



Title	マウス着床前胚のエピブラスト形成におけるTEAD-YAPの役割と標的遺伝子の制御機構の解析
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論文内容の要旨

氏 名 (廣 野 尚 暉)

論文題名

マウス着床前胚のエピブラスト形成におけるTEAD-YAPの役割と標的遺伝子の制御機構の解析
(Roles and target gene regulation of TEAD-YAP during epiblast formation in mouse preimplantation embryos)

Epiblast (EPI) is a pluripotent tissue produced in mouse preimplantation embryos. During EPI formation, the activity of the Hippo pathway transcription factor TEAD-YAP plays an important role. Coordinated regulation of TEAD-YAP activities and their target genes are required for proper EPI development. In the first part, I analyzed the role of TEAD-YAP in EPI formation, and in the second part, I analyzed the regulation of TEAD-YAP target genes.

In preimplantation embryos, EPI fate specification from the inner cell mass (ICM) is controlled by segregation of NANOG and GATA6 expression. The TEAD-YAP interaction is activated during EPI formation and is required for pluripotency factor expression. These events occur asynchronously with similar timing during EPI formation; however, their relationship remains elusive. Here, I examined the relationship between NANOG-GATA6 and TEAD-YAP. The nuclear accumulation of YAP takes place only in EPI-specified cells, and a positive feedback loop operates between NANOG and TEAD-YAP. The effects of TEAD-YAP on SOX2 upregulation in EPI-specified cells are likely indirect. EPI fate specification also alters the response of *Nanog*, *Sox2*, and *Cdx2* to TEAD-YAP. These results suggest that EPI-fate specification alters the transcriptional network from the morula-like to the EPI-specified state and activates TEAD-YAP to trigger a positive feedback loop with NANOG, which stabilizes the EPI fate. The coordinated occurrence of these processes in individual cells likely supports proper EPI formation under the condition of asynchronous EPI-fate specification.

In EPI-specified mid ICM cells, TEAD-YAP induces *Nanog*. Before EPI fate specification, however, the early ICM cells have a morula-like transcriptional network, and premature activation of TEAD-YAP results in activation of trophectoderm (TE)-specific genes. Here, I examined the mechanisms by which the TE-specific gene *Gata3* loses its competence to TEAD-YAP in EPI-specified cells. I first found that the expression of SOX2 in early ICM is required for loss of competence. I then identified the TE-specific enhancer (TEE) of *Gata3*. TEE was activated by TEAD-YAP and lost its competence to TEAD-YAP in a SOX2-dependent manner. Loss of competence of TEE to TEAD-YAP required SOX2 binding, and the effect of SOX2 required the corepressor protein TLE4 and the histone deacetylase HDAC1/2. Similar SOX2-dependent competence loss to TEAD-YAP was also observed for other TE-specific genes including *Cdx2* and *Krt8*. Taken together, I propose a model by which SOX2 proteins expressed in the early ICM bind to the enhancer of multiple TE-specific genes and close the chromatin structures by forming a complex of SOX2-TLE4-HDAC1/2. This mechanism likely contributes to the shift of transcriptional networks from morula-like to EPI-specified one during EPI fate specification.

Overall, this study clarified some mechanisms of how transcriptional network remodeling and dynamic regulation of TEAD-YAP cooperatively regulate EPI development.

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

本論文はHippoシグナル経路因子のTEAD-YAPに注目して、マウス着床前胚における細胞分化の制御機構について研究したものである。

前半では、内部細胞塊からエピブラストへの分化過程では、分化タイミングがばらつく中でも、運命が決まった細胞でTEAD-YAPとNANOGとのポジティブフィードバックループが働くことで、安定してエピブラストの分化が進行することを示した。この成果はDevelopment誌に掲載された。後半では、内部細胞塊でTEAD-YAPの標的遺伝子が栄養外胚葉の分化制御因子*Gata3*から*Nanog*へ切り替わる仕組みの一つとして、内部細胞塊特異的に発現するSOX2がTLE4, HDACとともに*Gata3*のエンハンサーに結合してクロマチンを閉じることで、*Gata3*のTEAD-YAPへの応答能を消失させることを示した。

本論文の成果は、発生におけるばらつきの克服機構および細胞の応答能の制御機構の解明に貢献する重要なものであり、博士の学位を授与するに値するものと認める。なお、チェックツール“iThenticate 2.0”を使用し、剽窃、引用漏れ、二重投稿等のチェックを終えていることを申し添えます。