Disordered proteins sensitive to environment, sequence changes

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Research published by IU bioinformaticist Predrag Radivojac, above, and two others has shown quantitative influence of small sequence changes and environment on disordered regions of proteins, raising questions about their influences on the regulation of protein function.

(PhysOrg.com) -- Research published by a team of Indiana University bioinformaticists has shown quantitatively the influence of small sequence changes and environmental conditions on the disordered regions of a protein.

The findings have led the team -- lead author and IU Bloomington School of Informatics and Computing assistant professor Predrag Radivojac, IU School of Medicine senior research professor Vladimir Uversky, and informatics Ph.D. candidate Amrita Mohan -- to suggest that function evolution in proteins, though with little actual protein

structure change, could be facilitated by the sensitivity of disordered regions to sequence changes.

Proteins are complex molecules that do most of the work in cells and are required for the structure, function and regulation of the body's tissues and organs. Single cells can contain thousands of different proteins, with each protein containing up to 20 different amino acids that are attached to one another in long chains that create a unique and stable three-dimensional structure. Disordered proteins lack a stable tertiary structure and challenge the traditional paradigm that structure defines protein function.

"We quantitatively showed what the influence of small sequence changes and environment can be on disordered regions in a protein," Radivojac said. "This leads us to speculate that since disordered regions are frequently involved in molecular recognition (binding), it raises questions about environmental regulation of protein function. This is a very unexplored area."

Changes in disordered regions of proteins as a result of mutation also are raising new questions about the evolvability of proteins through the sensitivity of disordered regions to sequence changes, he added.

"What we think is good about the paper is that it moves knowledge a bit forward and points to far more interesting questions in a systematic way," Radivojac said.

Using x-ray crystallography, the researchers studied and quantified the variability of intrinsically disordered protein regions under different external conditions like salinity, temperature and pH, and compared them to the variability introduced by small sequence changes. Results published in the paper, "Influence of Sequence Changes and Environment on Intrinsically Disordered Proteins," in *PLoS*

Computational Biology, found that both external conditions and sequence changes have strong impacts on the existence of disordered regions, and therefore could potentially regulate protein function by environmental factors or facilitating evolutionary change.

By developing methods for the characterization and prediction of a protein's structural and functional properties, including by automated inference of protein molecular and cellular function or disease associations from a protein's sequence, structure or interactions, researchers might one day be able to confirm a link between pathogenicity and the amount of disorder in the entire complement of proteins expressed by a cell, tissue or entire genome. Disordered proteins have been linked to human diseases like cancer, Parkinson's disease, Alzheimer's disease and several cardiovascular disorders.

Provided by Indiana University (news : web)