

Stromal cell-derived factor-1 G801A polymorphism and the risk factors for cervical cancer

ANDRZEJ ROSZAK^{1,2}, MATTHEW MISZTAL³, ANNA SOWIŃSKA⁴ and PAWEŁ P. JAGODZIŃSKI³

¹Department of Radiotherapy and Gynecological Oncology, Greater Poland Cancer Center, Poznań 61-866;
Departments of ²Electroradiology, ³Biochemistry and Molecular Biology, and ⁴Computer Science and Statistics,
Poznań University of Medical Sciences, Poznań 60-781, Poland

Received March 21, 2014; Accepted January 2, 2015

DOI: 10.3892/mmr.2015.3315

Abstract. Although certain studies have demonstrated no association between the stromal cell-derived factor-1 (*SDF1*-3') G801A single nucleotide polymorphism (SNP) and cervical carcinoma, the interactions between the *SDF1*-3' G801A SNP and contraceptive use, menopausal status, parity and tobacco smoking remain to be fully elucidated. Using polymerase chain reaction-restriction fragment length polymorphism, the distribution of *SDF1*-3' G801A genotypes in patients with cervical cancer (n=462) against control groups (n=497) was investigated. Logistic regression analysis, adjusting for age, pregnancy, oral contraceptive use, tobacco smoking and menopausal status, did not identify the *SDF1*-3' G801A polymorphism as a genetic risk factor for cervical cancer. The adjusted odds ratio (OR) for patients with the A/G, vs. G/G genotype was 1.203, with a 95% confidence interval (CI) of 0.909-1.591 (P=0.196). The adjusted OR for the A/A, vs. G/G genotype was 1.296 (95% CI=0.930-1.807; P=0.125) and for the A/A or A/G, vs. G/G genotype was 1.262 (95% CI=0.964-1.653; P=0.090). The P-value of the χ^2 test of the trend observed for the *SDF1*-3' G801A polymorphism was at the borderline of being statistically significant ($p_{\text{trend}}=0.0484$). Stratified analyses between the distribution of the *SDF1*-3' G801A genotypes and cervical cancer risks demonstrated that this polymorphism may be a risk factor for patients with a positive history of tobacco smoking (1.778; 95% CI=1.078-2.934; P=0.0235). These findings suggested that the *SDF1*-3' G801A polymorphism may be a genetic risk factor for cervical cancer in patients with a positive history of tobacco smoking.

Introduction

Cervical tumors are the most common type of gynecological malignancy worldwide and constitute the tenth most frequent type of cancer occurring in females in developed countries (1,2). The number of young females affected by cervical cancer has been increasing (1-3). Cervical carcinogenesis encompasses the transformation of normal cervical epithelium to cervical intraepithelial neoplasia (CIN), which may develop into an invasive cervical tumor (4,5). There are several risk factors for cervical cancer, including human papillomavirus, impairment of the immune system, expression of tumor suppressor genes and gain of function mutations in proto-oncogenes (4,5). In addition, contraceptive use, tobacco consumption, age and environmental exposures are also considered possible causative factors in cervical carcinogenesis (6). C-X-C motif chemokine 12 is a chemokine, also termed stromal cell-derived factor-1 (SDF1), which binds to the CXCR4/CXCR7 receptors (7).

The human *SDF1* gene is expressed as α and β alternative splice variants (8). SDF1 is involved in lymphopoiesis and myelopoiesis and attracts lymphocytes, megakaryocytes, endothelial cells and stem cells (9-11). In addition, the interaction of SDF1 with CXCR4 controls the embryonic growth of vascular, cardiac, neuronal and craniofacial systems (12). However, the binding of SDF1 to CXCR4 contributes to the progression of cancer of the colon, pancreas, ovaries, prostate, lung, stomach, mouth, breast and skin, in addition to cervical cancer (13-21).

SDF1 is present in common genetic variants due to a G801A transition in the 3'-untranslated region (rs 1801157) (22). The possible role of the *SDF1*-3' A variant in the increased levels of transcription and protein has been reported (22). Certain studies have demonstrated no association between the *SDF1*-3' G801A single nucleotide polymorphism (SNP) and cervical carcinoma (23,24), however, the interaction between the *SDF1*-3' G801A SNP with other known risk factors of cervical cancer remain to be fully elucidated. In the present study, the *SDF1*-3' G801A genotype and allele frequencies were investigated in patients with cervical cancer (n=462) and healthy controls (n=497) in the Polish population, stratified based on contraceptive use, menopausal status, parity and history of tobacco smoking.

Correspondence to: Dr Paweł P. Jagodzinski, Department of Biochemistry and Molecular Biology, Poznań University of Medical Sciences, 6 Święcickiego, Poznań 60-781, Poland
E-mail: pjagodzi@am.poznan.pl

Key words: cervical carcinoma, stromal cell-derived factor-1, polymorphisms

Table I. Clinical and demographic characteristics of patients and controls.

Characteristic	Patient (n=462) n (%)	Control (n=497) n (%)
Mean age (years) \pm SD ^a	52.4 \pm 9.4	51.9 \pm 11.2
Tumor stage		
IA	63 (13.6)	
IB	62 (13.4)	
IIA	56 (12.1)	
IIB	57 (12.3)	
IIIA	146 (31.6)	
IIIB	55 (11.9)	
IVA	11 (2.4)	
IVB	12 (2.6)	
Histological grade		
G1	89 (19.3)	
G2	147 (31.8)	
G3	101 (21.9)	
Gx	125 (27.0)	
Histological type		
Squamous cell carcinoma	383 (82.9)	
Adenocarcinoma	62 (13.4)	
Other	17 (3.7)	
Pregnancy		
Never	55 (11.9)	59 (11.9)
Ever	407 (88.1)	438 (88.1)
Oral contraceptive pill use		
Never	250 (54.1)	281 (56.5)
Ever	212 (45.9)	216 (43.5)
Tobacco smoking		
Never	298 (64.5)	328 (66.0)
Ever	164 (35.5)	169 (34.0)
Menopausal status		
Premenopausal	165 (35.7)	195 (39.2)
Postmenopausal	297 (64.3)	302 (60.8)
HPV genotype		
16 and 18	315 (68.2)	
16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68	362 (78.3)	

^aAge at first diagnosis. HPV, human papillomavirus; SD, standard deviation.

Patients and methods

Patients and controls. The patients consisted of 462 females with histologically-determined cervical carcinoma, according to the International Federation of Gynecology and Obstetrics. All the females were enrolled between April 2007 and January 2014 at the Department of Radiotherapy, Greater Poland Cancer Center (Poznań, Poland; Table I). The controls included 497 unrelated healthy female volunteers, who were matched by age to the patients (Table I). Data regarding pregnancy, oral contraceptive use, tobacco smoking and menopausal status were obtained during clinical interviews. All individuals were

Caucasian and were enrolled from the Wielkopolska (Greater Poland) area of Poland. The patients and controls provided written informed consent and the study was approved by the Local Ethical Committee of Poznań University of Medical Sciences (Poznań, Poland).

Genotyping. DNA was isolated from peripheral blood leucocytes using a salting-out procedure, in which 10 ml peripheral blood were obtained using BD Vacutainer® (Becton Dickinson, Franklin Lakes, NJ USA). The presence of the *SDF1*-3' G801A (rs 1801157) transition was determined by polymerase chain reaction (PCR) using Dream Taq DNA Polymerase (Thermo Scientific,

Table II. Association between the stromal cell-derived factor-1-3' 'G801A (rs 1801157) polymorphism and cervical cancer.

Genotype	Patient (frequency)	Control (frequency)	Odds ratio (95% CI)	P-value ^a	Adjusted odds ratio (95% CI) ^b	P-value ^a	P _{trend}
G/G	289 (0.63)	337 (0.68)	Referent	-	Referent		
A/G	149 (0.32)	144 (0.29)	1.207 (0.914-1.593)	0.1849	1.203 (0.909-1.591)	0.196	0.0484
A/A	24 (0.05)	16 (0.03)	1.749 (0.911-3.57)	0.0892	1.296 (0.930-1.807)	0.125	
A/G+A/A	173 (0.37)	160 (0.32)	1.261 (0.966-1.646)	0.0878	1.262 (0.964-1.653)	0.090	
Minor allele frequency	0.21	0.18					

^a χ^2 analysis. ^bOdds ratios were adjusted by age, pregnancy, oral contraceptive use, tobacco smoking and menopausal status. Significant results are highlighted in bold font. CI, confidence interval.

Vilnius, Lithuania) and a PTC-200 DNA Engine Thermocycler (MJ Research Inc, St. Bruno, QC, Canada). The primer sequence was as follows, 5'-TTATTGTACTTGCCCTATTAGAG-3' and 5'-GTAGTTCACCCCAAAGGACC-3'. The PCR was followed by digestion with *MspI* (C/CGG; Thermo Scientific) according to manufacturer's instructions. The *SDF1*-3' A allele remained uncut at 732 bp, whereas the *SDF1*-3' G allele was cleaved into 456 bp and 276 bp fragments. The DNA fragments were separated by electrophoresis on a 3% agarose gel and visualized with ethidium bromide staining (Sigma-Aldrich, Poznań, Poland). The presence of the *SDF1*-3' G801A transition was also confirmed by Sanger sequencing of 15% of the samples, which were randomly selected.

Statistical analysis. The distinction in genotypic and allelic prevalence between patients and controls, and their genotypic deviation from the Hardy-Weinberg (HW) equilibrium was evaluated using a χ^2 test. The polymorphism was assessed for association with cervical cancer incidence using a χ^2 test for trend (p_{trend}), odds ratio (OR) and 95% confidence intervals (CI). Unconditional logistic regression analysis was used to adjust for the effect of confounders, including age, pregnancy, oral contraceptive use, tobacco smoking and menopausal status. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Distribution of the *SDF1*-3' G801A polymorphism in females with cervical cancer. The prevalence of the *SDF1*-3' G801A genotypes did not exhibit a significant divergence from the HW equilibrium between the cases and controls. The distribution and adjusted analysis of the *SDF1*-3' G801A genotypes in females with cervical cancer are presented in Table II.

The frequency of the *SDF1*-3' A/A genotype was ~1.7-fold higher in patients compared with controls. The *SDF1*-3' A/G heterozygous genotype frequency was higher in patients with cervical cancer compared with controls, at 0.32 and 0.29, respectively. The *SDF1*-3' minor allele frequency was also higher in patients compared with controls, and was 0.21 and 0.18, respectively. The P-value of the χ^2 test of the trend observed for the *SDF1*-3' G801A polymorphism was at the borderline of being statistically significant ($p_{\text{trend}} = 0.0484$). Logistic regression analysis did not demonstrate that

the *SDF1*-3' G801A polymorphism was a risk factor for cervical cancer. The adjusted OR for patients with the A/G, vs. G/G genotype was 1.203 (95% CI=0.909-1.591; $P = 0.196$), the adjusted OR for A/A, vs. G/G was 1.296 (95% CI=0.930-1.807; $P = 0.125$) and for A/A or A/G, vs. G/G was 1.262 (95% CI=0.964-1.653; $P = 0.090$).

Stratified analysis between the *SDF1*-3' G801A genotypes and cervical cancer risks. The age adjusted analysis of the *SDF1*-3' G801A genotypes and cervical cancer risk, stratified by pregnancy, oral contraceptive use, tobacco smoking, and menopausal status is presented in Table III. An increase in cervical cancer risk was observed only among patients with a positive history of tobacco smoking for the adjusted OR with the A/A, vs. G/G genotype at 1.778 (95% CI=1.078-2.934; $P = 0.0235$). However, no significant association was observed between *SDF1*-3' G801A and smoking for the A/G, vs. GG (1.180; 95% CI=0.731-1.905; $P = 0.4975$) or A/A or A/G, vs. A/A genotype (1.352; 95% CI=0.862-2.122; $P = 0.1877$). Furthermore, no significant association was observed between *SDF1*-3' G801A and pregnancy, oral contraceptive use or menopausal status (Table III). No association was observed between the *SDF1*-3' G801A polymorphism and tumor stage, histological grade or type of tumor (data not shown) on stratification of the patients based on clinical characteristics.

Discussion

The *SDF1*-3' A gene variant has been suggested as a factor that upregulates SDF1 α levels, and the SDF1/CXCR4/CXCR7 axis is considered to contribute significantly to the biology and metastasis of several types of cancer (22,25). In addition, the SDF1-CXCR4 interaction has been demonstrated to be important in the progression of cervical cancer (26-30). Wei *et al* (26) suggested that the progression of cervical tumors is accompanied with an increased production of SDF1 α . In addition to these findings, Huang *et al* (27) demonstrated an increase in the co-expression levels of SDF1/CXCR4 in CIN and cervical carcinoma as a durative process in cervical cancerogenesis. The SDF1-CXCR4 axis initiates invasiveness via changes to the adhesion and secretion of matrix metalloproteinase-2. (OMIM *120360) and promotes the metastasis of tumor cells

Table III. Stratified analyses between the distribution of stromal cell-derived factor-1-3' *G801A* genotypes and cervical cancer risks: Pregnancy, oral contraceptive use, tobacco smoking and menopausal status.

Risk factor	Patient (n)			Control (n)			Adjusted odds ratio (95% CI) ^b	P-value ^d
	G/G	G/A	A/A	G/G	G/A	A/A		
Pregnancy								
Ever	255	132	20	297	127	14	1.200 (0.892-1.615) ^a 1.255 (0.879-1.790) ^b 1.245 (0.936-1.656) ^c	0.228 0.210 0.132
Never	34	17	4	40	17	2	1.635 (0.662-4.038) ^a 1.801 (0.694-4.677) ^b 1.898 (0.798-4.510) ^c	0.281 0.220 0.143
Oral contraceptive use								
Ever	131	69	12	146	63	7	1.210 (0.797-1.839) ^a 1.492 (0.907-2.453) ^b 1.293 (0.865-1.932) ^c	0.370 0.113 0.208
Never	158	80	12	191	81	9	1.083 (0.737-1.594) ^a 1.127 (0.713-1.783) ^b 1.117 (0.771-1.621) ^c	0.682 0.608 0.557
Smoking								
Ever	99	51	14	113	49	7	1.180 (0.731-1.905) ^a 1.778 (1.078-2.934) ^b 1.352 (0.862-2.122) ^c	0.498 0.025 0.189
Never	190	98	10	224	95	9	1.165 (0.822-1.653) ^a 1.139 (0.715-1.814) ^b 1.195 (0.853-1.674) ^c	0.390 0.582 0.300
Menopausal status								
Premenopausal	105	55	5	132	56	7	1.331 (0.839-2.111) ^a 1.003 (0.475 -2.119) ^b 1.322 (0.844-2.070) ^c	0.223 0.994 0.221
Postmenopausal	184	94	19	205	88	9	1.159 (0.812 -1.653) ^a 1.490 (0.986 -2.252) ^b 1.261 (0.898-1.770) ^c	0.415 0.058 0.181

^a(G/A vs. G/G); ^b(A/A vs. G/G); ^c(A/A and A/G vs. G/G), ^d χ^2 analysis. All P-values were adjusted by age. Significant results are highlighted in bold.

toward lymph nodes and the pelvic cavity in patients with cervical cancer (29,30). SDF1 α also provokes significant signal transduction events, including chemotaxis and rescue from apoptosis in cervical cancer cells (21,30). In addition to these findings Majka *et al* (21) demonstrated that SDF1 α augments cervical cancer cell scattering and supported the nuclear localization of the β -catenin gene and also increased its target gene expression, cyclin D1. In addition, it was observed that SDF1 α interacts with CXCR4 and leads to the activation of numerous downstream cytoplasmic signaling pathways, which support the invasiveness of cervical cancer (21).

Genetic variants of *SDF1* may have an impact on cervical cancer development and its clinicopathological variables. In the present study, the *SDF1*-3' G801A SNP was not identified as a risk factor for cervical cancer. The present observations are in agreement with those by Maley *et al* (23) and Tee *et al* (24), which also observed no association between the *SDF1*-3' G801A polymorphism and risk of cervical cancer. However, in

the present study, the P-value assessment of the trend observed for the *SDF1*-3' G801A polymorphism was on the borderline of statistical significance. In addition, the present study revealed that the *SDF1*-3' A/A genotype may be a risk for cervical cancer in females with a positive history of tobacco smoking. This is consistent with previous reports suggesting the possible causative role of tobacco consumption in cervical carcinogenesis (6,31,32). However, no other confounding variables, including contraceptive use, menopausal status or parity affected the *SDF1*-3' G801A polymorphism as a risk factor for cervical cancer.

The *SDF1*-3' G801A polymorphism has been reported as a risk factor in the development of breast, laryngeal, oral, lung, prostate and hepatocellular carcinoma, as well as lymphoma (33-39). The effect of the *SDF1*-3' G801A SNP on SDF1 α biosynthesis has been based mainly on the analysis of subjects infected with human immunodeficiency (HIV) (22). The *SDF1*-3' A variant has been suggested as a genetic variant,

which increases the production of SDF1 α (22). These findings were consistent with a study by Chang *et al* (40) who observed that fibroblasts from patients with colon cancer and the *SDF1-3'* GA or AA genotypes biosynthesized three times more SDF1 α transcript compared with fibroblasts with the GG genotype. In addition, Garcia-Moruja *et al* (41) demonstrated that the *SDF1-3'* A transcript variant exhibited a two-fold longer half-life than the *SDF1-3'* G transcript variant. By contrast, a study by Kimura *et al* (42), using Epstein-Barr virus-transformed lymphoblastoid cell lines, did not observe any effects of the *SDF1-3'* G801A SNP on the SDF1 α mRNA levels. In addition to these findings, Watanabe *et al* (43), using the syncytium model, also observed no correlation between the *SDF1-3'* G801A SNP gene variant and syncytium-inducing HIV (43).

In conclusion, the present genetic study is the first, to the best of our knowledge, to demonstrate that the *SDF1-3'* A gene variant may be a risk factor for cervical carcinoma in patients with a positive history of tobacco smoking; therefore this evaluation should be replicated in other independent ethnicities.

Acknowledgements

The present study was supported by Poznań University of Medical Sciences (grant no. 502-01-01124182-07474). The technical assistance of Ms. Alicja Pinczewska is gratefully acknowledged.

References

- Parkin DM, Bray F, Ferlay J and Pisani P: Global cancer statistics 2002. *CA Cancer J Clinicians* 55: 74-108, 2005.
- Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D: Global cancer statistics. *CA. Cancer J Clin* 61: 69-90, 2011.
- Kokawa K, Takekida S, Kamiura S, Kita M, Enomoto T, Kawaguchi R, Saito J, Horie A and Umesaki N: The incidence, treatment and prognosis of cervical carcinoma in young women: a retrospective analysis of 4,975 cases in Japan. *Eur J Gynaecol Oncol* 31: 37-43, 2010.
- Georgieva S, Iordanov V and Sergieva S: Nature of cervical cancer and other HPV-associated cancers. *J BUON* 14: 391-398, 2009.
- Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ and Muñoz N: Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 189: 12-19, 1999.
- Castellsague X and Munoz N: Chapter 3: Cofactors in human papillomavirus carcinogenesis-role of parity, oral contraceptives and tobacco smoking. *J Natl Cancer Inst Monogr* 20-28, 2003.
- Bleul CC, Fuhlbrigge RC, Casasnovas JM, Aiuti A and Springer TA: A highly efficacious lymphocyte chemoattractant, stromal cell-derived factor 1 (SDF-1). *J Exp Med* 184: 1101-1109, 1996.
- Shirozu M, Nakano T, Inazawa J, Tashiro K, Tada H, Shinohara T and Honjo T: Structure and chromosomal localization of the human stromal cell-derived factor 1 (SDF1) gene. *Genomics* 28: 495-500, 1995.
- Broxmeyer HE: Chemokines in hematopoiesis. *Curr Opin Hematol* 15: 49-58, 2008.
- Zou YR, Kottmann AH, Kuroda M, Taniuchi I and Littman DR: Function of the chemokine receptor CXCR4 in hematopoiesis and in cerebellar development. *Nature* 393: 595-599, 1998.
- Onai N, Zhang Y, Yoneyama H, Kitamura T, Ishikawa S and Matsushima K: Impairment of lymphopoiesis and myelopoiesis in mice reconstituted with bone marrow-hematopoietic progenitor cells expressing SDF-1-intrakinase. *Blood* 96: 2074-2080, 2008.
- McGrath KE, Koniski AD, Maltby KM, McGann JK and Palis J: Embryonic expression and function of the chemokine SDF-1 and its receptor, CXCR4. *Dev Biol* 213: 442-456, 1999.
- Kim J, Mori T, Chen SL, Amersi FF, Martinez SR, Kuo C, Turner RR, Ye X, Bilchik AJ, Morton DL and Hoon DS: Chemokine receptor CXCR4 expression in patients with melanoma and colorectal cancer liver metastases and the association with disease outcome. *Ann Surg* 244: 113-120, 2006.
- Maréchal R, Demetter P, Nagy N, Berton A, Decaestecker C, Polus M, Closset J, Devière J, Salmon I and Van Laethem J-L: High expression of CXCR4 may predict poor survival in resected pancreatic adenocarcinoma. *Br J Cancer* 100: 1444-1451, 2009.
- Kajiyama H, Shibata K, Terauchi M, Ino K, Nawa A and Kikkawa F: Involvement of SDF-1 α /CXCR4 axis in the enhanced peritoneal metastasis of epithelial ovarian carcinoma. *Int J Cancer* 122: 91-99, 2008.
- Akashi T, Koizumi K, Tsuneyama K, Saiki I, Takano Y and Fuse H: Chemokine receptor CXCR4 expression and prognosis in patients with metastatic prostate cancer. *Cancer Sci* 99: 539-542, 2008.
- Kijima T, Maulik G, Ma PC, Tibaldi EV, Turner RE, Rollins B, Sattler M, Johnson BE and Salgia R: Regulation of cellular proliferation, cytoskeletal function and signal transduction through CXCR4 and c-Kit in small cell lung cancer cells. *Cancer Res* 62: 6304-6311, 2002.
- Lee HJ, Kim SW, Kim HY, Li S, Yun HJ, Song KS, Kim S and Jo DY: Chemokine receptor CXCR4 expression, function and clinical implications in gastric cancer. *Int J Oncol* 34: 473-480, 2009.
- Oliveira-Neto HH, Silva ET, Leles CR, Mendonça EF, Alencar Rde C, Silva TA and Batista AC: Involvement of CXCL12 and CXCR4 in lymph node metastases and development of oral squamous cell carcinomas. *Tumour Biol* 29: 262-271, 2008.
- Yasuoka H, Tsujimoto M, Yoshidome K, Nakahara M, Kodama R, Sanke T and Nakamura Y: Cytoplasmic CXCR4 expression in breast cancer: induction by nitric oxide and correlation with lymph node metastasis and poor prognosis. *BMC Cancer* 8: 340, 2008.
- Majka M, Drukala J, Lesko E, Wysoczynski M, Jensen AB and Ratajczak MZ: SDF-1 alone and in co-operation with HGF regulates biology of human cervical carcinoma cells. *Folia Histochem Cytobiol* 44: 155-164, 2006.
- Winkler C, Modi W, Smith MW, Nelson GW, Wu X, Carrington M, Dean M, Honjo T, Tashiro K, Yabe D, Buchbinder S, Vittinghoff E, Goedert JJ, O'Brien TR, Jacobson LP, Detels R, Donfield S, Willoughby A, Gomperts E, Vlahov D, Phair J and O'Brien SJ: Genetic restriction of AIDS pathogenesis by an SDF-1 chemokine gene variant. *Science* 279: 389-393, 1998.
- Maley SN, Schwartz SM, Johnson LG, Malkki M, Du Q, Daling JR, Li SS, Zhao LP, Petersdorf EW and Madeleine MM: Genetic variation in CXCL12 and risk of cervical carcinoma: a population-based case-control study. *Int J Immunogenet* 36: 367-375, 2009.
- Tee YT, Yang SF, Wang PH, Tsai HT, Lin LY, Lee SK, Liao CL, Chang JT and Shih YT: G801A polymorphism of human stromal cell-derived factor 1 gene raises no susceptibility to neoplastic lesions of uterine cervix. *Int J Gynecol Cancer* 22: 1297-1302, 2012.
- Sun X, Cheng G, Hao M, Zheng J, Zhou X, Zhang J, Taichman RS, Pienta KJ and Wang J: CXCL12/CXCR4/CXCR7 chemokine axis and cancer progression. *Cancer Metastasis Rev* 29: 709-722, 2010.
- Wei M, Liang LZ, Zhang CQ, Xiong Y, Zhang Y, Shen Y and Li JQ: Correlation of CXCR4/CXCL12 overexpression to lymph node metastasis and chronic inflammation in cervical adenocarcinoma. *Ai Zheng* 26: 298-302, 2007.
- Huang Y, Zhang J, Cui ZM, Zhao J and Zheng Y: Expression of the CXCL12/CXCR4 and CXCL16/CXCR6 axes in cervical intraepithelial neoplasia and cervical cancer. *Chin J Cancer* 32: 289-296, 2013.
- Shen XY, Wang SH, Liang ML, Wang HB, Xiao L and Wang ZH: The role and mechanism of CXCR4 and its ligand SDF-1 in the development of cervical cancer metastasis. *Ai Zheng* 27: 1044-1049, 2008.
- Zhang JP, Lu WG, Ye F, Chen HZ, Zhou CY and Xie X: Study on CXCR4/SDF-1 α axis in lymph node metastasis of cervical squamous cell carcinoma. *Int J Gynecol Cancer* 17: 478-483, 2007.
- Yang YC, Lee ZY, Wu CC, Chen TC, Chang CL and Chen CP: CXCR4 expression is associated with pelvic lymph node metastasis in cervical adenocarcinoma. *Int J Gynecol Cancer* 17: 676-686, 2007.

31. Magnusson PK, Lichtenstein P and Gyllenstein UB: Heritability of cervical tumours. *Int J Cancer* 88: 698-701, 2000.
32. Moreno V, Bosch FX, Muñoz N, Meijer CJ, Shah KV, Walboomers JM, Herrero R and Franceschi S: International agency for research on cancer. Multicentric cervical cancer study group: Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. *Lancet* 359: 1085-1092, 2002.
33. de Oliveira KB, Oda JM, Voltarelli JC, Nasser TF, Ono MA, Fujita TC, Matsuo T and Watanabe MA: CXCL12 rs1801157 polymorphism in patients with breast cancer, Hodgkin's lymphoma and non-Hodgkin's lymphoma. *J Clin Lab Anal* 23: 387-393, 2009.
34. Razmkhah M, Doroudchi M, Ghayumi SM, Erfani N and Ghaderi A: Stromal cell-derived factor-1 (SDF-1) gene and susceptibility of Iranian patients with lung cancer. *Lung Cancer* 49: 311-315, 2005.
35. Chang CC, Chen SC, Hsieh YH, Chen YC, Chen TY, Chu YH, Ma HJ, Chou MC, Tsai HT and Yang SF: Stromal cell-derived factor-1 but not its receptor, CXCR4, gene variants increase susceptibility and pathological development of hepatocellular carcinoma. *Clin Chem Lab Med* 47: 412-418, 2009.
36. Vairaktaris E, Vylliotis A, Spyridonodou S, Derka S, Vassiliou S, Nkenke E, Yapijakis C, Serefoglou Z, Neukam FW and Patsouris E: A DNA polymorphism of stromal-derived factor-1 is associated with advanced stages of oral cancer. *Anticancer Res* 28: 271-275, 2008.
37. Hirata H, Hinoda Y, Kikuno N, Kawamoto K, Dahiya AV, Suehiro Y, Tanaka Y and Dahiya R: CXCL12 G801A polymorphism is a risk factor for sporadic prostate cancer susceptibility. *Clin Cancer Res* 13: 5056-5062, 2007.
38. Zafiroopoulos A, Crikas N, Passam AM and Spandidos DA: Significant involvement of CCR2-64I and CXCL12-3a in the development of sporadic breast cancer. *J Med Genet* 41: e59, 2004.
39. Kruszyna L, Lianeri M, Rydzanicz M, Szyfter K and Jagodziński PP: SDF1-3'A gene polymorphism is associated with laryngeal cancer. *Pathol Oncol Res* 16: 223-227, 2010.
40. Chang SC, Lin PC, Yang SH, Wang HS, Li AF and Lin JK: SDF-1alpha G801A polymorphism predicts lymph node metastasis in stage T3 colorectal cancer. *Ann Surg Oncol* 16: 2323-2330, 2009.
41. Garcia-Morujá C, Rueda P, Torres C, Alcamí J, Luque F and Caruz A: Molecular phenotype of CXCL12beta 3'UTR G801A polymorphism (rs1801157) associated to HIV-1 disease progression. *Curr HIV Res* 7: 384-389, 2009.
42. Kimura R, Nishioka T and Ishida T: The SDF1-G801A polymorphism is not associated with SDF1 gene expression in Epstein-Barr virus-transformed lymphoblastoid cells. *Genes Immun* 4: 356-361, 2003.
43. Watanabe MA, de Oliveira Cavassin GG, Orellana MD, Milanezi CM, Voltarelli JC, Kashima S and Covas DT: SDF-1 gene polymorphisms and syncytia induction in Brazilian HIV-1 infected individuals. *Microb Pathog* 35: 31-34, 2003.