for other dual bromodomain proteins such as Brd3 [11,12], Brd4 [13–15], Brd6 [Brdt; 16], the basal transcription factor $TAF_{II}250$ [17,18] and *Brd2* gene orthologs: *Saccharomyces BDFI* [19–21], *Arabidopsis GTE4* [22], *Drosophila female sterile* (1) *homeotic* (*fs*(*1*)*h*) [23–25], *Caenorhabditis bet-1* [26], and *Danio* and *Xenopus brd4* [27]. Dual bromodomain proteins thereby couple histone acetylation to transcription in a wide variety of organisms and transcriptional contexts.

This highly conserved family of transcriptional co-regulators is primarily known for function in cell fate during development, in cancer and the cell cycle. Dual bromodomain proteins have crucial functions in pattern formation in *Drosophila* [28–32] and mice [13,33,34]. Mutation of *fs(1)h* causes severe defects in differentiation and cell fate; $fs(1)h^{null}$ is lethal [23,29,35]. The *fs(1)h* locus is an upstream activator of *trithorax* in *Drosophila* [30,36], an important, homeotic control gene that positively regulates *Hox*-controlled differentiation in mice, countering repression by the Polycomb group (PcG) proteins. Disruption of human *BRD4* through t(15;19) chromosomal translocation generates aggressive midline carcinomas [37; reviewed in 38]. Brd2 and Brd4 control cell cycle in mice [13,39,40] and in cultured cells [5,41]. In the mouse, Brd4 is necessary for the G_2-to-M transition of the cell cycle, and $brd4^{(+/-)}$ mice show severe defects in differentiation and organogenesis. In mice, $brd4^{null}$ is lethal [13,42,43]. The $TAF_{II}250$ subunit of the TFIID basal transcription factor complex [44] is also crucial for cell cycle control through its regulation of *cyclin A*, which is a critical driver of S phase [45]. Brd2 transduces mitogenic signals [46,47], leading to increased proliferation [48]. Forced expression of Brd2 transcriptionally co-activates *cyclin A*, causing earlier S phase entry during cell cycle progression [5]. Brd2 constitutive expression in B cell progenitors causes a B cell malignancy in mouse models [40] that is most similar to human diffuse large B cell lymphoma [49,50]. Thus, the dual bromodomain proteins exert non-redundant, chromatin-based activities that are essential for growth, development, differentiation and cell cycle progression.

These proteins use a structural component, the bromodomain, to bring transcriptional functions to chromatin that has already been identified for transcriptional regulation through histone hyperacetylation or sequence-specific DNA-binding transcription factors. Virtually all of the nuclear HATs contain bromodomains [51,52], but not all bromodomain proteins are HATs. Instead, the enzymatic activities (HAT or ATP-dependent chromatin remodelase) are either encoded within the same polypeptide chain or are recruited to a multiprotein complex, including bromodomain proteins resident at the promoter, thereby coupling structure to function. Chromosomal translocation can decouple this system, targeting HAT activity to the wrong promoter [53], a genetic abnormality frequently associated with cancer [38,54–57].

3. The bromodomain motif

In 1992, the bromodomain was first noticed as a primary amino acid sequence present in certain proteins that have chromatin or transcription functions [58]. Many bromodomain-containing proteins are found in transcription complexes [51,52], where they perform scaffolding functions [59]. The bromodomain takes its name from *Drosophila* brahma (BRM), an important chromatin-modify-

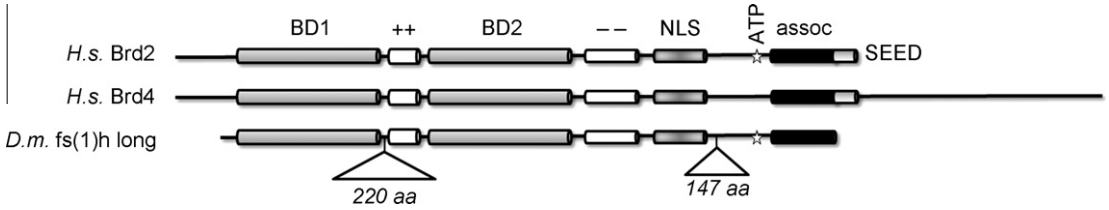

Fig. 1. Major forms of BET proteins. The structure of human Brd2 is compared to human Brd4 and the long form of *Drosophila* fs(1)h. Both Brd2 bromodomains (BD) are about 100 amino acids in length and are highly homologous to each other. They are separated by a basic domain (++), followed by an acidic domain (−−), a short nuclear localization sequence (NLS), an ATP binding/kinase domain (ATP), a multiprotein complex association domain (assoc) 164 amino acids in length and an acidic polyserine (SEED) domain. Brd2 BD1 is located between amino acid positions 75 and 175, and BD2 is located between 350 and 450. Brd4 possesses a long carboxyl-terminal region of unknown function that lacks association motifs. fs(1)h possesses a number of insertions, also of unknown function. The two largest insertions are shown. Mammalian BET proteins exhibit alternative start sites and splice sites, but tend to cluster into one of two subtypes: either a short form with dual bromodomains and an association domain (Brd2, Brd3, Brd6), or a long form with an unstructured carboxyl terminal tail (Brd4). [See Ref. [66] for more detailed discussion.]

ing factor discovered by Tamkun and colleagues [60] and discussed in a prescient 1994 paper of Randazzo and colleagues [61], who noted that brahma (*Snf2α*, *SMARCA2*) likely assists trithorax to overcome Polycomb repression of chromatin. Given the crucial role played by the human homolog of trithorax (*MLL*) in mixed lineage leukemias derived from 11q23 chromosomal translocations [62,63], they speculated that the brahma-related bromodomain protein BRG1 (*Snf2β*, *SMARCA4*), which is an essential catalytic component of the SWI/SNF complex (discussed in detail below), would be implicated in mammalian malignancy, as later work verified [64,65]. The conserved, ~110 amino acid bromodomain motif is comprised of four left-handed α helices bundled together and connected with two segments, the so-called ZA and BC loops. The structure was solved first by analysis of nuclear Overhauser effects in the P/CAF single bromodomain [8]. The field has enjoyed a number of excellent reviews that discuss the relationship between bromodomain protein structure and transcriptional co-activation or co-repression function [53,66–68].

4. Transcriptional co-activation and co-repression by bromodomain proteins

Bromodomain proteins that encode HAT activity, or recruit HAT enzymes to chromatin, establish a paradigm for transcriptional co-activation. The model also implies that a basal level of histone acetylation of nucleosomes is required to catalyze the initial association with bromodomain proteins. It is widely appreciated that histone hyperacetylation is a mark of transcription activation of promoter chromatin. Brd2 binds endogenous *cyclin A* promoter chromatin, but mutants of Brd2 with deleted bromodomains or carboxyl-terminal protein association domains do not transactivate [5]. Functional *cis*-acting E2F binding sites are required for Brd2-dependent transcriptional function on the *cyclin A* promoter [48], and overexpressed retinoblastoma protein (RB), which halts E2F-dependent cell cycle progression [69], ablates Brd2-driven transactivation [48]. E2F1 and E2F2 are present in Brd2 multiprotein complexes purified from nuclear extracts [48] and Brd2 works with E2Fs to recruit HAT activity and other epigenetic regulators, including Mediator complex proteins, and the hSWI/SNF component BAF155, to chromatin [4,5] thus to transactivate *cyclin A*. Dysregulation of this process leads to the classic disease of uncontrolled proliferation: cancer [40].

Transcriptional programs that promote cellular proliferation/cell cycle progression function in balance with programs that promote cellular differentiation/cell cycle exit. The balance between the two lies at the heart of cell decisions to grow, specialize or undergo apoptosis. Imbalances are pathogenic. For example, diverse leukemias arise in the bone marrow through defective differentiation closely coupled to abnormal proliferation [70–72]. The resultant leukemic blasts are often blocked at an early stage of differentiation, consistent with their continued active proliferation at the expense of normal differentiation. Important and effective therapies for certain leukemias take advantage of this transcriptional switch as a rationale to treat leukemic patients with differentiation-promoting agents, such as retinoic acid derivatives that force cell cycle exit and block proliferation [73,74].

Bromodomain proteins also play important roles in transcriptional co-repression, as first identified in studies showing that the bromodomain protein BRM contacts RB [75,76]. RB and its family members p107 and p130 bind to E2F proteins and block their transcription activation function to oppose cell cycle progression. RB also recruits a histone deacetylase (HDAC), as do p107 and p130, through contact with BRM and other proteins in the SWI/SNF complex [77–80]. Not all SWI/SNF complexes contribute to this repressive function, however. Indeed, recent studies indicate that a specific variant SWI/SNF complex (the ARID1A BAF complex) is important for repression of E2F activated cell cycle control genes, whereas another variant (the ARID1B BAF complex) contributes to the activation of these genes [81,82]. Until recently [3], there was no evidence of a role for Brd2 in mammalian transcriptional co-repression, although clues from studies of *Drosophila* development identified in *fs(1)h*, the homolog of Brd2, transcriptional repression functions that are essential for proper differentiation in the early embryo [38,83].

5. The SWI/SNF complex

As discussed above, local modification of histones on enhancers and promoters is required to activate gene expression [84,85]. Transcription factors that bind to nucleosome-free regions of DNA or to DNA within nucleosomes recruit enzymatic activities that also non-covalently modify the surrounding chromatin architecture. These ATP-dependent remodeling complexes may contribute to gene regulation through a variety of mechanisms, including movement in *cis* of nucleosomes away from or over regulatory elements, removal or deposition of nucleosomes in conjunction with cellular chaperones, changes in the histone composition of nucleosomes, regulation of covalent histone modifications, alteration of nucleosome structure, and/or changes in higher order chromatin folding. While these models mostly derive from in vitro biochemical studies, examples of many of these effects in gene regulation are beginning to accumulate [86].

The SWI/SNF complex offers an important example of an evolutionarily conserved, bromodomain-containing, ATP-dependent chromatin remodeling machine, with roles in both transcriptional activation and repression [65,87,88]. Mammalian SWI/SNF comprises a 2 MDa complex that possess the essential, catalytic proteins brahma-related gene 1 (BRG1) or BRM, and an additional 9–12 proteins called BRM/BRG1 Associated Factors (BAFs) [89; for review, see Ref. 90]. The function of SWI/SNF complexes can vary depending on the complex components. Two major classes of SWI/SNF complexes have been identified. The BAF complexes (most similar to *Saccharomyces* SWI/SNF) contain either the BRG1 or BRM ATPase subunit together with one of two variant BAF250/OSA/ARID1 subunits. These complexes contain a single bromodomain in their ATPase subunit. The choice of BAF250 subunit can dramatically alter complex function, such as the opposing effects of ARID1A versus ARID1B complexes in cell cycle control [81,82] and the specific function of ARID1A in stem cell renewal [91]. The choice of ATPase may also be critical, because BRG1 tends to be highly expressed in proliferating cells, whereas BRM is preferentially expressed in terminally differentiated tissues [92], and because the regulation of specific target genes is sometimes affected by only one ATPase or the other [93,94]. Furthermore, $Brg1^{-/-}$ mice are embryonic lethal [95], whereas $Brm^{-/-}$ mice show a relatively mild phenotype [96]. PBAF complexes (most similar to yeast RSC) contain BRG1, but not BRM, lack BAF250 and contain a BAF180/Polybromo subunit bearing six bromodomains.

Studies have shown that these variant SWI/SNF complexes have distinct, but often overlapping functions [90]. Variant forms of other subunits also exist, and show differential cell-type distributions and functions (such as the presence of BAF60a, but not BAF60c in the esBAF complex, that is critical for stem cell renewal [97]). The emerging model is that SWI/SNF complex composition varies by tissue and cell type [89,95,98], and that the distinct combinations of subunits enable these variant complexes to interact with distinct DNA-binding transcription factors and co-regulators, or to interact with histones that bear specific modifications to carry out tissue-specific, divergent functions.

The bromodomains in SWI/SNF complexes appear to play a critical role in maintaining the stable association of the complex with

chromatin. This interaction was shown for *Saccharomyces* SWI/SNF in an elegant set of in vitro experiments [99]. This mechanism is also evidenced, in mammalian cells, by the requirement of P/CAF-mediated acetylation to support SWI/SNF recruitment to the myogenin promoter [100]. However, relatively little is known about potential differential functions of the bromodomains in BRG1, BRM or Polybromo.

Determination of genes that require SWI/SNF enzymes for proper regulation has been accomplished in part by use of antibodies that function in co-immunoprecipitation (co-IP) and chromatin immunoprecipitation (ChIP) assays. These experiments show SWI/SNF components localized with specific activators and/or at specific gene sequences, indicating that the role of SWI/SNF in co-activation and co-repression is mediated by direct recruitment of the complex to target promoters [101–104]. SWI/SNF complexes bind to a wide variety of transcription factors, acting either as co-activators or co-repressors [for a recent review, see Ref. 105]. Of particular relevance to adipogenic differentiation, hSWI/SNF complexes bind to and serve as co-activators for many nuclear hormone receptors, including estrogen, glucocorticoid, retinoic acid receptor (RAR) families and PPARγ [102,103,106–109]. SWI/SNF and PPARγ are crucial for adipogenesis, as discussed below. Sequence-specific DNA-binding transcription factors are required to target individual adipogenic genes and marshal the transcriptional program, but the general transcriptional factors and non-sequence specific complexes, such as the bromodomain-containing chromatin remodeling factors and co-activators, are also critical. It is not well understood how these specific and general factors work together with chromatin remodeling enzymes on the promoters of adipogenic genes.

6. Functions of PPARγ and its transcriptional co-activators in adipogenesis

Not only is transcriptional control of proliferation subject to tight control, but differentiation must also be carefully regulated. Adipocyte differentiation from fibroblast-like progenitors, for example, is regulated by two well-studied families of transcriptional regulatory proteins: C/EBPs (CCAAT/enhancer binding protein) and PPARs (peroxisome proliferator-activated receptor), especially PPARγ, a master regulator of differentiation of white adipose tissue (WAT) and brown adipose tissue (BAT) [110–113]. To act as a transcription factor, PPARγ forms a complex with the retinoid X receptor (RXR) transcription factor [114–116]. Improper or deficient activation of PPARγ is associated with insulin resistance and T2D [117,118]. The transcriptional programs of adipogenesis have been effectively reviewed [119].

Nuclear receptors like PPARγ are Cys4-type Zn^{2+}-finger transcription factors. It has been proposed that this class prefers to interact with BRG1 subunits of SWI/SNF [104,120]. Seminal studies from the Imbalzano group [121] showed that the catalytic subunits of the SWI/SNF complex, BRG1 and BRM, are required for induction of adipogenic transcription programs. Specifically, they established that general transcription factors assemble at the promoter of the PPARγ2 gene. Upon subsequent association of SWI/SNF and TFIIH with the promoter, a preinitiation complex forms and is capable of transcription. This topic has been recently reviewed [122,123]. It is now clear that SWI/SNF and associated bromodomain-containing co-activator complexes are crucial for PPARγ function. Interestingly, expression of dominant negative PPARγ is capable of partially reversing terminal adipogenesis [124], suggesting that some basal form of ongoing chromatin maintenance or nucleosomal remodeling is required to maintain an adipogenic pattern of gene expression. This would come at high energetic cost to the adipocyte.

PPARγ co-activators, including members of the p160 family [125,126] must be regulated in their association with the chromatin-bound transcription complex. It is apparent that adipogenesis or differentiation of adipose tissue from progenitors during development could be severely affected by loss or dysregulation of this association. We speculate that these associated co-activator and SWI/SNF complexes localized on the chromatin of adipogenic genes are partially disassembled upon cessation of the adipogenic program. However, how this is achieved, to what extent, and the signal transduction events that prompt complex disassembly are obscure. For a model of this process, we have begun to analyze the stoichiometry and kinetics of Brd2-dependent transcriptional control of the *cyclin A* promoter [4], which requires complexes that must be activated and inactivated each time the cell traverses the cell cycle.

The dramatic adiposity of *brd2 lo* mice was completely unexpected. However, in retrospect the co-activator/co-repressor functions of bromodomain proteins make sense as a mechanism for regulating the adipogenic phenotype. The increased adipogenesis of 3T3-L1 pre-adipocytes in which Brd2 was knocked down [3] suggests PPARγ interactions with Brd2 are crucial. In addition, two important transcriptional targets of PPARγ and its co-activator PGC-1α are the genes that encode mitochondrial uncoupling protein-1 and -2 (*ucpl, ucp2*), which have been linked to obesity [127] in mice [128] and humans [129] and are important for thermogenesis in BAT. We noted that both ucp1 and 2 were dramatically elevated in *brd2 lo* mice [3]. Intriguingly, PCG-1α binds a transcriptional co-activator/co-repressor complex [130,131] that contains the Mediator complex [132] and Brd2 [4,133–135]. These observations reinforce the hypothesis that Brd2 levels regulate the transcription of genes that are targets of the PPARγ/PCG-1 family.

Certain crucial transcription co-factors are shared between Brd2 transcription complexes [4,5,48] (Fig. 1) and PPARγ-containing complexes (Table 1; *common factors shown in bold*) [123]. Net co-activation/co-repression depends on the relative abundance, targeting and activity of these associated factors [59] and their ability to switch the chromatin status of key metabolic genes. This insight suggested two easily testable hypotheses: that (1) Brd2 and PPARγ interact, either directly through protein–protein association, or indirectly through association in a ternary complex, and that (2) a drop in Brd2 levels in certain cell types, such as the pre-adipocyte, derepresses PPARγ-regulated transcription. Co-immunoprecipitation experiments showed that indeed, Brd2 and PPARγ associate, and Brd2 opposes the action of PPARγ on PPAR-responsive transcriptional elements in DNA [3]. Interestingly, mice harboring a knock-in mutation of 'silencing mediator of retinoid and thyroid hormone receptors' (SMRT), a nuclear co-repressor thought normally to antagonize PPARγ-directed transcription, exhibit a pro-adipogenic phenotype [136], as do mice harboring a knockout of estrogen receptor β [137]. This phenotype shares certain features with Brd2 knockdown, particularly the lower threshold for a PPARγ-directed program of transcription. This pattern also resembles the insulin-sensitizing action of glitazones and thiazolidinediones

Table 1
Transcriptional co-factors that interact with PPARγ.

Co-repressors	Co-activators
Mediator	**SWI/SNF**
HDACs	**p300/CBP**
RB	**CAF**
NCoR	PPAR-binding protein (PBP)
SMRT	PPAR-interacting protein (PRIP)
Sirt 1	PGC-1,2

Factors shared between Brd2 complexes and PPARγ complexes are shown in boldface.

(TZDs) [138]. Indeed, the observations suggest Brd2 might be a novel, useful, 'druggable' therapeutic target for insulin resistance. In addition, the thyroid hormone receptor-associated protein (TRAP)220 component of the Mediator complex (encoded by MED1) is important for PPARγ-directed adipogenesis [139]. The observation that Brd2 associates with a number of components of the Mediator complex [4] suggests that PPARγ and Brd2 may be functionally linked through Mediator. Thus, it will be important to verify the presence on chromatin of the Brd2 complex factors shared with PPARγ-associated complexes, and then test their function individually to understand the combined functions of Brd2 and PPARγ in transcriptional regulation of adipogenesis. Given the failure of intensive effort to identify an obvious endogenous ligand for PPARγ, we can reasonably speculate that specific post-translational modifications in response to nutritional signal transduction, such as phosphorylation of co-repressor proteins or acetylation/ubiquitylation of histones, might behave as a 'pseudo-ligand' for shifting co-repressor complex function and enable PPARγ-directed adipogenesis. If so, Brd2 may be poised to respond to these signals either as a target for modification or as a 'reader' of the resulting modifications, especially histone acetylation.

7. A model for the role of bromodomain proteins in adipocyte differentiation

Recent studies have shown that Brd2 cooperates with E2F1, stabilizing a transcriptional activation complex on acetylated chromatin at *cyclin A*. This complex also contains SWI/SNF, the association of which will be stabilized both through interaction with Brd2 and via binding of the bromodomain in its ATPase subunit to acetylated chromatin. By contrast, a combination of RB binding to E2F1 (that potentially recruits the inactivating ARID1A form of SWI/SNF), loss of *cyclin A* promoter acetylation and loss of Brd2 would silence *cyclin A* and slow growth of pre-adipocytes. In addition to the slowing of growth, adipocyte differentiation requires the upregulation of PPARγ, which requires SWI/SNF for increased transcription. PPARγ activation of its target genes is also likely to require SWI/SNF, although the specific variant complex involved has not been identified. Importantly, however, Brd2 can inhibit transactivation by PPARγ [3]. Thus, Brd2 is required both to activate genes that enable growth and to repress differentiation-specific genes in pre-adipocytes. Accordingly, it is not surprising that deletion of Brd2 leads to a near-complete elimination of mature adipocytes.

8. Important outstanding issues

1. *Signal transduction and specificity*. The mechanisms by which signal transduction pathways instruct the chromatin remodeling machinery to conduct an adipogenic program are very poorly understood. The notion that chromatin remodeling machines can function as effectors of signal transduction, particularly of mitogenic signals, has been discussed with respect to Mediator [134] and hSWI/SNF [140,141]. For example, mitogenic signals through the ras pathway [142] or inflammatory signals through the TLR pathway [143,144] convey information to chromatin to create a coherent transcriptional state that is also reversible. Conversely, it is reasonable to hypothesize that in response to an adipogenic differentiation signal, a specialized cell mobilizes a MDa transcriptional apparatus at a limited number of genes. This restricted response – only a few 'immediate early' adipogenic promoters – could explain why the global disruption of so fundamental a transcriptional cofactor as Brd2 generates a coherent response on PPARγ-responsive promoters and a clear, adipogenic transcriptional program in a pre-adipocyte. Most progenitor cells, such as pre-adipocytes, are already primed for a specific fate, thus, manipulation of global transcriptional and chromatin programs does not create transcriptional confusion, because the map of cell fate is restricted. It will be important to learn how, upon cell cycle exit and induction of differentiation, chromatin in the adipocyte resolves the differential responses to a combination of mitogenic and differentiation-promoting signal transduction pathways. It also remains to be explored whether epigenetic predetermination of adipogenic promoters is a major mechanism that defines the cell fate of the pre-adipocyte. More generally, a better, comprehensive knowledge of the signal transduction-mediated mechanisms of priming in progenitor cells will be critical if we wish to understand how lineage-specific transcription factors establish cell fate.
2. *Functional shifts in chromatin remodeling and histone modification complex composition*. Biochemical studies of SWI/SNF complexes sometimes identify BRG1 and BRM subunits associated with the same locus [121], reflecting the view that these subunits identify complexes that exhibit a combination of overlapping and specific functions. Differential recruitment of SWI/SNF subunits BAF155 and BAF170 to the same promoter in response to estrogen determines subsequent recruitment of a co-activator HAT or a co-repressor HDAC [145], suggesting that different mechanisms of PPARγ activation (which may include signal transduction pathways or as-yet unidentified endogenous ligands) could differentially regulate transcription factor/chromatin complexes formed during adipogenesis.

   The dramatic adipogenic phenotype of Brd2 deficiency strongly suggests that Brd2 and its associated bromodomain-containing transcriptional co-regulators (including SWI/SNF) are central to the decision to undergo adipogenic differentiation. During this process, the chromatin-associated SWI/SNF complexes likely change character in a coordinated fashion. These shifts will be most directly measurable with analysis of chromatin-modifying activities, along with DNA accessibility, associated with proliferative and adipogenic genes during adipogenesis (i.e. at the end of the clonal expansion) in 3T3-L1 adipocytes that have been induced to undergo adipogenic differentiation.

   It appears that E2Fs govern a link between proliferative signaling pathways and terminal adipocyte differentiation. E2Fs trigger clonal expansion, then, through RB-mediated repression and replacement of pro-proliferative E2Fs with pro-differentiation E2Fs, coherently switch a variety of promoters to the new program. Apart from the proposed role of E2F-1 in PPARγ1 transcription, to switch between proliferative, clonal expansion and terminal adipocyte differentiation through control of PPARγ levels [146], reviewed in [119], it is reasonable to hypothesize that reduced levels of Brd2 or a related bromodomain protein reprograms a panel of target genes, analogous to the result of *swi/snf* mutation in *Saccharomyces* [88], transcriptionally repressing the proliferative genes [5] and activating the adipogenic genes [3]. Likewise, transcriptionally activating SWI/SNF complexes may need to shift character to transcriptional repression complexes on the relevant promoters. It is unclear whether this switch would occur by swapping out subunits on chromatin-bound SWI/SNF or by exchanging one entire complex for another. However, given the rapid exchange seen for most transcription factors on and off chromatin [for review, see Ref. [147]] together with the strong association of SWI/SNF complex subunits in biochemical studies, the latter possibility seems most likely [148]. As discussed above, experiments in the 3T3-L1 model will be useful to define these mechanisms. It will be expected that patterns of histone and DNA methylation and acetylation, DNA accessibility, DNAse hypersensitivity and transcript levels will follow suit and reflect the differential functions of the variant chromatin-bound complexes.

3. *Cell fate and development*. Interesting recent work on adipose cell fate used an RNAi screen in *Drosophila* to identify candidate obesity genes and discovered an important, previously unappreciated role for hedgehog signal transduction [149]. Significantly, reported activators of the fat-specific obesity pathway included Nejire [a fly homolog of the well-known HAT p300/CREB (cyclic AMP-responsive element binding) binding protein (CBP)]; repressors included trr (trithorax-related histone methyltransferase), CG3075 (histone H2A), Su(fu) (an mSin3 co-repressor) and slmb (required for E2F function). These factors implicate chromatin modification in adipogenic transcriptional programs and should be studied in detail in mouse models. In this regard, developmental regulators such as the bone morphogenetic proteins (BMPs) [150] with morphogen roles first identified in *Drosophila* [151] and transcriptional co-activators such as PRDM16 [152] and PGC-1 [153] have newfound significance in adipogenic transcriptional programs and cell fate, particularly the crucial function of BMP-7 in BAT adipogenesis [154]. However, very little is known about how these developmental factors communicate with nucleosomes and chromatin remodeling machinery during an adipogenic program in adult progenitor cells.
4. *Maternal effect on adipogenesis*. The *Drosophila* homolog of Brd2, *fs(1)h*, is a maternal effect gene [23,30,31], which suggests the possibility that adipogenic transcriptional programs in humans are influenced by maternal effect inheritance of *BRD2*. Brd2 remains mitotically associated with chromatin [6], and Brd4 tethers virus episomes to host mitotic chromatin across cell divisions [155]. This behavior suggests a role for dual bromodomain proteins in inheritance, not only of specific histone modifications from one cell generation to the next, but also of chromatin-bound complexes, which likely has significance for epigenetic inheritance of predisposition to adiposity. Convincing evidence from epidemiological study of the Dutch 'Hunger Winter' of 1944–1945 establishes an *environmental* maternal effect of starvation during gestation. Specifically, maternal hunger promotes insulin insensitivity, obesity, an atherogenic lipid profile and elevates CVD risk in the surviving children as they age [156]. A number of animal models explore the effect of gestational stress on obesity, hypertension, insulin resistance and hyperinsulinemia in progeny [recently reviewed in 157]. However, there has been insufficient study of *genetic* maternal effect on obesity. It is likely that alleles of chromatin modification genes, or genes of the class II Major Histocompatibility Complex, within which *BRD2* resides, will be found to play a role in maternally inherited patterns of human adipogenesis and insulin sensitivity, independent of environment and nutrition status.

9. Future directions

Deficiency of *Brd2*, a gene that encodes a dual bromodomain protein in mice, generates an unexpected and dramatic adipogenic phenotype, revealing a pathway of transcriptional co-repression and chromatin modification that normally opposes the action of PPARγ. Heterozygous *brd2 lo* mice develop severe obesity but, surprisingly, completely avoid insulin resistance. These mice may provide a useful model for decoupling these two aspects of metabolic syndrome. The *Drosophila* homolog of *Brd2*, *female sterile (1) homeotic*, is a maternal effect, developmental gene and upstream activator of the trithorax complex, which opposes Polycomb action. These surprising connections suggest that research effort in humans that focuses on the adipocyte-specific functions of developmental and patterning genes will be fruitful, because the size and health of adipose tissue depots, body mass index, insulin sensitivity and WAT/BAT specification from progenitors are all likely to be affected by this pathway. This area of investigation is surprisingly underdeveloped, yet is of great medical significance because of the potential for new mechanistic insight into the 'metabolically healthy but obese' (MHO) human phenotype [158], which exhibits a reduced CVD risk and a diminished inflammatory profile [159]. Novel developmental pathways could be exploited to design a next generation of insulin-sensitizing drugs to treat obesity and its comorbidities, or re-direct energy storage from undesirable, central obesity to peripheral, subcutaneous depots of adipose tissue. In addition, this work highlights the connections between chromatin status, nucleosome positioning, histone modification and adipogenic transcription programs. Particularly, research effort should focus on the critical role of bromodomain-containing protein complexes, such as Brd2, SWI/SNF and their associated co-activator/co-repressor factors, in transcriptional reprogramming from proliferation in the pre-adipocyte to differentiation in the adipocyte. These epigenetic mechanisms have an importance at least equal to lineage-specific transcription factors in the determination of cell fate.

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