Original Article
Running Title: SDF-1 Genetic Variation in Endometrial Cancer
Received: February 14, 2024; Accepted: July 17, 2024

Stromal Cell-Derived Factor1 Genetic Variation at Locus 801 in Patients with Endometrial Cancer

Fateme Sadat Najib[*], MD, Elham Izanloo[**], MD, Maryam Aghdaki[**], MD, Soolmaz Khansalar[***], MSc, Mohammad Javad Fattahi[***], PhD, Zahra Oveisi[**], MD, Mohammad Reza Haghshenas[***♦], PhD

[*]*Obstetrics and Gynecology Department, Infertility Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*
[**]*Obstetrics and Gynecology Department, Shiraz University of Medical Sciences, Shiraz, Iran*
[***]*Shiraz Institute for Cancer Research, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*

♦Corresponding Author
Mohammad Reza Haghshenas, PhD
Shiraz Institute for Cancer Research,
Shiraz University of Medical Sciences,
Shiraz, Iran
Email: haghshenasmr@sums.ac.ir
vhaghshenas@yahoo.com

Abstract

Background: The gene's 3′ untranslated region of stromal cell-derived factor1 (SDF-1/ CXC chemokine ligand 12 (CXCL12)) contains a polymorphism, known as SDF1-3′A at location 801, and has been linked to various types of cancers. The present study aimed to evaluate the relationship between this polymorphism and genetic predisposition to endometrial cancer.

Method: In this case-control study, DNA was extracted from blood samples of 108 endometrial cancer patients and 123 healthy individuals through salting out method. Genotyping was done by restriction fragment length polymorphism-polymerase chain reaction method, and the data were analyzed using chi-square test.

Results: A total number of 67 (62%) patients emerged as GG genotypes, 35 (32.4%) with GA, and 6 (5.6%) with AA genotypes. The frequency of GG, GA and AA in healthy control group was found to be 68 (55.3%), 50 (40.6%) and 5 (4.1%), respectively. Furthermore, the most frequent allele in both patient (169 (78.25%)) and control (186 (75.6%)) groups was G allele. However, no significant difference was observed between genotypes and alleles frequencies between the two groups. Furthermore, no significant association was observed between genotypes distribution and menopausal status (P = 0.70), tumor size (P = 0.62), degree of tumor differentiation (P = 0.74), stage (P = 0.35), tumor type (P = 0.22), and myometrial invasion (P = 0.22).

Conclusion: Our results show that SDF1-3′A at location 801 may not enhance the risk of endometrial cancer. However, further research with a larger sample size is required to understand the molecular behavior of the SDF-1 gene polymorphism in endometrial cancer.

Keywords: Endometrial neoplasms, Stromal cell-derived factor1, Chemokine CXCL12, Genotype

Introduction

Endometrial cancer is the most common gynecologic malignancy in women around the world. More than 83% of uterine corpus cancers are endometrial, and both genetic and non-genetic agents may act as causal risk factors.[1] Aggressive types, including serous and papillary serous carcinomas, account for 4% to 6% of endometrial carcinomas, whereas clear cell carcinomas account for 1% to 2% of the cases.[2] The lifetime chance of acquiring endometrial cancer is approximately 2.8%.[3, 4]

The therapy choices for individuals with severe or recurring disease, or those who intend to protect their fertility, are restricted. As a result, it is critical to understand the cellular and molecular mechanisms of endometrial cancer in order to design and develop appropriate diagnostic and therapeutic targets.[5-7] Because solid tumors, including endometrial cancer, are made up of tumor cells and diverse kinds of stromal cells, tumor growth is influenced not only by the tumor cells but also by the tumor stroma.[8] Stromal cell-derived factor1 (SDF-1), also known as CXCL 12, is a chemoattractant cytokine with several physiological and pathological roles. Significant evidence suggests that SDF-1 plays critical roles in the cell proliferation, apoptosis, invasion, and metastasis of many types of cancer.[5, 9, 10] SDF-1 is engaged in inflammation and stem cell migration; Thus, it plays an important role in inflammation and hematopoiesis.[11] The gene encoding SDF-1 is found on chromosome 10.q.11.1. SDF-1 exists in two main isoforms. Because of alternative splicing, both are generated from the same gene. SDF-1 is released by bone marrow stromal cells and endothelial cells and is present in all organs.[12] SDF-1 is an essential chemokine that binds largely to its cognate receptor CXCR4 and hence regulates normal and malignant cell trafficking.[13]

A common polymorphism in SDF1 gene comprises a single nucleotide substitution in the 3'untranslated region (3'UTR) at the 801-nucleotide position (rs1801157), where guanine substitutes adenine (G / A).[14] Cis-acting factors that promote SDF1 expression target the A allele, and this was found to be related to enhanced mRNA expression and/or mRNA stability, which had a half-life twice as long as G allele, and it may influence disease progression in human immunodeficiency virus 1 (HIV-1).[14, 15] Additionally, it has been reported that allele A was associated with a remarkable loss of CD4+ lymphocytes HIV-1 infection.[16] To the best of our knowledge, no prospective study has addressed the SDF-1 genetic variation in endometrial cancer patients.

Given the importance of genetic variations in predisposing Iranian women to endometrial cancer, this case-control study was conducted to investigate the probable association of SDF1 gene polymorphism at position 801 (rs1801157) with endometrial cancer in comparison with peer control participants.

Methods and Materials

Target group and study design

This case-control study was conducted in the Obstetrics and Gynecology Department of Shiraz University of Medical Science, and Shiraz Institute for Cancer Research from November 2022 to May 2023. SDF-1 genetic variations in patients with endometrial cancer were compared with a healthy control group. This study consisted of 32 to 86-year-old endometrial cancer cases diagnosed based on pathological assessment referred to the Obstetrics and Gynecology Department and healthy participants who were selected from cases without current or history of endometrial cancer. According to the incidence of endometrial cancer in Iran, and sample size of previous studies with the ethnicity of Asian and Caucasian, 108 patients with endometrial cancer were

enrolled in this study.[17] The pathologic diagnoses were established based on hysterectomy material evaluated by expert pathologists. The surgical staging was performed according to the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) guidelines by expert gynecologists as determined by the International Federation of Gynecology and Obstetrics. Open total hysterectomy and bilateral salpingo-oophorectomy (TAH + BSO) and pelvic/paraaortic lymphadenectomy with or without omentectomy were the main surgical procedures. Demographic variables (age, parity, menopausal status, presenting symptoms, medical history) and clinicopathological variables (histopathological type, stage, the degree of myometrial invasion, lymph node involvement, lymphovascular space invasion, and survival outcomes) were evaluated and recorded on their files. Patients with a history of other malignancy and autoimmune disorders, missed to follow up, undergoing surgery in other hospitals, aged below 18 years or more than 80 years, and unwilling to continue participation were excluded from the study. We also excluded patients with uncompleted data. In addition, 123 age- and sex-matched healthy control individuals were included.

Ethics approval and consent to participate

An informed written consent, data on epidemiology, and medical history were collected prospectively at the time of inclusion. The protocol of the study, in accordance with the Declaration of Helsinki, was approved by the Ethics Committee of Shiraz University of medical sciences, Shiraz, Iran (IR.SUMS.MED.REC.1400.109).

DNA extraction and determining genotype at position 801G/A in SDF1 gene

5ml of venous blood sample was collected from both groups and transferred to tubes containing 0.5ml of EDTA for DNA extraction. Genomic DNA was extracted from peripheral blood cells by salting out method.

Restriction Fragment Length Polymorphism (RFLP)-Polymerase Chain Reaction (PCR) was used to determine the genotype of the participants in the 801G/A position in the SDF1 gene. To do so, two primers forward (F) (5 'CAG TCA ACC TGG GCA AAG CC 3') and reverse (R) (5 'AGC TTT GGT CCT GAG AGT CC 3') were used to amplify the desired region by thermo cycler instrument (Bio-Rad, Germany). The PCR product was then exposed to MSPI (HpaII) restriction enzyme (Fermatas, Lithuania).) and broken down into fragments (302bp, 202bp and 100bp). The results of RFLP for detection of SDF1 genotypes at locus 801(rs1801157) are shown in figure 1. The DNA genotype can be determined based on the size of the fragments obtained as run on 2% agarose gel in 1x TAE buffer, and visualized using a document gel apparatus.

Data analysis

The data were analyzed using Chi-square (X^2) test and SPSS 16, EPI Info 2000 and Arlequin statistical programs. Arlequin program version 2000 was used to check whether the groups in the study position followed Hardy-Weinberg equilibrium. The two tailed *P*-value less than 0.05 were considered significant.

Results

Demographic and pathological characteristics of the patients with endometrial cancer

In this study, 108 endometrial cancer cases and 123 healthy controls were included. As shown in table 1, mean age of the patients was 57.35 ± 11.15 years, and mean age of the control participants was 57.00 ± 11.01. The mean menstrual age of patients was 12.82 ± 1.52, and the mean menopausal age of patients was 49.43 ± 8.56. Among patients,

89 individuals (82.4%) had reached menopause at the time of endometrial cancer diagnosis and 19 (17.6%) had not reached menopause. The age of the control group was also selected in terms of menopause in such a way that it included both menopause and non-menopause. There was no significant difference in terms of age (P = 0.89), menstrual age (P = 0.95), menopausal age (P = 0.87), and menopausal status (P = 0.70) between the two groups. Most of the cases with endometrial cancer had a tumor size of equal or greater than 2 cm (71.3%) and had myometrial invasion lower than 50% (73.1 %). In terms of histological differentiation, the patients were divided into three groups of well differentiation, moderate differentiation and poorly differentiated. 57 (52.8%) were well-differentiated, 27 (25%) moderately-differentiated and 24 (22.22%) were poorly differentiated. In addition, patients were divided into three groups in terms of Figo stage. Statistical analysis showed that 63 (58.3%) of patients had tumor confined to the corpus uteri, 27 (25%) had invasive cervical stromal tumor, and 18 (16.7%) had local and / or regional spread of the tumor. The location of the tumor in all patients (100%) were endometrium. Furthermore, the patients were divided into two groups according to the type of tumor including endometroid type grade I, Ⅱ including 76 individuals (70.4%), and endometroid type grade Ⅲ clear cell undifferentiated papillary serous including 32 (29.6%). The data are summarized in table 1.

The comparison of genotypes and alleles frequencies in SDF-1 gene polymorphism at 801 G/A (rs1801157) between patients and controls

Genotype distribution in SDF-1 gene polymorphism at 801 G/A (rs1801157) in both patients and controls was observed to be in agreement with Hardy–Weinberg equilibrium (pv = 0.25 and pv= 1.28). The frequency of GG, GA and AA in 123 healthy control group was found to be 68 (55.3%), 50 (40.6%) and 5 (4.1%), respectively. Of 108 endometrial cancer patients, 67 (62%) emerged as GG genotypes, 35 (32.4%) with GA, and 6 (5.6%) with AA genotypes. However, statistical analysis revealed no significant differences in terms of genotypes between patients with endometrial cancer and healthy control group. Furthermore, the most frequent allele in both patient (169 (78.25%)) and control (186 (75.6%)) groups was G allele. However, no statistically significant difference was observed between the frequency of alleles between patient and control groups (P = 0.58). The data are illustrated in table 2.

Association between SDF-1 gene polymorphism at locus 801 G/A and demographic and pathological information of patients

Statistical analysis indicated no significant association between SDF-1 gene polymorphism at locus 801 and menopausal status (P = 0.70), tumor size (P = 0.62), degree of tumor differentiation (P = 0.74), Figo Stage (P = 0.35), tumor type (P = 0.22), and myometrial invasion (P = 0.22). The data are shown in table 3.

Discussion

This study demonstrated that genotypes and alleles frequencies of SDF-1 gene at +801 positions (rs1801157) did not differ between endometrial cancer patients and healthy controls. Furthermore, statistical analysis indicated no significant association between the 801 G/A locus of SDF-1 gene and menopausal status, tumor size, degree of tumor differentiation, Figo Stage, tumor type, and myometrial invasion. Therefore, based on our study, having certain genotypes and/or alleles of SDF-1 at +801 position may not increase the risk of endometrial cancer and/or disease progression.

According to earlier studies, polymorphism in genes of chemokines and/or chemokine

receptors may render genetic susceptibility and/or disease progression in different types of cancers, as we have previously observed in Iranian patients with thyroid cancer.[18] The 3′ untranslated region of mRNAs contains critical regulatory elements that can influence gene expression. Polymorphism in this area may affect the mRNA stability.[14] Accordingly, genetic variation in chemokine molecule of SDF-1 gene in the 3′ UTR may result in SDF-1 overexpression, which might be associated with the risk of cancer development in different types of solid tumors and hematological malignancies such as Lung cancer, Urologic cancer and Acute Myeloid Leukemia.[17, 19] Furthermore, the mRNA expression of SDF-1 was observed to be significantly higher in mucoepidermoid carcinoma of salivary gland tumors in comparison with benign subtypes.[20] The role of the CXCR4-CXCL12 (SDF-1) axis in the evolution of endometrial cancer has been established, and various studies have emphasized the role of SDF-1alpha in endometrial cancer proliferation and migration.[5] Despite such poor outcomes in endometrial cancer, the SDF1 801 gene polymorphism is thought to be a risk factor for cancer, more especially in Asian.[17] SDF-1 at protein level may also participate in cancer pathogenesis. Cancer-associated fibroblasts secrete SDF-1, which activates PI3K/Akt, MAPK/Erk, and matrix metalloproteinases-2 and 9 (MMP) signaling in endometrial cancer. SDF-1/CXCR4 overexpression has been linked to lymph node metastases, deep myometrial invasion, and a poor prognosis in endometrial cancer.[5, 21] Activation of the CXCL12-CXCR4 signaling axis may also promote Epithelial-Mesenchymal Transition (EMT) and cancer stem cell mobilization.[22] This inducer effect has been shown in a variety of cancers, including ovarian,[23] glioma,[24] and cervical cancer.[25] Increased level of CXCR4 on breast cancer cells also enhances metastasis to target tissues with high amounts of CXCL12 chemokine, such as the bone, lung, and lymph node. It may influence response to neoadjuvant chemotherapy and immunotherapy, and may affect survival rate.[26-29] In addition to tumor growth in solid tumors and hematological malignancies, SDF-1/CXCR4 expression has also been observed in normal physiological mechanism such as embryogenesis, wound healing, and proliferation.[13, 30, 31] However, we did not find a significant association between SDF-1 gene at +801 position and genetic susceptibility to endometrial cancer in a population from southern Iran. Similarly, several studies on the impact of the SDF1 801 G/A polymorphism have failed to find a significant association between possessing this genotype with cancer risk.[17] For example, no significant link between SDF-1 G/A polymorphism and increased cancer risk was found in Non-Small Cell Lung Carcinoma in the Chinese population.[32]Additionally, our previous study demonstrated that 801 G/A position was not associated with myasthenia gravis in Iran.[33] These differences might be due to a different sample size, different populations, differences in ethnicity and race and different inclusion and exclusion criteria. Moreover, the negative result of our study might arise from the relatively small sample size. In addition, investigations on only one single nucleotide polymorphism (SNP) may not be sufficient to detect the effect of SDF-1 G/A gene on cancer susceptibility to endometrial cancer. Study on a larger sample size as well as simultaneous exploration of different polymorphic areas of SDF-1 and other cytokines, chemokines, chemokine receptors and other immune related genes may help us disclose the exact role of genetic variations in the pathogenesis and/or genetic susceptibility to endometrial cancer.

As explained above, our study is a preliminary exploration dealing with SDF-1

gene and endometrial cancer. However, the investigation of only one SNP of SDF-1 gene and the relatively low sample size of the study participants are the main limitations of the present study.

Conclusions

Our study suggests that the SDF1 gene polymorphism at position 801 may not enhance the risk of endometrial cancer. However, because of the importance of SDF-1/CXCR4 in cancer development and metastasis, further research with a larger sample size, given different ethnicity and race groups, is required to understand the molecular behavior of the SDF-1 gene polymorphism in endometrial cancer.

Acknowledgments

This study was financially supported by a grant from Shiraz University of Medical Sciences (Grant No. 22509) and also a grant from Shiraz Institute for Cancer Research (No. ICR-100-503). This manuscript was derived from the MD thesis by Dr. Elham Izanloo at Shiraz University of Medical Sciences, Shiraz, Iran. We gratefully acknowledge the dedicated efforts of the investigators, coordinators, and volunteers who participated in this study. The authors would like to thank Dr. Nasrin Shokrpour for editorial assistance.

Funding

This study was conducted without external funding.

Authors' Contributions

F SN, M A, and MR H designed the study. E I collected the data; MR H and S Kh analyzed the data; E I and Z O interpreted the results; F S N, E I, M A, Mj F, and MR H conceived and designed the study. M A, FS N and MR H wrote the manuscript. All authors discussed the results and revised the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

None declared.

References

1. Katagiri R, Iwasaki M, Abe SK, Islam MR, Rahman MS, Saito E, et al. Reproductive factors and endometrial cancer risk among women. *JAMA Netw Open.* 2023;6(9):e2332296. doi: 10.1001/jamanetworkopen.2023.32296.
2. Mahdy H, Casey MJ, Crotzer D. Endometrial Cancer. 2022 Sep 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 30252237.
3. Constantine GD, Kessler G, Graham S, Goldstein SR. Increased incidence of endometrial cancer following the women's health initiative: An assessment of risk factors. *J Womens Health (Larchmt).* 2019;28(2):237-43. doi: 10.1089/jwh.2018.6956.
4. Cespedes Feliciano EM, Hohensee C, Rosko AE, Anderson GL, Paskett ED, Zaslavsky O, et al. Association of prediagnostic frailty, change in frailty status, and mortality after cancer diagnosis in the women's health initiative. *JAMA Netw Open.* 2020;3(9):e2016747. doi: 10.1001/jamanetworkopen.2020.16747.
5. Teng F, Tian WY, Wang YM, Zhang YF, Guo F, Zhao J, et al. Cancer-associated fibroblasts promote the progression of endometrial cancer via the SDF-1/CXCR4 axis. *J Hematol Oncol.* 2016;9:8. doi: 10.1186/s13045-015-0231-4.
6. Hogg JC, Timens W. The pathology of chronic obstructive pulmonary disease. *Annu Rev Pathol.* 2009;4:435-59. doi: 10.1146/annurev.pathol.4.110807.092145.
7. Restaino S, Paglietti C, Arcieri M, Biasioli A, Della Martina M, Mariuzzi L, et al. Management of patients diagnosed with

endometrial cancer: comparison of guidelines. *Cancers (Basel).* 2023;15(4):1091. doi: 10.3390/cancers15041091.
8. Naghibi AF, Daneshdoust D, Taha SR, Abedi S, Dehdezi PA, Zadeh MS, et al. Role of Cancer Stem Cell-Derived Extracellular Vesicles in Cancer Progression and Metastasis. *Pathol Res Pract.* 2023;247:154558. doi: 10.1016/j.prp.2023.154558.
9. Chen Y, Gou X, Kong DK, Wang X, Wang J, Chen Z, et al. EMMPRIN regulates tumor growth and metastasis by recruiting bone marrow-derived cells through paracrine signaling of SDF-1 and VEGF. *Oncotarget.* 2015;6(32):32575-85. doi: 10.18632/oncotarget.5331.
10. Feig C, Jones JO, Kraman M, Wells RJ, Deonarine A, Chan DS, et al. Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti–PD-L1 immunotherapy in pancreatic cancer. *Proc Natl Acad Sci U S A.* 2013;110(50):20212-7. doi: 10.1073/pnas.1320318110.
11. Lu L, Li J, Jiang X, Bai R. CXCR4/CXCL12 axis: "old" pathway as "novel" target for anti-inflammatory drug discovery. *Med Res Rev.* 2024;44(3):1189-220. doi: 10.1002/med.22011.
12. Cun Y, Diao B, Zhang Z, Wang G, Yu J, Ma L, et al. Role of the stromal cell derived factor-1 in the biological functions of endothelial progenitor cells and its underlying mechanisms. *Exp Ther Med.* 2021;21(1):39. doi: 10.3892/etm.2020.9471.
13. Sadri F, Rezaei Z, Fereidouni M. The significance of the SDF-1/CXCR4 signaling pathway in the normal development. *Med Res Rev.* 2024;44(3):1189-220. doi: 10.1002/med.22011.
14. Skeeles LE, Fleming JL, Mahler KL, Toland AE. The impact of 3'UTR variants on differential expression of candidate cancer susceptibility genes. *PLoS One.* 2013;8(3):e58609. doi: 10.1371/journal.pone.0058609.
15. Wei M, Rong C, Zhao J, Liu X, Yang F, Zeng J. Role of SDF-1 3'A polymorphism in HIV-1 disease progression: A systematic review and meta-analysis. *Gene.* 2018;677:182-8. doi: 10.1016/j.gene.2018.07.058.
16. Lima ÉRG, Queiroz MAF, Lima SS, Machado LFA, Cayres-Vallinoto IMV, Vallinoto ACR, et al. CCR5Δ32 and SDF1 3'A: Gene variants, expression and influence on biological markers for the clinical progression to AIDS among HIV-1 virus controllers in a mixed population of the Amazon region of Brazil. *Int J Mol Sci.* 2023;24(5):4958. doi: 10.3390/ijms24054958.
17. Tong X, Ma Y, Deng H, Wang X, Liu S, Yan Z, et al. The SDF-1 rs1801157 polymorphism is associated with cancer risk: An update pooled analysis and FPRP test of 17,876 participants. *Sci Rep.* 2016;6:27466. doi: 10.1038/srep27466.
18. Dabbaghmanesh MH, Rezaei B, Haghshenas MR, Montazeri-Najafabady N, Mohammadian Amiri R, Erfani N. CCR4 1014C/T and CCL22 16C/A genetic variations in Iranian patients with thyroid cancer. *Middle East J Cancer.* 2022;13(3):404-10. doi: 10.30476/mejc.2021.87469.1421.
19. Aladle DAAM, Ghannam MA, El-Ashwah S, Ghobrial FEI, Mortada MI. Association of SDF-1 gene polymorphism with increased risk of acute myeloid leukemia patients. *Asian Pac J Cancer Prev.* 2021;22(4):1035-43. doi: 10.31557/APJCP.2021.22.4.1035.
20. Haghshenas MR, Ashraf MJ, Khademi B, Ghaderi A, Erfani N, Razmkhah M. Chemokine and chemokine receptor patterns in patients with benign and malignant salivary gland tumors: a distinct role for CCR7. *Eur Cytokine*

Netw. 2017;28(1):27-35. doi: 10.1684/ecn.2017.0388.
21. Alsayed R, Khan AQ, Ahmad F, Ansari AW, Alam MA, Buddenkotte J, et al. Epigenetic regulation of CXCR4 signaling in cancer pathogenesis and progression. *Semin Cancer Biol*. 2022;86(Pt 2):697-708. doi: 10.1016/j.semcancer.2022.03.019.
22. Yang P, Hu Y, Zhou Q. The CXCL12-CXCR4 signaling axis plays a key role in cancer metastasis and is a potential target for developing novel therapeutics against metastatic cancer. *Curr Med Chem*. 2020;27(33):5543-61. doi: 10.2174/0929867326666191113113110.
23. Jaszczynska-Nowinka K, Rucinski M, Ziolkowska A, Markowska A, Malendowicz LK. Expression of *SDF-1* and *CXCR4* transcript variants and *CXCR7* in epithelial ovarian cancer. *Oncol Lett*. 2014;7(5):1618-24. doi: 10.3892/ol.2014.1897.
24. Chang S, Li S, Yang B, Yao K, Miao R, Liang G, et al. CXCL12 G801A polymorphism and susceptibility to glioma: a case–control study. *Genet Mol Res*. 2015;14(4):17399-405. doi: 10.4238/2015.December.21.9.
25. Roszak A, Misztal M, Sowińska A, Jagodziński PP. Stromal cell-derived factor-1 G801A polymorphism and the risk factors for cervical cancer. *Mol Med Rep*. 2015;11(6):4633-8. doi: 10.3892/mmr.2015.3315.
26. Okuyama Kishima M, de Oliveira CE, Banin-Hirata BK, Losi-Guembarovski R, Brajão de Oliveira K, Amarante MK, et al. Immunohistochemical expression of CXCR4 on breast cancer and its clinical significance. *Anal Cell Pathol (Amst)*. 2015;2015:891020. doi: 10.1155/2015/891020.
27. Wang RX, Ji P, Gong Y, Shao ZM, Chen S. SDF-1 expression and tumor-infiltrating lymphocytes identify clinical subtypes of triple-negative breast cancer with different responses to neoadjuvant chemotherapy and survival. *Front Immunol*. 2022:13:940635. doi: 10.3389/fimmu.2022.940635.
28. Zhou W, Guo S, Liu M, Burow ME, Wang G. Targeting CXCL12/CXCR4 Axis in Tumor Immunotherapy. *Curr Med Chem*. 2019;26(17):3026-41. doi: 10.2174/0929867324666170830111531.
29. Bouyssou JM, Ghobrial IM, Roccaro AM. Targeting SDF-1 in multiple myeloma tumor microenvironment. *Cancer Lett*. 2016;380(1):315-8. doi: 10.1016/j.canlet.2015.11.028.
30. Ladikou EE, Chevassut T, Pepper CJ, Pepper AG. Dissecting the role of the CXCL12/CXCR4 axis in acute myeloid leukaemia. *Cancer Lett*. 2016;380(1):315-8. doi: 10.1016/j.canlet.2015.11.028.
31. Tavernier E, Aanei C, Solly F, Flandrin-Gresta P, Campos L, Guyotat D. CXCR4: a new therapeutic target of the leukaemic cell? Role of the SDF-1/CXCR4 axis in acute myeloid leukaemia. *Bull Cancer*. 2014;101(6):593-604. doi: 10.1684/bdc.2014.1925.
32. Xu W, Cui R, Yu H. The association between SDF-1 G801A polymorphism and non-small cell lung cancer risk in a Chinese Han population. *Int J Clin Exp Med*. 2015;8(8):14065-9. eCollection 2015.
33. Yousefipour GA, Haghshenas MR, Yahyazadeh S, Erfani N. Stromal cell derived factor-1 genetic variation at locus 801 in patients with myasthenia gravis. *Iran J Immunol*. 2011;8(2):90-5. PMID: 21705836.

Table 1. Clinical and pathological characteristics of patients with endometrial cancer

Variables \ Group		Endometrial cancer (n=108)	Healthy control (n=123)	*P*-value
Age (year)		57.35 ± 11.15	57.00 ± 11.01	0.89
Menstrual age (year)		12.82 ± 1.52	12.78 ± 1.88	0.95
Menopausal age (year)		49.43 ± 8.56	48.38 ± 9.22	0.87
Menopausal status (%)	**Pre-menopause**	19(17.6)	24(19.5)	0.70
	Menopause	89(82.4)	99(80.5)	
Tumor size (%)	**<2cm**	31(28.7)	-	-
	≥2 cm	77(71.3)	-	
Degree of tumor differentiation (%)	**Well-differentiated**	57(52.8)	-	-
	Moderately-differentiated	27(25)	-	
	Poorly-differentiated	24(22.2)	-	
Figo Stage (%)	**Tumor confined to the corpus uteri**	63(58.3)	-	-
	Invasive cervical stromal tumor	27(25)	-	
	Local and / or regional spread of the tumor	18(16.7)	-	
Tumor type (%)	**Grade I, Ⅱ**	76(70.4)	-	-
	Grade Ⅲ, clear cell undifferentiated papillary serous	32(29.6)	-	
Myometrial invasion	**≥ 50%**	22(20.4)	-	-
	< 50%:	79(73.1)	-	
	Missing	7(6.5)	-	

FIGO: Fédération Internationale de Gynécologie et d'Obstétrique

Table 2. Genotypes and alleles distribution in SDF-1 gene polymorphism at locus 801 G/A in patients with endometrial cancer and the control group

SDF-1 polymorphism		Patients (n=108)	Controls (n=123)	*P*-value
Genotypes	**GG**	67(62)	68(55.3)	0.11
	GA	35(32.4)	50(40.6)	
	AA	6(5.6)	5(4.1)	
Alleles	**G**	169(78.25)	186(75.6)	0.58
	A	47(21.75)	60(24.4)	

P-value was measured by chi-square (X^2) test; SDF-1: stromal cell-derived factor1

Table 3. Association between the SDF-1 gene polymorphism at locus 801 G/A and clinical and pathological characteristics patients with endometrial cancer

Variables	Group	GG	GA	AA	*P*-value
Menopausal status (%)	**Premenopause**	12(63.2)	7(36.8)	0	0.70
	Menopause	55(61.8)	28 (31.5)	6 (6.7)	
Tumor size (%)	**<2cm**	21(67.7)	8 (25.8)	2 (6.5)	0.62
	≥2 cm	46(59.7)	27 (35.1)	4 (5.2)	
Degree of tumor differentiation (%)	**Well-differentiated**	38(66.7)	17 (29.8)	2 (3.5)	0.74
	Moderately-differentiated	16(59.3)	9 (33.3)	2 (7.4)	
	Poorly-differentiated	13(54.2)	9 (37.5)	2 (8.3)	
Figo Stage (%)	**Tumor confined to the corpus uteri**	43(68.3)	18 (28.5)	2 (3.2)	0.35
	Invasive cervical stromal tumor	14(51.9)	11 (40.7)	2 (7.4)	
	Local and / or regional spread of the tumor	10(55.6)	6 (33.3)	2 (11.1)	
Tumor type (%)	**Grade I, Ⅱ**	51(67.1)	21 (27.6)	4 (5.3)	0.22
	Grade Ⅲ, clear cell undifferentiated papillary serous	16(50)	14 (43.8)	2 (6.2)	
Myometrial invasion	**Up 50%**	10(45.5)	10 (45.5)	2 (9)	0.22
	Under 50%:	52(65.8)	23 (29.1)	4 (5.1)	

P-value was measured by chi-square (X^2) test; SDF-1: stromal cell-derived factor1; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique

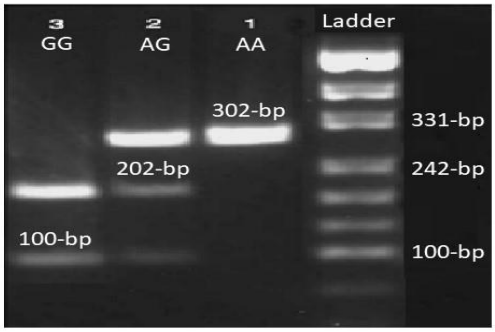

Figure 1. Results of RFLP for detection of SDF1 gene variation at locus 801. Lane1 is an undigested fragment (302bp) and presented as AA genotype. Lane 2 is included the fragments of 302, 202 and 100bp and is known as AG heterozygote genotype. Lane 3 is included digested fragments of 202 and 100bp and is emerged as GG genotype.

M: Molecular size marker; RFLP: Restriction fragment length polymorphism; SDF-1: stromal cell-derived factor1