Role of Macrophage Migration Inhibitor Factor in Endometriosis

Hu YuHong,
Jian Li,
Sadichha Thapa

Department of Gynecology and obstetrics, the 1st affiliated Hospital of Jiamusi University, Jiamusi city, Heilongjiang, P.R. China

Corresponding Author: Jian Li

Department of Gynecology and obstetrics, the 1st affiliated Hospital of Jiamusi University, Jiamusi city, Heilongjiang, P.R. China

✉ liamjiam@gmail.com

Tel: 3351440618

Abstract

Endometriosis is a common gynecological disease among women of reproductive age, which affects approximately 6 ~10 percent of females, but the pathogenesis of endometriosis is still ambiguous. Until now, the prevailing theory concerning the etiology of endometriosis is the retrograde menstruation hypothesis put forward by Sampson in 1921. However, it can't illustrate completely the etiology and pathology of the endometriosis. In recent years, immune-inflammatory factor is a hot point of endometriosis field. Many studies demonstrated that the numbers and level of cytokines in the peritoneal fluid of endometriosis patients, namely the macrophage migration inhibitor factor (MIF) which is one of the cytokines described previously, is increased. This has been observed to have a crucial role during the pathology of endometriosis as well as pelvic pain and infertility which are responsible for endometriosis. Therefore, MIF might be the target of new approach to diagnosis and therapy endometriosis.

Keywords: MIF, Cytokine, Endometriosis

Introduction

Endometriosis is characterized by endometrial glands and stroma located outside of the uterine cavity. It's prevalence is nearly 6~10 percent [1] among reproductive female and shows an increase trend during the past few years. The patients suffering from pain, infertility or both is as high as 35~50 percent. The etiology and pathology of endometriosis has not yet been elucidated. Several factors contribute to the development of endometriosis such as disturbance of hormonal condition, familial and genetic factors and immune-inflammatory factor [2]. In the past decade, evidence based on immunologic study indicates that MIF plays an important role in the process of endometriosis development, which possibly acts as a biomarker for diagnosis of endometriosis. Hence, MIF might be the key of a new way to diagnosis and therapy endometriosis [3-5].

The effection of MIF during the endometriosis development

In 1966, Bloom et al named firstly the cytokine secreted by activated T cell that inhibits the random migration of macrophage for macrophage migration inhibitor factor. The MIF gene is a highly conserved sequence, it's protein exists as a homo-trimer and displays enzymatic action. MIF combines with CD74 then involves sustained activation of the ERK-1/2 family of mitogen-activated protein kinases (MAPK), which results in increased levels of the precursors of pro-inflammatory prostaglandins, leukotrienes and cells proliferation. MIF is secreted mainly by activated lymphocytes and macrophage, endometriotic glandular and stromal cells. MIF is a important component of congenital immunity that described as a pro-inflammatory cytokine firstly, and subsequently identified having diverse biological functions, which are involved in immunity, inflammatory, cells proliferation, and angiogenesis.

The pathogenesis of endometriosis is based on three steps: adhesion, migration, and angiogenesis. The angiogenic process is a critical step for endometriosis development [6-9]. Researchers observed that the peritoneal fluid of endometriosis patients displayed a greater angiogenic activity both in vivo and in vitro using the model of endothelial cell proliferation [10]. Some angiogenic factors may contribute to the neovascularization of ectopic endometrial implants; for instance, Tumor Necrosis Factor alpha (TNF-a), interleukin-8 (IL-8) and Vascular Endothelial Growth Factor (VEGF),whose concentration have already documented to be increased in the peritoneal fluid of women suffering from endometriosis. However, if the ectopic endometrial cells can produce angiogenic factors by itself to ensure their survival and development, Yang, et al. [11] analyzed one bioactive fraction that markedly enhanced endothelial cell proliferation in vitro showing 100% homology with MIF, then the protein was testified as MIF by a specific anti-MIF antibody. The investigation reveals that MIF can be released by endometriotic cells and acts as a potent mitogenic factor for human endothelial cells to stimulate

cells proliferation directly for its angiogenic activity or indirectly, by stimulating endometriotic stromal cells to produce potent angiogenic factors. As we know the angiogenicability with MIF, it is a critical for ectopic endometrial cells survival and proliferation with endometriosis. Thus, In 2002, Akoum, et al. [7] for the first time reported that women with endometriosis have a high level of MIF in peritoneal fluid and there was a 238% increase of MIF in those patients as compared to healthy females. MIF concentrations were more significantly increased in infertile than in fertile women with endometriosis. So, MIF may contribute to endometriosis-associated infertility and angiogenesis through its effects on endothelial cell proliferation. This indicates that MIF might have a great relationship with the neovascularization of ectopic endometrial implants. In 2005, Akoum, et al. [12-16] using ELISA to measure peripheral blood MIF of women suffering from endometriosis, the result showed that the level of MIF in peripheral blood of women with endometriosis increased by 364% than normal controls. It rose significantly in the earlier stage and reached its peak level in the advanced stages (III–IV); those findings elucidated a plausible link between MIF and the disease progress. On the other hand, MIF can also stimulate endometriotic stromal cells to produce potent angiogenic factors. MIF promotes monocyte/macrophage activation and it is required for the optimal expression of TNF-a, MCP-1,IL-1,IL-8, and VEGF through the MAPK pathway [9,13-16]. Leng, et al. [17] in their work reported that CD74, a Type II transmembrane protein, was the receptor for MIF, after MIF binding to the extracellular domain of CD74, it will induce activation of the extracellular signal–regulated kinase–1/2 MAP kinase cascade, cell proliferation, and PGE2 production [4,14,18]. MIF might function to stimulate secretion of angiogenic factors by exerting a indirect effect on endometrial cell growth. At the same time, some cytokines can conversely up-regulate expression of MIF, for example, IL-1andTNF-avia the kB nuclear transcription factor (NFkB) could up-regulate the expression of MIF in endometrial stromal cells. MIF combining with CD74 induces activation of MAPK/ERK pathway which markedly increase the expression of angiogenic factors, such as MCP-1, IL-8, VEGF, TNF-a, which are involved in the pathologic process of endometriosis development. Some of them will enhance secretion of MIF conversely, based on the cycle [18-20]. Those factors eventually establish a feedback positive loop to survive the ectopic endometrial cells which might play a considerable role in the development of endometriosis. Recently, Shahhosein, et al. [21] performed the real-time polymerase chain reaction to evaluate the expressions of MIF, CD74, and COX-2 in normal, ectopic, and eutopic endometrium. The result showed that relative mRNA expression of MIF, CD74, and COX-2 was significantly higher in ectopic endometrium than in eutopic and control endometrium. When MIF binding to CD74, inducing activation of the NF-kB pathway, will give rise to over-expression of B-cell lymphoma–extra-large (Bcl-XL) and Bcl-2, which are both essential factors in apoptosis inhibition, MIF binding to CD74 also results in over-expression of Toll-like receptor 4 (TLR4), which is one of the receptors of the macrophage surface in response to bacterial lipopolysaccharides. Some studies show that TLR4 could activate NF-kB and mitogen-activated protein kinase (MAPK) pathways to regulate expression of COX-2 [22-24], which will cause a large amount of prostaglandins release contributing to

endometriosis relative pelvic pain [22-24]. Last year, Rakhilae, et al. [25] used knockout (KO) genetic approaches forming MIF gene knockout mice(MIF-KO) model to identify the function of MIF in establishing ectopic endometrium lesions they noted that the number and size of endometriosis-like lesions from MIF-KO mice reduced significantly as compare to control mice, when MIF add-back to MIF-KO mice as well as when WT mice were treated with a selective specific inhibitor of MIF (ISO -1), and then the outcome was opposite. In addition, the expression of VEGF, COX2, BCL2, which are important mediators of angiogenesis, adhesion and cells survival, is down-regulated in the endometriosis implants and those from WT mice treated with ISO -1, these results coincided with Shahhoseini et al. Those evidences demonstrate that MIF plays a crucial role in the endometriosis development.

There are few studies to focus on the progress of endometriosis, the result contradict with each other as well. In 2010, Zhang, et al. [16] investigated whether there is a correlation between MIF variation and disease stage. However, the date showed that a large amount of elevation MIF concentration in the endometriosis female, however, there was no significantly association between MIF expression and American Fertility Society staging of endometriosis, the result is obviously different from previous that Akoum, et al. [12] reported and consistent with Gupta, et al. [26] research. The contradiction conclusion may due to the different numbers and disease stage of patients included in the study and method. We have acknowledged that the expression of MIF markedly increased in women with endometriosis, but it is still unclear if there is a parallel link between MIF expression and American Fertility Society staging of endometriosis, which need to be identified by further clinical research.

The role of the MIF in diagnosis of endometriosis

The gold standard approach for diagnosis of endometriosis currently is laparoscopy that is direct visualization of endometriotic implants [27]. However, it is an invasive and expensive means; thus, there is a low compliance in women with endometriosis, though some certain biochemical characteristics related to endometriosis, none of these subjects have adequate sensitivity or specificity for clinical application. Hence, endometriosis maybe definitively diagnosed after 6 to7 years from onset of symptoms [1], therefore, it is urgent to look for a way for early diagnosis of endometriosis at the moment; serum biomarkers is possibly an available replacement. At present, the main serum biomarker used for diagnosis of endometriosis is CA125, which is mostly responsible for epithelial ovarian cancer. It may have value in monitoring the progression of disease or recurrence during therapy, while there is low sensitivity for a screening test about endometriosis [28-30]. Previous studies indicated that the concentration of MIF in peritoneal fluid and peripheral blood of women suffering from endometriosis markedly increased as compared to the control group. The difference has statistical significance and thus, the problem is whether the variation of serum MIF concentration can act as one of the biomarkers used for early diagnosis of endometriosis [28-30]. Seeber, et al. [31] verified the panel of markers can accurately predict endometriosis

including seven cytokines, those cytokines play a role in the development of endometriosis in some degree capable of the potential as a diagnostic marker [26]. The date indicate that the individual diagnostic performance of each of the markers is poor, a three-marker panel of CA-125, macrophage chemotactic protein-1, and leptin could diagnose 51% of subjects as to the presence of endometriosis with 89% accuracy, when adding MIF, the panel could diagnose 48% of subjects with 93% accuracy, it may be a effective method to diagnose endometriosis using panel of markers. last year, the findings on diagnostic potentials of nine different biomarkers in endometriosis including MIF was reported by Ozhan, et al. [32]. The result showed that the level of CA125, LN-1, STX-5 had a statistically significant difference as compared to the control, the sensitivity and specificity of CA125 is higher than others and there was a lack of diagnostic potential value in endometriosis about the level of MIF and other biomarkers. Although we received a negative result for the variation of serum MIF in diagnosis of endometriosis, which seems that MIF lack the value of diagnostic potential in endometriosis and we hope it will be elucidated in the future.

The inhibitor of MIF in endometriosis therapy

Amongst the inhibitor of MIF including antibody, inhibitor of MIF enzymatic activity and inhibitor purification from plant, the scholar put their emphasis on inhibitor of MIF enzymatic activity, which could suppress the activity of MIF isomerase and oxidoreductase, (S, R)-3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid methyl ester (ISO-1), a selective specific of MIF, which has been identified by numbers of laboratories worldwide. Like neutralizing anti-MIF antibodies, ISO-1 significantly improves survival and reduces disease progression and/or severity in multiple murine models where MIF is implicated [16,33,34]. Rakhila, et al. [25] through the endometriosis murine model that implanted human endometrial tissue into murine peritoneal cavity to establish endometrial lesions. After the endometriotic-like lesions development, they gave a IS0-1 treatment to the mice with endometriosis to assess the effect of IS0-1 on endometriotic-like lesions, the consequence showed that the number and size of endometriotic-like lesions reduced markedly and the expression of VEGF、IL8、COX2、Bcl2 was down-regulated in endometriotic-like lesions from mice treated with IS0-1. This coincided with Mahdian, et al. [21] reported, these result suggest that inhibition of MIF activity can eventually reduce endometriotic implant size and give rise to a speculation that a similar approach of targeting MIF may prove useful in treating endometriosis in humans. Perhaps IS0-1 could be used to treat endometriosis clinically many years later and might be the key to a novel way for endometriosis treatment.

In conclusion, based on the concentration of MIF significantly increased in eutopicand ectopic endometrial tissue, peritoneal fluid, as well as peripheral blood, it was revealed that MIF plays a crucial role on the endometriosis development, especially at early stage of the disease. Over expression of BCL2 induced high level of MIF in the eutopic endometrial cells contributed to retrograde endometrial cells survival, the high concentration of MIF in the peritoneal fluid retained and activated macrophage, later up-regulated the expression of VEGF, MMP-2, IL-8, MCP-1, Those factors eventually establish a feedback positive loop to survive the ectopic endometrial cells which might play a considerable role in the development of endometriosis. In the condition of high level MIF in peritoneal fluid; those cytokines take part in the pathology of endometriosis. Although the serum levels of MIF were elevated in women with endometriosis, there seems to be a lack of data to support MIF possessing diagnostic potential in endometriosis at present. The number and size of endometriotic-like lesions significantly reduced in murine model after treatment with IS0-1, which might provide a new approach to therapy endometriosis. The mechanism of MIF involved in endometriosis is still inconclusive, which may be explained following advanced researches [33,34].

References

1   Burney RO, Giudice LC (2012) Pathogenesis and pathophysiology of endometriosis. Fertil Steril 98: 511-519.

2   Manolova N, Zasheva D, Stamenova M (2011) Immunobiology of endometriosis. Acta Medica Bulg 38: 38-50.

3   Cohen S, Shoshana OY, Zelman-Toister E, Maharshak N, Binsky-Ehrenreich I, et al. (2012) The cytokine midkine and its receptor RPTPζ regulate B cell survival in a pathway induced by CD74. J Immunol 188: 259-269.

4   Leng L, Metz CN, Fang Y, Xu J, Donnelly S, et al. (2003) MIF signal transduction initiated by binding to CD74. J Exp Med 197: 1467-1476.

5   Bach JP, Deuster O, Balzer-Geldsetzer M, Meyer B, Dodel R, et al. (2009) The role of macrophage inhibitory factor in tumorigenesis and central nervous system tumors. Cancer 115: 2031-2040.

6   Mahutte NG, Matalliotakis IM, Goumenou AG, Koumantakis GE, Vassiliadis S, et al. (2004) Elevations in peritoneal fluid macrophage migration inhibitory factor are independent of the depth of invasion or stage of endometriosis. Fertil Steril 82: 97-101.

7   Kats R, Collette T, Metz CN, Akoum A (2002) Marked elevation of macrophage migration inhibitory factor in the peritoneal fluid of women with endometriosis. Fertil Steril 78: 69-76.

8   Nishihira J (2000) Macrophage migration inhibitory factor (MIF): its essential role in the immune system and cell growth. J Interferon Cytokine Res 20: 751-762.

9   Mitchell R, Metz CN, Peng T, Bucala R (1999) Sustained mitogen-activated protein kinase (MAPK) and cytoplasmic phospholipase A2 activation by macrophage migration inhibitory factor (MIF). Regulatory role in cell proliferation and glucocorticoid action. J Biol Chem 274: 18100-18106.

10   Taylor RN, Ryan IP, Moore ES, Hornung D, Shifren JL, et al. (1997) Angiogenesis and macrophage activation in endometriosis. Ann N Y Acad Sci 828: 194-207.

11   Yang Y, Degranpre P, Kharfi A, Akoum A (2000) Identification of macrophage migration inhibitory factor as a potent endothelial cell growth-promoting agent released by ectopic human endometrial cells. J Clin Endocrinol Metab 85: 4721-4727.

12   Morin M, Bellehumeur C, Therriault MJ, Metz C, Maheux R, et al. (2005) Elevated levels of macrophage migration inhibitory factor in the peripheral blood of women with endometriosis. Fertil Steril 83: 865-872.

13   Ogawa H, Nishihira J, Sato Y (2000) An antibody for macrophage migration inhibitory factor suppresses tumour growth and inhibits tumour-associated angiogenesis. Cytokine 12: 309-314.

14   Calandra T, Roger T (2003) Macrophage migration inhibitory factor: a regulator of innate immunity. Nat Rev Immunol 3: 791-800.

15   Ren Y, Chan HM, Li Z (2004) Upregulation of macrophage migration inhibitory factor contributes to induced N-Myc expression by the activation of ERK signaling pathway and increased expression of interleukin-8 and VEGF in neuroblastoma. Oncogene 23: 4146-4154.

16   Veillat V, Carli C, Metz CN, Al-Abed Y, Naccache PH, et al. (2010) Macrophage migration inhibitory factor elicits an angiogenic phenotype in human ectopic endometrial cells and triggers the production of major angiogenic factors via CD44, CD74, and MAPK signaling pathways. J Clin Endocrinol Metab 95: 403-412.

17   Lin W, Chen S, Li M, Wang B, Qu X, et al. (2010) Expression of macrophage migration inhibitory factor in human endometriosis: relation to disease stage, menstrual cycle and infertility. J Obstet Gynaecol Res 36: 344-351.

18   Carli C, Metz CN, Al-Abed Y, Naccache PH, Akoum A (2009) Up-regulation of cyclooxygenase-2 expression and prostaglandin E2 production in human endometriotic cells by macrophage migration inhibitory factor: involvement of novel kinase signaling pathways. Endocrinology 150: 3128-3137.

19   Cao WG, Morin M, Metz C, Maheux R, Akoum A (2005) Stimulation of macrophage migration inhibitory factor expression in endometrial stromal cells by interleukin , beta involving the nuclear transcription factor NFkappaB. Biol Reprod 73: 565-570.

20   Cao WG, Morin M, Sengers V (2006) Tumour necrosis factor-alpha up-regulates macrophage migration inhibitory factor expression in endometrial stromal cells via the nuclear transcription factor NF-kappaB. Hum Reprod 21: 421-428.

21   Mahdian S, Aflatoonian R, Yazdi RS, Yaghmaei P4, Ramazanali F, et al. (2015) Macrophage migration inhibitory factor as a potential biomarker of endometriosis. Fertil Steril 103: 153-159.

22   Young SL, Lyddon TD, Jorgenson RL, Misfeldt ML (2004) Expression of Toll-like receptors in human endometrial epithelial cells and cell lines. Am J Reprod Immunol 52: 67-73.

23   Herath S, Fischer DP, Werling D, Williams EJ, Lilly ST, et al. (2006) Expression and function of Toll-like receptor 4 in the endometrial cells of the uterus. Endocrinology 147: 562-570.

24   Kajihara H, Yamada Y, Kanayama S, Furukawa N, Noguchi T, et al. (2011) New insights into the pathophysiology of endometriosis: from chronic inflammation to danger signal. Gynecol Endocrinol 27: 73-79.

25   Rakhila H, Girard K, Leboeuf M, Lemyre M, Akoum A (2014) Macrophage Migration Inhibitory Factor Is Involved in Ectopic Endometrial Tissue Growth and Peritoneal-Endometrial Tissue Interaction In Vivo: A Plausible Link to Endometriosis Development. PLoS One 9: e110434.

26   Gupta S, Agarwal A, Sekhon L, Krajcir N, Cocuzza M, et al. (2006) Serum and peritoneal abnormalities in endometriosis: potential use as diagnostic markers. Minerva Ginecol 58: 527-551.

27   Vercellini P, Viganò P, Somigliana E, Fedele L1 (2014) Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol 10: 261-275.

28   Mol BW, Bayram N, Lijmer JG, Wiegerinck MA, Bongers MY, et al. (1998) The performance of CA-125 measurement in the detection of endometriosis: a meta-analysis. Fertil Steril 70: 1101-1108.

29   Chen FP, Soong YK, Lee N, Lo SK (1998) The use of serum CA-125 as a marker for endometriosis in patients with dysmenorrhea for monitoring therapy and for recurrence of endometriosis. Acta Obstet Gynecol Scand 77: 665-670.

30   Kitawaki J, Ishihara H, Koshiba H, Kiyomizu M, Teramoto M, et al. (2005) Usefulness and limits of CA-125 in diagnosis of endometriosis without associated ovarian endometriomas. Hum Reprod 20: 1999-2003.

31   Seeber B, Sammel MD, Fan X, Gerton GL, Shaunik A, et al. (2008) Panel of markers can accurately predict endometriosis in a subset of patients. Fertil Steril 89: 1073-1081.

32   Ozhan E, Kokcu A, Yanik K, Gunaydin M3 (2014) Investigation of diagnostic potentials of nine different biomarkers in endometriosis. Eur J Obstet Gynecol Reprod Biol 178: 128-133.

33 Lubetsky JB, Dios A, Han J, Aljabari B, Ruzsicska B, et al. (2002) The tautomerase active site of macrophage migration inhibitory factor is a potential target for discovery of novel anti-inflammatory agents. J Biol Chem 277: 24976-24982.

34 Nothnick WB, Colvin A, Cheng KF, Ya A (2012) Inhibition of macrophage migration inhibitory factor reduces endometriotic implant size in mice with experimentally induced disease. J Endometr 29: 997-1003.