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The paradox of IL-10-mediated modulation in cervical cancer (Review)

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Abstract. Interleukin-10 (IL-10) has opposing effects as an anti-inflammatory (potentially cancer-promoting) and antiangiogenic (potentially cancer-inhibiting) agent. The role of IL-10 in cervical cancer is also dual. Here, we review the IL-10-mediated tumor-promoting effect and tumor-inhibiting effects in cervical cancer, among which, human papilloma virus (HPV), human leukocyte antigen-G (HLA-G) and IL-10 polymorphisms are associated with the development of cervical cancer. IL-10 is also used for the therapy of cervical cancer through enhancing proliferation, expression of immunologically important surface molecules and increasing Th1 cytokine production and cytotoxic potential in HPV-specific CD8 (+) cytotoxic T lymphocytes.

Contents

1. Introduction

Cervical cancer is the second most common cause of cancer mortality among women worldwide (1). Chronic infection of the keratinocytes of the uterine cervix by the human papilloma virus (HPV) is associated with the development of cervical cancer (2). However, HPV infection alone is not sufficient for cancer development, since the majority of women with HPV infection do not develop cervical cancer (1,3). Cytokines, especially interleukin-10 (IL-10), play an important role in the development of cervical cancer.

The role of IL-10 in cancer remains unclear. IL-10 is a multifunctional cytokine, exhibiting immunosuppressive and anti-angiogenic properties. Consequently, IL-10 plays a dual, controversial role in human carcinogenesis, as a tumor-promoting and -inhibiting factor (4,5). Available information on IL-10 production in freshly excised human tumors, including carcinomas of the ovary, breast, kidney, lung and skin, including melanoma, has been previously reported (6). In colorectal carcinogenesis, IL-10 promotes rather than inhibits cancer growth, through its immunosuppressive activity (7). Previous studies suggested that increased IL-10 levels may control inflammatory responses and cancer development (8) and constitute a risk factor for carcinogenesis. However, in certain types of cancer, low IL-10 expression may constitute a risk factor for disease or disease progression (9). For example, certain studies have demonstrated that IL-10 has the ability to inhibit tumor growth and metastasis in several types of cancer (10-12). The IL-10 low-producer haplotype (ATA) is associated with a higher risk of gastric adenocarcinoma, which may be related to the role of IL-10 as an anti-inflammatory cytokine that downregulates IL-1β, tumor necrosis factor (TNF)-α, immunoreactive fibronectin (IFN)-γ and other pro-inflammatory cytokines (13). Furthermore, low IL-10 levels are associated with a higher risk of prostatic cancer (14).

It has been demonstrated that IL-10 is highly expressed locally in biopsies from patients with premalignant lesions and cervical cancer and may induce a local state of immunosuppression. An increased number of IL-10-positive cells was detected in the cervix of patients with cervical intraepithelial neoplasia (CIN), associated with the grades of dysplasia (15). Furthermore, an increase in the levels of IL-10 was observed in cervical cancer and CIN grade III patients, compared to those with early CIN grades and healthy controls (16). The genotype predisposing to the production of high levels of IL-10 is more commonly observed in cervical cancer patients, compared to healthy women (17). However, findings of a previous suggested that the variants of chemokine receptor 2 and IL-4 receptor, rather than IL-10 or Fas ligand, increase the risk of cervical cancer (18).

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Furthermore, decreased IL-10 levels are also associated with the risk of cervical cancer (19), supporting the clinical use of IL-10 in combination with IL-2 in the treatment of cervical cancer (20). These studies suggested that IL-10 expression may play an important role in the development of cervical cancer. The dual biological function of IL-10 as anti-inflammatory (potentially cancer-promoting) and anti-angiogenic (potentially cancer-inhibiting agent reflects the conflicting data in cervical cancer.

2. IL-10 exerts a tumor-promoting effect in cervical cancer

IL-10 mRNA and/or protein have been found to be enhanced in several types of human cancer, such as renal, hepatocellular and ovarian cancer, as well as squamous and basal cell carcinoma of the skin (21-24), human gliomas (25) and melanoma (26). Furthermore, IL-10 is elevated in squamous intraepithelial lesions (SILs), which are considered as preneoplastic stages of cervical cancer (27), as well as in true cervical cancer. For example, it has been demonstrated that mononuclear cells collected from peripheral blood samples of patients with cervical SIL and true cervical cancer patients, produced higher levels of IL-10 (2,28-30). Increased serum levels and peri-tumoral IL-10 production have been reported in a number of malignancies, which have been interpreted to support the role of IL-10 in tumor escape from the immune response. The persistence of IL-10 in SILs may tolerize the immune system and permit the progression of the premalignant lesion to cancer. Expression of IL-10 in cervical lesions was most commonly upregulated in high-grade CIN. This immunosuppressive cytokine may play an important role in creating a microenvironment that favors progressive cervical disease and immune evasion by high-risk HPV (31) and may also explain the immunosuppressive state of cervical cancer patients (32). Women who are genetically programmed to produce high or moderate levels of IL-10 are more likely to develop cancer of the uterine cervix, compared to individuals genetically predisposed to low IL-10 production, suggesting that the genetically acquired ability to produce higher levels of IL-10 may be a significant factor in the development of cervical cancer (17). Therefore, one potential candidate that possesses the ability to reduce the expression of IL-10 may be effective in the treatment of cervical cancer. However, the possible mechanism of IL-10-induced tumor-promoting effect in cervical cancer is complicated.

HPV infection is the major etiological factor in cervical cancer patients. Certain investigators have hypothesized that higher IL-10 levels promote HPV growth, viral replication and malignant transformation of infected cells in women infected with the virus, which offers a possible explanation for some women with HPV developing cervical cancer, whereas others do not (19). In particular, IL-10 is highly expressed in tumor cells and its expression is directly proportional to the development of HPV-positive cervical cancer, suggesting an important role of HPV proteins in the expression of IL-10. IL-10 expression in the cervical tissues of Mexican women demonstrated a clear tendency to increase with advancing cervical cancer stage (low-grade SIL, high-grade SIL and true cancer) (33). Furthermore, IL-10 is highly expressed in the tumor cells of all patients and its expression is directly proportional to the development of HPV-positive cervical cancer, suggesting a distinct association between IL-10, HPV and the stage of cervical cancer disease (33). The elevated expression of IL-10 may allow for virus persistency, transformation of cervical epithelial cells and, consequently, cancer development (34). The upregulated production of IL-10 may inhibit immune responses against HPV infection in early cervical lesions, whereas upregulated TNF-α and uncoordinated cytokine production (elevated Th1 and Th2 cytokine levels) may reflect impaired or invalid responses in advanced-stage lesions. The detection of IL-10 and TNF-α in cervical secretions may be a useful indicator of local immune response and of the stage of the cervical lesions induced by HPV infection (35). The maintenance of IL-10 expression may contribute to the initiation of SIL, by allowing HPV to subvert the innate immunological surveillance and the efficient tumor escape mechanisms (2). In the HPV16 TC-1 tumor mouse model, IL-10 produced by tumor macrophages induces the development of a regulatory phenotype of T cells, an immune escape mechanism that facilitates tumor growth, suggesting a correlation between higher IL-10 expression and risk of cervical cancer development in HPV-infected women (36). IL-10 was found to function as an anti-inflammatory agent in the presence of HPV oncoprotein (37). Two viral oncoproteins of HPV-16, E6 and E7, play an active role in the malignant growth properties of cervical cancer cells and may be ideal targets for antigene therapy (38). When E6 oncoprotein activity is high, IL-10 is found to promote tumor growth (39). Additionally, the HPV E2 protein binds to the regulatory region of the human IL-10 gene (-2054 nt) and induces the expression of elevated levels of IL-10 mRNA in HPV-infected cells. Prophylactic vaccines against HPV infection are based on aluminum adjuvanted virus-like particles. Vaccines have been shown to protect against HPV infection and the subsequent risk of cervical cancer development (40-42), whereas transplantable tumors have long been used to demonstrate vaccine efficacy in preclinical trials in mice (43). Dendritic cells in a 3D culture model exert a notable effect on the enhancement of the immune response to the HPV16 DNA vaccine and indicate that the dendritic cell-based 3D model is a novel approach to the study of the HPV vaccine (44).

Results of a previous study demonstrated that human leukocyte antigen-G (HLA-G) and IL-10 mRNA and protein expression in cervical cancer tissues were significantly increased (45), suggesting that HLA-G and IL-10 may play an important role in cervical cancer progression. IL-10 contributes to the impairment of the anti-tumor immune response, either by downregulating human leukocyte antigen Class I expression or by increasing HLA-G expression in human trophoblasts and monocytes (46,47) and certain cancer models, such as lung cancer (48). HLA-G is known to inhibit the cytotoxic activity of T lymphocytes and natural killer (NK) cells (49,50), which is associated with cancer development and immune tolerance. High HLA-G mRNA expression may be correlated with early carcinogenesis, since it was associated with early-stage cervical cancer (45). It was demonstrated that HLA-G expression was progressively higher in patients with CIN 1 to CIN 2/3 and was the highest in patients with cervical cancer, suggesting that HLA-G expression in cervical lesions may be associated with carcinogenesis, HPV infection and host immune response (51).

Polymorphisms in cytokine genes may influence the immune response to HPV infection, possibly altering the risk of cervical cancer. IL-10 polymorphisms affect the clearance of infection with high-risk HPV types (52). The IL-10-1082 gene polymorphism may serve as a marker of genetic susceptibility to cervical cancer among Japanese women (53). The IL-10-1082 GA genotype was found at a significantly increased frequency among 77 Zimbabwean women with histologically proven cervical cancer (17). Other studies supported that the IL-10 promoter polymorphisms at -1082, -819 and -592 sites was not associated with a higher cervical cancer risk in Korean women (54,55) and did not affect the early stages of cervical carcinogenesis, but may determine the differences in susceptibility to other cervical abormalities, unrelated to HPV infection (56). Moreover, passive smokers among North Indian women, exhibiting IL-10 AC genotypes, had an increased risk of developing cervical cancer (57). Therefore, the role of IL-10 polymorphism in the development of cervical cancer needs to be elucidated by further studies.

3. IL-10 exerts a tumor-inhibiting effect in cervical cancer

The dual biological function of IL-10 as an anti-inflammatory (potentially cancer-promoting) and anti-angiogenic (potentially cancer-inhibiting) agent reflects the conflicting data in cervical cancer. IL-10 levels were found to be high in almost all cervical cancer cases (28-30). However, several gene transfection studies on IL-10 have demonstrated that IL-10 has the ability to inhibit tumor growth and metastasis in several types of cancer, although the mechanisms have yet to be elucidated. IL-10 may act by inhibiting angiogenetic factors, such as vascular endothelial growth factor, IL-1β, TNF-α, IL-6 and metalloproteinases, or by enhancing NK cell-dependent tumor cell lysis (10-12). The IL-10 ATA haplotype is associated with an increased risk of gastric adenocarcinoma and this may be related to the role of IL-10 as an anti-inflammatory cytokine that downregulates IL-1β, TNF-α, IFN-γ, as well as other pro-inflammatory cytokines (13). A small synthetic peptide derived from IL-10 may increase tumor sensitivity to NK cells in human melanomas, which may prove relevant in the designing of future strategies for cancer immune therapy (58). Low IL-10 levels are associated with a higher risk of prostatic cancer (14). Furthermore, decreased IL-10 levels are also associated with a higher risk of cervical cancer (19). Previous studies suggested that higher levels of IL-10 may prevent cervical neoplasia by assisting in the elimination of HPV (59). IL-10 enhances the proliferation and expression of immunologically important surface molecules and increases Th1 cytokine production and the cytotoxic potential of HPV-specific $CD8^+$ cytotoxic T lymphocytes, supporting the clinical use of IL-10 in combination with IL-2 in the treatment of cervical cancer (20). However, there are no *in vivo* data to support this hypothesis, since Th1 cytokine levels are always decreased in the presence of high IL-10 levels (20).

4. Conclusion

IL-10 is widely known as an immunosuppressive cytokine by virtue of its ability to inhibit macrophage-dependent, antigen-specific T-cell proliferation and macrophage-dependent production of cytokines by T cells (60,61). However, increasing evidence has challenged the perception of IL-10 solely as an immunosuppressive cytokine affecting T lymphocytes (62,63). Clinical evidence demonstrated that the high-producing IL-10 genotype was significantly increased among Zimbabwean cervical cancer patients (17) and North Indian women exhibiting the high-producing IL-10 genotype had an increased risk of developing cervical cancer (57). Other clinical studies demonstrated that the administration of IL-10 in combination with IL-2 following antigen stimulation, consistently increased the intracellular expression of Th1 cytokines, proliferation, intracellular perforin levels, cytotoxic activity and IFN-γ expression in cytotoxic T lymphocyte cultures, supporting the clinical use of IL-10 in combination with IL-2, for the *in vitro* expansion and potentiation of tumor-specific cytotoxic T lymphocytes for the treatment of cervical cancer (20). These studies resulted in conflicting data regarding IL-10-mediated modulation in cervical cancer by immunosuppressive and immunoenhancing effect. However, clinical evidence from other studies suggested that IL-10 was not associated with a higher cervical cancer risk in Korean women (54,55) and did not affect the early stages of cervical carcinogenesis, but may determine differences in susceptibility to other cervical abnormalities, unrelated to HPV infection (56). Therefore, the role of IL-10 in cervical cancer development requires further investigation.

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