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Significance of SHP-1 and SHP-2 Expression in Human Papillomavirus Infected *Condyloma acuminatum* and Cervical Cancer

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Abstract

Human papillomaviruses (HPVs) are a group of DNA viruses that infect the skin and mucous membranes. Type HPV6/11 is closely related to *Condyloma acuminatum*, while HPV16/18 is the principal cause of cervical cancer. In this study, we examined the expression of protein tyrosine phosphatases SHP-1 and SHP-2 in *Condyloma acuminatum*, cervical cancer and the relationship between SHP-1/SHP2 expression and HPV infection. Forty *Condyloma acuminatum* cases, 20 cervical cancer cases and 20 normal human foreskins were examined for HPV infection by in situ hybridization and the expression of SHP-1 and SHP-2 were examined by immunohistochemistry. Results demonstrated that positive expression rates of HPV6/11, HPV16/18, and HPV31/33 were 98%, 10%, and 7.5% in *Condyloma acuminatum*, 10%, 85%, and 25% in cervical cancer. Only one normal foreskin demonstrated positive staining for HPV16/18. Positive expression rates of SHP-1 and SHP-2 were 80% and 85% in *Condyloma acuminatum*, 85% and 90% in cervical cancer. The SHP-1 and SHP-2 expressions were mainly distributed in the prickle layer of

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Condyloma acuminatum and were diffusely distributed in cervical cancer cells. Only 35% and 30% of foreskins demonstrated weak staining in the basal layer cells. There were statistically significant correlations among the infection of HPV and the expression of SHP-1 and SHP-2 in both *Condyloma acuminatum* and cervical cancer ($P<0.05$). SHP-1 expression has a positive correlation with SHP-2 expression. Our results demonstrate putative roles of SHP-1 and SHP-2 in the progression of both *Condyloma acuminatum* and cervical cancer after HPV infection.

Keywords

Cervical cancer; *Condyloma acuminatum*; Human papillomavirus; Protein tyrosine phosphatase

Introduction

Human papillomaviruses (HPVs) are a group of DNA virus that infect the skin and mucous membranes. Over 100 HPV types have been identified, among them, at least 35 are related to genitourinary tract infections [1, 2]. A strong tropism for epithelia is the feature of HPV and the effects of this tropism depends on the type of HPV involved. Low-risk HPVs 6/11 always results in focal hyperplasia, such as *Condyloma acuminatum* (CA), whereas high-risk HPV16, HPV18, HPV31, and HPV33 are causative for dysplasia and cervical cancer [3, 4].

Condyloma acuminatum is a hyperplastic lesion of skin and mucosa that is caused by several types of HPVs. Approximately 90% of genital warts are caused by HPV6/11 [5]. The pathological features after HPV infection include hypertrophy of the spinous layer, the appearance of koilocytes in granular and upper spinous layers, and parakeratosis and papillomatous hyperplasia.

Over 99% of cervical cancer cases are a result of HPV infection [6], and of those approximately 70% are a result of infection with HPV16/18 [5].

A vaccine targeting quadrivalent HPV types 6, 11, 16, and 18 [5] has been approved by the USA Food & Drug Administration to prevent HPV associated diseases.

Despite the fact that a causal relationship exists among HPV infection, cervical cancer and genital warts, the exact mechanism by which HPV induces *Condyloma acuminatum* and cervical cancer is still largely unknown.

Cellular events are tightly controlled by intracellular signaling processes initiated by extracellular signals, in which protein phosphorylation (conducted by protein kinases) and dephosphorylation (conducted by protein phosphatases) are central events [7–9]. Several protein kinase pathways, including the MAPK pathway, have been implicated in *Condyloma acuminatum* and cervical cancer formation after HPV infection. It has been reported that infection by HPV may interfere with MAPK cellular signal transduction via Erk, JNK/SAPK, p38/RK and BMK1/Erk5 in keratinocytes [10]. Little is known about the role of protein phosphatases, i.e., SHP-1 and SHP-2 in *Condyloma acuminatum* and cervical cancer after HPV infection.

SHP-1 was identified as a cytosolic non-receptor type SH2 domain containing protein tyrosine phosphatase (also known as PTPN6) and functions in cellular proliferation and differentiation [11, 12]. SHP-2 (also known as PTPN11) is another member of the non-receptor protein tyrosine phosphatases [13], and is thought to participate in a variety of cytokine and growth factor initiated signal transduction processes [14–16]. Both SHP-1 and SHP-2 act downstream of receptor and cytoplasmic tyrosine kinases to propagate signal relay. Despite a high homology between SHP-1 and SHP-2, their functions are distinct. SHP-1 plays a negative regulatory role in intracellular signaling processes, and inhibits cell proliferation. Activated SHP-1 may terminate signaling processes by JAK2 dephosphorylation, and inhibit cellular proliferation [17]. SHP-1 also induces cell cycle arrest and apoptosis through the Bax pathway after γ-irradiation [18]. On the other hand, SHP-2 plays a positive regulatory role in signal transduction, and has been reported to stimulate cell proliferation and differentiation [19–21]. Ke and coworkers demonstrated that deletion of SHP-2 in the brain leads to defective proliferation and differentiation of neural stem cells [19].

In order to explore whether there are different changes of SHP-1 and SHP-2 in *Condyloma acuminatum* and examine their relationship to HPV infection, 40 cases of *Condyloma acuminatum*, 20 cases of cervical cancer, and 20 foreskin samples were used in this study. HPV6/11, HPV16/18 and HPV31/3 infections were identified by in situ hybridization and the expression and distribution of SHP-1 and SHP-2 were examined by immunohistochemistry. Results support a putative role(s) of SHP-1 and SHP-2 in both *Condyloma acuminatum* and cervical cancer pathogenesis after HPV infection.

Materials and Methods

Tissue Specimens

Forty consecutive cases (23 male; 17 female) of *Condyloma acuminatum* were entered in this study. Patient age ranged from 17 to 69 years, with an average age of 39 years. *Condyloma acuminatum* was excised at the Department of Dermatology and the diagnosis confirmed at the Pathology Department of Zhejiang Province People's Hospital, Hangzhou, China. Twenty cervical cancer (age 32–61 years, average age 43 years) and 20 foreskin samples (age 17–37 years, average age 25 years) were collected in the Pathology Department for comparison. The follow up period was approximately 2 years.

In situ Hybridization

In situ hybridization for HPV6/11, HPV16/18 and HPV31/33 was carried out on 4 μm thick paraffin sections using a biotinylated HPV DNA probe kit (Zhongshan Goldenbridge Biotechnology Co. LTD, Beijing, China) following the manufacturer's protocol. Briefly, sections were heated at 60°C for 1 h, deparaffinized, digested with proteinase K at 37°C for 15 min, and dehydrated in a series of graded ethanol. The probes were added and the slides were heated at 90°C for 10 min for DNA denaturation and then incubated at 37°C overnight. Visualization of the hybridized probe was achieved by incubating the sections with anti-biotin, followed by biotin-conjugated anti-immunoglobulin, each for 20 min at 37°C. Finally, peroxidase-labeled streptavidin was added for 20 min at 37°C and staining was

visualized by chromogen substrate 3-amino-9-ethyl carbazole and counterstained with hematoxylin.

Immunohistochemistry

Five micrometer sections were deparaffinized and rehydrated. Antigen retrieval was performed by autoclaving the slides in citrate buffered solution at 121°C for 5 min. Endogenous peroxidase activity was blocked by incubating the sections with 0.5% hydrogen peroxide in phosphate-buffered saline for 15 min at room temperature. After blocking non specific binding sites by incubation with non-immune rabbit serum for 30 min at room temperature, primary antibodies were applied: anti-SHP1 monoclonal antibody (Santa Cruz Biotec, USA) at a 1:100 dilution; anti-SHP2 monoclonal antibody (Santa Cruz Biotec, USA) at a 1:500 dilution. The slides were washed and incubated with biotinylated rabbit anti-mouse antibody at a 1:700 dilution. Visualization was by avidin–biotin–peroxidase complex method (Maixin Biotec, China) using 3,3′-diaminobenzidine tetrahydrochloride as chromogen and counterstaining with Harris's hemotoxylin.

Method for Interpretation of in situ Hybridization and Immunohistochemistry

Diagnosis of *Condyloma acuminatum* and cervical cancer were confirmed by pathological examination of parallel H&E slides. In situ hybridization and immunohistochemistry results were evaluated independently by two pathologists. In situ hybridization of HPV6/11, HPV16/18 and HPV31/33 were assessed as positive when the cell nuclei stained purple [22]. Immunohistochemistry staining of SHP-1 or SHP-2 were considered positive when the cytoplasm were stained brown yellow or pale yellow. Arbitrary grades [23] were used to evaluate the immunohistochemistry staining results. Staining was first evaluated for percentage of positive cells and staining intensity. Positive cell percentage ≤10% marked as zero; 11~25% marked as 1; 26~50% marked as 2; 51~75% marked as 3; and ≥76% marked as 4. Staining intensity score was marked as follows: no stain, zero; pale yellow stain, 1; yellow stain, 2; brown yellow stain, 3. The final staining grade for immunohistochemistry was determined by multiplying the percentage positive cell score and the staining intensity score: grade negative (−) means zero, weak positive (+) means 1~4; positive (++) means 6~8; strong positive (+++) means 9~12.

Statistical Analysis

SPSS14.0 software was used for statistical analysis. Comparison of HPV infection rates, SHP-1/SHP-2 expression levels among *Condyloma acuminatum*, cervical cancer and normal skin was performed using χ^2 test. Spearman correlations were used to examine the correlations between HPV infection and positive expression of SHP-1 and SHP-2, and the correlation between SHP-1 expression and SHP-2 expression. We used K Independent Samples to determine if there were differences in SHP-1 and SHP-2 expression among various age groups of *Condyloma acuminatum* and cervical cancer patients.

Results

High HPV Infection Rates in *Condyloma acuminatum* and Cervical Cancer

By in situ hybridization, HPV infection as indicated by blue purple staining in the cell nucleus were seen in all *Condyloma acuminatum* and cervical cancer samples (Fig. 1). In *Condyloma acuminatum*, positive staining was seen in the upper prickle layer or granular layer cells, mainly in koilocytes; while in cervical cancer, positive diffuse staining was seen in cancer cells. Only one case of normal foreskin showed positive staining for HPV16/18 (5%). Multiple HPV subtype infections could be found in six samples of *Condyloma acuminatum* (three with HPV6/11 and HPV16/18 infection, two with HPV6/11 and HPV31/33 infection, and one with HPV 16/18 and HPV 31/33 infection), and in four samples of cervical cancer (one with HPV6/11 and HPV16/18 infection, one with HPV6/11 and HPV31/33 infection, and two with HPV 16/18 and HPV 31/33 infection). *Condyloma acuminatum* cases were mainly infected with HPV6/11 (98%), and cervical cancer with HPV16/18 (85%). No cervical cancer samples were infected by HPV6/11 alone (Table 1).

Expression of SHP-1 and SHP-2 in *Condyloma acuminatum* and Cervical Cancer

Thirty-two *Condyloma acuminatum* cases (80%) revealed positive cytoplasmic staining for SHP-1. Staining intensity was strong in most cases and staining was predominantly located in the superficial layer, mainly in koilocytic cells. SHP-1 expression also was diffuse in the cytoplasm of the cervical cancer cells in 17 cases (85%). In contrast, there were only seven (35%) positive SHP-1 cases of normal human skin where the staining localized in the cytoplasm of some basal layer cells of the epithelia and the staining intensity was low in most cases (6/7). There were statistically significant differences in SHP-1 expression rates between *Condyloma acuminatum* and foreskin (χ^2= 11.87, P<0.05) as well as between cervical cancer and foreskin (χ^2=10.42, P<0.05). Although the positive expression rate in cervical cancer was higher than that in *Condyloma acuminatum*, there was no statistical difference (χ^2=0.22, P>0.05) (Table 2, Fig. 2).

Thirty-four (85%) *Condyloma acuminatum* cases are SHP-2 positive. The expression pattern was similar to that observed in SHP-1 staining. Strong immunostaining was seen in the upper epithelial layer with many koilocytic cells staining positive. Strong SHP-2 immunostaining also was found in 18 (90%) cervical cancer samples. Only six (30%) normal foreskins showed SHP-2 positive staining in basal keratinocytes. The expression, which was localized to the cytoplasm in five out of the six positively stained cases, was weak. There was a statistically significant difference in the expression rate for SHP-2 between *Condyloma acuminatum* and foreskin (χ^2=18, P<0.05) as well as between cervical cancer and foreskin (χ^2=15, P<0.05). Though the positive SHP-2 expression rate in cervical cancer was higher than that in *Condyloma acuminatum*, the difference was not statistically significant (χ^2=0.29, P>0.05).

Correlation Among HPV Infection and Expression of SHP-1 and SHP-2 in *Condyloma acuminatum* and Cervical Cancer

In order to determine whether or not there were correlations among HPV infection and positive expression of SHP-1 and SHP-2, the Spearman correlation was used to analyze the

expression of SHP-1 and SHP-2 in HPV infected *Condyloma acuminatum*/cervical cancer compared with non HPV infected foreskin (excluding the case positive to HPV16/18 infection). There was a correlation among HPV infection and SHP-1/SHP-2 expression in *Condyloma acuminatum* (rs=0.449/rs=0.556, both $P<0.05$), and cervical cancer (rs=0.562/rs=0.682, both $P<0.05$). As *Condyloma acuminatum* were mainly infected with HPV6/11 and cervical cancer with HPV16/18, we also analyzed the correlation with respect to HPV subtype. There are statistically significant correlations among HPV6/11 infection (except for the six cases with multiple HPV infection) and SHP-1/SHP-2 expression in *Condyloma acuminatum* (rs=0.511/rs=0.547, both $P<0.05$), and between HPV16/18 infection (except for the six cases with no or multiple HPV infection) and SHP-1/SHP-2 expression in cervical cancer (the former rs=0.600/rs=0.695, both $P<0.05$) (Fig. 3).

Correlation Among the Expression of SHP-1 and SHP-2 in *Condyloma acuminatum* and Cervical Cancer

Spearman correlation analysis demonstrated a correlation among the expression of SHP-1 and SHP-2 in *Condyloma acuminatum* (rs=0.331, $P<0.05$), and in cervical cancer (rs=0.570, $P<0.05$).

SHP-1 and SHP-2 Expression in HPV Infected *Condyloma acuminatum* and Cervical Cancer According to Age Groups

HPV infected *Condyloma acuminatum* and cervical cancer patients were divided into three groups according to their ages: ≤35, 36~45 and >45. K Independent samples demonstrated no differences for the expression of SHP-1 and SHP-2 among various age groups with HPV infection or HPV6/11 infected *Condyloma acuminatum*. There also were no differences with HPV infection or HPV16/18 infected cervical cancer (all $P>0.05$).

Consequences of HPV Infected *Condyloma acuminatum*

The 40 *Condyloma acuminatum* patients had been followed up for approximately 2 years at the time this manuscript was prepared. None of the patients progressed to cervical carcinoma or other epithelial cancers. Two patients (one with HPV6/11 and 16/18 infection; the other one with HPV16/18 and 31/33 infection) were diagnosed with Bowenoid papulosis.

Discussion

Previous reports demonstrated that 90% of genital warts are caused by HPV types 6 and 11 infection, and that approximately 70% of cervical cancers are associated with HPV types 16 and 18 infection [5, 24]. In agreement with previous reports, we found that the predominant HPV types for *Condyloma acuminatum* are HPV 6 and HPV11 (98%), and the main HPV types associated with cervical cancer are HPV16 and HPV18 (85%). All cervical cancer cases were infected by at least one cancer causing HPV type (HPV11/16 and/or HPV31/33). Multiple infections which include at least one cancer related HPV type (HPV16/18 and/or HPV31/33) infection were found in six out of 40 *Condyloma acuminatum* cases. After a 2-year follow up, two of the six *Condyloma acuminatum* cases developed Bowenoid papulosis. Bowenoid papulosis is a highly characteristic condition of the anogenital region

which is histologically similar to Bowenoid carcinoma in situ, and is often associated with the oncogenic high-risk HPV types 16, 18, 31 and 33 [25, 26]. None of the six cases progressed to cervical cancer or other epithelial cancers; neither did the HPV6/11 infected *Condyloma acuminatum* cases. However this does not exclude malignant changes at a later time point, since the development, maintenance and progression of precursor lesions evolve slowly into invasive cancer, typically over a period of more than 10 years [27]. Yoneta and co-workers reported that a patient with Bowenoid papulosis involving HPV31, 67 infection developed invasive squamous cell carcinoma (SCC) 8 years following the Bowenoid papulosis' diagnosis [28]. Therefore a longer follow up time may be valuable for those *Condyloma acuminatum* patients who experienced HPV16/18 and/or HPV31/33 infection. These data also suggests screening of *Condyloma acuminatum* patients with high carcinogenic HPV type infections, and administration of immunotherapy prior to development of cancer. The single case of HPV16/18 infected foreskin suggests that males could be infected by HPV and remain asymptomatic, and serve as a source of HPV infection for a female partner.

SHP-1 has been proposed as a candidate tumor suppressor gene in lymphoma, leukemia and other cancers, since it functions as an antagonist to the growth-promoting and oncogenic potential of tyrosine kinases [17, 18, 29]. Zapata and colleagues reported that overexpression of SHP-1 inhibited growth of human prostate adenocarcinoma cell line PC-3 cell [30], and that the anti-proliferative effect of somatostatin on prostate cancer was mediated by SHP-1. [31] Massa et al. [32] have shown that SHP-1 is a critical factor in controlling virus replication in the CNS glia and virus-induced demyelination. In contrast, SHP-2 plays an important role in cancer progression [19–21]. Fibroblasts lacking a functional SHP-2 were impaired in their ability to spread and migrate on fibronectin compared with wild-type cells [33, 34]. Coyne et al. [35] have reported that receptor-induced signals promote virus entry and suggest a role for SHP-2 in viral pathogenesis [19–21].

Since both *Condyloma acuminatum* and cervical cancer are proliferative lesions, we expected to observe decreased SHP-1 expression and increased SHP-2 expression in *Condyloma acuminatum* and/or cervical cancer tissues. However, our data demonstrate that both SHP-1 and SHP-2 expression are significantly higher in *Condyloma acuminatum* as well as in cervical cancer when compared to normal human skin (Table 2). SHP-1 expression and SHP-2 expression are correlated in all the samples examined, i.e., high SHP-1 expression correlated with high SHP-2 expression. There are statistically significant correlations between the expression of SHP-1/SHP-2 and HPV6/11 infection in *Condyloma acuminatum*/HPV11/16 infection in cervical cancer (Fig. 3). These data suggest a possible role for the cytosolic non-receptor type SH2 domain containing protein tyrosine phosphatase (SHP), in particular, SHP-1 and SHP-2 in HPV induced *Condyloma acuminatum* as well as in cervical cancer. SHP-1 inhibits and SHP-2 promotes cell proliferation. Therefore, their correlated positive expression in *Condyloma acuminatum* and cervical cancer was unexpected and may imply a cell defense reaction (SHP-1) to recover from the abnormality caused by HPV infection. The increase in SHP-2 may be correlated to the excessive hyperplasia or malignant transformation, whereas increased SHP-1 expression may be a response to counteract these changes. Abnormal expression and/or unbalanced expression of

SHP-1 and SHP-2 may reflect a cascade reaction of certain cellular signaling pathways, which in turn result in tissue remodeling and even malignant change.

Our current data does not provide a mechanism for the increase in both SHP-1 and SHP-2 expression following HPV16/18 infection which eventually leads to malignant change, and HPV6/11 infection induced *Condyloma acuminatum*. Further cell/animal model based studies may reveal the mechanisms involved.

This is the first report on SHP-1/SHP-2 expression in *Condyloma acuminatum*. Our data suggest possible roles for SHP-1 and SHP-2 in HPV infected diseases like *Condyloma acuminatum* and cervical cancer.

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References

1. zur Hausen H. Roots and perspectives of contemporary papillomavirus research. J Cancer Res Clin Oncol. 1996; 122:3–13. [PubMed: 8543590]
2. Dupin N. Genital warts. Clin Dermatol. 2004; 22:481–486. [PubMed: 15596319]
3. Leung AK, et al. Genital infection with human papillomavirus in adolescents. Adv Ther. 2005; 22:187–197. [PubMed: 16236680]
4. Moscicki AB. Impact of HPV infection in adolescent populations. J Adolesc Health. 2005; 37:S3–S9. [PubMed: 16310138]
5. Bryan JT. Developing an HPV vaccine to prevent cervical cancer and genital warts. Vaccine. 2007; 25:3001–3006. [PubMed: 17289220]
6. Walboomers JM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999; 189:12–19. [PubMed: 10451482]
7. Denu JM, et al. Form and function in protein dephosphorylation. Cell. 1996; 87:361–364. [PubMed: 8898189]
8. Hunter T. Signaling—2000 and beyond. Cell. 2000; 100:113–127. [PubMed: 10647936]
9. Tonks NK, Neel BG. From form to function: signaling by protein tyrosine phosphatases. Cell. 1996; 87:365–368. [PubMed: 8898190]
10. Yu WM, et al. Catalytic-dependent and -independent roles of SHP-2 tyrosine phosphatase in interleukin-3 signaling. Oncogene. 2003; 22:5995–6004. [PubMed: 12955078]
11. Adachi M, et al. Mammalian SH2-containing protein tyrosine phosphatases. Cell. 1996; 85:15. [PubMed: 8620532]
12. Su MW, et al. Targeting Src homology 2 domain-containing tyrosine phosphatase (SHP-1) into lipid rafts inhibits CD3-induced T cell activation. J Immunol. 2001; 166:3975–3982. [PubMed: 11238643]
13. Huang Q, et al. The novel role of the C-terminal region of SHP-2. Involvement of Gab1 and SHP-2 phosphatase activity in Elk-1 activation. J Biol Chem. 2002; 277:29330–29341. [PubMed: 12011040]
14. Ahmad S, et al. A widely expressed human protein-tyrosine phosphatase containing src homology 2 domains. Proc Natl Acad Sci U S A. 1993; 90:2197–2201. [PubMed: 7681589]
15. Feng GS, et al. SH2-containing phosphotyrosine phosphatase as a target of protein-tyrosine kinases. Science. 1993; 259:1607–1611. [PubMed: 8096088]

16. Vogel W, et al. Activation of a phosphotyrosine phosphatase by tyrosine phosphorylation. Science. 1993; 259:1611–1614. [PubMed: 7681217]
17. Klingmuller U, et al. Specific recruitment of SH-PTP1 to the erythropoietin receptor causes inactivation of JAK2 and termination of proliferative signals. Cell. 1995; 80:729–738. [PubMed: 7889566]
18. Hsu HC, et al. Mutation of the hematopoietic cell phosphatase (Hcph) gene is associated with resistance to gamma-irradiation-induced apoptosis in Src homology protein tyrosine phosphatase (SHP)-1-deficient “motheaten” mutant mice. J Immunol. 2001; 166:772–780. [PubMed: 11145649]
19. Ke Y, et al. Deletion of Shp2 in the brain leads to defective proliferation and differentiation in neural stem cells and early postnatal lethality. Mol Cell Biol. 2007; 27:6706–6717. [PubMed: 17646384]
20. Voena C, et al. The tyrosine phosphatase Shp2 interacts with NPM-ALK and regulates anaplastic lymphoma cell growth and migration. Cancer Res. 2007; 67:4278–4286. [PubMed: 17483340]
21. Xu R. Shp2, a novel oncogenic tyrosine phosphatase and potential therapeutic target for human leukemia. Cell Res. 2007; 17:295–297. [PubMed: 17404595]
22. Gillison ML, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst. 2008; 100:407–420. [PubMed: 18334711]
23. McDonald JS, et al. nm23-H1 expression in squamous cell carcinoma of the head and neck. Pathol Oncol Res. 1996; 2:34–36. [PubMed: 11173580]
24. Skerlev M, et al. PL9 The HPV-genital (and oral?) infections—how are we standing now? Oral Dis. 2006; 12(Suppl 1):2.
25. Richter ON, et al. Bowenoid papulosis of the vulva-immunotherapeutical approach with topical imiquimod. Arch Gynecol Obstet. 2003; 268:333–336. [PubMed: 14504882]
26. Wigbels B, et al. Imiquimod: a new treatment possibility in bowenoid papulosis? Hautarzt. 2001; 52:128–131. [PubMed: 11244890]
27. Wang KL. Human papillomavirus and vaccination in cervical cancer. Taiwan J Obstet Gynecol. 2007; 46:352–362. [PubMed: 18182340]
28. Yoneta A, et al. Development of squamous cell carcinoma by two high-risk human papillomaviruses (HPVs), a novel HPV-67 and HPV-31 from bowenoid papulosis. Br J Dermatol. 2000; 143:604–608. [PubMed: 10971337]
29. Wu C, et al. The function of the protein tyrosine phosphatase SHP-1 in cancer. Gene. 2003; 306:1–12. [PubMed: 12657462]
30. Zapata PD, et al. Autocrine regulation of human prostate carcinoma cell proliferation by somatostatin through the modulation of the SH2 domain containing protein tyrosine phosphatase (SHP)-1. J Clin Endocrinol Metab. 2002; 87:915–926. [PubMed: 11836342]
31. Zapata PD, et al. Phosphotyrosine phosphatase SHP-1, somatostatin and prostate cancer. Actas Urol Esp. 2004; 28:269–285. [PubMed: 15248398]
32. Massa PT, et al. Critical role for protein tyrosine phosphatase SHP-1 in controlling infection of central nervous system glia and demyelination by Theiler’s murine encephalomyelitis virus. J Virol. 2002; 76:8335–8346. [PubMed: 12134038]
33. Manes S, et al. Concerted activity of tyrosine phosphatase SHP-2 and focal adhesion kinase in regulation of cell motility. Mol Cell Biol. 1999; 19:3125–3135. [PubMed: 10082579]
34. Yu DH, et al. Protein-tyrosine phosphatase Shp-2 regulates cell spreading, migration, and focal adhesion. J Biol Chem. 1998; 273:21125–21131. [PubMed: 9694867]
35. Coyne CB, et al. Poliovirus entry into human brain microvascular cells requires receptor-induced activation of SHP-2. EMBO J. 2007; 26:4016–4028. [PubMed: 17717529]

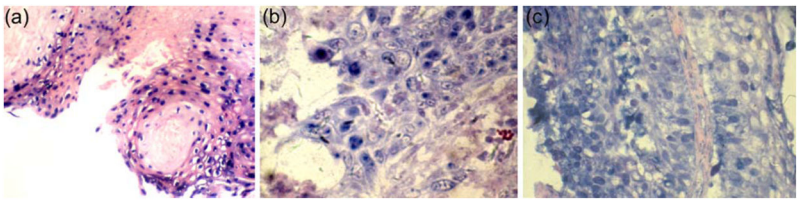

Fig. 1.

Micrographs showing representative HPV in situ hybridization staining. **a** HPV6/11 expression in *Condyloma acuminatum*, showing positive nuclear staining in the upper epithelial layers (principally in koilocytes) (original magnification: ×200). **b** HPV16/18 expression in cervical cancer (original magnification: ×400). **c** HPV31/33 expression in cervical cancer (original magnification: ×240)

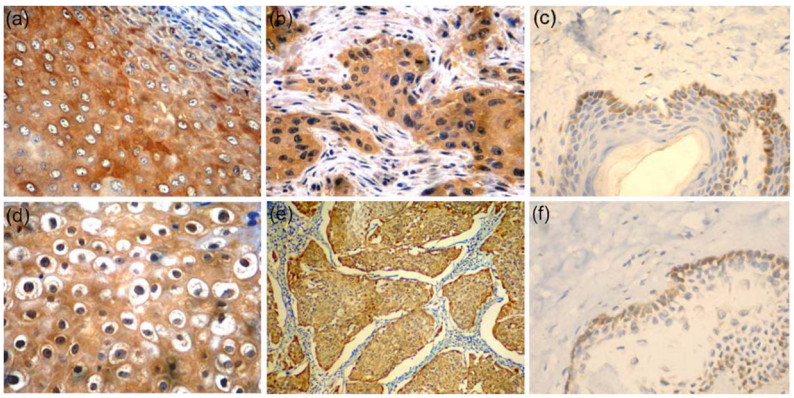

Fig. 2.

Micrographs showing representative SHP1/SHP-2 immunohistochemical staining. **a** SHP-1 expressed in koilocytic cells of *Condyloma acuminatum* (original magnification: ×240). **b** Strong expression of SHP-1 in cervical cancer (original magnification: ×240). **c** Weak SHP-1 expression in basal layers of foreskin (original magnification: ×200). **d** SHP-2 expression in koilocytic cells of *Condyloma acuminatum* (original magnification: ×400). **e** Strong SHP-2 expression in cervical cancer (original magnification: ×200). **f** Weak SHP-2 expression in basal layers of foreskin (original magnification: ×200)

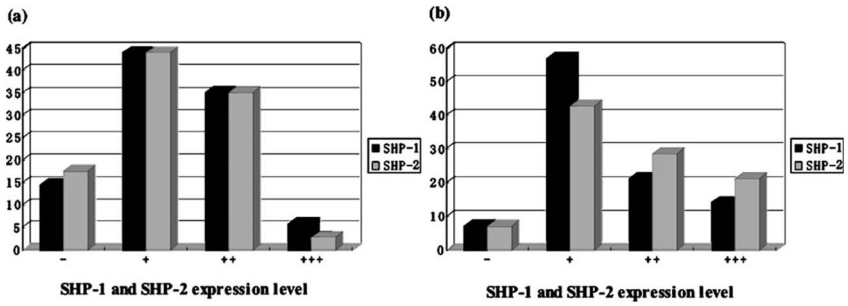

Fig. 3.

a Both SHP-1 and SHP-2 expression are higher in HPV6/11 infected *Condyloma acuminatum* compared to foreskin without HPV infection. Spearman correlation demonstrated the expression of SHP-1 and SHP-2 associated with HPV infection in *Condyloma acuminatum* (both $P<0.05$). There is also a correlation between SHP-1 expression and SHP-2 expression in *Condyloma acuminatum* ($P<0.05$). **b** SHP-1 and SHP-2 expression are higher in HPV16/18 infected cervical cancer compared to foreskin without HPV infection. Spearman correlation demonstrates the expression of SHP-1 and SHP-2 associated with HPV infection in cervical cancer (both $P<0.05$). There is also a correlation between SHP-1 expression and SHP-2 expression in cervical cancer ($P<0.05$)

Table 1

Number of HPV6/11, HPV16/18 and HPV31/33 infection in different tissue samples (percent)

Pathologic diagnosis	Total cases	HPV6/11	HPV16/18	HPV31/33
Condyloma acuminatum	40	39 (98)	4 (10)	3 (7.5)
Foreskin	20	0 (0)	1 (5)	0 (0)
Cervical cancer	20	2 (10)	17 (85)	5 (25)

Table 2

The expression of SHP-1 and SHP-2 in *Condyloma acuminatum*, cervical cancer and foreskin

Pathologic diagnosis	Total cases	SHP-1				SHP-2			
		−	+	++	+++	−	+	++	+++
Condyloma acuminatum	40	8	18	12	2	6	16	15	3
Foreskin	20	13	6	1	0	14	5	1	0
Cervical cancer	20	3	8	5	4	2	7	6	5

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