Structural basis for non-catalytic signalling mechanisms of Eph receptor pseudokinase EphA10

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The erythropoeitin-producing human hepatocellular (Eph) receptors are a large family of transmembrane, cell surface proteins with intracellular tyrosine kinase domains [1]. Interactions between Eph receptors and their membrane-bound ephrin ligands occur across cell-cell junctions and promote the assembly of dynamic clusters that amplify intracellular phsophorylation to propagate downstream signalling [2]. In addition to their tyrosine kinase activity, Eph receptors rely heavily on non-catalytic mechanisms to transduce signals across the cell membrane. Moreover, two members of the Eph receptor family, EphA10 and EphB6, are classified as pseudokinases and lack phosphotransferase activity due to substitutions of conserved residues in their kinase fold [3]. Dysregulation of EphA10 and EphB6 expression is associated with the onset and progression of multiple aggressive cancers, however, the specific roles of these pseudokinases in physiology and disease are still emerging, revealling complex mechanisms of regulation that challenge the development of Eph-targeted therapies [4,5]. We hypothesise that gaining a molecular-level understanding of the non-catalytic signalling mechanisms of Eph receptor pseudokinases will provide new opportunities for the design of effective Eph-targeted therapeutic strategies. Using advanced, integrated light and electron microscopy techniques, this work aims to determine the key structural features that drive non-catalytic signalling functions of Eph receptor pseudokinase EphA10.

References

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