

Unfolded proteins collapse when exposed to heat and crowded environments

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Proteins are important molecules in our body and they fulfil a broad range of functions. For instance as enzymes they help to release energy from food and as muscle proteins they assist with motion. As antibodies they are involved in immune defence and as hormone receptors in signal transduction in cells. Until only recently it was assumed that all proteins take on a clearly defined three-dimensional structure – i.e. they fold in order to be able to assume these functions. Surprisingly, it has been shown that many important proteins occur as unfolded coils. Researchers seek to establish how these disordered proteins are capable at all of assuming highly complex functions.

Ben Schuler's research group from the Institute of Biochemistry of the University of Zurich has now established that an increase in temperature leads to folded proteins collapsing and becoming smaller. Other environmental factors can trigger the same effect. The crowded environments inside cells lead to the proteins shrinking. As these proteins interact with other molecules in the body and bring other proteins together, understanding of these processes is essential "as they play a major role in many processes in our body, for instance in the onset of cancer", comments study coordinator Ben Schuler.

Measurements using the "molecular ruler"

"The fact that unfolded proteins shrink at higher temperatures is an indication that cell water does indeed play an important role as to the



spatial organisation eventually adopted by the molecules", comments Schuler with regard to the impact of temperature on <u>protein structure</u>. For their studies the biophysicists use what is known as single-molecule spectroscopy. Small colour probes in the protein enable the observation of changes with an accuracy of more than one millionth of a millimetre. With this "molecular yardstick" it is possible to measure how molecular forces impact <u>protein</u> structure.

With computer simulations the researchers have mimicked the behaviour of disordered proteins. They want to use them in future for more accurate predictions of their properties and functions.

Correcting test tube results

That's why it's important, according to Schuler, to monitor the proteins not only in the test tube but also in the organism. "This takes into account the fact that it is very crowded on the molecular level in our body as enormous numbers of biomolecules are crammed into a very small space in our cells", says Schuler. The biochemists have mimicked this "molecular crowding" and observed that in this environment disordered proteins shrink, too.

Given these results many experiments may have to be revisited as the spatial organisation of the molecules in the organism could differ considerably from that in the <u>test tube</u> according to the biochemist from the University of Zurich. "We have, therefore, developed a theoretical analytical method to predict the effects of <u>molecular crowding</u>." In a next step the researchers plan to apply these findings to measurements taken directly in living cells.

More information: Andrea Soranno, Iwo Koenig, Madeleine B. Borgia, Hagen Hofmann, Franziska Zosel, Daniel Nettels, and Benjamin Schuler. Single-molecule spectroscopy reveals polymer effects of



disordered proteins in crowded environments. *PNAS*, March 2014. DOI: <u>10.1073/pnas.1322611111</u>

René Wuttke, Hagen Hofmann, Daniel Nettels, Madeleine B. Borgia, Jeetain Mittal, Robert B. Best and Benjamin Schuler. Temperaturedependent solvation modulates the dimensions of disordered proteins. *PNAS*, March 2014. DOI: 10.1073/pnas.1313006111

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