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cell survival and apoptosis through the generation of bioactive lipids (Oskouian and Saba, 2010).

The new findings have several clinical implications. The authors propose that PAFAH1B3 may serve as a useful prognostic marker in newly diagnosed patients, and, considering that silencing PAFAH1B3 in breast cancer cells results in profound growth inhibition, it may represent a novel therapeutic target for breast cancer, especially in high risk patients harboring tumors positive for TAZ and/or PAFAH1B3. It will be important to determine whether inhibiting the normal activity of PAFAH1B3 is safe and well tolerated in humans. Whether PAFAH1B3 will also be a downstream mediator of YAP/TAZ in other cancers in which Hippo has been implicated also remains to be determined.

Although promising, the study raises several important questions that have not yet been directly addressed. First, how does the Hippo pathway influence PAFAH1B3 activity? Second, is the activity of PAFAH1B3 fundamental to TAZ's ability to confer self-renewal capability to breast cancer cells? Considering a recent report demonstrating that Hippo regulates the transition from differentiated to undifferentiated state in liver cells (Yimlamai et al., 2014), it seems likely that a direct impact on the "stemness" of cancer stem cells could be mediated by TAZ targets. Third, what PAFAH substrates/products mediate tumorigenicity? Last, this study identified a number of other genes and proteins that were differentially expressed or activated in response to TAZ overexpression in this cancer progression model. Although not pursued by the authors, these targets may be relevant in the biology of breast cancer progression, and thus additional hypotheses may emerge from this interesting data set.

In conclusion, Mulvihill et al. (2014) present exciting work that opens a new dimension for cancer research and therapeutics. Overall, the intriguing results demonstrate the utility of metabolism-focused investigations to dissect the biology of the cancer cell and identify new targets.

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Nonequivalent Response to Bromodomain-Targeting BET Inhibitors in Oligodendrocyte Cell Fate Decision

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The tandem bromodomains (BD1 and BD2) of the BET family proteins BRD2, BRD3, BRD4, and BRDT are structurally conserved but not functionally equivalent. In this issue of *Chemistry & Biology*, Gacias and colleagues report that a BD1-specific chemical inhibitor, Olinone, enhances oligodendrocyte differentiation, contrasting the reverse process triggered by broad BD1/BD2-targeting inhibitors, highlighting distinct roles of BD1 and BD2 in cell fate decision.

The amino acid sequences and 3D structures of the tandem acetyl-lysine (Kac)-binding bromodomains (BD1 and BD2) present in the bromodomain and extra-terminal (ET) domain-containing BET family proteins are evolutionarily conserved (Wu and Chiang, 2007; Filippakopoulos et al., 2012). Nevertheless, the finding of two additional conserved regions with one containing the N-terminal cluster of casein kinase II phosphorylation sites (NPS) and one harboring basic

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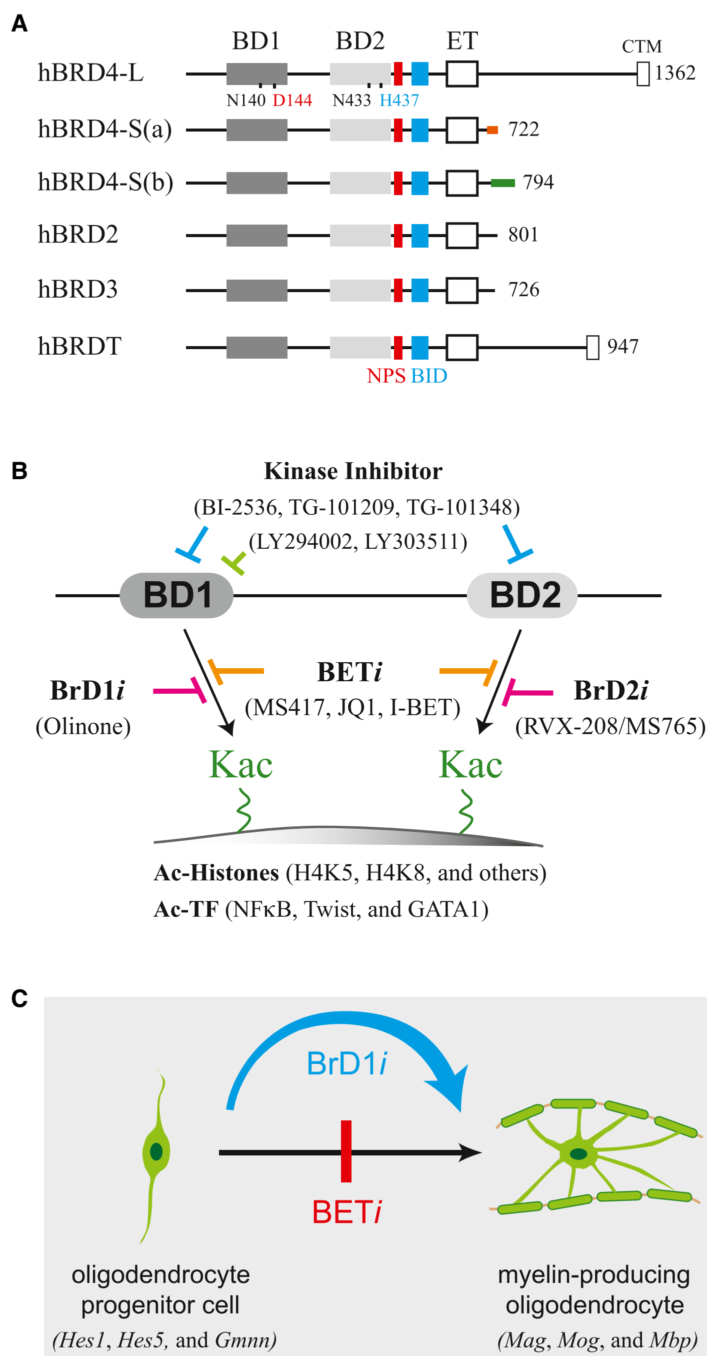

Figure 1. Differential Effects of BET Inhibitors on Oligodendrocyte Differentiation

(A) Human BET family proteins. The evolutionarily conserved regions, including bromodomain I (BD1), bromodomain II (BD2), extraterminal domain (ET), C-terminal motif (CTM), N-terminal cluster of CK2 phosphorylation sites (NPS), and basic residues-enriched interaction domain (BID) are schematized with conserved N140 and N433 as well as diverged D144 and H437 residues between BD1 and BD2 also indicated. The full-length long (L) and two short (S) forms (a and b) of human BRD4 with common amino acids 1–719 but different 3′ regions generated by alternative splicing are also shown.

(B) Chemical inhibitors targeting BD1 and/or BD2 of BET proteins. BrD1*i* and BrD2*i* are respective BD1-specific and BD2-specific inhibitors, whereas BET*i* represents broad inhibitors binding to both BD1 and BD2. Acetylated (Ac) histones and transcription factors (TF) binding to BD1 and/or BD2 are indicated on the bottom.

(C) BrD1*i* promotes, but BET*i* inhibits, oligodendrocyte differentiation. Representative genes expressed in oligodendrocyte progenitor cells and myelin-producing cells are indicated in respective cells in parentheses.

residues-enriched interaction domain (BID) situated downstream of the BD2 in all the BET family proteins (Figure 1A) predicts that BD1 and BD2 are differentially regulated by posttranslational modification that, in turn, recruits different partner proteins to regulate BET protein function in diverse cellular processes (Wu et al., 2013).

Using a structure-guided design to synthesize and screen for small compounds binding selectively to the BD1 of bromodomain-containing protein 4 (BRD4), Gacias et al. (2014) identified a high-affinity compound containing an acetyl moiety linked by four methylene groups to a tricyclic tetrahydro-pyrido indole scaffold that exhibits over 100-fold higher binding affinity to BD1 (K_d ~3.4 μM) than BD2 (K_d > 300 μM). This compound, named Olinone, shows comparable binding affinity to BRD2-BD1 and BRD3-BD1 and equal reluctance of association with the second bromodomains of the other BET proteins. Olinone occupies the hydrophobic Kac-binding pocket in a configuration and surface contact similar to that seen with a diacetyl histone H4 lysine 5 (K5) and lysine 8 (K8) peptide binding to BRD4-BD1, as revealed by X-ray crystallography at 0.94 Å. Although the asparagine 140 (N140) residue of BD1 crucial for contacting Kac and Olinone is likewise present in BD2 (N433, Figure 1A), a nonconserved histidine residue (H437) at BD2 poses a steric clash for Olinone contact complementarily mediated by aspartate 144 (D144) at the comparable position in BRD4-BD1. This structural insight elegantly explains the binding selectivity of Olinone for the BD1 of BET proteins. Conversely, H437 provides crucial contacts with the K73/K76-diacetylated Twist transcription factor that recruits BRD4 via BD2-specific association to enhance epithelial-to-mesenchymal transition in basal-like breast cancer cells, and conversion of D144 to histidine allows BD1 interaction with acetylated Twist (Shi et al., 2014), further highlighting the importance of BD1-specific D144 and BD2-specific H437 for bromodomain selectivity in drug design and recruitment of transcription factors. Other than Twist, the structural similarity for BET bromodomain binding to acetylated histone tails and acetylated nonhistone proteins has also been illustrated with BRD3-BD1-specific contact with K312/K315-diacetylated hematopoietic transcription factor

GATA1 (Gamsjaeger et al., 2011) and individual BD1 and BD2 of BRD4 association with the K310-acetylated RelA subunit of inflammatory transcription factor NF-κB (Zou et al., 2014).

The availability of BD1-selective chemical inhibitor (BrD1*i*) Olinone, distinct from the previously characterized broad BET inhibitors (BET*i*) MS417, JQ1, and I-BET that target both BD1 and BD2 and a BD2-selective inhibitor (BrD2*i*) MS765/RVX-208 (Figure 1B), allows the use of these pharmacological agents to address the target selectivity and functional significance of BD1 and BD2. Using mouse oligodendrocyte progenitor cells (OPCs) that can differentiate into myelin-producing oligodendrocytes, Gacias et al. (2014) found that treating OPCs with Olinone promotes oligodendrocyte differentiation, as reflected by enhanced myelin-specific *Mag*, *Mog*, and *Mbp* gene expression, accompanied by reduced progenitor *Hes1*, *Hes5*, and *Gmnn* marker expression; but, surprisingly, treating oligodendrocytes with broad BET inhibitors such as MS417 that target both BD1 and BD2 actually hinders differentiation (Figure 1C). This observation was further confirmed via the use of additional bromodomain-selective BET inhibitors, including MS611 BrD1*i* and RVX-208/MS765 BrD2*i* (Figure 1B). Enhanced myelin formation by BrD1*i*, but not BrD2*i* and BET*i*, highlights the need to develop more selective bromodomain inhibitors to enrich our molecular understanding of BD1- and BD2-specific function in gene targeting and disease treatment. It would be interesting to determine whether oligodendrocyte lineage gene expression is indeed regulated by BRD2 that is predominantly expressed in these cells and whether BRD4 and BRD3 could independently or collaboratively regulate progenitor and differentiated oligodendrocyte gene expression with BRD2. The existence of other evolutionarily conserved regions (e.g., ET, NPS, and BID) that regulate chromatin binding and partner association of the BET family proteins also predicts new drug development targeting other functionally important regions of the BET proteins. The recent finding that many protein kinase inhibitors targeting PLK1 (e.g., BI-2536), JAK2 (e.g., TG-101209 and TG-101348), PI3K (e.g., LY294002 and LY303511), and other kinases also exhibit strong binding affinity to both BD1 and BD2 or specifically to BD1 (Ciceri et al., 2014; Dittmann et al., 2014; Ember et al., 2014; see Figure 1B) raises not only interest in developing dual kinase/BET inhibitors for cancer therapeutics but also concerns of off-target effects that require further mechanistic studies of drug action in various biological systems.

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Lighting up FGFR Signaling

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In this issue of *Chemistry & Biology*, Kim and colleagues describe their work on optogenetic control of fibroblast growth factor receptor (FGFR) signaling. By engineering a chimeric receptor, the authors demonstrate that FGFR intracellular signaling can be controlled in space and time by blue light.

Intracellular signal transduction transmits external signals into the cell interior to ensure proper cellular decision making. Fibroblast growth factor receptor (FGFR) signaling belongs to a classical family of signal transduction pathways that regulates a wide spectrum of biological events such as development, wound healing, and angiogenesis. Dysregulation of FGFR signaling has been associated with developmental disorders and cancers.

Puzzlingly, many of the key cellular signaling modules initiated by membrane-bound receptor tyrosine kinases, like FGFR, activate overlapping sets of downstream pathways, but with distinct outcomes. Consequently, a central

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