A nonhormonal target for endometriosis to explore

We have read and analyzed the manuscript "Sphingosine-1-phosphate receptor 3 is a nonhormonal target to counteract endometriosis-associated fibrosis," recently published in *Fertility and Sterility* (1). The investigators conducted exceptional research in which they correlated the amount of fibrosis with this receptor's expression levels. Despite the conclusion being strictly based on the study's results, which is appropriate for comprehensive scientific work, we highlight the importance of identifying a nonhormonal, single molecule as a target for endometriosis.

Gold-standard treatment of endometriosis is focused on estrogenic signaling by reducing estradiol levels or activating progesterone receptors. In this context, nonhormonal treatments are scarce and have been restricted to pain relief therapies or anti-inflammatory drugs. An honorific mention is antioxidants, which have reported effects on the three entities of endometriosis known: deep (polydatin, resveratrol-3-O-β-mono-D-glucoside); peritoneal (polydatin, resveratrol-3-O-β-mono-D-glucoside); and ovarian (melatonin) (2). Other examples are noncoding ribonucleic acids (3), which do not focus on endocrine targets and point to reducing disease onset or progression. However, they are not specific to endometriosis; most emerge for cancer and fibrosis research and are directed at wide-spectrum processes (invasion, epithelial-mesenchymal transition, and cell damage), which are the basis for other pathologies.

In this scenario, S1PR3 is highly relevant because it is a single molecule (not a whole process), which the investigators proved to be directly related to disease progression by promoting fibrosis. It represents an opportunity for targeted therapy, considered the cornerstone of precision medicine that has higher efficacy and lower side effects. The most evident alternative is the direct blockage of S1PR3, with drugs such as fingolimod, ozanimod (mentioned by the investigators), siponimod, and ponesimod or newly developing drugs such as etrasimod and amiselimod. To date, there are no trials of these drugs in patients with endometriosis. Finally, the investigators contribute to associating extracellular signal-regulated kinase (ERK) 1 and 2 and erzin signaling as downstream targets of the receptor, adding new treatments related to the ERK pathway, such as direct inhibitors or inactivation of the BRAF and mitogen-activated protein kinase (MEK) pathways. However, these routes are frequently involved in other cellular processes. Therefore, side effects, resistance development, and efficacy may not be optimal for clinical requirements.

In summary, the article published by Bernacchioni et al. (1) represents a new cutting-edge piece of research on endometriosis therapy, where S1PR3 emerges as the most promising single molecule target for treatment, which may be involved since the early stages of the disease.

CRediT Authorship Contribution Statement

Renan Orellana-Walden: Conceptualization, Writing – original draft. **Manuel E. Cortés:** Formal analysis, Writing – review & editing.

Declaration of Interests

R.O.-W. has nothing to disclose. M.E.C. has nothing to disclose.

Renan Orellana-Walden, Ph.D.[a]
Manuel E. Cortés, Ph.D.[b]
[a] Integrative Center of Chemistry and Biology (CIBQA), Bernardo O'Higgins University, Santiago, Chile; [b] Research Direction, Vicerectorate for Academic Affairs, Bernardo O'Higgins University, Santiago, Chile

https://doi.org/10.1016/j.fertnstert.2024.08.352

REFERENCES

1. Bernacchioni C, Rossi M, Vannuzzi V, Prisinzano M, Seidita I, Raeispour M, et al. Sphingosine-1-phosphate receptor 3 is a non-hormonal target to counteract endometriosis-associated fibrosis. Fertil Steril 2024;121:631–41.
2. Nagayasu M, Imanaka S, Kimura M, Maruyama S, Kobayashi H. Nonhormonal treatment for endometriosis focusing on redox imbalance. Gynecol Obstet Invest 2021;86:1–12.
3. Brichant G, Laraki I, Henry L, Munaut C, Nisolle M. New therapeutics in endometriosis: a review of hormonal, non-hormonal, and non-coding RNA treatments. Int J Mol Sci 2021;22:10498.