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Scientists uncover evolutionary origins of prion disease gene

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A University of Toronto-led team has uncovered the evolutionary ancestry of the prion gene, which may reveal new understandings of how the prion protein causes diseases such as bovine spongiform encephalopathy (BSE), also known as "mad cow disease."

Diseased prion proteins are responsible for the fatal neurodegenerative Creutzfeldt-Jakob disease (CJD) in humans, and BSE, scrapie and chronic wasting disease (CWD) in livestock. Overall, this work holds promise for efforts to reveal the physiological function of members of the prion protein family and may provide insights into the origins and underlying constraints of the conformational changes associated with prion diseases. The study was published today, September 28, 2009, in the online journal PLoS ONE.

Principal investigator Gerold Schmitt-Ulms (Centre for Research in Neurodegenerative Diseases; Department of Laboratory Medicine and Pathobiology, U of T) and his graduate student Sepehr Ehsani teamed up with Holger Wille and Joel Watts (University of California, San Francisco) and David Westaway (University of Alberta) for this project. "The prion protein was discovered over twenty years ago and has been studied intensively. Nobody, however, knew its evolutionary origin and much confusion surrounds its physiological function," says Prof. Schmitt-Ulms. The team's analysis suggests that the prion gene is descended from the more ancient ZIP family of metal ion transporters. Members of the ZIP protein family are well known for their ability to transport zinc and other metals across cell membranes.

The U of T laboratory initially demonstrated the physical proximity of two metal ion transporters, ZIP6 and ZIP10, to mammalian prion proteins in living cells. As with the normal cellular prion protein, ZIP6 and ZIP10 exhibit widespread expression in biological tissues with high transcript levels in the brain. Schmitt-Ulms then made the startling discovery that prion and ZIP proteins contain extensive stretches of similar amino acid sequence. The researchers next documented that the respective segments within ZIP and prion proteins are computationally predicted to acquire a highly similar three-dimensional structure. Finally, the team uncovered multiple additional commonalities between ZIP and prion proteins which led them to conclude these molecules are evolutionarily related.

Most proteins do not act in isolation but partner with other proteins to exert their biological roles. The relationship between ZIP-family and prion proteins may thus provide a new angle from which to study the biology of the prion protein in health and disease. The level of shared characteristics between these protein families, in addition to the presence of prion protein genes in most chordate (i.e., backboned) species, place the split from the ZIP-like ancestor gene at the base of the chordate lineage.

Although no single evidence firmly established the phylogenetic relationship between ZIP and prion genes, Schmitt-Ulms is confident that the many corroborating pieces of evidence collected and, equally important, the absence of any conflicting observations, allow no other conclusion to be drawn.

Source: University of Toronto (news : web)