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Structural and Functional Insight into the Epigenetic Regulator SMCHD1

Thursday, 24 November 2016 14:00 (15 minutes)

Structural Maintenance of Chromosomes flexible Hinge Domain-containing 1 (SMCHD1) is a non-canonical SMC protein that plays critical roles in epigenetic regulation. Recently, heterozygous loss of function mutations in SMCHD1 were identified in facioscapulohumeral muscular dystrophy (FSHD) patients, leading to failure of epigenetic silencing of the disease-causing gene DUX4 in muscle cells. While the importance of SMCHD1 is well-described, there is limited understanding about how SMCHD1 protein mediates epigenetic control at the molecular level.

We performed small-angle X-ray scattering (SAXS) studies of the two recognisable domains of SMCHD1, namely the SMC hinge domain that is responsible for nucleic acid binding and the putative GHKL ATPase domain. We demonstrated that the hinge domain of SMCHD1 assembles into an unconventional dimeric arrangement flanked by intermolecular coiled-coil. Furthermore, we showed the N-terminal region of SMCHD1 that encapsulates the ATPase domain grossly resembles the crystal structure of full-length Hsp90 protein. Importantly, we found the ATPase domain of SMCHD1 is catalytically active. Therefore, similar to Hsp90's ATP-binding dependent conformational changes, we envisage that SMCHD1 dimer may undergo energy-dependent conformational changes to engage with chromatin. Additionally, ongoing characterisation of recombinant proteins incorporating patient-derived SMCHD1 mutations have provided potential explanations for the underlying pathogenesis. Finally, our study has formed the basis of exploring activation of SMCHD1 as a potential therapeutic treatment for FSHD.

Keywords or phrases (comma separated)

SMCHD1, Epigenetic regulation, FSHD, SMC hinge, GHKL ATPase, SAXS

Are you a student?

No

Do you wish to take part in the Student Poster Slam?

No

Are you an ECR? (<5 yrs since PhD/Masters)

Yes

What is your gender?

Female

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