KAP1 is an antiparallel dimer with a natively functional asymmetry

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KAP1 (KRAB-domain associated protein 1) plays a fundamental role in regulating gene expression in mammalian cells by recruiting different transcription factors and altering the chromatin state. In doing so, KAP1 acts both as a platform for macromolecular interactions and as an E3 SUMO ligase. Using an integrative modelling approach, we sheds light on the overall organization of the full-length protein combining solution scattering diffraction data and single-molecule experiments. We show that KAP1 is an elongated antiparallel dimer with a native asymmetry at the C-terminal domain. This conformation supports our finding that the RING domain contributes to KAP1 auto-SUMOylation. Importantly, this intrinsic asymmetry has key functional implications for the KAP1 network of interactions, as the heterochromatin protein 1 (HP1) occupies only one of the two putative HP1 binding sites on the KAP1 dimer, resulting in an unexpected stoichiometry, even in the context of chromatin fibers.