Acceptance speech

20 June 2024

Arthur Horwich, awardee in the Biology and Biomedicine category (16th edition)

I'm deeply honored and humbled to receive a Frontiers of Knowledge Award in Biology and Biomedicine alongside my collaborator, Ulrich Hartl, concerning discovery of a molecular machine that carries out protein folding in the cell, and along with Kazutoshi Mori and Peter Walter who discovered signaling pathways that direct a "stress response" when wrongly folded proteins are present.

Proteins carry out the myriad of functions within cells, each assuming a characteristic folded form that is biologically active. Recently it has become possible to predict such forms from just the sequence of the 20 different amino acids that comprise a given protein chain, accomplished by last year's Biology and Biomedicine awardees. Does that mean that proteins, initially synthesized like strands of spaghetti, can fold on their own into the final active form? A test tube experiment of the late 1950s indicated that, remarkably, that can occur: an enzyme was unfolded in a test tube and, astonishingly, was able, upon removal of unfolding agents, to refold on its own into its active form. But, increasingly, it became clear that in living cells, at physiological temperature and in a dense "goo" of molecules, this does not necessarily occur – that is, proteins can misfold. They start to "ski" down an energy landscape toward the final active form at the bottom, but get "stuck" in a trap – they fail to reach active form. The trapped forms expose greasy so-called hydrophobic surfaces that would lie in the core of a fully folded protein – the greasy surfaces cause "misfolded" proteins to aggregate with each other, as can occur, for example, in sickle cell disease or in neurodegenerative diseases.

We asked, could there be such a thing as a "machine" that prevents such aggregation from occurring during protein folding and produces the active form? With my student Ming Cheng, we looked for, and found, a miraculous mutant of baker's yeast that affected such a machine – inside of the mutant cells the protein chains did not fold correctly, as we observed with Ulrich, and complete deletion of the machine blocked cell growth. The molecular machine itself is a specialized protein molecule composed of two back-to-back rings. Such ring machines are found broadly in nature, including in humans. X-ray

crystallography of the bacterial machine with the late Paul Sigler revealed the inside of each ring has a cavity lined with a greasy surface that could capture a misfolded protein via its own exposed greasy surface. A detachable lid structure then covers the ring and reshapes it to release the bound protein into what is now an encapsulated watery chamber where the protein can fold correctly in solitary confinement, without any chance of aggregation. Then, after some seconds, through the action of ATP, the lid is detached, and out pops the folded protein as if from a jack-in-the-box. The beauty of the machine and its mechanism leaves an indelible impression of the power of Mother Nature.

A few thanks must be shared. To my parents who cultivated my love of Science first via books describing wonderful scientists and their experiments, and then through supporting my tinkering with ham radio. They did, however, take exception when I wanted to put a dish antenna on top of the house to bounce signals off of the moon. To my mentor Mike Czech at Brown University where I was an undergraduate, who taught me how to design, carry out, and interpret experiments to test a hypothesis, and how, accordingly, to modify a hypothesis. To Tony Hunter who taught me likewise in the context of Molecular Biology, himself a Frontiers awardee in 2014 – I watched him discover tyrosine phosphorylation. To additional collaborators, Helen Saibil for cryoEM snapshots of states of the folding machine and Kurt Wuthrich for daring to look at the huge machine by solution NMR. To my senior staff, Wayne, Krystyna, George, who piloted the many experimental directions. To all of my students and postdocs. And last and most importantly, to my wife, Martina, for all of her love and support in the midst of her own biomedical career, given to both me and my three kids, and now five grandkids. And finally to the BBVA Foundation and the Frontiers committee, my deepest gratitude for this recognition.