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EDITORIAL

Metabolomics analysis in endometriosis patients: is it a step toward the future?

Endometriosis is a condition in which abnormal endometrial tissue grows outside the uterus, mainly in the pelvis. It is an estrogen-dependent disease that can cause chronic pelvic pain, dysmenorrhea, and infertility. It affects around 5-10% of women, most commonly diagnosed between 25 and 35 [1]. The current methods used to diagnose endometriosis are often inaccurate, and the diagnostic delay is an important clinical problem. Moreover, in some patients, available treatments have many limitations in controlling symptoms and disease progression [1]. Therefore, new methods that can improve the diagnosis and treatment of endometriosis are urgently needed.

Metabolomics is a field of research aimed at analyzing metabolites present in biological samples and has emerged as a promising tool for the understanding of the underlying mechanisms related to the pathogenesis of endometriosis and for the developing of more personalized therapies [2]. Various types of biological samples can be utilized in metabolomic studies. Commonly used samples in endometriosis research include serum, urine, endometrial tissue (ectopic or eutopic), and follicular, peritoneal or endometrial fluid. The choice of sample depends on the experimental aim and dictates the appropriate analytical technique used to provide results. Nuclear magnetic resonance and mass spectrometry are the most commonly employed analytical techniques [2].

Recent research in endometriosis and metabolomics has shown that women with endometriosis have altered metabolic profiles, indicating changes in lipid metabolism, oxidative stress, inflammation, and other metabolic pathways [3–10]. Compared to healthy controls, women with endometriosis exhibit significant differences in the levels of specific amino acids, including alanine, phenylalanine, leucine, proline, and arginine [3–7]. These results suggest that analyzing the levels of specific amino acids may have a potential as a diagnostic tool for endometriosis and provide valuable insights into the disease's pathogenic mechanisms. The increased demand for energy may explain the changes in amino acid levels observed in endometriosis due to the rapid proliferation of endometrial cells and the need for tissue repair. This process requires higher protein turnover rates, which can lead to the release of amino acids into the bloodstream [3–7].

The heightened energy demand and rapid growth of endometrial cells may be analogous to tumor cells. This similarity is supported by the fact that specific metabolites, such as taurine and myo-inositol, are present at high levels in the tissue of advanced stages of endometriosis and certain tumor tissues [2,3,6]. Another resemblance between endometriosis and cancer is the alteration of the pyruvate metabolism, which leads to high anaerobic metabolism characterized by increased lactate and decreased serum glucose levels [4,7]. Also, patients with endometriosis have reduced levels of antioxidative enzymes, resulting in inadequate levels of reduced glutathione. Consequently, ophthalmate synthesis occurs, producing a byproduct known as 2-hydroxybutyrate [4,7]. Elevated levels of this byproduct found in the serum of patients with endometriosis suggest the involvement of reactive oxygen species (ROS) related to chronic inflammation and associated tissue damage [4–7]. Identifying altered lipid metabolism has also been a key finding in metabolomic studies of endometriosis. Dysregulation of the levels of various lipid species, including phospholipids, sphingolipids, and fatty acids, has been demonstrated in women with endometriosis [8–10]. Some of these lipids, such as the phosphatidic acid (PA), are involved in cellular processes such as cell proliferation, survival, and transformation. Higher PA levels have been found in eutopic endometrium of endometriosis patients [10]. It is possible that PA serves as a critical mediator for the transformation, survival, and proliferation of endometriotic cells outside the uterus and can stimulate oxidative burst, producing ROS [9,10]. Elevated concentrations of different sphingomyelins have also been found in the plasma of patients affected by endometriosis. This phenomenon may be attributed to the denervation and re-innervation of the ectopic endometrium of these patients [8]. The dysregulation of the lipid metabolism has been identified as a potential pathogenetic factor in the disease and may be a potential target for new therapeutic approaches. In particular, the study by Vouk et al. [8] highlights how high concentrations of plasmanylcholines found in endometriosis patients, appear to be associated with an increased demand for platelet-activating factor (PAF) or PAF-like molecules in macrophages or neutrophils. PAF is an inflammatory mediator, promoting, through its receptors, the synthesis, and release of neoangiogenic factors, such as vascular endothelial growth factor. PAF synthesis increases in the ectopic endometrial tissue due to the increased activity of various isoforms of the phospholipase A2 (PLA-2) enzyme. This enzyme converts plasmanylcholines in to lysoPAF, which is subsequently converted into PAF by lysophosphatidylcholine-acyltransferase 4 (LPCAT4). This discovery suggests a possible therapeutic strategy by inhibiting LPCAT4 and the hyper-expressed forms of PLA2 [8].

Despite the potential in applying metabolomics in the study of endometriosis, there still are challenges facing medical researchers. These challenges include: the standardization of the sample collection and analysis protocols, the validation of biomarkers in different populations and platforms, and the integration of metabolomic related data to other 'omic' data (genomics, transcriptomics), which may provide a more comprehensive understanding of the disease.

In conclusion, metabolomics could be a promising approach that may improve the diagnosis, treatment, and understanding of endometriosis. By identifying specific metabolic markers associated with the disease, metabolomics could aid in the development of more personalized and effective therapies and enhance our understanding of the underlying pathogenic mechanisms of endometriosis. Further research is needed to address the challenges and validate the potential of metabolomics for the management of endometriosis.

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