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Motor domain β-sheet motifs contribute to diversification of kinesin-microtubule interactions

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There is a growing appreciation for the importance of correlated motions within β-sheets of enzymatic proteins. Case in point, kinesin ATPases have α/β organization with a central β-sheet that physically separates the two ligand-binding sites: The active and microtubule (MT)-binding sites. Meta-analysis of existing kinesin X-ray structures revealed that a change in motor function is correlated with a change in β-sheet twist. We hypothesized that the change in twist was due to key sequence differences that occurred within the central β-sheet during the evolution of the kinesin nanomotor. We first identified three β-sheet motifs in which sequence changes correlate with different kinesin functional outputs. These motifs were structurally and functionally validated. X-ray structures of both β-sheet substitution and an active site surface loop substitution were generated. We show that single-site substitution of the central β-sheet results in loss of β-strand and changes in twist that are propagated across the β-sheet. Our functional assays provide evidence that these substitutions alter communication between the enzyme's active and MT-binding sites. While correlated motions in β-sheets are predominately studied in terms of backbone interactions, we show that side chain identity contributes to these motions. We conclude that β-sheet sequence changes promote enzyme specialization and are likely a universal design principle in NTPases.

Biography

Jessica Richard has completed her PhD in Biochemistry and Molecular Biology at Louisiana State University Health Sciences Center in New Orleans, LA in May 2016. She is currently a Post-doctoral fellow in the laboratory of Dr. Sunyoung Kim. She is investigating the evolution of sequence-structure-function relationships in kinesin motor proteins.

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