Revising the meaning of 'prion'

October 4 2016

A team of Whitehead Institute and Stanford University scientists are redefining what it means to be a prion—a type of protein that can pass heritable traits from cell to cell by its structure instead of by DNA.

Although prions are infamous for causing Creutzfeld-Jakob disease, fatal familial insomnia, and bovine spongiform encephalopathy, commonly known as mad cow's disease, the present study indicates that prions identified in yeast, and possibly in plants, and other organisms may be beneficial.

All prions identified thus far share defining characteristics, including the ability to fold into a self-perpetuating conformation, efficient transmission when the contents of a prion-containing cell are injected into a "naïve" cell (a technique known as cytoplasmic transfer), and the ability to form large aggregates of similarly folded proteins, called amyloids. The biological importance of these molecules is underscored by the presence of cellular machines that evolved to propagate prions. One helper protein, called Hsp104, dices up prion aggregates into smaller "seeds" that are passed from a mother to all or almost all daughter cells and confer dominant traits.

To assess the breadth of such protein-based inheritance, the lab of Whitehead Member Susan Lindquist lab devised an unbiased screen that examines all proteins in yeast for those capable of producing stable phenotypes that are passed from mother to daughter cells for at least 100 generations. The screen and its outcome are described in this week's issue of the journal *Cell*.

When they scrutinized the results, the team noted that most of the 46 prion prospects lack some conventional characteristics, specifically amyloid formation and the dependence on a helper protein to transform the amyloid into heritable seeds. Nevertheless, their protein-conformation dependent traits are dominantly inherited from mother cells to all daughter cells and could be transmitted via cytoplasmic transfer—two key prion traits. Interestingly, most of the identified "molecular memories" help yeast cells adapt to varied stressful environments.

Unlike canonical prions, which are noted for creating specific structures, these proteins contained large sections that are intrinsically disordered, meaning that those domains lack a fixed three-dimensional architecture. In this way, they are related to human proteins that also have prion-like characteristics. According to Sohini Chakrabortee, lead author of the *Cell* paper, the physical flexibility of intrinsically disordered proteins could allow them to fulfill a variety of roles in a cell, from an enzyme to a chaperone protein like Hsp70. When the team examined the human cognates of the prion-proteins, the intrinsically disordered domains were conserved over hundreds of millions of years.

"This conservation over millennia could be because these proteins are vastly beneficial in nature," says Chakrabortee, who is currently Research Development Officer for European and International Funding for the University of Birmingham, United Kingdom.

For Chakrabortee, the unbiased screen has called into question the fundamental assumptions surrounding prions.

"We don't know how deep is the ocean," she says about the pool of potential prions. "This opens up new directions, and we're just starting to look into what these proteins do and their impact. This screen just gives us a taste of the breadth of prions and protein-based inheritance."

More information: "Intrinsically disordered proteins drive emergence and inheritance of biological traits" *Cell*, October 6, 2016.

Provided by Whitehead Institute for Biomedical Research