New role of important factor in early embryonic development identified

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In collaboration with Stanford University, a working group from MedUni Vienna's Division of Cell and Developmental Biology, led by Mark Wossidlo, has identified the role of a factor involved in early embryonic development. This is the Zscan4 protein, which has now been shown to protect the early embryo from DNA damage and DNA strand breaks during activation of the first of its own genes. Up until this time, it was not known why there is such high expression of Zscan4 during so-

called embryonic genome activation—i.e. when the embryo's genome is activated for the first time—and what role it plays.

"In our study, we were able to identify a mechanism that evolution has set up to protect the early embryo from lethal DNA damage during times of high genomic stress," explains epigeneticist and embryologist Mark Wossidlo, who started this work using an animal model when he was a post-doc at Stanford University in the U.S. and has now completed it in collaboration with the working group of Joanna Wysocka at MedUni Vienna. "If, in these very early stages of life, in the first few hours or days, the early embryo is unable to activate its own genes safely, there cannot be any life."

Important protection during the stressful phase of early embryos

The fertilized oocyte, the zygote, is a so-called "jack-of-all-trades" from which all the other cells necessary to create new life can develop. This capacity is known as "totipotency." Totipotency is also retained after the first division in the next stage of development, the two-cell stage. In contrast, the cells of the later embryo in the blastocyst are merely pluripotent, and are capable of forming many cell types, but not all.

Embryonic genome activation takes place in this totipotent two-cell stage (in the mouse model), the two-cell embryo becoming a multi-cell blastocyst over the course of a few days with the involvement of its own embryonic genes. "Shortly after fertilization, thousands of embryonic genes are simultaneously activated for the first time. During this process, the DNA in the cells comes under huge stress, which can result in unstable DNA folding and even lethal DNA damage," says Wossidlo. This is prevented by the Zscan4 protein, which docks onto so-called microsatellites (repetitions of short, uncoded DNA sequences) and

ensures protection of the genome and its long-term stability during activation of the embryonic genome by preventing zigzag-shaped Z-DNA from forming, as this is very prone to DNA strand breaks and can lead to genetic instability.

In the laboratory, the scientists demonstrated that the Zscan4 protein specifically binds to these microsatellites, protecting them from the formation of a Z-DNA structure. They also showed that, if Zscan4 is removed during embryonic genome activation, this type of lethal genetic damage occurs in the two-cell embryo.

Wossidlo says, "Thus, we have identified another important mechanism that increases our understanding of the mechanisms that help to ensure successful development of a new living being in the very early stage of life."

The general aim of this basic research working group at MedUni Vienna is to find out what processes are involved in reprogramming the germ cells of life shortly after fertilization to become these "all-rounders," and what effects faulty reprogramming could have on future generations. The group is primarily concentrating on the role of epigenetics, that is to say, the inheritable modification of DNA, which can affect gene activity without changing the DNA sequence.

More information: Rajini Srinivasan et al. Zscan4 binds nucleosomal microsatellite DNA and protects mouse two-cell embryos from DNA damage, *Science Advances* (2020). DOI: 10.1126/sciadv.aaz9115

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