REELIN IS A HEPARIN BINDING PROTEIN: IN VITRO TESTING AND IN SILICO ANALYSIS - (session: Structural Genomics)

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Reelin is a large molecule of the extracellular matrix (ECM) which regulates neuronal positioning during the early stages of cortical development in vertebrate species1,2,3. The localization of Reelin in the ECM, its modular assembly and its role in the regulation of neuronal migration led us to suppose a function for its modules in binding to polysaccharides commonly found on proteoglycans of the ECM, similar to that observed for the repeat modules of Laminins and Thrombospondins. We investigated whether Reelin could interact with the polysaccharide heparin using an affinity chromatography approach followed by immuno-blot analysis. The results obtained indicate an important specific interaction between Reelin and the heteropolysaccharide heparin; moreover the data support the involvement of the Reelin subrepeats in the binding. Further bioinformatic analysis and three-dimensional modeling of the Reelin subrepeat regions confirm the presence of structural features common to polysaccharide binding modules, like an ASP-BNR hairpin loop, large aromatic residues and a series of basic arginine residues, located on the surface cleft of the 3D model of a Reelin subrepeat, and potentially involved in the binding to polysaccharides. These findings provide new insights into the structural organisation of Reelin and novel hypothesis concerning the molecular function of this large ECM molecule, that could be tested experimentally. Finally, this work points to new directions in the research of therapeutic compounds that can modulate the activity of Reelin, given the importance of this protein in several human neurodevelopmental disorders.

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