Exploring ATAD2 Bromodomain Structure And Function Differences In The Dynamic Epigenetic Landscape

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The ATPase family, AAA-domain containing protein 2 (ATAD2) is highly overexpressed in unrelated cancers and associated with poor patient outcomes. ATAD2 contains a C-terminal bromodomain that "reads" post-translational modifications (PTM) that occur on histone proteins present in the nucleosome core particle. The bromodomain is a structurally conserved motif consisting of a left-handed alpha helical bundle with a deep binding pocket that is known to recognize acetylated lysine. The epigenetic landscape forms a combinatorial code on histone proteins, which contain multiple modifications at any given time. Yet, it is unknown how the presence of other modifications adjacent to the acetylated lysine residues impact bromodomain protein recognition and function. We hypothesized that the presence of nearby post-translational modifications including methylation and phosphorylation would modulate the ability of the ATAD2 bromodomain to recognize its acetylated lysine binding partners. Previously, we systematically screened for multiple PTM combinations recognized by the ATAD2 bromodomain. In our current study, we characterized the interactions with these histone ligands using isothermal titration calorimetry (ITC), and solved structures of the bromodomain-ligand complexes using X-ray crystallography. Our results indicate that the histone binding activity of the ATAD2 bromodomain is impacted by the presence of nearby PTMs, which is likely due to changes observed in the binding pocket interactions. Our results provide new insights on how the bromodomain functions to target the ATAD2 protein to chromatin, and how this interaction may be fine-tuned via dynamic changes in the epigenetic landscape