Targeting epigenetics: structure-guided design of histone demethylase inhibitors for cancer therapy.

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Epigenetic mechanisms in tumorigenesis have attracted considerable attention in the development of anticancer therapy. High expression levels of histone lysine demethylases of subfamily 4 (KDM4s) are linked to oncogenesis in common cancers such as breast, lung, and colorectal cancer. The ability to reverse epigenetic modifications offers a promising therapeutic strategy to transform a pathological state into a normal one.

All KDM4s share a structurally conserved catalytic domain, including the 2-oxoglutarate (2OG) binding site, as confirmed by numerous crystal structures of this subfamily. Nevertheless, to achieve higher binding affinity and selectivity toward subfamily 4 members, we postulate leveraging structure-based exploration of the histone binding site to support the design of compounds that can reach this less conserved region.

To test our hypothesis, we applied a structure-based strategy that combined rational design with high-throughput fragment screening using X-ray crystallography. Focusing on the distal histone binding site, we employed known scaffolds—such as nicotinic acid and tetrazolylhydrazides—tailored with flexible extensions to probe this less conserved region. As part of a broad crystallographic fragment screening campaign, we screened F2X-Entry and FragMAXlib fragment libraries comprising over 250 compounds, along with the EU-OpenScreen collection of 1,000 chemically diverse molecules. This effort yielded numerous hits: some fragments targeted the histone binding site directly, while others revealed novel interaction hotspots across the KDM4D protein surface. We also uncovered a variety of functional groups engaging key residues within and around the catalytic pocket. These binding modes—several of which offer new handles for inhibitor optimization—are being further investigated.

With these critical interactions pinpointed, our design efforts are now focused on sculpting novel lead compounds. We are confident this refined approach will culminate in a selective KDM4 inhibitor, heralding a new therapeutic possibility.

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