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BET proteins in abnormal metabolism, inflammation and the breast cancer microenvironment

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Abstract

Obesity and its associated pathology Type 2 diabetes are two chronic metabolic and inflammatory diseases that promote breast cancer progression, metastasis and poor outcomes. Emerging critical opinion considers unresolved inflammation and abnormal metabolism separately from obesity; settings where they do not co-occur can inform disease mechanism. In breast cancer, the tumor microenvironment is often infiltrated with T effector and T regulatory cells programmed by metabolic signaling. The pathways by which tumor cells evade immune surveillance, immune therapies and take advantage of anti-tumor immunity are poorly understood, but likely depend on metabolic inflammation in the microenvironment. Immune functions are abnormal in metabolic disease, and lessons learned from pre-clinical studies in lean and metabolically normal environments may not translate to patients with obesity and metabolic disease. This problem is made more urgent by the rising incidence of breast cancer among women who are not obese but who have metabolic disease and associated inflammation, a phenotype common in Asia. The BET proteins, comprising BRD2, BRD3 and BRD4, are new critical regulators of metabolism, co-activate transcription of genes that encode pro-inflammatory cytokines in immune cell subsets infiltrating the microenvironment, and could be important targets in breast cancer immunotherapy. These transcriptional co-regulators are well known to regulate tumor cell progression, but only recently identified as critical for metabolism, metastasis and expression of immune checkpoint molecules. We consider interrelationships among metabolism, inflammation and breast cancer aggressiveness relevant to the emerging threat of breast cancer among women with metabolic disease, but without obesity.

Summary.

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AUTHORSHIP

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CONFLICT OF INTEREST DISCLOSURES

The authors declare no conflict of interest.

Type 2 diabetes is an understudied contributor to progression of breast cancer; disease-associated chronic inflammation by BET proteins is a dangerous modifier of tumor microenvironments.

Keywords

Type 2 diabetes; metabolic disease; chronic inflammation; breast cancer; BET proteins

Introduction

Chronic inflammation is well recognized as a potent cause for the development of cancer [1–4]. Persistent bacterial or viral infections, and chemical irritants have been firmly implicated as causative agents, and anti-inflammatory drugs have been convincingly demonstrated to have chemopreventive value for cancer [5]. However, the focus of this review will be to discuss the relationships between *metabolic inflammation* and breast cancer, and mechanisms by which a new class of transcriptional co-regulators, the Bromodomain and ExtraTerminal (BET) proteins, mediate several critical aspects of this relationship. Fifteen years ago, metabolically abnormal adipose tissue in insulin-resistant obesity was recognized to be infiltrated with immune cells [6, 7]. In adults with obesity, many local and systemic factors become abnormally high (*e.g.*, fasting glucose, insulin, leptin, free fatty acids, pro-inflammatory cytokines) or low (*e.g.*, adiponectin, cardioprotective cytokines), but one significant area of recent focus for cancer research has been persistent, low-level inflammation, arising locally in part from these infiltrating immune cells that contact the adipocytes of the fat depot. Exposure of adipocytes and muscle cells to pro-inflammatory cytokines was shown to directly cause (not ‘associate with’) insulin resistance [8, 9]. Chronic, systemic imbalances in pro-inflammatory and anti-inflammatory cytokines also characterize metabolic abnormalities such as Type 2 diabetes (T2D) and are critical for disease pathogenesis [10–14]. BET proteins also critically regulate transcription of many cytokine genes. Given the preponderance of evidence directly linking metabolic inflammation to cancer initiation and progression, molecular and cellular models of insulin resistant obesity are being explored to understand mechanisms that drive risks for cancer incidence and progression in obesity. These studies will undoubtedly build on observations made in population studies when obesity was first recognized as an inflammatory disease [15–17]. Furthermore, new molecular insights are revealing how stromal, non-malignant cells of the tumor microenvironment, particularly immune infiltrates and adipocytes, where BET proteins are also crucial for function, are abnormal in T2D and drive tumor promotion and metastasis [18–20]. Here, we will discuss how the BET proteins are critical players in breast cancer progression [21], as well as in abnormal function of the stromal cells of the tumor microenvironment.

BET PROTEINS IN CANCER

Histone acetylases and deacetylases are critical to control condensation of chromatin, adding acetyl groups to specific peptides of nucleosomal histones that permit recruitment of co-activators to the target genes. These acetyl groups are ‘read’ by the bromodomain motif [22], comprised of four, bundled, anti-parallel α -helices connected by two loops [23]. The loops

bind to the acetyl groups of the histones with nanomolar affinity constants. The motif is found in an estimated 42 human proteins [24] and is highly conserved across eukaryotes [25]. This 110-amino acid structure occurs in the BET family as two tandem, mutually related bromodomains at the amino terminal end of the polypeptide, accompanied by an 'extraterminal' protein interaction domain that is always positioned carboxyl-terminal to the dual bromodomains [26, 27]. The BET family is comprised of three somatic proteins BRD2, BRD3, and BRD4, and a testis-specific form BRDT [24]. Enzyme or co-activator functions that are part of a polypeptide containing the bromodomain are thereby recruited to chromatin to change transcriptional activity [28, 29]. Thus, an individual BET protein can bind to acetylated histones at promoter chromatin through its bromodomains, and through its extraterminal domain or other carboxyl terminal domain. The BET protein can then recruit co-activators/histone acetylases to upregulate transcription of the target gene or co-repressors/histone deacetylases to downregulate transcription of the target gene in a versatile fashion [30–33]. In addition to epigenetic types of regulation through histone-modifying enzymes, these recruited proteins include transcription factors critical for cell cycle gene regulation and mitosis, such as E2F proteins [30, 32, 34], p53 and Myc [35] or P-TEFb [36, 37]; or also central for epithelial-to-mesenchymal transition (EMT), such as Twist [38]; or inflammation, such as NF- κ B [39].

BET proteins have long been known as drivers of human cancer [40], sometimes through mutation but more commonly through overexpression. Specific, reproducible and reciprocal translocations of chromosomes that break the *BRD3* and *BRD4* genes drive aggressive carcinomas of the midline in humans [41]. BRD4 function in particular has been implicated in mitotic control [42–45], BRD2 in cyclin gene transcription [46] and BRD3 in GATA1 transcription [47, 48]. Mistargeting of chromatin regulators and transcription-modifying enzymes [30, 31, 49] through chromosomal translocation is likely an essential step in this type of oncogenic transformation, which leads to deregulation of genes like cyclin D1 that are important for breast cancer [50]. The discovery of small molecule “pan-BET” inhibitors (BETi), such as JQ1 [51] and I-BET [39], which displace all BET proteins from promoter chromatin at low nanomolar concentrations, has generated significant excitement. Chromatin is now demonstrated to be ‘druggable’ [52] and epigenetic therapeutics for diverse cancers may be possible [53]. The roles of BET bromodomain proteins and the potential utility of pan-BETi in diverse cancers have been well reported, including for myeloma [54], lymphoma and leukemia [55–58], neuroblastoma [59], prostate [60], lung [61] and other tumor types.

In human breast cancer subtypes, several epigenetic factors are overexpressed [62, 63] and inhibition of BET proteins shows promise [64]. In some studies, triple negative cell lines show sensitivity to pan-BETi, blocking proliferation and promoting apoptosis [65]. Unfortunately, those experiments were conducted at physiologically irrelevant concentrations (2–20 μ M) and did not discriminate among BRD2, BRD3 and BRD4, which have overlapping and sometimes opposing functions [53]. Interestingly, estrogen receptor (ER) α -positive breast cancer that is resistant to tamoxifen may be amenable to BETi approaches, by blocking recruitment of the histone H3K36 methyltransferase WHSC1, which regulates ER α transcription and is overexpressed in certain poor-prognosis breast tumors [66]. This mechanism appears to involve BRD3 and BRD4 but not BRD2. New

results also show that BRD4 controls invasion and migration behaviors of several types of breast cancer [67]. The mechanisms of BET protein misregulation that contribute to obesity-associated breast cancer are an emerging focus of investigation [68].

BET PROTEINS IN METABOLIC INFLAMMATION AND BREAST CANCER IN OBESITY

DNA-binding transcription factors are essential for regulation of genes that control production of inflammatory cytokines, such as NF- κ B, and of genes that control adipocyte differentiation, such as PPAR γ . In addition to *cis*-acting transcription factors, these genes also require epigenetic regulators that modify chromatin and enable RNA polymerase access to promoters; these regulators include the BET proteins. In insulin-resistant obesity and T2D, BET proteins play important roles in the metabolism of cell types that are critical for disease progression, including pancreatic β -cells. Here, the co-repressor function of BET proteins is pertinent [21, 28, 29, 69, 70]. Reduced expression of Brd2 increases insulin transcription, likely through transcriptional de-repression [71] in both cell lines and animal models [72], and improves β -cell metabolism [73], while reduced expression of BRD4 also increases β -cell insulin content [73].

BET proteins are functionally critical for inflammation and adipogenesis. Here, we focus on two stromal cell types in the breast tumor microenvironment that are crucial in T2D: T cell subsets and white adipocytes (Fig. 1). BET proteins interact with both NF- κ B [74] and PPAR γ [71] in ternary complexes [75] and can co-activate or co-repress target genes, depending on the enzymatic activities in the ternary complex [30–34]. Interestingly, BET proteins appear to co-activate the NF- κ B-regulated target genes reported so far [39, 58, 74–78], whereas BET proteins co-activate [79] or co-repress [71, 80] PPAR γ -regulated target genes (Fig. 2). The evidence base for BET protein regulation of adipocyte functions is still emerging, compared to what is already well established about BET proteins in inflammation.

T2D, a chronic inflammatory disease, increases risk of breast cancer incidence [81] and mortality [82]. Inflammation also contributes to breast cancer aggressiveness and metastasis [83]. It is likely that the increased breast cancer risk in post-menopausal women with T2D is exacerbated by inflammatory processes. In obesity-driven T2D, adipose tissue produces pro-inflammatory cytokines and adipokines that alter the breast tumor microenvironment, increasing progression of invasive, metastatic cancer. Specifically, the inflammatory status of breast adipose tissue is positively correlated with tumor aggressiveness [18–20, 84]. Furthermore, ‘metabolically healthy’ adults, who show less local and systemic inflammation [85] than obese adults with co-morbid T2D and hypertension, have reduced incidence of certain cancers [86, 87]. The chronic inflammation of mammary adipose tissue in T2D is defined in part by infiltration with specific immune cells, *e.g.*, CD68+ macrophages that form histologically distinct ‘crown-like’ structures (CLS) that encircle stressed adipocytes in the fat depot [84, 88, 89]. These pro-inflammatory CLS correlate with poor prognostic features, higher tumor grade, decreased disease-free survival and increased risk for metastasis, and produce important cytokines that locally alter the tumor microenvironment.

Such microenvironments are breast cancer subtype- and patient-specific and likely differ in ways that impact tumor expansion and dissemination.

Several cytokines and chemokines are implicated in both obesity-driven T2D and breast cancer [90]. Interleukin (IL)-6, for example, is characteristically elevated in T2D [91] in a chronic manner and the gene is positively co-regulated by BET proteins [74]. In breast cancer, IL-6 is well established to promote proliferation [92] in breast cancer cells, as well as migration, invasion [67, 93], stemness [94] and epithelial-to-mesenchymal transition [95, 96]. Metabolic inflammation in breast adipose tissue associates with increased aromatase expression and activity (the enzyme central to the biosynthesis of estrogen) [84] and signaling to increase tumor aggressiveness [97–99]. Cytokine signaling is unquestionably an important contributor to breast cancer aggressiveness and chemoresistance in patients with metabolic inflammation.

Other pro-inflammatory cytokines and chemokines produced by immune cells, such as the Th17 cytokines (*e.g.*, IL-17A/F, IL-21, IL-22) [100–103] are also deregulated in T2D and are important for tumor cell migration, invasion, survival and proliferation [104–108]. The genes that encode many of these cytokines and chemokines are also positively regulated by one or more BET proteins [109–111]. These reports suggest that new, small molecule BETi can also improve the inflammatory microenvironment for therapeutic benefit, especially in patients with T2D and other chronic inflammatory diseases that are co-morbid with their cancers. Given the potent anti-inflammatory action of BETi, through their effects on transcription of NF- κ B target genes [39, 74] and STAT target genes [112], these approaches represent potentially effective avenues for intervention in inflammation and metastasis in breast cancer.

METABOLIC INFLAMMATION AND BREAST CANCER *WITHOUT* OBESITY

New research is forcing consideration of the disturbing possibility that ‘obesity-associated’ breast cancer is rising worldwide in women who are not apparently obese. Within the last year, work has shown that certain lean women show elevated biomarkers of inflammation both systemically and locally in breast adipose tissue, which associate with increased aromatase and breast cancer risk [113, 114]. These insights provoke a radical hypothesis: obesity *per se* is less important for cancer risk than *metabolic inflammation*, which need not accompany expanded fat depots or elevated body mass at all. This hypothesis represents a major paradigm shift, because previous research in obesity-associated cancers has tended to focus wholly on obesity itself, rather than the abnormal metabolism and inflammation that often accompany obesity [115]. Two well-established drivers of breast cancer progression, leptin, adiponectin (and their ratio), are deregulated in obesity, but generally are not abnormal in lean women, although they are abnormal in metabolic disease [116, 117]. Similarly, obese animal models of breast cancer may be inadequate or misleading [115, 118]. Chronic cytokine imbalances and abnormal immune infiltrates in breast tumors likely represent new mechanisms critical to cancer progression in lean women with metabolic disease.

Abnormal metabolism and chronic, systemic inflammation arising from metabolic disease, but in adults without apparent obesity, is creating an emergent, alarming public health crisis worldwide. This crisis is propelled partly by economic forces. Increased disposable income in Asia-Pacific countries, including India and China, for example, is boosting calorie consumption and curtailing physical activity. These transformations are taking place against a background of evolutionary pressure that selected for human populations with high insulin sensitivity and superb ability to store or metabolize glucose. A severe metabolic imbalance has quickly emerged in Asia over the last fifteen years. As economies have improved, the calorie-activity equilibrium of centuries has been upset. This well described economic change now drives a major shift in incidence patterns for cardiometabolic disease [119]. Macroeconomic forces such as urbanization and rising incomes are increasing sedentary behavior [120] and stimulating consumption of high-glycemic index foods, which together promote T2D. The relative impact of infectious diseases is decreasing, whereas chronic inflammatory conditions like T2D increasingly dominate the disease patterns in these regions [121]. Furthermore, unlike European-origin or African-origin adults, fat deposition in South Asians, Koreans, Chinese and other Pacific groups of people is not necessarily into discrete depots, but internally and ‘ectopically’ into visceral organs like liver, kidney and heart. Such a distribution is long known to endocrinologists as the ‘metabolically obese normal weight’ phenotype [122, 123]. Such adults need not reach high body weights to experience dangerous risks for T2D. Throughout the Asia-Pacific region, T2D and metabolic inflammation is rising quickly among adults who are underweight, lean, normal weight and slightly overweight [124].

With respect to breast cancer in India, incidence has been rising rapidly among younger women, and population-based cancer registries show significant increases in age-adjusted incidence rates for breast cancer from 2011–2014 [125]. Breast cancers in these younger patients also tend to take more aggressive forms. Several problems concern this emerging field. Different kinds of obesity carry different cancer risks [86, 87]. Whether T2D in obesity and T2D in lean women is the same disease with respect to breast cancer incidence and progression is yet to be explored. More broadly, it is not yet possible to leverage our current knowledge of metabolic inflammation to understand cancer progression in different types of patients. Emerging critical opinion [126] recognizes that the same subtype of cancer behaves quite differently depending on whether the patient is lean and metabolically normal, obese and diabetic, or lean and diabetic. In each case, the nature of T2D-associated inflammatory cytokines and cellular infiltrates likely makes a critical difference. New thinking will be required to address this emerging crisis of breast cancer driven by metabolic disease and chronic inflammation, but in patients who are relatively lean, about whom little is known.

As yet, there have been no clinical observational studies to test correlation of the expression of BET proteins with metabolic disease or cancer progression among Asian adults. However, the arguments presented here support a hypothesis that personalized profiling of BET proteins in T cell subsets of peripheral blood of Asian adults, particularly who have co-morbid metabolic disease, would be helpful to stratify risks for tumor progression and dissemination. High expression of one or more BET family members would be predicted to associate positively with tumor development and metastasis risk. Furthermore, if sufficiently selective small molecule inhibitors can be developed among the next generation of BETi to

enable discrimination among BET family members [53], these inflamed patients could benefit from chemoprevention for tumor progression and metastasis through reduced inflammation in the microenvironment of their tumors.

BET PROTEINS AND METFORMIN IN BREAST CANCER

One of the most successful and inexpensive treatments for T2D in obesity has been metformin (1,1-dimethylbiguanide), which has long been used effectively in the clinic. Metformin inhibits the mitochondrial complex I in diverse tissues [127], depleting the cell of ATP, which alters the balance of ATP and adenosine monophosphate (AMP). A secondary consequence of this shift is mobilization of an AMP sensing system, which activates 5' AMP-activated protein kinase (AMPK). Activated AMPK reprograms metabolic enzymes to stimulate fatty acid oxidation, thus to tap sources of energy and reverse storage pathways. Several cancer clinical trials have reported improvements in complete response and overall survival in breast cancer patients with diabetes who were treated with metformin [128, 129]. These trials built on compelling results from animal and cellular model studies [130]. Furthermore, AMPK activation can reverse EMT [131] and proliferation [132]. In addition to their role as co-activators of cytokine gene transcription, BET proteins also appear to play a role in AMPK energy sensing. For example, selective knockdown of BRD2 in pancreatic β -cells specifically increases fatty acid oxidation [73], illustrating a pathway that is likely conserved across diverse cell types. Activated AMPK is consistent with observed increases in fatty acid oxidation [73]. BRD2 has been shown to regulate catabolic genes in cachectic mice by modulating transcription of IL-6. Reduction of IL-6 prevents AMPK activation in the skeletal muscles of these mice [133]. The BET proteins likely reprogram breast cancer cell metabolism through these pathways.

Additional investigation has shown that AMPK activation promotes the formation of mammospheres in breast cancer cellular assays, and reduces apoptosis arising from matrix detachment of breast cancer cells [134]. Because mammosphere formation is also a feature of stem-like cancer cells, it is likely that AMPK activation additionally exacerbates the stemness character of breast cancer cells to promote drug resistance. An ability to overcome anoikis, cell death triggered by matrix-detachment, is critical for the survival of circulating tumor cells: solid tumor cells shed into circulation that seed metastasis. Circulating tumor cells are also more drug-resistant [135]. Thus, rapid AMPK activation after matrix detachment [136] can serve as an adaptable switch to alter cellular metabolism [137] and promote tumor cell survival in the circulation [138]. Furthermore, high grade breast cancers show elevated AMPK activation [136] and are associated with hypoxia, which both drives EMT [139] and activates AMPK [140]. Ongoing research strongly supports a role for AMPK in promoting EMT downstream of several stimuli. These processes are pro-tumorigenic, suggesting a troubling possibility that metformin treatment may have undesirable, pro-metastatic side effects for certain breast cancer patients.

BET PROTEINS IN METABOLIC INFLAMMATION AND IMMUNE EXHAUSTION

Tumor cells can escape the immune system by expressing diverse molecules that activate immune checkpoints, particularly against antitumor T cells. The most studied inhibitory receptors that tune the antitumor immune response are cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death 1 (PD-1). PD-1, a member of the CD28/CTLA-4 family, is expressed in activated T cells and represses their activation in the peripheral tissues under inflammatory responses to limit autoimmunity [141]. Therefore, PD-1 constitutes a major immune response inhibitor within the tumor microenvironment [142]. PD-1 is expressed by activated T cells and by tumor-infiltrating lymphocytes (TILs) [143], and is elevated in patients with T2D [144]. PD-1 has two ligands, programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2). PD-L1 is expressed in a variety of epithelial cancers including breast cancer [145], where it is associated with poor prognosis [146], and is also elevated in patients with T2D [144]. Moreover, chronic antigen exposure in cancer can lead to persistent high-level PD-1 expression on antigen-experienced T cells, impairing effector function and upregulating inhibitory receptors, termed “T cell exhaustion” [147]. PD-L1 expression is associated with poor prognosis and fewer TILs in several cancer types. Cancer cell-induced activation of this pathway might also explain why, in ongoing studies that investigate cancer vaccination, there is no tumor growth control despite the induction of cancer-specific T cells [148]. These observations provide a strong rationale to target PD-1 or its ligand PD-L1 with antibodies capable of inhibiting this pathway, an approach that has already shown promise for triple negative breast cancer [149]. BET proteins (Fig. 1) are newly implicated in the expression of PD-L1 in ovarian cancer [150] and B cell lymphoma [151]. New approaches that target family members individually will reveal mechanisms that are obscured by pan-BETi [53], and could then be leveraged with checkpoint inhibitors in innovative combinations. Thus, a new therapeutic opportunity has arisen to exploit BETi in immunotherapy.

As discussed above, the breast tumor microenvironment is characterized by the chronic presence of pro-inflammatory molecules and immune cell infiltration that exacerbates tumor progression. PD-1 is increased in CD8⁺ T cells before their activation in response to pro-inflammatory cytokines such as IL-6, IL-12 or interferon- γ and signaling through JAK/STAT [152]. Therefore, chronically elevated inflammatory cytokines within the breast tumor microenvironment in T2D may elicit PD-1 expression in breast tumor-infiltrating T cells. Evidence supports a mechanism for metformin treatment in T2D to improve PD-1 exhaustion [153]. Based on these considerations, it is reasonable to hypothesize that BET proteins regulate PD-1 expression in T cells in the breast tumor microenvironment. In recently published work, we showed that BRD4, but not BRD2 or BRD3, is critical for Notch1 signaling activation in a triple negative breast cancer model [67]. Thus, we hypothesize that Notch1-mediated PD-1 expression [154] is critically dependent on BET proteins, likely BRD4. Moreover, as described above, BET proteins are crucial regulators of pro-inflammatory cytokines production and signaling. Therefore, we expect to find that BET inhibition in activated T cells prevents inflammatory cytokine-driven PD-1 expression in the

breast tumor microenvironment. These insights will be important to explore in breast cancer patients with co-morbid T2D.

CONCLUSIONS

BET proteins are likely to play important roles in metabolic inflammation in breast cancer and might be usefully combined with metformin or other well-established treatments for T2D. Our mechanistic understanding of cancer progression, immune exhaustion and metabolic signaling is incomplete to enable accurate interpretation and clinical decision making in cancer patients with different types of obesity and co-morbid metabolic disease. The burden of these co-morbid conditions worldwide is going to increase in the near future, and our biomedical and clinical tools are underprepared to deal with these developments.

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Abbreviations

AMP	adenosine monophosphate
AMPK	AMP protein kinase
BET	Bromodomain and ExtraTerminal domain
BETi	BET inhibitor
BRD	Bromodomain
CLS	crown-like' structures
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
EMT	epithelial-to-mesenchymal transition
ER	estrogen receptor
IL	interleukin
NF-κB	nuclear factor kappa light chain enhancer of activated B cells
p-AMPK	phosphorylated AMP-activated protein kinase
PD-1	programmed cell death 1
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PPARγ	peroxisome proliferator-activated receptor gamma
T2D	Type 2 diabetes

Th17	T helper 17 cell
TILs	tumor-infiltrating lymphocytes

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Figure 1. Cellular crosstalk in the breast tumor microenvironment.

Tumor cells engage in paracrine signal transduction networks with nearby white adipocytes and pro-inflammatory T cell subsets that infiltrate the adipose tissue depot. The functions of these non-tumor cell types are highly abnormal in T2D and likely drive tumor progression. BET bromodomain proteins regulate tumor cell proliferation, invasiveness, migration and metastatic potential in response to these signals from the microenvironment cells, as well as immune exhaustion markers (*e.g.*, PD-L1) that are elevated in metabolic inflammation. These non-tumor cells both upregulate immune exhaustion markers on lymphocytes (*e.g.*, PD-1) in response to metabolic inflammation [144], and produce cytokines, under the control of the same subset of BET bromodomain proteins. Therefore, small molecule inhibitors that selectively ablate production of pro-metastatic factors could reduce the risks for tumor progression, improve immune exhaustion in metabolic disease and ‘cure’ the microenvironment, as well as reduce tumor proliferation and cell-intrinsic metastatic programs like EMT.

Figure 2. BET proteins function as co-activators or co-repressors, depending on the cell type and signaling context.

Small molecule BET inhibitors (BETi) or shRNA against individual BET proteins perturb both transcriptional co-activation and co-repression processes. Cell proliferation, inflammation and immune exhaustion genes are positively regulated by the three BET proteins, thus inhibition or knockdown reduces their expression. However, certain other genes are activated upon BETi treatment or shRNA knockdown, including the insulin gene and targets of PPAR γ . Small molecule approaches must therefore be sufficiently selective to carefully avoid undesirable on-target effects in nearby non-tumor cells of the microenvironment or elsewhere in the patient [53]. Ac: acetyl groups, Pol II: RNA Polymerase II, TAF: TATA-binding protein associated factor.