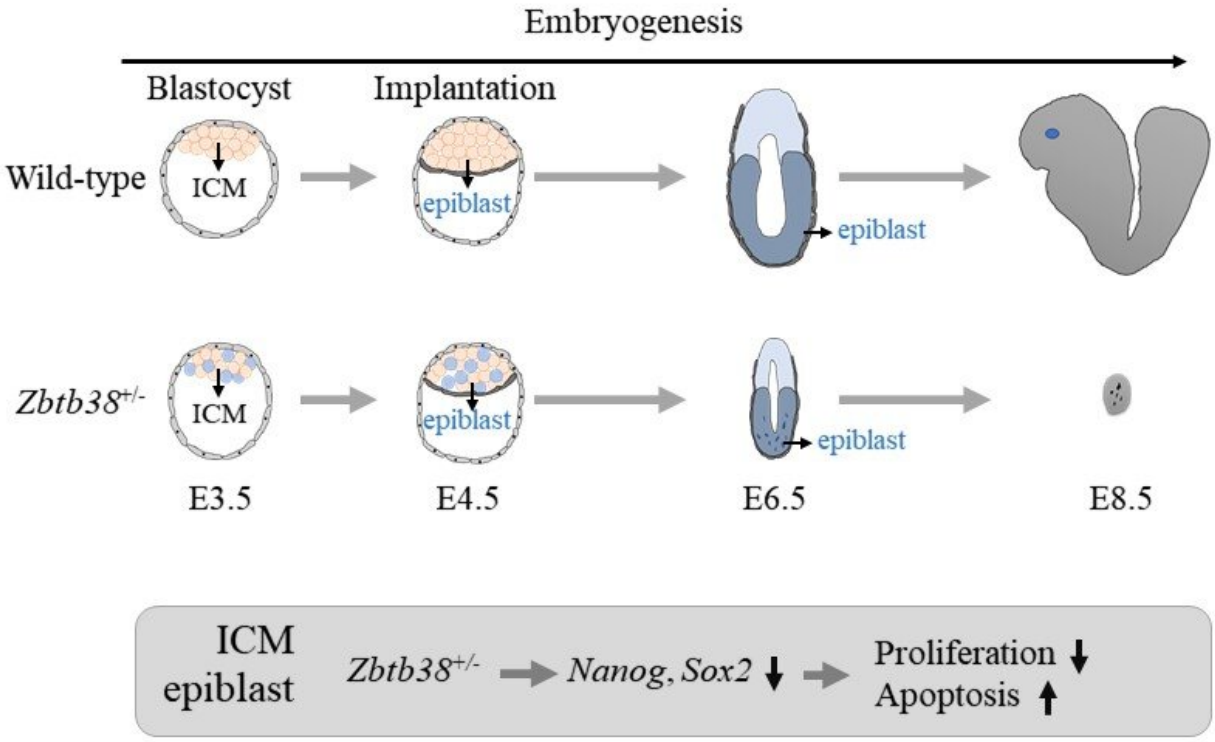
A single allele deletion in gene encoding Zbtb38 leads to early embryonic death

April 18 2022



Heterozygous loss of the Zbtb38 (Zbtb38+/-) decreased epiblast cell proliferation and increased apoptosis shortly after implantation (E4.5~), leading to early embryonic lethality. Nanog and Sox2 expressions were reduced in the Zbtb38+/- embryos. ICM: inner cell mass. Credit: Eishou Matsuda

DNA methylation is a major epigenetic modification that is crucial for mammalian development. For instance, DNA methylation is central to

inexhaustible biological processes, such as gene regulation and cell fate decisions. In mammals, DNA methyltransferases are key for blastocysts to re-establish global DNA methylation patterns during implantation. This is critical for passing on epigenetic information to the next generation.

On the other hand, the role of methyl-CpG binding proteins (MBPs) that bind methylated CpG as part of the DNA methylation processes is still unclear. However, a previous study conducted by researchers at Nara Institute of Science and Technology (NAIST), Japan, clarified that; Zbtb38, also known as CIBZ, is a zinc finger type of MBP that is pivotal for the growth of mouse embryonic stem (ES) cells. They further demonstrated that Zbtb38 facilitates the expression of Nanog, which is fundamental for the growth of ES cells. However, what Zbtb38 does in real life is still a mystery.

In a further quest to solve this mystery, the same scientists at NAIST, led by Eishou Matsuda, used Cre-loxP technology to make conditional Zbtb38 knockout mice. Their research revealed that a single Zbtb38 allele deletion in the germline led to a decrease in epiblast cell growth and an increase in apoptosis soon after implantation, which led to early embryonic death. Nanog, Sox2 and genes that control epiblast growth and differentiation became dysfunctional when Zbtb38 was lost in heterozygous embryos.

"Our findings indicate that germline loss of the Zbtb38 single allele reduces epiblast cell proliferation and increases apoptosis shortly after implantation, resulting in early embryonic lethality. Heterozygous Zbtb38 deficiency reduced the expression of Nanog, Sox2 and genes involved in epiblast proliferation, differentiation and cell viability. This finding shows that a methyl-CpG binding protein has a role in controlling embryonic phenotype," explains Matsuda.

"For the first time we demonstrated a link to an embryonic function for a protein that has long been known to bind methyl-CpG," says co-author Yasumasa Ishida. "This presents a huge opportunity for further research to find out how Zbtb38 works during embryogenesis. More research needs to be done to elucidate the specific molecular mechanisms. Zbtb38 is found in all tissues, and it is linked to height, cancers, neurodegenerative diseases and rheumatoid arthritis, etc. Thus, the creation and analysis of tissue-specific Cre-mediated knockout mice will help us understand Zbtb38's physiological functions and Zbtb38-linked diseases," concludes Matsuda.

The findings of this work will interest developmental biologists as it emphasizes the epigenetic significance of DNA methylation during the early stages of pregnancy.

The research was published in *Cell Proliferation*.

More information: Miki Nishio et al, Heterozygous loss of Zbtb38 leads to early embryonic lethality via the suppression of Nanog and Sox2 expression, *Cell Proliferation* (2022). DOI: 10.1111/cpr.13215

Provided by Nara Institute of Science and Technology