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Original Research

Expression and therapeutic potential of macrophage migration inhibitory factor and CD74 in ovarian cancer

Y. S. Lee[1], J. M. Baek[2], E. K. Park[1], C. J. Kim[1], H. J. Lee[3], J. O. Kim[4]
[1]Department of Obstetrics and Gynecology, [2]Department of General Surgery, College of Medicine, The Catholic University of Korea, Seocho-gu, Seoul; [3]Department of Pathology, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Wonmi-gu, Bucheon, Gyeonggi-do
[4]Department of Pathology, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Jung-gu, Daejeon (Republic of Korea)

Summary

Purpose of Investigation: To evaluate macrophage migration inhibitory factor (MIF) and CD74 expression in ovarian cancer, and to explore whether these expression levels correlate with clinicopathologic parameters. *Materials and Methods:* A total of 151 tissue samples were collected from May 2009 through May 2015. The collected samples included ten normal ovaries, 41 benign epithelial ovarian tumors, 38 borderline tumors, and 62 malignant epithelial ovarian tumors. CD74 and MIF expression was assessed by immunohistochemistry and a retrospective study was conducted. *Results:* Immunohistochemical analysis showed that MIF and CD74 expression was significantly higher in ovarian tumors, including ovarian cancer, than in normal ovary tissues. Furthermore, high MIF expression was correlated with lymph node metastasis ($p = 0.048$) and ovary surface invasion ($p = 0.039$). *Conclusion:* The present findings suggest that co-expression of MIF and CD74 in ovarian cancer is associated with poor clinical parameters and may serve as a therapeutic target for the treatment of ovarian cancer.

Key words: Ovarian tumor; CD74; Macrophage migration inhibitory factor (MIF); Immunohistochemistry

Introduction

Ovarian cancer is one of the major cancers affecting females. Despite various treatment efforts, including extensive surgery and combined chemotherapy, ovarian cancer remains a disease with an unfavorable prognosis. Recently, some immunotherapeutic agents have been introduced with impressive results, but their use is still at an early stage.

Macrophage migration inhibitory factor (MIF) is a critical pleiotropic inflammatory cytokine generated by cells of the innate and adaptive immune systems [1]. The potent proinflammatory effect of MIF may stimulate cancer progression [2, 3]. MIF may also directly inhibit tumor cell apoptosis by inactivating the p53 tumor suppressor [4]. Although increased MIF expression has been frequently observed in several cancer types, the mechanisms of action for MIF involvement in tumor progression remain to be fully clarified [3, 5-10]. Furthermore, MIF has been proposed as a novel potential tissue marker and drug target in cancer [11]. CD74, the HLA-DR antigen-associated invariant chain, is involved in several key immune system processes including antigen presentation, B-cell differentiation, and inflammatory signaling. Moreover, CD74 is upregulated in cancer cells, indicative of a role in tumorigenesis and angiogenesis [7, 12]. Recent evidence suggests that CD74 is the receptor for MIF, which, when bound to CD74, initiates survival pathways and cell proliferation [7, 13]. The binding of MIF to CD74 induces cell proliferation and cell cycle events, including antagonism of p53. MIF also prevents apoptosis and promotes tumor cell survival by directly activating the AKT pathway [4, 14]. Moreover, CD74 is suggested to be a new prognostic factor for malignancy and marker for predicting toxicity after chemotherapy [5, 9]. MIF and CD74 co-expression levels could be an alternative marker for the efficacy of anti-angiogenic drugs [8]. However, expression of MIF and CD74 in ovarian cancer, and their role in ovarian cancer pathogenesis, remains unclear.

The aim of this study was to determine the expression of MIF and CD74 in normal ovarian tissue, borderline ovarian tumor tissue, and epithelial ovarian cancer tissue and to identify the potential of MIF and CD74 for cancer immunotherapy targets. Furthermore, the authors aimed to estimate the potential of MIF and CD74 as prognostic markers by comparing their expression with clinical characteristics in epithelial ovarian carcinoma.

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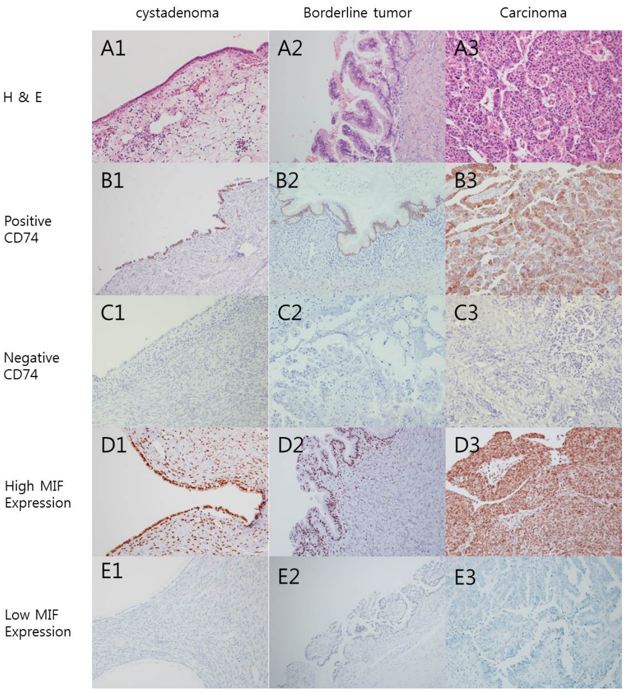

Figure 1. — Hematoxyin and Eosin staining (A1-3) and immunohistochemical staining for CD74 and MIF in the different ovarian tissues (B1-E3). Serous cystadenoma lined by single benign cuboidal epithelial cells (A1), mucinous borderline tumor shows stratified columnar epithelial cells and papillae of epithelia (A2), and endometrioid adenocarcinoma showing tubular structures and solid carcinoma component (A3). Positive cytoplasm expression for CD74: positive CD74 in serous cystadenoma (B1), mucinous borderline tumor (B2), and serous carcinoma (B3). Negative CD74 staining in serous cystadenoma (C1), seromucinous borderline tumor, (C2) and serous carcinoma (C3). High MIF expression: MIF positive cytoplasm and nuclei in serous cystadenoma (D1), positive nuclei in mucinous borderline tumor (D2), and nuclear and cytoplasmic expression in serous carcinoma (D4). Low MIF expression in mucinous cystadenoma (E1), mucinous borderline tumor (E2), and serous carcinoma (E3) (original magnification ×200).

Materials and Methods

A total 151 tissue samples were collected from the gynecology and pathology departments at Daejeon St. Mary's Hospital in Korea, between May 2009 and May 2015. The samples consisted of ten normal ovarian tissues, 41 benign epithelial ovarian tumors, 38 borderline tumors, and 62 malignant epithelial ovarian tumors. A retrospective study was conducted that included a review of medical records to assess the patients' clinicopathologic characteristics. All patients underwent primary surgery for ovarian tumor and did not receive chemotherapy and/or radiation before surgery. Normal ovarian tissue was obtained from patients with ovarian surgery due non-tumorous disease. Tissue specimens were obtained at the time of surgery. After resection, the fresh tissue was fixed in 10% neutral buffered formalin. All tissues were made of Hematoxylin and Eosin slides and diagnosed by a pathologist. The research protocol was approved by the institutional review board (IRB approval number: DIRB-00076_2-001). All instructions and processes performed in this study were in accordance with the ethical standards set forth in the Declaration of Helsinki.

Hematoxylin and Eosin slides were reviewed under a microscope by one pathologist and one slide was selected for each of the ten non-tumorous ovarian diseases (normal ovarian tissue), 41 benign epithelial ovarian tumors, 38 borderline tumors, and 62 malignant epithelial ovarian tumors (Figure 1).

Immunohistochemical studies were performed on 4-μm sections from formalin-fixed and paraffin-embedded tissue using an autostaining protocol and an autostainer as per the manufacturer's instructions. Deparaffinization and antigen retrieval were conducted as an automated program of the autostainer. The primary antibodies used were CD74 (1:200) and MIF (1:100). CD74 was positively expressed in the cytoplasm and nucleus. CD74 expression was evaluated based on Ishigami's classification. Based on the percentage of positive tumor cells, cases were divided into two groups: the negative group showed CD74 expression in less than 10% of cells, and the positive group included samples with CD74 expression in 10% or more of the cells [15]. MIF was mainly expressed in the cytoplasm, although expression was also noted in the nucleus in some samples. Evaluation of MIF expression was achieved by measuring stain intensity and stain area (double scoring system). Stain intensity was defined as follows: score 0, no staining, score 1, weak staining, score 2, moderate staining, and score 3, strong staining. Staining area is defined as: staining in ≤ 30% of tumor cells, score 1, staining in 31-75% of tumor cells, score 2, and staining in ≥ 75% of cells, score 3. Samples were assigned to the MIF high-expression category when their immunostaining score was ≥ 4 (stain intensity score x stain area score), and samples with a stain intensity score < 4 were assigned to the low-expression category, as described previously (Figure 1) [16].

The data are expressed as mean ± standard deviation (SD) for continuous variables and as number of cases (n) and percentage of occurrence (%) for categorical variables. Continuous data were analyzed using Student's *t*-test or Welch's *t*-test, and categorical data were analyzed using Chi-square test or Fisher's exact test. Statistical analyses were performed using SAS 9.2. All tests were two tailed, and $p < 0.05$ was considered statistically significant.

Results

Immunohistochemical staining showed that ten normal ovarian tissues were negative for CD74 expression. CD74 expression was observed in 16 (39.0%) of 41 benign tumors, seven (18.4%) of 38 borderline tumors, and 48 (77.4%) of 62 ovarian cancer tissues. CD74 expression in normal ovarian, benign tumor, borderline tumor, and ovarian cancer tissues was differed significantly ($p < 0.001$) (Table 1).

Immunohistochemical staining also showed that MIF expression was low in ten normal ovarian tissues and high in 38 (92.7%) of 41 benign tumor, 24 (63.2%) of 38 borderline tumor, and 50 (80.7%) of 62 ovarian cancer tissues. MIF expression in normal ovarian, benign tumor, borderline tumor, and ovarian cancer tissues differed significantly ($p < 0.001$) (Table 1).

To investigate the influence of CD74 and MIF on tumor behavior, the authors evaluated the relationship between

Table 1. — *Immunohistochemical staining for CD74 and MIF in different ovarian tissues.*

Variable	Normal ovary (n=10)	Benign tumor (n=41)	Borderline tumor (n=38)	Ovarian cancer (n=62)	*p* value
CD74					
Negative	10 (100.0)	25 (61.0)	31(81.6)	14 (22.6)	<0.001
Positive	0 (0.0)	16 (39.0)	7 (18.4)	48 (77.4)	
MIF					
Low	10 (100.0)	3 (7.3)	14 (36.8)	12 (19.3)	<0.001
High	0 (0.0)	38 (92.7)	24 (63.2)	50 (80.7)	

Table 2. — *Correlation between expression of CD74 and MIF and clinicopathological parameters in patients with ovarian cancer (n=62).*

Ovarian cancer (n=62)	No.Cases	CD74 expression		*p* value	MIF expression		*p* value	CD74 and MIF		*p* value
		Positive n (%)	Negative n (%)		High n (%)	Low n (%)		Positive & high n(%)	Others n(%)	
Age (years)				0.054				N=40	N=22	
< 50	26	17(65.4)	9(34.6)		24(92.3)	2(7.7)	0.048*	16(61.5)	10(38.55)	0.677
≥ 50	36	31(86.1)	5(13.9)		26(72.2)	10(27.8)		24(66.7)	12(33.3)	
Pathologic type				0.117			0.004*			0.009*
Serous	44	37(84.1)	7(15.9)		39(88.6)	5(11.4)		34(77.2)	10(22.8)	
Mucinous	11	7(63.6)	4(36.4)		6(54.5)	5(45.5)		3(27.2)	8(72.8)	
Endometrioid	5	3(60.0)	2(40.0)		5(100.0)	0(0.0)		3(60.0)	2(40.0)	
Transitional cell	1	1(100)	0(0.0)		0(0.0)	1(100.0)		0(0.0)	1(100)	
Squamous and mixed	1	0(0.0)	1(100)		0(0.0)	1(100.0)		0(0.0)	1(100)	
Tumor size (volume)				0.070						
< 300	32	28(87.5)	4(12.5)		23(71.9)	9(28.1)	0.071	23(71.8)	9(28.2)	0.211
≥ 300	30	20(66.7)	10(33.3)		27(90.0)	3(10.0)		17(56.7)	13(43.3)	
Degree of differentiation				>0.999						
Well	6	5(83.3)	1(16.7)		5(83.3)	1(16.7)	0.800	4(66.7)	2(33.3)	0.767
Moderate	26	20(76.9)	6(23.1)		22(84.6)	4(15.4)		18(69.2)	8(30.8)	
Poor	30	23(76.7)	7(23.3)		23(76.7)	7(23.3)		18(60.0)	12(40.0)	
FIGO Stage										
I	22	15(68.2)	7(31.8)	0.655	16(72.7)	6(27.3)	0.670	12(54.5)	10(45.5)	0.685
II	7	6(85.7)	1(14.3)		6(85.7)	1(14.3)		5(71.4)	2(28.6)	
III	23	18(78.3)	5(21.7)		20(87.0)	3(13.0)		16(69.6)	7(30.4)	
IV	10	9(90.0)	1(10.0)		8(80.0)	2(20.0)		7(70.0)	3(30.0)	
Lymph node metastasis				0.592			0.048*			0.231
No	36	27(75.0)	9(25.0)		26(72.2)	10(27.8)		21(58.3)	15(41.7)	
Yes	26	21(80.8)	5(19.2)		24(92.3)	2(7.7)		19(52.7)	7(47.3)	
Lymphovascular space invasion				0.871			0.526			0.677
No	36	28(77.8)	8(22.2)		30(83.3)	6(16.7)		24(66.7)	12(33.3)	
Yes	26	20(76.9)	6(23.1)		20(76.9)	6(23.1)		16(61.5)	10(38.5)	
Ovary surface invasion				0.365			0.039*			0.012*
No	8	5(62.5)	3(37.5)		4(50.0)	4(50.0)		2(25.0)	6(75.0)	
Yes	54	43(79.6)	11(20.4)		46(85.2)	8(14.8)		38(70.3)	16(29.7)	
Optimal surgery				0.409			0.358			0.035*
No	9	6(12.5)	3(21.4)		6(12.0)	3(25.0)		3(33.3)	6(66.7)	
Yes	53	42(87.5)	11(78.6)		44(88.0)	9(75.0)		37(69.8)	16(30.2)	
Recurrence				0.524			0.520			0.385
No	21	15(31.2)	6(42.9)		16(32.0)	5(41.7)		12(57.1)	9(42.9)	
Yes	41	33(68.8)	8(57.1)		34(68.0)	7(58.3)		28(68.3)	13(31.7)	

*FIGO: International Federation of Gynecology and Obstetrics. *χ^2 test.*

their expression and clinicopathological features in 62 ovarian cancer cases. As shown in Table 2, no clinicopathological parameter was associated with CD74 expression. CD74 expression did not change based on age. However, there was a statistically significant difference in MIF expression based on age. High MIF expression was observed in 72.2% of samples from patients ≥ 50 years and in 92.3% of samples from patients < 50-years-old. CD74 expression did not differ based on histologic type. MIF expression differed based on histologic type. In serous carcinoma, 88.6% of samples had high levels of MIF expression. Moreover, 84.1% of serous carcinoma samples expressed CD74. Co-expression was highest in serous carcinoma, with 77.2% of samples coexpressing MIF and CD74 (Table 2). Samples expressing CD74 and MIF did not show any differences in tumor size, degree of differentiation, clinical stage, or lymphovascular space invasion (Table 2). Expression of CD74 was not associated with lymph node metastasis or ovary surface invasion, but expression of MIF was increased in the lymph node metastasis and ovary surface invasion groups (Table 2). Additionally, there was no correlation between CD74 and MIF expression and patients having gone with or without optimal surgery, or with complete remission after chemotherapy, recurrence after treatment, or current survival status. CD74 expression and high MIF expression were observed in 40 cases, and this simultaneous increase in expression was associated with ovary surface invasion.

Discussion

It has been suggested that MIF, CD74, and their pathway could play a role in the pathogenesis of various cancers. However, to date, the expression of MIF and CD74 has not been clearly studied in ovarian cancer. Here, the authors confirmed that MIF and CD74 are overexpressed in ovarian tumors, including ovarian cancer. While the increase in CD74 and MIF expression was not proportional to the increase in ovarian lesion severity, compared to normal ovarian tissue, expression of CD74 and MIF was significantly increased in tumor tissue. These results suggest the involvement of MIF pathways in ovarian tumorigenesis.

To minimize toxicity, molecular treatment targets are required to be minimally expressed in normal tissues and highly expressed in target tissues. Based on these criteria, both CD74 and MIF show potential as therapeutic targets. In fact, the restricted expression of CD74 in normal tissues and its rapid internalization make CD74 an attractive therapeutic target for cancer therapy [17]. Increased CD74 expression has been noted in several cancer tissues, with no expression in corresponding normal tissues, highlighting the potential of CD74 as a target for treatment of hematologic malignancy. An anti-CD74 humanized monoclonal antibody, milatuzumab, has been developed, and is currently in a phase I-II clinical trial [18-20]. Milatuzumab has demonstrated activity in patients with relapsed and refractory B-cell non-Hodgkin's lymphoma and refractory chronic lymphocytic leukemia [18-20].

To date, few studies have examined the expression of CD74 in ovarian cancer, and those that have been rudimentary [21]. Recently, bevacizumab, a humanized monoclonal antibody directed against the vascular endothelial growth factor, and some immunotherapeutic agents have been introduced to treat ovarian cancer with impressive results. However, ovarian cancer treatments are still at an early stage compared to those for other cancers, including breast cancer. Results of ovarian cancer treatment remain at an unsatisfactory level. Therefore, the possibility of applying CD74 antibodies, which are already under clinical trial, to the treatment of ovarian cancer could be an attractive proposition.

MIF is a proinflammatory cytokine affecting the regulatory function of many biological processes in various cells. MIF may influence the prognosis of ovarian cancer by inhibiting the antitumor response of immune cells. Unlike normal cells, cancer cells secrete significant amounts of MIF and serum MIF concentrations are significantly elevated in ovarian cancer patients [2]. The levels of MIF in ascites and serum of patients with ovarian cancer correlates with common prognostic parameters such as tumor stage or platinum sensitivity, and with CD8 T and NK-cell infiltration in tumor tissue [22]. Hagemann *et al.* reported that MIF increased macrophage-mediated ovarian cancer cell invasiveness and suggested that autocrine production of MIF by ovarian cancer cells stimulates other cytokines, chemokines, and angiogenic factors [23]. Together, these factors may promote colonization of the peritoneum and neovascularization of tumor deposits [23]. The present results are consistent with those of Hagemann *et al.*, which showed that normal ovarian surface epithelium does not express MIF, but borderline tumor and ovarian carcinoma cells do [23]. MIF also appears to mediate angiogenesis and the development of metastasis and locoregional lymph node metastasis, which are often associated with a poor prognosis [24]. The present results showed that MIF expression is related to lymph node metastasis and ovary surface invasion. These results suggest that serum MIF level and MIF expression in ovarian tissues could play a prognostic role in ovarian cancer.

Contrary to the results obtained investigating other cancer types, the present authors did not find any significant correlation between ovarian cancer histoprognostic factors and CD74 expression [5, 9, 12]. However, increased MIF expression and co-expression of MIF and CD74 were associated with ovary surface invasion. These results suggest that the MIF/CD74 pathway could be related to early-stage invasiveness of cancer development. In cervical cancer, either MIF or CD74 expression has previously been shown to be positively associated with higher microvessel density [10]. Considering that there was no significant difference in clinicopathological parameters between CD74-positive and CD74-negative tumors, MIF probably plays a minor role in ovarian cancer development and progression.

The limitation of this study was the sample size. However, the results presented here are important, as very few studies have investigated tissue CD74 and MIF expression in ovarian cancer.

The present findings show that MIF and CD74 expression is significantly higher in ovarian tumors, including ovarian cancer, than in the normal samples, highlighting their potential role as therapeutic targets. Additionally, co-expression of MIF and CD74 was associated with some poor clinical parameters and might be involved in the etiology and progression of ovarian cancer.

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Corresponding Author:
JONG OK KIM, M.D.
Department of Pathology, Daejeon St. Mary's Hospital
College of Medicine, The Catholic University of Korea
64 Daeheung-ro, Jung-gu, Daejeon
34943 (Republic of Korea)
e-mail: jkim@catholic.ac.kr