PRESS RELEASE

When it's just right: Keeping the balance in protein aggregation

(Mainz, 7 Aug 2018) *Scientists from the Institute of Molecular Biology (IMB) in Mainz, Germany, in the laboratory of Prof. René Ketting, have discovered a method by which cells regulate the aggregation of proteins. In neurodegenerative diseases such as Alzheimer's, the uncontrolled clumping together of proteins into large aggregate structures is a common feature. In an article published yesterday in the journal* Developmental Cell*, Ketting and his team describe how cells in the embryos of zebrafish specifically trigger the aggregation of a certain protein (Bucky ball). This process leads to defining which cells become reproductive cells. Their research gives a rare glimpse into the regulation of protein aggregation processes, which may shed light on what goes wrong in disease.*

Diseases caused by protein aggregation, such as the prion disease CJD (Creutzfeldt–Jakob disease, the human form of mad cow disease) and Alzheimer's disease, have created the idea that aggregation is an undesirable process to be either avoided or repaired. More recently, however, we have learned that the process of proteins sticking together into denser clusters is actually a vital part of our biology. Scientists have found that different types of aggregates—ranging from a fluid state to a very solid, dense form—are found in completely healthy cells. The term for this phenomenon is "phase separation" and refers to the separation of protein mixtures into two non-mixing forms (like oil in water). Studying this process in biology is an emerging field of research that will have major implications for how we understand the normal functions of a cell. One of the main questions currently is: how does a cell ensure that the right proteins, in the right amounts and at the right time form and control the correct type of aggregate?

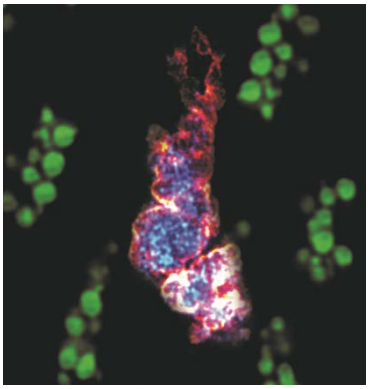

Image: Zebrafish embryos stained for protein and RNA. Aggregates of Buc (green) in early embryos. Tdrd6a (red) is present in the germ plasm of later embryos, indicated by germ plasm-specific RNA aggregates (blue).

It is in this area of normally occurring protein aggregation that Prof. René Ketting, who is a Scientific Director at IMB, and his team made their discovery. The team uses zebrafish to study "germ cells" (the cells that create both sperm and eggs) and tries to understand how these cells are formed and how they function. Interestingly, inside the egg cells of zebrafish, proteins are aggregated in a specific region. This part of the cell is needed after fertilisation to make new germ cells in the resulting embryo, thereby ensuring that the offspring can also reproduce. After the sperm and the egg fuse, this aggregate changes from the very solid form in the egg into a more fluid-like structure in the embryo.

"What's fascinating about these structures is that they are densely packed with the specific proteins and RNA needed to make a germ cell", explains Prof. Ketting. "In the egg, this structure actually resembles aggregates seen in protein aggregation diseases. However, in this case, it is specifically formed to concentrate the material needed to form germ cells into one place. In fact, it seems likely that disease-causing aggregations in humans may just be extreme versions of what we see occurring normally here."

So how do cells manage these aggregates properly? Prof. Ketting and his team discovered that a key protein in the germ cell aggregates called Bucky ball (Buc) is chemically modified in the germ cells. This modification then allows Buc to bind to another protein, Tdrd6a. It is this interaction that is critical in properly aggregating the Buc protein. “Buc is a prion-like protein, meaning it can easily aggregate with itself”, explains Elke Roovers, the lead author on the study. “However, without Tdrd6a, this process runs uncontrolled resulting in defects in germ cell formation. Essentially, Tdrd6a fine-tunes the aggregation properties of Buc, allowing the growth of functional germ cell aggregates.”

Of course, questions remain, such as: how exactly does Tdrd6a modulate Buc aggregation? Prof. Ketting continues, “It’s a good question and right now we don’t know for sure. What we do know is that Tdrd6a, in contrast to Buc, is a very mobile protein, even when present in aggregates. We think Tdrd6a may literally drag Buc around in the aggregates, preventing the formation of aggregates that are too stiff or too condensed.”

In the context of protein aggregation disease, it is exactly this type of regulation that we need to understand if we want to grasp what goes wrong. Similar systems are likely to be in place to prevent other functional aggregates transforming into a pathological form. As Prof. Ketting elaborates, “Knowing just how aggregation can be regulated inside a living organism is going to be highly relevant in the study of protein aggregation diseases. I think the system we are using is dynamic and powerful enough to give us a good idea of how protein aggregation is regulated in both time and space and it will grow our understanding of this process”.

Further details

The research paper used as the basis for this article can be found here.

Prof. René Ketting is a Scientific Director at IMB and a Professor in the Faculty of Biology at the Johannes Gutenberg University, Mainz. Further information about research in Prof. Ketting’s lab can be found at www.imb.de/ketting

About the Institute of Molecular Biology gGmbH

The Institute of Molecular Biology gGmbH (IMB) is a centre of excellence in the life sciences that was established in 2011 on the campus of Johannes Gutenberg University Mainz (JGU). Research at IMB is focused on three cutting-edge areas: epigenetics, developmental biology, and genome stability. The Institute is a prime example of successful collaboration between a private foundation and government: The Boehringer Ingelheim Foundation has committed 154 million euros to be disbursed over between 2009 and 2027 to cover the operating costs of research at IMB. The State of Rhineland-Palatinate has provided approximately 50 million euros for the construction of a state-of-the-art building and a further 52 million in core funding until 2027. For more information about IMB, please visit: www.imb.de.

Boehringer Ingelheim Foundation

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Press contact for further information

Dr Ralf Dahm, Director of Scientific Management
Institute of Molecular Biology gGmbH (IMB), Ackermannweg 4, 55128 Mainz, Germany
Phone: +49 (0) 6131 39 21455, Fax: +49 (0) 6131 39 21421, Email: press@imb.de