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A BAF'ling Approach to Curing HIV

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Abstract

Latency is the primary barrier to the development of a long-sought cure for HIV-1. In this issue of **Cell Chemical Biology,** Marian et al., (2018) describe the development of novel compounds targeting the BAF chromatin remodeling complex to reverse HIV latency, with the potential to provide a functional cure.

Remodeling of chromatin structure is a critical step in key cell-fate decisions, including cell cycle regulation, differentiation, and development. The human genome encodes four different families of chromatin remodeling complexes: SWI/SNF, ISWI, NURD/Mi-2/CHD, and INO8O, which each contain a core catalytic ATPase subunit and multiple accessory proteins (Mayes et al., 2014). The mammalian switch/sucrose nonfermenting (mSWI/ SNF) complexes, which are critical for cellular differentiation, pluripotency, adhesion, and cell cycle regulation, utilize two central ATPase subunits, either SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 4 (SMARCA4, also called Brg1) or SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 2 (SMARCA2, also called BRM) (Mayes et al., 2014). Therapeutic targeting of SWI/SNF complexes has long been of interest for the treatment of various cancers and neurological diseases.

Interestingly, viruses also exploit the activities of chromatin remodeling complexes such as SWI/SNF. A prime example is the human immunodeficiency virus (HIV-1), which upon reverse transcription of its RNA genome and integration into the host genome, is chromatinized and subject to transcriptional control by host chromatin-modifying and -remodeling enzymes (Hakre et al., 2011). In latent infections, transcription of the integrated provirus is silenced, allowing the virus to evade detection by the immune system and escape antiretroviral therapy, which only targets the active form of viral infection. Currently, latency is the primary barrier to an effective HIV cure, leaving most infected individuals to endure life-long therapy.

The influence of chromatin structure on HIV transcriptional activity was first recognized in studies mapping the nucleosome positioning of the long-terminal repeat (LTR) structures at the 5′ end of the provirus, the site of the enhancer/promoter (Verdin et al., 1993). This work

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showed that the nucleosome structure is not determined by where the virus integrates into the human genome and uncovered a key role of the +1 nucleosome (nuc-1) situated immediately downstream of the transcription start site, which is significantly remodeled upon induction of viral transcription. Follow-up studies showed that treatment with histone de-acetylase (HDAC) inhibitors led to the same remodeling of nuc-1 and induced transcriptional activation, underscoring the importance of chromatin for transcriptional control of HIV and laying the groundwork for the use of HDAC inhibitors in therapeutic reactivation of latent HIVas part of the “shock and kill” strategy (Van Lint et al., 1996). The principle of this approach is to pharmacologically activate viral transcription from latent viral reservoirs so that the reactivated virus can be eliminated through the natural immune response and concurrent antiretroviral therapy. However, clinical studies of HDAC inhibitors as a monotherapy have encountered a number of issues including low levels of reactivation, loss of effectiveness after prolonged treatment, and immunosuppressive side effects that blunt the “kill” part of the approach (Kim et al., 2018).

In this issue of *Cell Chemical Biology,* Marian et al. (2018) provide evidence that another epigenetic regulator could be a target for the shock and kill approach: the mammalian SWI/SNF-A complex, known as BAF. The BAF complex consists of 15–20 subunits and has been shown to play a role in HIV latency by positioning nuc-1 to repress HIV transcription (Rafati et al., 2011). Interestingly, the SWI/SNF-B complex, known as PBAF, has the opposite function, supporting the transcriptional activity of HIV in conjunction with the HIV-specific trans-activator Tat (Mahmoudi et al., 2006; Rafati et al., 2011). Notably, BAF and PBAF complexes share most subunits including the Brg1 ATPase, which had previously been proposed as a therapeutic target for HIV latency (Rafati et al., 2011). However, the functionally opposing roles of Brg1-containing BAF and PBAF complexes in HIV transcription make inhibitors of Brg1 less attractive as shock and kill agents.

Marian et al. tackled this problem by focusing on BAF-specific subunits of SWI/SNF (Figure 1). They developed a robust phenotypic screen to identify, in a high throughput manner, inhibitors of BAF-regulated transcription from a screen of ~350,000 compounds in murine embryonic stem cells (mESCs). Following a secondary quantitative PCR-based screen, the top hit compounds contained a macrocyclic scaffold structure similar to a 12-membered macrolactam (Figure 1). Further optimization of the hits led to the development of three potent compounds (BRD-K98645985, BRD-K25923209, and BRD-K80443127). These compounds effectively inhibited BAF-dependent transcription at low concentrations (EC_{50} <10 μM) and displayed very little cytotoxicity (CC_{50} value >30 μM).

To validate that the compounds specifically altered BAF-regulated genes, the authors compared gene expression profiles between compound-treated cells (30 μM BRD-K98645985) and cells in which the BAF-specific component BAF250A (ARID1A) was knocked out, and observed significant overlap. Biochemical assays further confirmed that ARID1A was the molecular target of the macrolactam compounds.

The authors next tested the compounds in *ex vivo* models of HIV latency and observed robust reactivation of HIV-1 transcription. In primary $CD4^+$ T cells *ex vivo* infected with a luciferase reporter strain of HIV (pNL4.3-Luc) and maintained in a latent state, treatment

with one of the BAF inhibitors (5 μM BRD-K98645985) induced ~30-fold induction in luciferase activity, while combinations with low doses of HDAC inhibitors (350 nM suberoylanilide hydroxamic acid [SAHA] or 2 nM Romidepsin) or activators of the protein kinase c pathway known to reverse HIV latency (300 nM Prostratin or 1 nM Bryostatin) amplified this induction and led to up to 600-fold activation. Moreover, when latently infected $CD4^+$ T cells isolated from HIV-infected individuals were exposed to combinations of BAF inhibitors and Prostratin (10 μM BRD-K80443127 and 200 nM Prostratin), this treatment resulted in significantly greater increase in the number of HIV RNA copies compared to treatment with the BAF inhibitor alone. No spontaneous T cell activation or significant cytotoxicity was observed with the treatment of the BAF inhibitor alone in primary T cells. Using Jurkat T cell lines harboring latent HIV (J-Lat), the group showed that treatment with BAF inhibitor (50 μM BRD-K80443127) resulted in decreased nuc-1 nucleosome occupancy, underscoring the critical role of active positioning of nuc-1 in the suppression of HIV transcription during latency (Figure 1).

Identification of these macrolactam compounds specifically targeting the BAF complex opens new avenues for the development of a novel class of latency-reversing agents in the quest for a functional cure for HIV-1. Additionally, the ability of these compounds to target the ARID1A subunit, which is unique to BAF, makes them exciting research tools to further probe the role of the BAF complex in cellular processes like neurogenesis, tumorigenesis, tumor suppression, and antiviral responses. However, as always, many questions remain. The precise mechanism of action for these compounds remains elusive. Since ARID1A has no catalytic activity within SWI/SNF, these inhibitors most likely disrupt its structure, a hypothesis which needs to be further investigated. While the finding of little cytotoxicity in treated cells is remarkable, the central role of the BAF complex in regulating many basic cellular processes presents a caveat in developing these macrolactam compounds as therapeutics. Last, but not least, the risk associated with the activation of chronic viruses, herpes viruses, or endogenous retroviral sequences found in the human genome need to be evaluated. Herpes viruses use SWI/SNF complexes for reactivation (Herrera and Triezenberg, 2004) and endogenous retroviral sequences are continually occupied by SWI/SNF complexes (Conrad et al., 2017), suggesting that modulation of BAF could also influence the activation of these viral elements in HIV-infected individuals.

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REFERENCES

Conrad RJ, Fozouni P, Thomas S, Sy H, Zhang Q, Zhou MM, and Ott M (2017). The short isoform of BRD4 promotes HIV-1 latency by engaging repressive SWI/SNF chromatin-remodeling complexes. Mol. Cell 67, 1001–1012.e6. [PubMed: 28844864]

Hakre S, Chavez L, Shirakawa K, and Verdin E (2011). Epigenetic regulation of HIV latency. Curr. Opin. HIV AIDS 6,19–24. [PubMed: 21242889]

Herrera FJ, and Triezenberg SJ (2004). VP16-dependent association of chromatin-modifying co-activators and underrepresentation of histones at immediate-early gene promoters during herpes simplex virus infection. J. Virol. 78, 9689–9696. [PubMed: 15331701]

Kim Y, Anderson JL, and Lewin SR (2018). Getting the “kill” into “shock and kill”: strategies to eliminate latent HIV. Cell Host Microbe 23, 14–26. [PubMed: 29324227]

Mahmoudi T, Parra M, Vries RG, Kauder SE, Verrijzer CP, Ott M, and Verdin E (2006). The SWI/SNF chromatin-remodeling complex is a cofactor for Tat transactivation of the HIV promoter. J. Biol. Chem. 281, 19960–19968. [PubMed: 16687403]

Marian CA, Stoszko M, Wang L, Leighty MW, de Crignis E, Maschinot CA, Gatchalian J, Carter BC, Chowdhury B, Hargreaves DC, et al. (2018). Small molecule targeting of specific BAF (mSWI/SNF) complexes for HIV latency reversal. Cell Chem. Biol. 25, this issue, 1443–1455. [PubMed: 30197195]

Mayes K, Qiu Z, Alhazmi A, and Landry JW (2014). ATP-dependent chromatin remodeling complexes as novel targets for cancer therapy. Adv. Cancer Res. 121, 183–233. [PubMed: 24889532]

Rafati H, Parra M, Hakre S, Moshkin Y, Verdin E, and Mahmoudi T (2011). Repressive LTR nucleosome positioning by the BAF complex is required for HIV latency. PLoS Biol. 9, e1001206.

Van Lint C, Emiliani S, Ott M, and Verdin E (1996). Transcriptional activation and chromatin remodeling of the HIV-1 promoter in response to histone acetylation. EMBO J. 15, 1112–1120. [PubMed: 8605881]

Verdin E, Paras P Jr., and Van Lint C (1993). Chromatin disruption in the promoter of human immunodeficiency virus type 1 during transcriptional activation. EMBO J. 12, 3249–3259. [PubMed: 8344262]

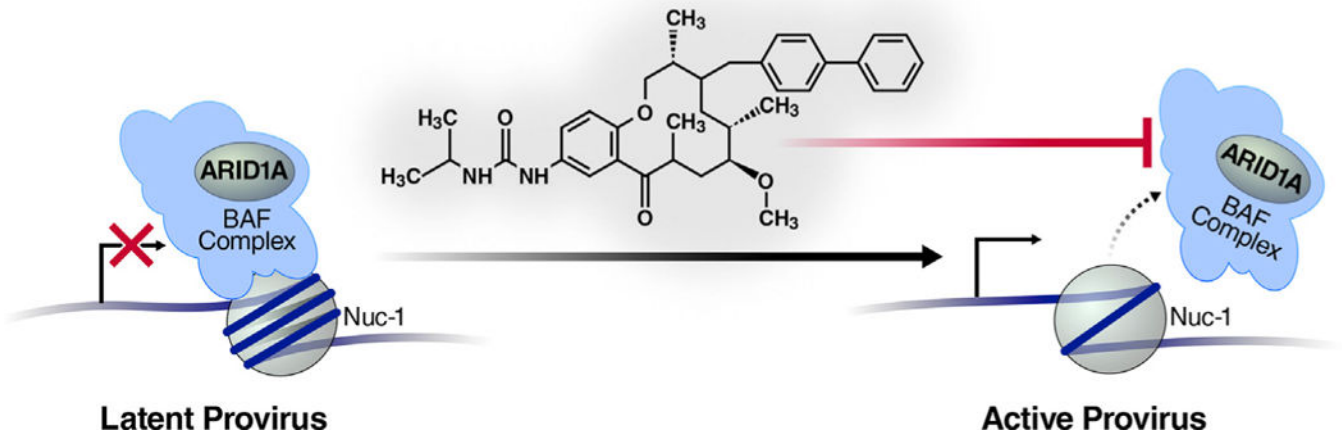

Figure 1.

TreatmentwithARID1A-Targeting Macrolactam Compounds Causes Re-positioning of Nuc-1 and Supports HIV-1 Latency Reversal through the Suppression of the BAF Complex