Comparing ATAD2/B Bromodomain Structure-Function Differences in The Dynamic Epigenetic Landscape

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ATAD2 (ATPase family, AAA-domain containing protein 2) is overexpressed in many cancers and is associated with poor patient outcomes. Both ATAD2 and its closely related paralog ATAD2B, contain sequentially and structurally conserved C-terminal bromodomains that can "read" post-translational modifications (PTMs) that occur on histone tails. Bromodomains are structurally conserved motifs consisting of a left-handed alpha-helical bundle with a deep hydrophobic binding pocket that recognizes acetylated lysine residues.

The histone epigenetic landscape forms a combinatorial code containing multiple modifications, like acetylation, methylation, and phosphorylation, at any given time. Our goal is to understand how crosstalk between combinatorial histone PTMs affects the bromodomain activity of ATAD2/B. We are also interested in how sequence variation in the histone tail in histone variants or "onco" mutations impacts crosstalk. We have previously shown that the ATAD2/B bromodomains recognize mono- and di-acetylated lysine residues on histone H4, however the effect of adjacent PTMs on the "reading" of acetylated lysine remains unknown. We hypothesized that the presence of nearby post-translational modifications or mutations would impact the acetylated lysine ligand recognition ability of the ATAD2/B bromodomains.

In this study, we have combined various biochemical and biophysical techniques to gain insights into how the combinatorial histone PTM readout modulates the ATAD2/B bromodomain activity. Using isothermal titration calorimetry (ITC) we show that the presence of nearby PTMs, sequence variation due to histone variants, and "onco" mutations impacts bromodomain binding activity of ATAD2/B. Our novel X-ray crystallography structures of the ATAD2/B bromodomains demonstrate a unique binding mode of ATAD2 compared to its paralog ATAD2B. Overall, our results illustrate how the ATAD2/B bromodomains differ in their preference for the recognition of specific histone PTMs in the epigenetic landscape. Additionally, we provide insight into how dynamic changes or mutations in the epigenetic landscape may modify how the ATAD2/B bromodomains are targeted to chromatin.