Computer modeling used to study protein involved with cancer, aging and chronic disease

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(PhysOrg.com) -- A new biophysical and biochemical study may lead to better understanding of how structural flexibility controls the interaction of a protein that is closely involved with cancer, aging and other chronic diseases -- thereby facilitating future development of better therapeutic strategies, according to a Kansas State University biochemist.

Jianhan Chen, an assistant professor of biochemistry, was one of the researchers on a collaborative project that took a combined computational and experimental approach to understand how protein p21 functions as a versatile regulator of cell division. Their latest findings, "Intrinsic disorder mediates the diverse regulatory functions of the Cdk inhibitor p21," were published in a recent edition of Nature Chemical Biology.

The study used computer simulation to rationalize results from biochemical and biophysical experiments, and provided further insights that would guide future investigations, Chen said. In this case, the focus is human protein p21 and its ability to function as an inhibitor of normal cell growth.

The protein has been shown to be an intrinsically disordered protein. This means it lacks a well-defined three-dimensional structure, characteristics that, until roughly a decade ago, were thought to be necessary for the protein to function.

"For a long time it was believed that proteins must fold to function and it was hard to imagine how an unfolded protein could play a role in crucial cellular areas," Chen said. "What researchers before me found was that by lacking a stable structure, this actually turned out to be really, really important to how these proteins function."

Along with being an intrinsically disordered protein, p21 is a versatile cyclin-dependent kinase, or Cdk, inhibitor -- meaning it adapts to and inhibits a range of Cdk-cyclin complexes that regulate eukaryote cell division. It also has been connected to cancer and aging. For example, Chen said p21 is a principal trans-activation target of the p53 tumor suppressor protein and contributes to p53-dependent tumor suppression.

"This protein is extremely challenging to study. It's highly dynamic and it's heterogeneous," Chen said. Because of this, mechanistic studies of intrinsically disordered proteins like p21 have been limited. Experiment alone is not sufficient and computer modeling is necessary to provide important missing details, he said. A tight integration of both could lead to a precise understanding of how structural flexibility influences function of p21 and other intrinsically disordered proteins.

"For me this is one of the most interesting IDPs," Chen said. "I'm a theorist and I want to use this system to understand the principles of how this type of proteins can perform their functions. Even though they are disordered, they are not random; there is no chaos. They still have some type of residual structures and certain features which allow function to be controlled in a precise way, and I want to understand the underlying mechanism of how this occurs."

Chen is continuing work with p21 and other small proteins that regulate cell cycles.

Provided by Kansas State University