MORC2 is a phosphorylation-dependent DNA compaction machine

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The Microrchidia (MORC) family of chromatin-remodelling ATPases is pivotal in forming higher-order chromatin structures that suppress transcription. The exact mechanisms of MORC-induced chromatin remodelling have been elusive. Here, we report an in vitro reconstitution of full-length MORC2, the most commonly mutated MORC member, linked to various cancers and neurological disorders. MORC2 possesses multiple DNA binding sites that undergo structural rearrangement upon DNA binding. MORC2 locks onto the DNA using its C-terminal domain (CTD) and acts as a sliding clamp. A conserved phosphate-interacting motif within the CTD was found to regulate ATP hydrolysis and cooperative DNA binding. Importantly, MORC2 mediates chromatin remodelling via ATP hydrolysis-dependent DNA compaction, regulated by the phosphorylation state of its CTD. These findings position MORC2 CTD phosphorylation as a critical regulator of chromatin remodelling and a promising therapeutic target.