Proteomics
Clinical Applications
www.clinical.proteomics-journal.com

Proteomics in the Diagnosis of Endometriosis: Opportunities and Challenges

Simone Ferrero

The non-surgical diagnosis of endometriosis is still challenging for the clinician. Ultrasonography and magnetic resonance imaging can be used to diagnose ovarian endometriotic cysts and deep infiltrating endometriosis; but their performance is poor in the diagnosis of initial stages of endometriosis. CA-125 and other serum markers (such as CA 19-9, serum protein PP14, interleukins, and angiogenetic factors) have been measured in women with endometriosis but they are not reliable for the diagnosis of the disease. Although several studies used proteomics technologies to identify plasmatic markers of endometriosis, the non-invasive diagnosis of endometriosis is far from being achieved. In this issue, Manousopoulou et al. compare the integrated quantitative proteomic profile of eutopic endometrium and serum of women with endometriosis and controls. 1214 proteins are differentially expressed in the eutopic endometrium and 404 proteins in the serum of the two study groups. 21 proteins are aberrantly expressed in both eutopic endometrium and serum of women with endometriosis. More work is needed to assess if the differentially expressed proteins identified in this study can be used as clinical markers of endometriosis.

Endometriosis is a benign gynecological condition that is characterized by the presence of endometriotic glands and stroma outside the uterine cavity. It affects at least 4% of reproductive age women causing pain symptoms (such as dysmenorrhea, non-menstrual pelvic pain, deep dyspareunia, and dyschezia).[1] The diagnosis of endometriosis is based on the visualization of the lesions during laparoscopy (**Figure 1**); the histologic confirmation of at least one lesion should ideally be obtained.[2] However, laparoscopy is a surgical procedure with potential risks. Ultrasonography and magnetic resonance imaging can be used to diagnose ovarian endometriotic cysts and deep infiltrating endometriosis, a particular form of the disease that penetrates >5 mm under the peritoneal surface.[3] However, the diagnostic performance of imaging techniques is dependent on the experience of the examiners. Furthermore, imaging techniques are inefficient in the diagnosis of initial stages of endometriosis. Many attempts have been made to use serum markers to diagnose endometriosis without surgery. CA-125 is the most widely used biomarker for endometriosis, but its diagnostic performance in detecting endometriosis is unsatisfactory. Several other serum markers (such as CA 19-9, serum protein PP14, interleukins, and angiogenetic factors) have been measured in endometriosis, but they are not reliable for the diagnosis of the disease.[4] Therefore, patients often suffer pain and infertility for years before endometriosis is diagnosed. Early diagnosis is crucial for treatment and prevention of disease progression. In addition, persistence or recurrence of endometriosis often happens also after adequate treatment. Therefore, the benefits of non-invasive, biochemical diagnostic markers for the detection of endometriosis are evident.

Over the last 10 years, several authors applied proteomic technologies to the research of biomarkers for the diagnosis of endometriosis.[5] These studies examined the proteome of eutopic endometrium,[6,7] peritoneal lesions,[6] peritoneal fluid,[8–10] urine,[10,11] and menstrual blood[12] obtained from women with and without endometriosis, reporting differential expression of various molecules. As a diagnostic tool, serum markers are of special interest, because serum is easily accessible for a screening test. Although several studies used proteomics technologies to identify plasmatic markers of endometriosis and promising findings were reported,[8,13] the application of proteomics technology to the clinical diagnosis of endometriosis is far from being achieved.

In this issue, Manousopoulou et al.[14] compared the integrated quantitative proteomic profile of eutopic endometrium and non-depleted serum of women with surgical diagnosis of endometriosis and controls. The authors found that 1214 proteins were differentially expressed in the eutopic endometrium and 404 proteins in the serum of the two study groups. Bioinformatics analysis showed that these molecules were mainly related to immune response, inflammation, cell adhesion and migration, and blood coagulation. 21 proteins were either upregulated or downregulated in both eutopic endometrium and serum of women with endometriosis. In the future, more work is needed to confirm the findings of this study and to assess if the

Prof. S. Ferrero
Academic Unit of Obstetrics and Gynecology
IRCCS Ospedale Policlinico San Martino
Largo Paolo Daneo 3, 16132 Genova, Italy
E-mail: simone.ferrero@unige.it
Prof. S. Ferrero
Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI)
University of Genoa
Italy

See accompanying article by Antigoni Manousopoulou et al. https://doi.org/10.1002/prca.201800153

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/prca.201800183

DOI: 10.1002/prca.201800183

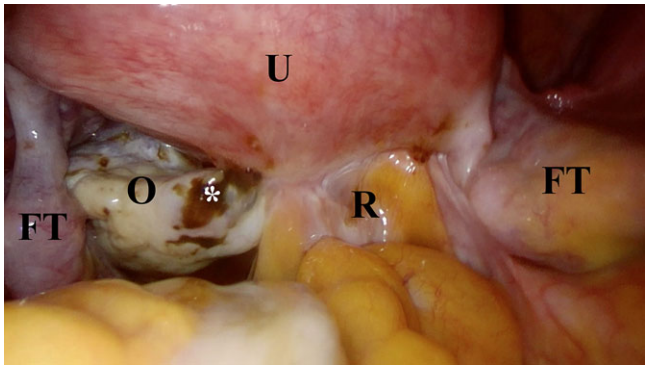

Figure 1. Laparoscopic diagnosis of endometriosis. The left ovary (O) and the rectum (R) are adherent to the posterior wall of the uterus (U). An ovarian endometriotic cyst (*) can be observed. FT, Fallopian tube.

differentially expressed proteins identified in this study can be used as markers of the disease. A diagnostic test should ideally have good sensitivity, specificity, and satisfactory positive and negative predictive values. In clinical practice, the various forms of the endometriosis (superficial, ovarian, or deep lesions), the variable severity of the disease, the use of hormonal therapies may significantly change protein expression. While these factors are commonly controlled in experimental studies, they may significantly interfere with the clinical diagnosis of endometriosis.

Conflict of Interest

The author declares no conflict of interest.

Keywords

biomarkers, diagnosis, endometriosis, proteomics, serum

Received: December 9, 2018
Published online:

[1] S. Ferrero, E. Arena, A. Morando, V. Remorgida, *Int. J. Gynaecol. Obstet.* **2010**, *110*, 203.
[2] G. A. Dunselman, N. Vermeulen, C. Becker, C. Calhaz-Jorge, T. D'Hooghe, B. De Bie, O. Heikinheimo, A. W. Horne, L. Kiesel, A. Nap, A. Prentice, E. Saridogan, D. Soriano, W. Nelen, *Hum. Reprod.* **2014**, *29*, 400.
[3] a) S. Guerriero, G. Condous, T. van den Bosch, L. Valentin, F. P. Leone, D. Van Schoubroeck, C. Exacoustos, A. J. Installe, W. P. Martins, M. S. Abrao, G. Hudelist, M. Bazot, J. L. Alcazar, M. O. Goncalves, M. A. Pascual, S. Ajossa, L. Savelli, R. Dunham, S. Reid, U. Menakaya, T. Bourne, S. Ferrero, M. Leon, T. Bignardi, T. Holland, D. Jurkovic, B. Benacerraf, Y. Osuga, E. Somigliana, D. Timmerman, *Ultrasound Obstet. Gynecol.* **2016**, *48*, 318; b) V. Nisenblat, P. M. Bossuyt, C. Farquhar, N. Johnson, M. L. Hull, *Cochrane Database Syst. Rev.* **2016**, *2*, CD009591.
[4] V. Nisenblat, P. M. Bossuyt, R. Shaikh, C. Farquhar, V. Jordan, C. S. Scheffers, B. W. Mol, N. Johnson, M. L. Hull, *Cochrane Database Syst. Rev.* **2016**, CD012179.
[5] S. Ferrero, D. J. Gillott, V. Remorgida, N. Ragni, P. L. Venturini, J. G. Grudzinskas, *Expert Rev. Proteomics* **2008**, *5*, 705.
[6] C. M. Kyama, D. T'Jampens, A. Mihalyi, P. Simsa, S. Debrock, E. Waelkens, B. Landuyt, C. Meuleman, V. Fulop, J. M. Mwenda, T. M. D'Hooghe, *Fertil. Steril.* **2006**, *86*, 203.
[7] a) P. A. Fowler, J. Tattum, S. Bhattacharya, T. Klonisch, S. Hombach-Klonisch, R. Gazvani, R. G. Lea, I. Miller, W. G. Simpson, P. Cash, *Proteomics* **2007**, *7*, 130; b) S. Ten Have, I. Fraser, R. Markham, A. Lam, I. Matsumoto, *Proteomics Clin. Appl.* **2007**, *1*, 1243; c) P. Rai, V. Kota, M. Deendayal, S. Shivaji, *J. Proteome Res.* **2010**, *9*, 4407; d) A. Fassbender, N. Verbeeck, D. Bornigen, C. M. Kyama, A. Bokor, A. Vodolazkaia, K. Peeraer, C. Tomassetti, C. Meuleman, O. Gevaert, R. Van de Plas, F. Ojeda, B. De Moor, Y. Moreau, E. Waelkens, T. M. D'Hooghe, *Hum. Reprod.* **2012**, *27*, 2020.
[8] S. Ferrero, D. J. Gillott, V. Remorgida, P. Anserini, K. Price, N. Ragni, J. G. Grudzinskas, *Fertil. Steril.* **2005**, *83*, 1536.
[9] a) S. Ferrero, D. J. Gillott, V. Remorgida, P. Anserini, K. Y. Leung, N. Ragni, J. G. Grudzinskas, *J. Proteome Res.* **2007**, *6*, 3402; b) S. Ferrero, D. J. Gillott, P. Anserini, V. Remorgida, K. M. Price, N. Ragni, J. G. Grudzinskas, *J. Soc. Gynecol. Investig.* **2005**, *12*, 272.
[10] K. E. Williams, O. Miroshnychenko, E. B. Johansen, R. K. Niles, R. Sundaram, K. Kannan, M. Albertolle, Y. Zhou, N. Prasad, P. M. Drake, L. C. Giudice, S. C. Hall, H. E. Witkowska, G. M. Buck Louis, S. J. Fisher, *J. Proteomics* **2015**, *113*, 194.
[11] M. M. El-Kasti, C. Wright, H. K. Fye, F. Roseman, B. M. Kessler, C. M. Becker, *Fertil. Steril.* **2011**, *95*, 1261.
[12] J. H. Hwang, J. J. Oh, T. Wang, Y. C. Jin, J. S. Lee, J. R. Choi, K. S. Lee, J. K. Joo, H. G. Lee, *Mol. Med. Rep.* **2013**, *8*, 183.
[13] a) H. Zhang, Y. Niu, J. Feng, H. Guo, X. Ye, H. Cui, *Fertil. Steril.* **2006**, *86*, 274; b) L. Wang, W. Zheng, J. K. Yu, W. Z. Jiang, L. Mu, S. Z. Zhang, *Fertil. Steril.* **2007**, *88*, 1700; c) H. Liu, J. Lang, Q. Zhou, D. Shan, Q. Li, *Fertil. Steril.* **2007**, *87*, 988; d) L. Wang, W. Zheng, L. Mu, S. Z. Zhang, *Int. J. Gynaecol. Obstet.* **2008**, *101*, 253; e) M. Nabeta, Y. Abe, L. Kagawa, R. Haraguchi, K. Kito, N. Ueda, A. Sugita, M. Yokoyama, Y. Kusanagi, M. Ito, *Proteomics Clin. Appl.* **2009**, *3*, 1201; f) B. Seeber, M. D. Sammel, X. Fan, G. L. Gerton, A. Shaunik, J. Chittams, K. T. Barnhart, *Fertil. Steril.* **2010**, *93*, 2137; g) M. Dutta, E. Subramani, K. Taunk, A. Gajbhiye, S. Seal, N. Pendharkar, S. Dhali, C. D. Ray, I. Lodh, B. Chakravarty, S. Dasgupta, S. Rapole, K. Chaudhury, *J. Proteomics* **2015**, *114*, 182.
[14] A. Manousopoulou, M. Hamdan, M. Fotopoulos, D. J. Garay-Baquero, J. Teng, S. D. Garbis, Y. Cheong, *Proteomics Clin. Appl.* **2018**, e1800153.