Expression of AMHR2 and C-KIT in cervical lesions in Uyghur Women of Xinjiang, China

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Abstract

Background: Cervical cancer is one of the most common malignant tumors in women. Anti-Müllerian hormone receptor 2 (AMHR2) and C-Kit were two members of protein kinase which were reported increased in some cancers like ovarian carcinoma and breast cancer. The present study aimed to assess the expression of AMHR2 and C-Kit in cervical cancer of different differentiated degrees as well as in cervicitis sections.

Methods: All the lesions were collected randomly during clinical observations in hospitals located in Xinjiang, China. Polymerase chain reaction (PCR) and immunohistochemical staining were used to detect AMHR2 and c-Kit expression in cervical samples from women who had been infected with human papilloma virus (HPV16). The expression rate was compared between cervical cancer of well, moderately and poorly differentiated and cervicitis.

Results: The average age of the patients was 45 years; ranged from 23 to 80. For AMHR2, all 17 cervicitis samples ranged from (+) to (+++), while cervical cancer showed 11 (+), 9 (++), 15 (+++), 9 (++++), and 8 (++++), which showed AMHR2 expression was lessen with the poorer of differentiation degree of cervical cancer (P < .05). For c-Kit, 18 cervicitis samples mainly expressed as (−) with none showed (+++) or (+++), while cervical cancer samples showed 7 (−), 6 (+), 1 (++), 2 (+++), and 8 (++++), which indicated c-Kit’s expression increased with the reduction of cervical cancer’s differentiation degree (P < .05).

Conclusion: AMHR2 might have some correlation with self defense of our body, while c-Kit might link with the potential invasive capacity of cervical cancer.

Abbreviations: AMH = anti-Müllerian hormone, CC = cumulus cells, EOCs = epithelial ovarian carcinomas, GC = granulose cells, GIST = gastrointestinal stromal tumor, GISTs = gastrointestinal stromal tumors, HPV = human papilloma virus, PCR = polymerase chain reaction, PTs = phyllodes tumors, SCG = squamous cell carcinoma, SCF = stem cell factor, SCLC = small-cell lung cancer, TGF-β = transforming growth factor-beta.

Keywords: AMHR2, biomarkers, cervical cancer, c-Kit, HPV16

1. Introduction

Cervical cancer is one of the most common malignant tumors that bring an ominous threat to women’s health around the world.[1] In Xinjiang (China), Uyghur women are one of the highest risk groups of cervical cancer, whose morbidity and mortality are much higher than that of other ethnic groups in the same region.[2] Moreover, cervical cancer tends to develop in younger ages recent years.[11] The essential pathogenic factor in cervical cancer is the infection of human papilloma virus (HPV), especially the high-risk type — HPV16.[1] Other risk factors include early age at first sexual intercourse, multiple sexual partners, and cigarette smoking.[11]

The successful treatment of some tumours with Kit-based inhibitors such as advanced gastrointestinal stromal tumors with imatinib mesylate and acute myeloid leukemia with dasatinib, has raised the expectation that whether other tumours could also be treated similarly.[15,6] Protein kinases are enzymes related to many important roles in cells, such as apoptosis, cell cycle progression, et al.[7] Many studies have proved that enzyme mutations or abnormal expressions could lead to cancers. Also as 2 members of protein kinase, anti-Müllerian hormone receptor 2 (AMHR2) and C-kit were reported have some links with cervical cancer’s occurrence and development.

Anti-Müllerian hormone (AMH) is a dimeric glycoprotein and a member of the transforming growth factor-beta (TGF-β) superfamily.[7] It is produced by Sertoli cells directing regression of the paired Mullerian ducts. It is also produced by granulosa cells of the early developing follicles in the ovary affecting two major regulatory steps of folliculogenesis—the inhibition of primordial follicle recruitment and the modification of the FSH sensitivity of small antral follicles.[3,8] AMH expresses its biological effects mostly through AMHR2, phosphorylates and activates a TGF-β type I receptor and process the intracellular transduction.[9] However, it is reported that AMH was synthesized and expressed at higher levels in cumulus cells (CC) as compared with granulose cells (GC) in human large antral and pre-ovulatory follicles.[10] AMHR2 is a...
differentiation protein expressed in 90% primary epithelial ovarian carcinomas,[11] indicating it might have some roles in female reproductive system. In SEONG JIN HWANG team's study, AMH inhibited growth of cervical cancer cells through cellular apoptosis. In this way, targeted therapy may be feasible in AMHR-expressing cervical tumors in the future.[12]

C-Kit belongs to the type-III receptor tyrosine kinase family.[13] It is a 145 kD transmembrane glycoprotein that appears in embryonic and fetal stage in humans.[14] C-Kit and its ligand stem cell factor (SCF) exerts multiple biological effects that leading to the regulation of apoptosis, cell differentiation, proliferation, chemotaxis, and cell adhesion.[15] In a variety of tissues ranging from embryonic cells to germ cells and epithelial cells, C-Kit expression had been found before. It is also expressed in primitive germ cells during embryonic development and in the placental tissue during pregnancy, as well as in astrocytes, melanocytes, and CD34-cells in bone marrow.[15,16]

Moreover, it reported to appear in several kinds of cancers, like small-cell lung cancer (SCLC), gastrointestinal stromal tumor (GIST), ovarian and endometrial cancer, breast cancer, prostate cancer,[9,17,18] and was thought to promote tumor development. The receptor tyrosine kinases like EGFR and HER2 became more attractive and promising rational targets for cancer therapy,[13] but the therapeutic importance of c-Kit is not completely clear. Han's team found strong and diffuse c-Kit immunoreactivity in the tumour nests of uterine cervix's squamous cell carcinoma (SCC), but negative immunoreactivity in the overlying epithelial layer which limited the use of imatinib in SCC patients.[15] And this may help doctors choose applicable treatments for different types of cervical cancer patients.

The present study aimed at evaluating the expression rate of AMHR2 and c-Kit in cervical samples from women who had been infected with HPV16 through Polymerase chain reaction (PCR) and immunohistochemical staining. We also evaluated whether they could serve as biomarkers for screening early stage of cervical cancer along with other indexes, and giving us ideas about new treatment options for cervical cancer.

2. Material and methods

2.1. Specimen collection and ethics approval

Tissue specimens were collected from a total number of 70 patients (average age: 45 years, range: 23–80 years), of whom 52 were cervical cancer patients (9 was poorly differentiation, 32 was moderately differentiation and 11 was well differentiation) and 18 were cervicitis patients which was set as the age-matched control group. All the samples were collected during clinical observations between 2002 and 2007 in the First Affiliated Hospital of Xinjiang Medical University (Urumqi, Xinjiang, China) and the First People’s Hospital of Kashgar District (Kashgar, Xinjiang, China), which were collected upon obtaining signed consent forms. Patients aged >18 years, whose cervical cancer type was squamous cell carcinoma and was infected with HPV16, and also had not treated with preoperative radiotherapy or chemotherapy prior on the time of sample collection were eligible. Exclusion criteria included previous cancer history, pregnancy, cervical surgery history, and severe liver or kidney disease. According to the eligibility and exclusion criteria, 52 patients were involved from 73 cervical cancer patients. The tissues were formalin fixed and paraffin embedded, and the diagnosis was histologically confirmed by experienced pathologists from the Xinjiang Medical University.

The most common type of HPV to infect Uyghur women is HPV16, and all of the tissues were proved to be positive for it through polymerase chain reaction (PCR) as shown in Figure 1.

All the clinical materials used in this study were approved by the Medical Ethics Committee of Xinjiang Medical University (20160828-01).

2.2. Reagents

The rabbit polyclonal antibodies used in this study were anti-AMHR2 antibody [MIG7] (ab64762, abcam, Shanghai, China) and anti-c-Kit antibody (ab115801, abcam, Shanghai, China). Other major chemicals and Kits were: TaKaRa Ex Taq Polymerase (DRR001A, TaKaRa Biotechnology [Dalian] Co. Ltd, Dalian, China), agarose gel (A600014-0050, Sangon Biotech, Shanghai, China), QIAamp DNA Mini Kit (Qiagen, Hilden, Germany), Permount Mounting Medium (Thermo Fisher Scientific, Waltham, MA), DNTP mix (Life Technologies, Beijing, PR China), citrate-buffered solution (MVS-0066, MAIXIN Bio, Fuzhou, China), the endogenous peroxidases (SP KIT-A2, MAIXIN Bio, Fuzhou, China), phosphate-buffered saline (PBS-0060, MAIXIN Bio, Fuzhou, China), biotinylated goat anti-rabbit antibody (KIT-5004, MAIXIN Bio, Fuzhou, China), DAB (diaminobenzidine) Horseradish Peroxidase Color Development Kit (DAB-0031, MAIXIN Bio, Fuzhou, China), etc.

2.3. PCR

We cut small pieces of tissue samples from the paraffin-embedded sections. Then we used the QIAamp DNA Mini Kit to isolate the DNA from the tissue samples according to the manufacturer’s instructions. The quantity of the DNA samples through optical density was at 260 nm. The quality of the DNA samples was validated by amplification of a 110-bp fragment of the hemoglobin beta-chain (HBB) gene.[19] Infection with HPV was examined by PCR amplification with HPV-specific DNA sequences. This step used a universal HPV primer pair (“consensus primer”) which was specific for HPV 16. The sequences of primers were:

- Forward 5’-GGTCGGTGACCGGGTCATG-3’
- Reverse 5’-GCAATGTAGGTGTATCTCCA-3’

The main courses of PCR were as follows: the PCR reaction system’s total volume was 50 μL, which contained: DNA (500 ng/mL, 5 μL), TaKaRa Ex Taq Polymerase (5U/μL, 3 μL), Mg2+ (5 μL), dNTP Mixture (2.5 mm/each, 4 μL), 2 μL of each primer

![Figure 1. PCR amplification of HPV16 from the DNA samples extracted from the cervical cancer lesions. The lanes from left to right: M: molecular marker, 1: positive control sample (96 bp), 2: negative control sample (96 bp), 3–13: examined tissue samples (96 bp), and of them 8, 10–13 were positive for HPV 16. HPV = human papilloma virus, PCR = polymerase chain reaction.](image-url)
(200pmol/mL), and then added DEPC to 50μL. The cycling conditions were denaturation at 95°C lasted for 3 minutes, then 40 cycles of denaturation at 95°C for 15 seconds. Next, primer was annealed at 60°C for 20 seconds, and extension at 72°C for 25 seconds, followed by a final extension at 72°C for 7 minutes.[20] To analyze the PCR results, 5μL of each PCR reaction product was resolved by electrophoresis in 1.5% agarose gel, and the images were recorded through Gel Doc 2000 system (BioRad, Hercules, CA). The PCR experiment was replicated 7 times.

2.4. Immunohistochemistry

The immunohistochemical staining[21] was briefly described as: Sections of 4-μm were dewaxed in xylol and alcohol. Then antigen epitopes were unmasked by microwave heating at 98.5°C for 15 minutes in 0.01 M citrate-buffered solution (pH 6.0), and cooled to room temperature in the same solution for 30 minutes. Next, the sections were rinsed in wash buffer (PBS with 0.05% polysorbate 20 surfactant) for 20 minutes. The endogenous peroxidases were blocked by keeping the slides for 15 minutes. Next, the sections were rinsed in wash buffer, the slides were incubated with DAB (Diaminobenzidine) Horseradish Peroxidase Color Development Kit for 5 minutes at room temperature. At last, the sections were counterstained with hematoxylin and mounted in Permount Mounting Medium.

The experiment was replicated 3 times. The sections with known positive tissue sections were used as positive controls, and target proteins in tissue sections were stained brown in cytoplasm as shown in Figure 2. Sections stained with isotype-matched immunoglobulin molecules as well as cervix tissues did not show the staining effect by this method with an excess of the respective antigen but showed no brown staining were set as negative controls as shown in Figure 2.

AMHR2 and C-kit expressed in cervical cells’ cytoplasm. Brown immunohistochemical staining in the cytoplasm under the microscope was defined as positive for the target protein. The images of the sections were taken through Nikon microscope (Nikon Corporation, Tokyo, Japan), and analyzed by Image Pro Plus software Version 6.0 which can get information obtained by photograph or scanned documents and can collect intensity data from the area of interest. This method can offer good results with less operator dependency and can increase efficiency, so has been used in many studies.[22]

2.5. Statistical analysis

The statistical analysis was implemented through the SPSS software version 17.0 (Chicago, IL). The data were first evaluated through the Homogeneity of variance test. The significant standard was set at P > .05. Then comparisons between groups were carried out with 2-independent-samples test and Kruskal–Wallis test. The significant standards were set at P < .05.

3. Results

3.1. Evaluation standards

We used PCR to detect the HPV Infection in cervical tissues. Line 1 in Figure 1 showed an unusual clear band different from the background in 96 bp was defined as positive control for HPV16, and Line 2 showed no clear band was defined as negative control. According to this standard, samples showed similar band in 96 bp were considered as positive. All samples used in this study were proved to be squamous cell carcinoma, and was infected with HPV16 as was showed in Figure 1.

In order to test the distribution characteristic and staining intensity of AMHR2 and C-kit in cervix and cervical cancer samples, specific antibodies were used to localize the two kinases. Typical presentations were showed in Figure 2, and the target proteins in the tissue sections were stained brown in cytoplasm.

To search further, immunohistochemistry staining results were scored based on the staining intensity: score 0: no staining; score 1: light yellow; score 2: brownish yellow and score 3: tan.[23] Then, the samples were scored based on the positive areas occupied by the target antigens at 400× magnification: score 0: <5% of positive staining; score 1: 5% to 25% of positive staining; score 2: 26% to 50% of positive staining; score 3: 51% to 75% of positive staining; and score 4: more than 75% of positive staining. The degree of staining was calculated by multiplying the staining intensity score and the percentage of positive staining score. Finally, the overall degree of staining was defined as follows: negative (−): score 0; weak positive (+): score 1–3; positive (++): score 4–6; strong positive (+++): score 7–9; and extreme strong positive (++++): score 10–12.

3.2. Expression of AMHR2

Because of sample loses during the staining course, results were obtained from 52 cervical cancer tissues (9 was poorly differentiated, 32 was moderately differentiated and 11 was well differentiated) and 17 cervix tissues. AMHR2 mostly expressed in muscular tissues, connective tissues and vascular walls, little were observed in gland, but none in epithelium. In cervix and well-differentiated samples, the muscular tissues and connective tissues were nearly filled with the stained cells. The distributions were quite even with similar strong staining. As the differentiation went poorer, the stained areas became smaller and lighter.

Positive expression of AMHR2 was apparently decreased in cervical cancer sections (84.6%) compared with cervix sections (100.0%) as a whole (Z = -4.04, P < .01) (Table 1). The homogeneity of variance test showed P < .05 which meant unequal variance. So we used the Kruskal–Wallis test (P < .05), which showed there were meaningful distinctions in AMHR2 expression between cervical cancer and cervix. As could see from Table 2, all samples of the cervix group were positive (100.0%) ranged from (+) to (+++), and mostly gathered in the extreme strong positive (++++) group (76.5%). While cervical cancer groups ranged from (−) to (++++): of all 52 samples, 11 showed (+) (21.2%), 9 showed (+++) (17.3%), 15 showed (++++) (28.8%), 9 showed (++++) (17.3%) as well as 8 showed (−) (15.4%). From the statistic, we could infer that the expression of AMHR2 were lessen with the cervical cancer’s differentiation became poorer.

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Table 1

The comparison of c-Kit and AMHR2’s expression between cervicitis and cervical cancer sections (N, \( \bar{x} \pm s \)).

| AMHR2          | c-Kit          |
|----------------|----------------|
| poorly         |                |
| moderately     |                |
| well           |                |
| cervicitis     |                |
| negative       |                |
| control        |                |

| Comparison | N | IOD (\( \bar{x} \pm s \)) | z   | P      |
|------------|---|---------------------------|-----|--------|
| AMHR2      |   |                           |     |        |
| Cervical cancer | 52 | 13855.46 ± 19113.50 | -4.04 | <.01   |
| Cervitis   | 17 | 20358.31 ± 18735.75 |     |        |
| c-Kit      |   |                           |     |        |
| Cervical cancer | 24 | 20677.89 ± 40100.77 | -5.93 | <.01   |
| Cervicitis | 18 | 6948.10 ± 22965.16    |     |        |

AMHR = anti-Müllerian hormone receptor.

Figure 2. Expression of AMHR2 and c-Kit in the cervical tissues from patients with cervical cancers of different differentiation grades and cervicitis. (400× magnification). 1 muscle tissue 2 around the vein 3 arterial wall 4 around the artery 5 around the gland 6 connective tissue. AMHR = anti-Müllerian hormone receptor.
3.3. Expression of C-Kit

Results were gained from 24 cervical cancer tissues (4 was poorly differentiated, 15 was moderately differentiated, and 5 was well differentiated) and 18 cervicitis tissues. C-Kit was widely expressed in glands, epithelium, muscular tissues, connective tissues and vascular walls, but was rather dispersive. Stained cells mostly gathered in the basilar part of epithelium and glands or in the muscular tissues which close to epithelium, glands or vessels. Deserve to be mentioned, the vascular walls especially arterial walls were extremely strong stained.

Positive expression of c-Kit was obviously increased in cervical cancer sections (70.8%) compared with cervicitis sections (27.8%) (Z = -5.93, P < .01) (Table 1). The homogeneity of variance test showed P < .05. Then we used the Kruskal–Wallis test (P < .05), which indicated the statistical difference between cervical cancer and cervicitis in c-Kit expression. In Table 3 we could see that cervicitis samples were mainly expressed as negative (72.2%), and there were none showed (+++) or (++++). At the same time, as for the 24 cervical cancer samples, 7 were (−) (29.2%), 6 were (+) (25.0%), 1 were (+++) (4.2%), 2 were (+++) (8.3%), and 8 were (++++) (33.3%). Basically, we could deduce that c-Kit expressed increasingly as the cervical cancer’s differentiation degree decreased.

4. Discussion

Cervical cancer is one of the most common malignant tumors in women. It brings an ominous threat to women’s health. The successful treatment of advanced gastrointestinal stromal tumors (GISTs) with Kit-based inhibitors has raised the hope that other successful treatment of advanced gastrointestinal stromal tumors (GISTs) with Kit-based inhibitors has raised the hope that other

AMHR2 expresses in granulosa and theca cells activates AMH exerting its biological effects. AMHR2’s protein expression is up-regulated in female embryos treated with estrogen synthesis inhibitor fadrozole. It is reported that AMHR2 is a differentiation protein which expressed in 90% of primary epithelial ovarian carcinomas (EOCS)—the most deadly gynecologic malignancy. In our study, AMHR2 was distinctly reduced in cervical cancer samples compared to cervicitis samples. This might indicate that the normal biological effects of AMH was restrained and disturbed in the cervical cancer tissues. This caused a series of hormonal disorders and dysfunction which end up with some clinical symptoms such as irregular menstruation and infertility. The lessen expression of AMHR2 along with poorer of the differentiation indicated the inhibition became more seriously. But on the other hand, there were reports uncovered TGF-β members like AMH played a role as inhibitors of normal epithelial and endothelial cell proliferation, but they contributed to cancer progression in later stages. The decrease of AMHR2 in cervical cancer might be a mark of early stage or self defense implemented by human body. Furthermore, according to Sakalar and his team’s report, AMHR2 could also served as a useful target for vaccination against EOCS for it significantly inhibited ID8 tumor growth under the help of CD4+ T cell without much side effects. The TGF-β/BMP family which AMHR2 belongs to is associated with lung malignancies strongly, and a determinant of prognosis as well. In Tim N. Beck’s report, TGF-β/BMP family’s signaling is significantly influenced by context, with TGF-β signaling altering from tumor-suppressive to metastasis-promoting in response to the contributions of diverse cell intrinsic and cell extrinsic factors, and this might be a possible therapeutic management for lung cancers. Whether AMHR2 can act as a target for cervical cancer needs further researching. C-Kit is a protein encoded by KIT gene in humans. Altered forms of this receptor may be associated with neoplasms such as GIST, human glablastoma, feline sarcoma. Also it affects melanocyte physiology and influences melanogenensis in other reports. Furthermore, c-Kit is a mutagenic effective proto-

### Table 2

|                | Poorly differentiation | Moderately differentiation | Well differentiation | Cervicitis |
|----------------|------------------------|----------------------------|---------------------|------------|
| −              | 5 (55.6%)              | 1 (3.1%)                  | 2 (18.2%)           | 0          |
| +              | 1 (11.1%)              | 7 (21.9%)                 | 3 (27.2%)           | 0          |
| ++             | 2 (22.2%)              | 5 (15.6%)                 | 2 (18.2%)           | 1 (5.9%)   |
| +++            | 0                      | 13 (40.6%)                | 2 (18.2%)           | 3 (17.6%)  |
| ++++           | 1 (11.1%)              | 6 (18.8%)                 | 2 (18.2%)           | 13 (76.5%) |
| Total          | 9                      | 32                         | 11                  | 17         |

AMHR = anti-Müllerian hormone receptor.

### Table 3

|                | Poorly differentiation | Moderately differentiation | Well differentiation | Cervicitis |
|----------------|------------------------|----------------------------|---------------------|------------|
| −              | 0                      | 6 (40.0%)                  | 1 (20.0%)           | 13 (72.2%) |
| +              | 1 (25.0%)              | 3 (20.0%)                  | 2 (40.0%)           | 3 (16.7%)  |
| ++             | 0                      | 1 (6.7%)                   | 0                   | 2 (11.1%)  |
| +++            | 0                      | 1 (6.7%)                   | 1 (20.0%)           | 0          |
| ++++           | 3 (75.0%)              | 4 (26.6%)                  | 1 (20.0%)           | 0          |
| Total          | 4                      | 15                         | 5                   | 18         |
oncogene with a stem-cell factor (SCF) as a ligand, and it leads to tumor growth through impairment of cellular growth regulation. In our study, c-Kit increased in cervical cancer sections obviously while cervicitis sections were mainly expressed negatively. And it expressed increasingly as the cervical cancer’s differentiation degree decreased. According to Sara Franceschi’s report, c-KIT overexpressing cells showed a regression of typical morphological features of malignancy in papillary thyroid carcinoma and might be involved in the differentiation of thyroid cells and in tumor progression. This might show c-Kit link with the potential invasive capacity of cervical cancer. Other reports about presents of c-Kit positivity increased the risk of tumor growth and invasion in Kaposi sarcoma, follicular thyroid carcinoma and prostate cancer showed the same result. And also reported to be correlated with the capacity of cell self-renewal and cancer progression. As for the distribution of c-Kit, Liu’s team found c-Kit’s expression in the stroma of phyllodes tumors (PTs) was positively associated with malignancy, while epithelial positivity was inversely correlated, which was anastomosed with our report. In our study, the arterial walls were extremely strong stained with c-Kit. This might show it affected the vascular epithelial cells’ function and changed their permeability, which created favorable conditions for cancer metastasis. Also this feature even considered as a potential target for therapy of some diseases.

There were some limitations in the present study: First, our sample size was small. Due to the difficulties on sample collecting and tissue size, we only collected materials from two hospitals and could not expand the number of samples. So studies with much larger patient population was needed to confirm our results. Second, we only collected Uyghur women, this special minority’s cervical tissues. More researches about other ethnic groups were needed to draw a decent conclusion.

In conclusion, our study evaluated expressions of c-Kit and AMHR2 in cervical cancer and cervicitis. According to the results of our investigation, c-Kit and AMHR2 might become biological markers of cervical cancer and give us ideas about new therapeutic options for tumors in further studies. Although cervical biopsy using Pap smear test remains the gold standard for diagnosis of cervical cancer, situations sometimes happen when it is difficult to make an exact diagnose. To deal with this, referring to biomarkers such as AMHR2 and c-Kit may be a good choice.

5. Conclusions
The presence of AMHR2 was lessen with the cervical cancer’s differentiation degree became poorer, which might indicate it had some connection with self defense of our body. While c-Kit increased with the reduction of cervical cancer’s differentiation degree, which might link with the potential invasive capacity of cervical cancer. The possibility of being used as biomarkers needs to be verified by further studies.

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