What drove the cow mad? Lessons from a tiny fish

March 10 2009

For over twenty years, scientists have known that a normal protein in the brain, PrP, or prion protein, can turn harmful and cause deadly illnesses like Creutzfeldt-Jakob disease (CJD) in humans, and bovine spongiform encephalopathy (BSE) in cattle. What they could not explain is why large amounts of this normal protein are produced by our bodies in the first place. In a new study published in this week's *PLoS Biology*, researchers from the University of Konstanz in Germany reveal that PrP indeed plays a beneficial role for the organism - PrP helps cells communicate with one another during embryonic development.

In prion diseases, what transforms the normal PrP protein into a life-threatening substance is the abnormal alteration of its chemical structure. Moreover, prions have the treacherous ability to replicate by imprinting their abnormal structure into healthy PrPs, thereby generating new pathogenic particles.

While this "conversion" process explains how prions are disseminated, "An abnormal function of the prion protein is considered to be one of the reasons for neuronal degeneration," explains Dr. Edward Málaga-Trillo, leader of the study in Konstanz. However, the normal function of PrP has remained an unsolved mystery for many years. Until now, all previous experiments in genetically modified mice had failed to provide conclusive evidence, as these animals lacking PrP seemed perfectly healthy. A dead end?

By no means. The scientists from Konstanz were able to show that the

lack of PrP can cause clear physiological abnormalities in a living animal and the trick was to use the tiny zebrafish as a model.

When the researchers from Konstanz microinjected zebrafish eggs with morpholinos, DNA-like molecules that prevent the normal production of PrP, the treated zebrafish embryos were unable to develop normally and eventually died. The proteins in the fish embryos normally found at cell-to-cell contact sites disappeared, rendering these cells unable to communicate and carry out the differentiation program that shapes the major structures of the body, including the nervous system.

"We were then able to prove that PrP serves as a glue element, bringing cells together and keeping them in contact," explains co-author Dr. Gonzalo Solis, member of the team at the laboratory of Prof. Claudia Stürmer. "When two neighboring cells make contact, they become able to exchange important signals that affect the function of a tissue in the body."

Although the work by Málaga-Trillo, Solis, and colleagues does not offer an immediate cure for CJD or BSE, the team from Konstanz has fit together the first pieces of a complex puzzle, which may widen our understanding of prion diseases and provide hope for their effective treatment.

More information: Málaga-Trillo E, Solis GP, Schrock Y, Geiss C, Luncz L, et al. (2009) Regulation of embryonic cell adhesion by the prion protein. PLoS Biol 7(3): e1000055. doi:10.1371/journal.pbio.1000055 biology.plosjournals.org/perls … journal.pbio.1000055

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