TEAD3 and TEAD4 exhibit redundant roles in morula-to-blastocyst transition during bovine early embryonic development

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Members of the TEA domain family are specifically expressed in the trophectoderm of mammals at the blastocyst stage. The role of TEAD4 in promoting trophectoderm lineage specification has been clarified during the transition from morula to blastocyst in mice. However, TEAD4 knockout (KO) does not impair embryo development in cattle, suggesting a species-specific function of TEA domain family members. Given that TEAD3 is uniquely expressed in the trophectoderm of cattle but not in mice, this study aims to identify the functional roles of TEAD3 and TEAD4 in bovine early embryos and the mechanisms involved. TEAD3 knockdown (KD) and TEAD4 KO embryos are constructed using RNA interference and a cytosine base editor, respectively. While TEAD3 KD does not affect embryo development, embryos with concurrent TEAD3 KD and TEAD4 KO fail to develop past the morula stage, implying an overlapping function of TEAD3 and TEAD4 during morula-to-blastocyst transition in cattle. RNA-seq analysis reveals dysregulation in 215 genes, with 53 being upregulated and 162 downregulated in bovine embryos deficient of TEAD3 and TEAD4. This analysis shows a decrease in trophectoderm genes KRT8, KRT18, and EZR in the TEAD3 KD and TEAD4 KO embryos, along with a reduction in the HIPPO signaling pathway gene WWC3. These changes suggest that developmental failure stems from impaired trophectoderm epithelium function and altered Hippo signaling. Immunofluorescence analysis corroborates the minimal presence of KRT8 in the treated group. Notably, the combined KD of TEAD3 and KO of TEAD4 does not affect the expression of trophectoderm lineage-specific factors such as TFAP2C and GATA3 or inner cell mass lineage-specific factors like OCT4, which contrasts with TEAD4's role in mice. In summary, our research demonstrates that TEAD3 and TEAD4 have redundant functions during the morula to blastocyst transition in cattle, highlighting species-specific roles in early embryonic development.