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EPIGENETIC DRUGS

New modulators of readers and erasers

The post-translational modification of lysine residues on histones, resulting in epigenetic changes in gene expression, is linked to several disorders including cancer, inflammation and viral infection. Two recent papers report the identification of new modulators of specific epigenetic proteins.

The first study, reported in *Nature Chemical Biology*, identified a novel small-molecule probe for a methyl-lysine 'reader' domain (which recognizes and binds to lysine modifications).

The authors focused their search for a modulator of methyl-lysine reader activity on the MBT (malignant brain tumour) domain-containing proteins because of the potential druggability of the interaction between this domain and lysine residues.

Synthesis of ligands and subsequent structure–activity relationships yielded a compound — named UNC1215 — that had high affinity (120 nM) and selectivity for L3MBTL3.

Next, the authors investigated the mechanism of action of UNC1215. The crystal structure of the compound complexed with L3MBTL3 showed that binding resulted in a 2:2 complex of these two molecules, and was mediated by the domain 1 and domain 2 binding pockets of the MBT protein. Cellular studies showed that the binding of UNC1215 to L3MBTL3 displaces native cellular methyl-lysine-containing targets.

Finally, the authors looked for proteins that interact with L3MBTL3 to see whether the interaction could be inhibited by UNC1215. One such protein was BCL-2-associated transcription factor 1, which interacts with the BCL-2 family of apoptosis-regulating proteins. The interaction between these two proteins was indeed disrupted by UNC1215.

The second paper, published in *Science Translational Medicine*, showed that a new inhibitor of a Jumonji domain-containing protein 2 (JMJD2; an 'eraser') prevented herpes simplex virus (HSV) infection and prevented viral reactivation from latency.

The initiation of cellular infection by HSV is dependent on the activity of lysine-specific histone demethylase 1 and JMJD2 proteins that promote transcriptional activation of viral genes (by removing repressive histone marks). So the authors used an *in vitro* compound screen to find new JMJD2 inhibitors that might modulate HSV infectivity.

Out of a series of newly identified JMJD2 inhibitors, ML324 inhibited viral immediate-early gene expression with a half-maximal inhibitory concentration of ~10 μM, and was chosen for further studies.

In cells infected with HSV, ML324 reduced viral yields, even when infection levels were high, and the compound blocked the transcription of viral immediate-early genes when administered after infection. Moreover, ML324 suppressed the formation of HSV plaques and reduced the spread of infection to adjacent cells.

The authors next assessed ML324 in mouse sensory ganglia infected with latent HSV, where it reduced the level of viral reactivation and suppressed the spread of reactivated viral infection.

These studies, which describe the first small-molecule probe for L3MBTL3 and show that a new JMJD2 inhibitor can control HSV infection and recurrence, widen the window of potential epigenetic targeting.

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ORIGINAL RESEARCH PAPERS James, L. I. *et al.* Discovery of a chemical probe for the L3MBTL3 methyllysine reader domain. *Nature Chem. Biol.* 6 Jan 2013 (doi:10.1038/nchembio.1157) | Liang, Y. *et al.* Targeting the JMJD2 histone demethylases to epigenetically control herpesvirus infection and reactivation from latency. *Sci. Transl. Med.* **5**, 167ra5 (2013)

FURTHER READING Arrowsmith, C. H. *et al.* Epigenetic protein families: a new frontier for drug discovery. *Nature Rev. Drug Discov.* **11**, 384–400 (2012)