Utilizing AI for the identification and validation of novel therapeutic targets and repurposed drugs for endometriosis

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Introduction

Endometriosis affects over 190 million women globally. Dysregulated steroidogenesis is one commonly studied mechanism, emphasizing hormonal therapy as an effective treatment for the disease, but their long-term effects still remain unknown. Thus, a pressing, unmet clinical need exists to develop new, effective as well as safe therapeutics for endometriosis.

Materials and Methods

We utilized an artificial intelligence (AI)-driven target discovery platform, PandaOmics, to identify novel druggable targets and analyze approved drugs that could be repurposed to treat endometriosis. To validate these targets, we conducted targeted knockdown experiments using siRNA on proliferation and apoptosis of ectopic endometrial cells both in-vitro and in-vivo. Furthermore, an approved drug was identified as a candidate drug through PandaOmics and evaluated as repurposing drug with therapeutic value in treating endometriosis in-vitro and in-vivo.

Results

We identify two unreported therapeutic targets, guanylate-binding protein 2 (GBP2) and hematopoietic cell kinase (HCK), along with a drug repurposing target, integrin beta 2 (ITGB2) for the treatment of endometriosis. GBP2, HCK, and ITGB2 are upregulated in human endometriotic specimens. siRNA-mediated knockdown of GBP2 and HCK significantly reduced cell viability and proliferation while stimulating apoptosis in endometrial stromal cells. In subcutaneous and intraperitoneal endometriosis mouse models, siRNAs targeting GBP2 and HCK notably reduced lesion volume and weight, with decreased proliferation and increased apoptosis within lesions. Both subcutaneous and intraperitoneal administration of Lifitegrast, an approved ITGB2 antagonist, effectively suppresses lesion growth. Collectively, these data present Lifitegrast as a previously unappreciated intervention for endometriosis treatment and identify GBP2 and HCK as novel druggable targets in endometriosis treatment.

Conclusion

The study leveraged an AI target discovery platform to analyze transcriptomic datasets from patients with endometriosis and healthy controls. This innovative approach identified multiple novel targets and drug repurposing opportunities, underscoring AI's potential to accelerate the discovery of novel drug targets and facilitate the repurposing of treatment modalities for endometriosis.

Key words
[artificial intelligence, target discovery, drug repurposing]