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Small spatial motifs within a surface-exposed loop in kinesin motor proteins codes for mechanochemical coupling

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In kinesins, loop-5 is implicated in mechanochemistry and widely noted for its allosteric druggability. Yet, its native role has been obscured by its sequence variability and irregular conformations: No signature sequence in function or ligand-binding has been defined. Here we hypothesize that the loop-5 protein backbone is shaped by small spatial motifs in a catalytically-dependent manner. Mining of small motifs, <5 residues in length and based on amide hydrogen-bonding and phi/psi angles showed that loop-5 of two different processive kinesin motor proteins have variable and conserved ordered structures that are not dependent on amino acid identity. Mutation of conserved, inter-linked loop-5 niches is shown to selectively deregulate mechanical output and catalysis of both motors. Analysis of 55 reported substitutions in 6 kinesins complemented our experiments; disruption of mechanochemical coupling is correlated with mutation in small motifs and not within classical secondary structures. Thus, loop-5 has a conserved function as a kinesin transducer but we redefine it as a series of variable and conserved 3D motif switches that can encode a spectrum of mechanocoupling strategies. Modular organization of a series of small spatial motifs is extendable to other loops in motor proteins specifically and NTPases more broadly.

Biography

Rebecca S Buckley has completed her PhD in 2016 from Louisiana State University Medical School & Health Sciences Center. She is currently a Postdoctoral fellow in the lab of Sunyoung Kim where she is continuing her work on the functional characterization of a surface-exposed, drug-binding loop and its role in kinesin mechanochemistry and oligomerization.

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