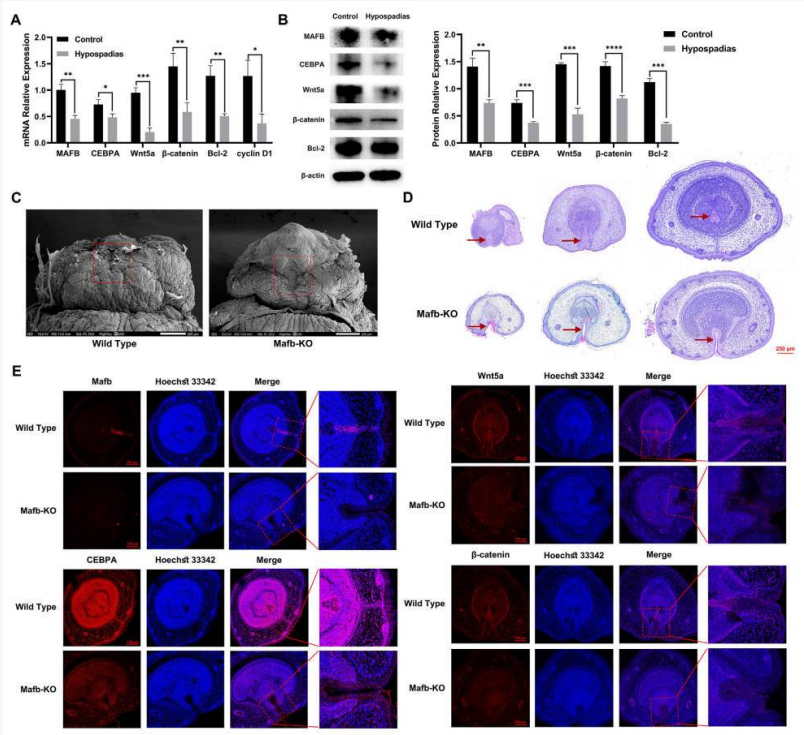
New genetic insights into hypospadias: MAFB and CEBPA's role in urothelial growth

GA, UNITED STATES, March 25, 2025 /EINPresswire.com/ -- A recent study has unveiled the critical roles of two transcription factors, MAFB and CEBPA, in the development of hypospadias, a common congenital malformation affecting male urethral development. The research reveals that MAFB and CCAAT/enhancer-binding protein alpha (CEBPA) regulate urothelial cell growth via the Wnt/β-catenin signaling pathway, offering new insights into the genetic mechanisms underlying this condition. These findings pave the way for innovative therapeutic strategies and a deeper understanding of the genetic and molecular foundations of hypospadias.



Changes in hypospadias foreskin and Mafb-KO mice GT.

Hypospadias is characterized by an ectopic urethral opening and abnormal penile curvature, affecting approximately 1 in 200 live male births. While its origins are believed to stem from a combination of genetic and environmental factors, androgen signaling pathways are thought to play a significant role in the condition's development. Despite progress in identifying the genetic components, the precise molecular mechanisms remain poorly understood. Previous studies have suggested that the Wnt/β-catenin signaling pathway is involved in urethral development, but the specific contributions of transcription factors such as MAFB and CCAAT/enhancer-binding protein alpha (CEBPA) have yet to be fully explored. This gap in understanding highlights the need for in-depth research to elucidate the pathways involved in hypospadias.

On September 13, 2024, a study (DOI: 10.1016/j.gendis.2024.101432) published in Genes & Diseases and led by researchers from the Children's Hospital of Chongqing Medical University in China identified MAFB and CEBPA as crucial regulators of urothelial cell growth. By influencing

cell proliferation and apoptosis through the Wnt/β-catenin signaling pathway, MAFB and CEBPA play a significant role in the genetic mechanisms of hypospadias. This research lays a strong foundation for future studies aimed at developing targeted therapies for this prevalent congenital condition.

The study focused on the roles of MAFB and CEBPA in urothelial cell growth, utilizing human foreskin samples and mouse models. The researchers found that expression levels of MAFB and CEBPA were significantly reduced in the foreskin tissues of hypospadias patients. Using RNA sequencing and Western blot analysis, they discovered that MAFB knockdown led to suppressed CEBPA protein expression, inhibiting the Wnt/β-catenin pathway and causing cell cycle arrest and increased apoptosis in urothelial cells. Furthermore, MAFB overexpression promoted cell proliferation and activated the Wnt/β-catenin pathway, while CEBPA knockdown reversed these effects. These findings highlight the pivotal role of the MAFB-CEBPA axis in regulating urothelial cell growth and suggest that disruptions in this pathway may contribute to hypospadias development. The study also pinpointed potential therapeutic targets for future interventions.

Dr. Xing Liu, the corresponding author of the study, commented, "Our findings provide a deeper understanding of the molecular mechanisms underlying hypospadias. By identifying the roles of MAFB and CEBPA in urothelial growth, we have uncovered potential targets for therapeutic intervention, which could lead to improved outcomes for patients with this condition."

The discovery of the MAFB-CEBPA regulatory pathway holds immense potential for advancing the treatment and prevention of hypospadias. By targeting this pathway, researchers could develop novel therapies to correct or prevent the malformation during early development. Additionally, the study opens exciting new avenues for exploring the genetic and molecular underpinnings of other congenital disorders related to urethral development. Future research may focus on identifying additional genetic factors and environmental influences that interact with the MAFB-CEBPA pathway, further advancing our understanding of hypospadias and related conditions.

DOI
10.1016/j.gendis.2024.101432

Original Source URL
https://doi.org/10.1016/j.gendis.2024.101432

Funding information
This work was financed by the National Natural Science Foundation of China (No. 81970571), the Natural Science Foundation of Chongqing Municipality, China (No. CSTB2022NSCQ-MSX1001), and the Program for Youth Innovation in Future Medicine, Chongqing Medical University (No. W0109).

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