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In situ immunopathological events in human cervical intraepithelial neoplasia and cervical cancer: Review

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ABSTRACT

Neoplasia of the cervix represents one of the most common cancers in women. Clinical and molecular research has identified immunological impairment in squamous intraepithelial cervical lesions and cervical cancer patients. The in-situ expression of several cytokines by uterine epithelial cells and by infiltrating leukocytes occurs during the cervical intraepithelial neoplasia and cervical cancer. Some of these cytokines can prevent and others can induce the progression of the neoplasm. The infiltrating leukocytes also produce cytokines and growth factors relate to angiogenesis, chemotaxis, and apoptosis capable of modulating the dysplasia progression. In this review we analyzed several interleukins with an inductive effect or blocking effect on the neoplastic progression. We also analyze the genetic polymorphism of some cytokines and their relationship with the risk of developing cervical neoplasia. In addition, we describe the leukocyte cells that infiltrate the cervical uterine tissue during the neoplasia and their effects on neoplasia progression.

Introduction

Cervical cancer ranks third in cancer incidence worldwide and is the most frequent gynecological cancer in developing countries [1, 2]. The relationship between the immune system and cancer has been studied for many years. Rudolf Virchow [3] proposed this relationship centuries ago. Thus, immune factors such as infiltrating cells, types of cytokines, and other molecules related to the immune system have been characterized as predictive factors in the evolution of cancers. It is generally accepted that inflammation and its cells and soluble mediators are involved in the evolution of cancerous lesions, some inducing progression and others inducing inhibiting of tumor evolution [4, 5]. There are well known mechanisms during inflammation that lead to tumor growth. These include DNA damage and the disruption of the extracellular matrix by reactive oxygen species [6] and metalloproteinases [7] respectively, and the stimulation of tumor growth by cytokines such as IL-1B [8] and IL-8 [9]. In addition, the immune system during inflammation leads to modifications of both the tumor cells and the microenvironment. In this regard, cytokines such as vascular endothelial growth factor (VEGF) induce neoangiogenesis, along with disruption of the extracellular matrix, tumor cell migration, and metastasis [10]. The main cells that infiltrate cancerous tumors and modify their evolution are monocytes/macrophages (Mn/MΦ) and lymphocytes. Mn/MΦ, which represent the major component of tumor infiltrates, produce high amounts of cytokines such as IL-1β, IL-6, IL-23, and TNF-α, which are important in tumor modulation during inflammatory processes [10, 11].

Besides the relationship between inflammation and tumorigenesis, there are other cells of the immune system that produce mediators capable of modulating tumor evolution. The expression of tumor antigens on cancerous cells induces the formation of CD8+ lymphocyte clones with cytotoxic activity and capable of slowing tumor growth, and together with the activity of CD4+ lymphocytes represent the most important anti-tumor activity. In this regard, CD8+ lymphocytes induce tumor cell apoptosis using granzymes [12] and CD4+ lymphocytes produce cytokines and chemokines such as IFN-γ, IL-12, CXCL9 and CXCL10 inducing activation and accumulation of CD8+ lymphocytes [13, 14]. Tumor cells in response to these anti-tumor activities can produce mediators that induce immunosuppressive effects on the immune system. The production of cytokines such as IL-10 and TGF-B, can inhibit the cytotoxicity and proliferation of T-lymphocytes [15]. Tumoral cells can also express ligands such as PDL1 and PD-L2 which when binding to PD-1 receptors on T lymphocytes inhibit their activity [16, 17]. Tolerance to tumor antigens mediated by the activity of CD4+ Treg lymphocytes and myeloid suppressor cells has also been demonstrated [15]. In this way,

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this interconnected network of cells (lymphoid, myeloid, endothelial, lymphatic, and stromal cells) represents the tumor microenvironment, that is involved in anti-tumor and pro-tumor responses by the activation or inhibition of immune system, respectively.

Approximately one third of cancerous tumors are linked to inflammation induced by microorganisms. In this respect and focusing on this review the human papillomavirus (HPV) is highly involved in the induction of cervical and neck cancer [18, 19]. HPV is a small DNA virus that can infect the skin and respiratory and anogenital tract with the ability to induce cancers [20]. According to their ability to promote malignancy are classified into low- risk and high-risk viruses. Viral proteins E6 and E7 have been evaluated for their ability to induce alterations in the proliferation and differentiation of cells that invade. High-risk HPV types 16 and 18 are involved in 99% of cervical cancers [20]. After viral cell invasion the proteins E6 and E7, bind and inactivate the tumor-suppressor gene product p53, and the retinoblastoma tumor-suppressor protein (pRb), respectively [21], these proteins are required for malignant conversion. These facts support the hypothesis that E6 and E7 are related to the onset and maintenance of human cervical cancers.

In addition to the pro-tumor effect induced by HPV, the immune system response to this infection occurs. Both the innate and adaptive immune systems are involved in the defense against HPV infection and the induced cervical neoplasia [22, 23]. Viral protein-specific CD4+ *T* lymphocytes interact with both early and late viral peptides in the context of their binding to the histocompatibility complex class II (HLA II) on antigen-presenting cells (dendritic cells, Mn/MΦ) [22, 23]. Activation of CD4+ *T* cells leads to the production of various cytokines that can inhibit or promote HPV infection and neoplastic lesions. In this regard, Th1 cytokines (INF-gamma, IL-2 and TNF-beta) have a beneficial effect because they reduce neoplastic lesions, while Th2 cytokines (IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13) produce a deleterious effect promoting neoplastic lesions; however, IL-4 and IL-5 can generate development of B-lymphocytes and induce strong antibody production [24].

Cytolytic T lymphocytes (CD8+) play an important role in HPV infection and cervical neoplasia, both by destroying the cells that possess the viral antigens in conjunction with HLA class I and by destroying cells presenting neoplastic antigens. The cytotoxic action of CD8+ cells requires signals sent by dendritic cells and activated CD4+ cells [25]. The HPV viral proteins E6 and E7 appear to be very important in the action of CD8+ cytolytic cells. However, more studies are needed to determine the role of CD8+ cytotoxic lymphocytes in the regression of cervical neoplasia [26]. These immune factors are reflected in cervical biopsies from patient with HPV infection, and from patients with different degrees of cervical intraepithelial neoplasia (CIN) and cervical cancer. In this regard, histological analysis of cervical lesions shows that HPV infection is restricted to the cervical epithelium, and high infiltration of Mn/MΦ, NK cells, and CD4+ and CD8+ *T* lymphocytes into the epithelial layer is observed. This infiltration is accompanied by increased expression of adhesion molecules (E-selectin and VCAM) in blood vessel endothelial cells and the production of chemokines such as RANTES [27, 28]. In cases of CIN and cervical cancer, a reduction of Langerhans cells is seen in both cases. These epithelial dendritic cells are important as antigen presenting cells, necessary for the activation of T lymphocytes. The absence or decrease of these cells may result in T-lymphocytes with a greater capacity for tolerance than for cytolytic activity [29, 30]. Diminished Langerhans' cells have been associated with HPV infection [31].

The evolution of CIN is unpredictable and histopathological analyses cannot predict it. Analysis of biomarkers may be useful to determine progression or regression of the lesions. These biomarkers include viral factors (viral genotype, viral DNA methylation), host factors (human leukocyte antigen, markers of lymphoproliferation, amplification of telomerase and epigenetic effects induced by HPV and cellular factors (Ki-67, p53 and pRb) [32]. Cervical cancer is a major gynecological problem in developing and underdeveloped countries. Despite the significant advancement in early detection and treatment modalities, several patients often show poor prognosis and significantly high mortality rates especially recurrent cervical cancer [33]. The development of non-invasive biomarker with the potential to provide more specific tumor characterization before treatment begins or during therapy may permit clinicians to administer a more individualized anti-cancer treatment. At present, new biomarker techniques have appeared for an efficient diagnosis of cervical neoplasia. Radiomics is a mathematical-statistical procedure extracting information from medial images, which has the potential for prediction of staging, histological type, node status, relapse, and survival in patients with cervical cancer [34]. Deoxyribonucleic and ribonucleic acids have been used as biomarkers in the diagnosis and prognosis of cervical neoplasia. In this regard, several DNA methylation markers such as ANKRD18CP, C13ORF18, EPB41L3, JAM3, SOX1 and ZSCAN1 have high sensitivity and specificity to detect CIN2 [35]. Other host-cell DNA methylation markers (*ASCL1, LHX8, ST6GALNAC5, GHSR, SST* and *ZIC1*) have high sensitivity and specificity for CIN3 and cancer of HPV-positive women [36]. The efficacy of high-risk human papillomavirus (HR-HPV) and DNA image cytometry (DNA-ICM) status have been used to identify CIN2 and CIN3 [37]. MicroRNA (miRNA) are involved in carcinogenesis and response to viral infections. Human papillomaviruses induce aberrant expression of many cellular miRNAs, this dysregulation could be used as a marker in early diagnosis of HR-HPV infection, CIN and cervical cancer [38]. Aberrant expression of lncRNAs (transcripts) has been used as a key factor in cervical tumorigenic process [39]. Recently it has been realized that non-coding RNAs (ncRNA), including long noncoding RNAs (LncRNAs), microRNAs, circular RNAs and piRNAs (PIWI-interacting RNAs), can all play a role in gynecological cancer and several clinical trials are underway looking at these biomarkers and therapeutic roles [40]. For histological diagnosis of high-grade cervical lesions, $p16^{INK4a}$ immunostaining has proven to be useful. Therefore, $p16^{INK4a}$ immuno-cytology may be applicable as a favorable technology for cervical cancer screening [41].

The *in-situ* localization of factors that modulate the progression of CIN to cancer in the cervical tissues have been extensively studied [31]. Immunological and other factors associated or not with HPV infection have been shown in cervical biopsies from women with different degrees of cervical injury. Genital infection with certain strains of HPV is associated with a high risk of malignant transformation, and HPV-associated CIN can become invasive cancer. Host factors are critical in regulating tumor growth by expressing different modulating factors including immune response [42]. This review focuses on the possible *in situ* role of cytokines and leukocytes on the evolution of cervical neoplasia (Table 1).

In-situ cervical cytokines in CIN and cervical cancer

Cytokines are low molecular weight proteins which have a complex regulatory influence on inflammation and immunity. They have a role in development of immune and inflammatory response involving hematopoietic cells, lymphoid cell, and various pro-inflammatory and anti-inflammatory cells [43]. About 200 cytokines are recognized to date. Cytokines are categorized on the basis from which they are produced either from Th1 cells (Interleukin-2: IL-2, interferon-gamma: IFN-γ, tumor necrosis alpha: TNF-α), Th2 cells (IL-4, IL-5, IL-6, IL-9, IL-13), Th17 (IL-17, IL-22, IL-21,IL-25) and T regulatory cells (Treg: IL-10, IL-35, TGF-β) [44]. According to their secretion, cytokines can be lymphokines (secreted by T cells and regulate the immune response), proinflammatory (amplify and perpetuate the inflammatory process), anti-inflammatory (negatively modulate the inflammatory response), growth factors (promote cell survival) and chemokines (chemotactic for inflammatory cells) [45]. In addition to inflammation, immunity and infections, cytokines have now expanded their domain to atherosclerosis and cancer [46].

Chronic inflammation is associated with cancers including cervical cancer. During the inflammation, the upregulation of cytokines and the presence of immune cells in cervical tissue modulate the incidence of inflammation and the progression or regression of cervical dysplasia

Table 1
Effect of cytokines on the evolution of cervical intraepithelial neoplasia.

Cervical neoplasia	Cytokines
Prevent progression	IL-2, INF-γ, IL-12, IL-21, IL-10, IL-32, IL-37, and TGF-β1
Induce progression	IL-1, IL-6, IL-8, IL-10, IL-17, IL-32, TGF-β1, MCP-1, and RANTES
Dual effect	IL-10, IL-32, and TGF-β1

[47]. The production of cytokines by various cervical cells and by infiltrating leukocytes can be triggered by antigenic stimuli, including HPV infection. In this regard, significantly lower levels of IL-1α, IL-2, IL-4 and TNF-α are detected in cervical samples obtained from HPV infected patients with low-grade dysplasia when compared to samples obtained from high-grade dysplasia [48]. HPV is capable of inducing down-regulation in the expression of interferon and upregulation of IL10 and transforming growth factor (TGF-β1) to produce a local immunosuppressive environment, which, along with altered tumor surface antigens, forms an immunosuppressive network that inhibits the antitumor immune response [49]. However, controversial findings regarding to the role of HPV have been reported. In this regard, patients with precancerous lesions of the uterine cervix showed prevail of type Th1 cytokines (IL-2 and IFN-γ) in relation to Th2 (IL-4 and IL-6), whether they are HPV positive or negative [50], suggesting that the type of immune response may be independent of HPV infection. Immunological *in situ* events can be reflected in the microenvironment, since high levels of IL-12p40, IL-10, TGF-β1, TNF-α and IL-1β have been found in cervicovaginal washing fluid from patients with cervical cancer infected by HPV [51]. In general, the production of cytokines in the cervical tissue during the malignant transformation can induce, suppress, or have both effects on the progression of the neoplasm.

Interferon-gamma

The involvement of the immune response in the progression of human uterine cervix cancer has been documented. The *in-situ* presence of cytokines in cervical tissues from patients with CIN and cervical cancer support this hypothesis. The Th1 cytokines IL-2 and IFN-γ are immunostimulatory thus capable of limiting tumor growth. The Th2 cytokines interleukin 4 (IL-4) and interleukin 10 (IL-10) are immunoinhibitory and are thus capable of stimulating tumor growth [52]. IFN-γ expression and IFN-γ mRNA were reported increased in HPV-positive high-grade CIN, suggesting the inducer effect of this infection on IFN-γ production [53, 54]. In this regard, HPV persistent infection induced an immunologic dissonance with decreasing expression of Th1 cytokines (INF-γ), that is aggravated with the progression of the disease [52]. In addition, IFN-γ treatment is an effective therapeutic method to reduce CIN lesions [55, 56].

Interleukin-1

The involvement of IL-1 in tumorigenesis, cancer progression, metastasis, and even in the response to cancer treatment (*i.e.*, chemotherapy, surgery, or radiation) has been studied extensively. IL-1 dysregulation has been shown to be associated with almost all types of human malignancies [57]. IL-1 plays an important role in inflammation and inflammation plays a role in the pathogenesis of cancer in two different pathways, an intrinsic pathway, where genetic mutations activate oncogenes and cause neoplasia, and an extrinsic pathway, where an inflammatory environment increases the susceptibility to cancer [58]. The expression of IL-1 is higher in CIN compared to healthy cervix uteri tissue [59], and it is even higher in CIN3 compared to CIN1 [48, 59]. IL-1 can induce normal and tumor cell growth [60]. In CIN with a co-existent HPV infection, an increased number of cells expressing IL-1 are seen, because HPV16, −18 stimulates IL-1 release in keratinocytes, and IL1 stimulates proliferation of immortal and malignant cervical epithelial cells [60]. Single and IL-1 gene-cluster polymorphisms have been suggested to be associated with cervical cancers [61]. However, some studies show increase in the risk of progression of pre-neoplastic lesions to *cervical tumor* in women with lower IL-1β gene expression [62].

Interleukin 2

IL-2 is a cytokine produced by T cells during an immune response, it is necessary for the growth, proliferation, and differentiation of naïve T cells into effector T cells. This cytokine is used as a therapeutic cytokine in cancer [63, 64]. The expression of IL-2 and its receptor in cervical cancer cells have been documented. Previous studies have shown an inverse relationship between IL-2 expression and CIN progression in patients with cervical dysplasia; as the degree of cervical lesions increased, the expressions of IL-2 decreased, and IL-10 increased [65]. This association could be a potential factor that influence the pathogenicity of HPV infection and the occurrence and development of cervical lesions [65, 66]. This inverse association between degree of CIN and IL-2 has also been demonstrated in vaginal immune factor [67]. Different concentrations of IL-2 could activate effector cells of the immune system cells. Low concentrations of IL-2 may promote the regulatory microenvironment and tumor growth. High concentrations of IL-2 activate immune system cells, such as CD8+, CD4+, and $\gamma\delta$ T cells and NK cells with capacity to eliminate tumor cells [68]. The anti-tumoral effect of IL-2 is based not only on the ability of this cytokine to stimulate cellular-mediated immunity, but also because of its direct effects on tumor cells [69].

Interleukin-6

Interleukin 6 (IL-6) is produced in response to infections and tissue injuries and contributes to host defense through the stimulation of acute phase responses, hematopoiesis, and immune reactions. IL-6 plays a pathological effect on chronic inflammation and autoimmunity [70]. IL-6 has recently shown to act *in vitro* as a growth factor for cervical carcinoma cell lines, and increased IL-6 gene and protein expression has been reported associated to severity of cervical neoplasia and in invasive cervical cancer, suggesting a role in the pathogenesis of the uterine cervix neoplasia and in advanced neoplastic cervical lesions [71]. This effect of IL-6 may be associated to the capacity of this cytokine to promote tumor angiogenesis and the development of cervical cancer [71]. Production of IL-6 might also contribute to a local immunosuppressive effect in cervical dysplasia, silencing an autocrine IL-6 response and preventing constitutive production of the mononuclear cell-attracting chemokine (MCP-1). Both mechanisms might help the tumor to escape from the immune system [72]. In addition, dysplasia severity has been shown associated with IL-6 levels and inversely associated with IL-2 levels (an anti-tumor cytokine) [73]. Circulating levels of this cytokine have been associated to the degree of cervical dysplasia in patients with persistent low-grade squamous intraepithelial lesion, suggesting an additional biomarker for early cervical neoplasia [74].

Interleukin-8

Interleukin-8 (IL-8), a proinflammatory chemokine, induces neutrophil chemotaxis and degranulation and it is a regulatory factor within the tumor microenvironment. IL-8 activates multiple intracellular signaling after interactions with G protein-coupled receptors (CXCR1 and

CXCR2) on cell surface [75]. Increased expression of IL-8 and/or its receptors has been characterized in cancer cells, endothelial cells, infiltrating neutrophils, and tumor-associated macrophages [76]. Therefore, IL-8 serves an important function in chronic inflammation and cancer development. Enhanced expression of IL-1β and IL-8 indicates (Th2 inflammatory response) has been reported in uterine cervical region associated to the progression of CIN lesions [77]. The upregulation of IL-8 in cervical cancers correlates with angiogenesis, monocyte/macrophage infiltration and it is a prognostic indicator of cancer evolution [78]. *In vitro* analysis shows that exogenous IL-8 was capable of inducing IL-8 receptors (IL-8RA, IL-8RB) on Hela cells and increasing migratory and proliferative efficiencies of those cells [79]. In addition to, blockade of IL-8 with an antibody or small hairpin RNA demonstrated significant anti-tumor effects in a xenograft model and in cellular cultures [80].

Interleukin-10

IL-10 is a cytokine with multiple, pleiotropic effects in immunoregulation and inflammation. It downregulates the expression of Th1 cytokines, mayor histocompatibility complex (MHC) class II antigens, and co-stimulatory molecules on macrophages [81]. The up-regulated expression of IL-10 can inhibit immune responses may be inducing an immunosuppressive environment by upregulating HLA-G expression and downregulating HLA class I expression [82]. In general, the higher levels of IL-10 suggest a potential down-modulation of tumor-specific immune responses to HPV-infected lesions. This phenomenon appears to provide a tumor 'progressive' microenvironment in these patients with cervical neoplasia [83]. Bypassing the local immunological defense reactions in the cervix is one of the prerequisites for HPV infections to progress to CIN. IL-10 over-expression along with HPV infection is one of the independent covariates of CIN2/3, creating a microenvironment that favors progressive cervical disease and immune evasion by HPV [84].

Interleukin-17

IL-17 is a cytokine with diverse functions in host defense and in the pathology of autoimmune disorders, chronic inflammatory diseases, and cancer. IL-17-producing cells may play a role in antitumor immunity. However, recently Th17 cells and their cytokines have been implicated in both pro and anti- tumorigenic processes. Expression of IL-17 and IL-23 (a major inducer of IL-17) has been reported elevated in human HPV-infected patients with cervical epithelial hyperplasia suggesting an immunosuppressive role for IL-17 in HPV-associated epithelial hyperplasia [85]. According with this, increased levels of IL-17 in supernatant of cervical tissue homogenate from patients with CIN infected by high-risk HPV showed the tendency to progression of CIN with high-risk HPV infection [86]. Other studies show association of IL-17 with other molecules in cervical dysplasia. Human leukocyte antigen G (HLA-G) and IL-17 expression in specimens with CIN 1 has been reported, suggesting that these molecules have a contribution towards cervical progression. These data suggest that HLA-G and IL-17 expression may be an early marker for assessing the progression of cervical lesions [87]. Increased number of IL-17-positive cells and MTA1 (metastasis associated 1) expression in CIN and cervical cancer compared to normal cervical tissues have been reported. The number of IL-17-positive cells was positively correlated with MTA1 suggesting progression of dysplasia. Analysis in cellular cultures show that IL-17 upregulates MTA1 mRNA and protein expression to promote HeLa and DU-145 cells migration and invasion [88]. In addition, IL-17A was observed upregulated in the cervical mucus from patients with cervical cancer and CIN associated with more severe cervical neoplasia [89].

Interleukin-21 and interleukin-12

Interleukin-21(IL-21) stimulates cytotoxicity and IFN-γ production in natural killer (NK) cells suggesting effective anti-tumor action) [90]. Interleukin-12 (IL-12) is a potent stimulator of T-cell function. IL-12 is known to stimulate effector cell populations, such as cytotoxic T cells and natural killer cells with anti-tumor effect [91, 92]. Cervical cancer cells are known to produce an extensive range of cytokines and chemokines, including IL-12 [93]. IL-21 and IL-12 have been known to be effective antitumor agents, enhancing the cytotoxicity of peripheral blood mononuclear cells in patients with CIN3 and cervical cancer and the possible mechanisms may be due to down-regulated Treg and Th17 cell differentiation [94]. IL-12 treatment in women with cervical cancer and HPV infection improved lymphoproliferative responses to HPV in a clinical trial, suggesting specific activation of lymphocytes by this cytokine [95].

Interleukin-32

Interleukin 32 (IL-32) was initially identified in activated natural killer (NK) and T cells, and its expression is strongly augmented by microbes, mitogens, and other pro-inflammatory cytokines. IL-32 is an amplifier of inflammation through its stimulatory effects on pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α. Since IL-32 expression is increased in inflammatory diseases and amplifies inflammatory cytokines, it is conceivable that IL-32 is strongly associated with various cancers related to inflammation [96]. IL-32 is present at substantial levels in cervical cancer tissues and in HPV-positive cervical cancer cells. The high-risk variant of HPV induces IL-32 expression via E7-mediated cyclooxygenase 2 stimulation [97]. IL-32 may indirectly promote tumor angiogenesis via inducing other cytokines and growth factors that it is crucial in the pathogenesis and progression of cancer [98].

Interleukin-33

Interleukin 33 (IL-33) is a dual function cytokine that also acts as a nuclear factor. IL-33 resides in the nucleus of the cells and upon tissue damage, necrosis, or injury, it is quickly released into extracellular space where it binds to its receptor suppression of tumorigenicity 2 (ST2) on the membrane of target cells to potently activate a Th2 immune response. The IL-33/ST2 axis is emerging as a potent modulator of the microenvironment. By recruiting a cohort of immune cells, it can remodel the microenvironment to promote malignancy or impose tumor regression [99-101]. It has shown the essential protective anti-viral immunity role of IL-33 that it is upregulated by IFN-γ. IL-33 may play a role in the pathogenesis of HPV induced cervical neoplasia by the effect of IL-33/ST2 on HPV infection. In this regard, diminished expression of IL-33 and IL33/ST2 has been reported in progression of CIN and carcinogenesis mediated by HPV infection. This defective anti-viral immunity may be related to diminished local production of IFN-γ [102, 103].

Interleukin 37

Interleukin (IL-37), a new IL-1 family member, is expressed in various normal cells and tissues and is regulated by inflammatory stimuli and pro-cytokines via different signal transduction pathways. This cytokine is expressed in a variety of cancers, chronic inflammatory and autoimmune disorders, and exerts anti-inflammatory effects [104]. Growing evidence has indicated that IL-37 is a potential anticancer molecule that mainly plays an inhibiting role in different kinds of cancers. Analysis of the effect of IL-37 on Hela cell cultures show this cytokine as a potential anticancer cytokine. IL-37 upregulated Bim (Bcl-2 family member Bim is required for apoptosis) in cervical cancer cells promoting apoptosis [105]. In addition, IL-37 suppressed cell proliferation and invasion of cervical cancer (Hela cells) and STAT3 is involved in this process. These data suggest that IL-33 is an anticancer cytokine in cervical neoplasia [106].

Transforming growth factor beta1

Transforming growth factor β1 (TGF-β1) is a multifunctional cytokine that plays important roles in cervical neoplasia formation, invasion, progression, and metastasis. TGF-β1 functions as a tumor inhibitor in precancerous lesions and early-stage cancers of cervix whereas as a tumor promoter in later stage. This switch from a tumor inhibitor to a tumor promoter might be due to various alterations in TGF-β signaling pathway, such as mutations or loss of expression of TGF-β receptors and Smad proteins. Additionally, the oncoproteins of HPV have been shown to stimulate TGF-β1 expression, which in turn suppresses host immune surveillance. Thus, in addition to driving tumor cell migration and metastasis, TGF-β1 is believed to play a key role in promoting HPV infection by weakening host immune defense [107]. Cervical carcinomas consist of tumor cell nests surrounded by varying amounts of intra-tumoral stroma containing different quantities and types of immune cells. TGF-β1 is involved in the formation of stroma and extracellular matrix and in immunosuppression. An inverse relationship between TGF-β1 mRNA expression in tumor cells and the extent of the tumor infiltrate has been demonstrated suggesting decreased neoplasia progression [108]. Alterations of the TGF-β1 signaling pathway by HPV-16 E7 protein plays an important role during the development of cervical cancer by immuno-inhibition and stimulation of tumor cell proliferation through the TGF-β1 /Smads signaling pathway [109, 110]. It has been attributed a beneficial effect to beta-carotene in relation to the risk of cervical cancer. In this respect, patients in the highest quartiles of dietary beta-carotene intakes had significantly lower cervical cancer risks than those in the lowest quartiles [111].

Chemokines

Chemokines play a role in tumor-inflammation and angiogenesis that could be involved in cervical tumor progression. IL-8 is a chemokine that was previously explained in topic 2.5. This cytokine can be expressed in CIN in conjunction with other chemokines. In this regard, monocyte chemoattractant protein-1 (MCP-1) and IL-8 expression were found increased in CIN accompanied by an increment of lymphocyte infiltration co-expressing CD3/MCP-1 and CD3/IL-8 according to the CIN evolution [112]. The presence of an eosinophilic infiltrate in patients with cervical squamous carcinoma has been shown to correlate with a worse overall survival, suggesting a less effective immune response in these cases. Type 2 cytokines such as IL-4 and IL-5 known to attract eosinophilic granulocytes, have been reported up-regulated in cervical cancer, findings that might explain the worse clinical outcome seen in cervical cancer patients with an eosinophilic tumor infiltrate [113, 114]. The expression of chemokines has also been reported in liquid based cervical samples. In this regard, increased IL-8 (neutrophil granulocyte attractant) was found in liquid based cervical samples and associated with cervical cancer [115]. Examination of co-expression patterns of chemokines in relation to HPV infection status in the cervical mucus from patients with cervical cancer and CIN showed upregulation of RANTES (Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted) and MCP-1 associated with more severe cervical neoplasia [89]. Fig. 1 shows the trend of the different cytokines in the modulation of cervical dysplasia progression.

Cytokine genetic polymorphisms

Results from cytokine genetic polymorphisms and cervical dysplasia studies are sometimes conflicting, and the association is not always clear. Polymorphisms in regulatory and coding regions of cytokine genes have been associated with susceptibility to cervical neoplasia. In this regard, it has been reported that TNFA -308A allele is associated with susceptibility to HPV infection and IL18 -607A allele confer protection against HPV infection [116]. TGF-β1 −509T allele confers marginal protection for early stage 1B but risk for stage II of cervical cancer

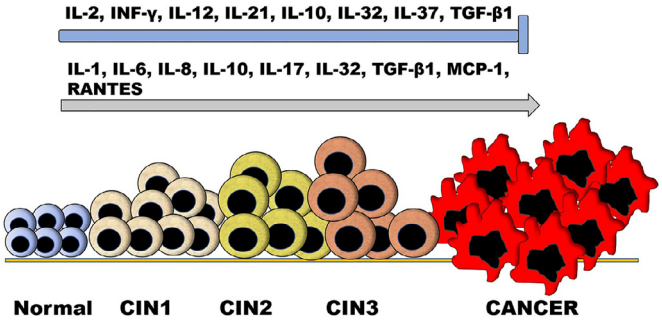

Fig. 1. Effect of cytokines on the progression of cervical neoplasia. In general, cytokines have the effects of slowing or preventing the progression of the neoplasm, inducing its progression, or having a dual effect according to the circumstances. Cytokines that prevent progression of the malignancy (⊤) include: IL-2, INF-γ, IL-12, IL-21, IL-10, IL-32, IL-37, and TGF-β1; those that induce progression (↑): IL-1, IL-6, IL-8, IL-10, IL-17, IL-32, TGF-β1, MCP-1, and RANTES; and those that may have a dual effect: IL-10, IL-32, and TGF-β1.

[117]. Several studies suggest that some polymorphic sites change the cytokines levels and influence the cancer development in HPV infected patients. Evaluation of functional polymorphisms at +874 (T/A) IFNγ and +1188 (A/C) IL-12B genes in cervical smears samples did not show significant differences between CIN patients and control groups on IFN-γ allelic polymorphism [118]. Resistance to apoptosis through the Fas pathway might enable many cancers to escape the immune system. A possible role for the IL-10 gene (for the A-allele of the IL-10-592 polymorphism) in CIN progression and squamous cell cervical cancer has been reported. In addition, a role for the Fas gene (polymorphism at position −670 of the Fas promotor) in the development of adenocarcinoma of the cervix has also been reported [119]. IL-10 -1082 gene polymorphism has been shown as a marker of genetic susceptibility to cervical cancer among Japanese women [120]. IL-6-*597A/G* and TNF-α-308G/*A* polymorphisms showed increased risk of cervical cancer [121]. Single and IL-1 gene-cluster polymorphisms have been suggested to be associated with cervical cancers [61]. Plasma IL-1β level and IL-1β C-511T polymorphism may consider as candidate biomarkers for cervical cancer in Egyptian women [121, 122]. However, the IL1β gene, encoding IL-1β cytokine, contains several single nucleotide polymorphisms and IL*1B* -511 C/C genotypes were significantly associated with a decreased risk of cervical cancer in korean population [123]. IL-12A rs568408 polymorphism contributed to increasing risk of cervical cancer, providing evidence that IL-12 polymorphisms may play a potential role in cancer risk [124].

Circulating cytokine positive leukocytes

In situ cytokines events in cervical tissues can be reflected in the circulation. In this regard, circulating mononuclear leukocytes from HPV 16 and 18 status patients showed decline levels of IL-2 in high-grade CIN and cancer patients, whereas IFN-γ levels were decreased only in patients with advanced cancer of cervix. In addition, an increase in the levels of IL-4 and IL-10 in leukocytes was found in all cancer cervix and CIN3 patients, as compared to those with early CIN grades and healthy controls. The type 2 and type 1 cytokine levels were significantly correlated with HPV status [125]. In other studies, the progress of CIN2 in patients infected by HPV was accompanied with increasing levels of IFN-γ, IL-10 and TNFα positive leukocytes in the circulation [126].

In situ presence of leukocytes in human cervical intraepithelial neoplasia and cervical cancer

Extensive studies have been conducted on the role of cytokines in CIN and cervical cancer [127]. The presence of cytokines in association with both infiltrating and cervical tissue cells is an important aspect

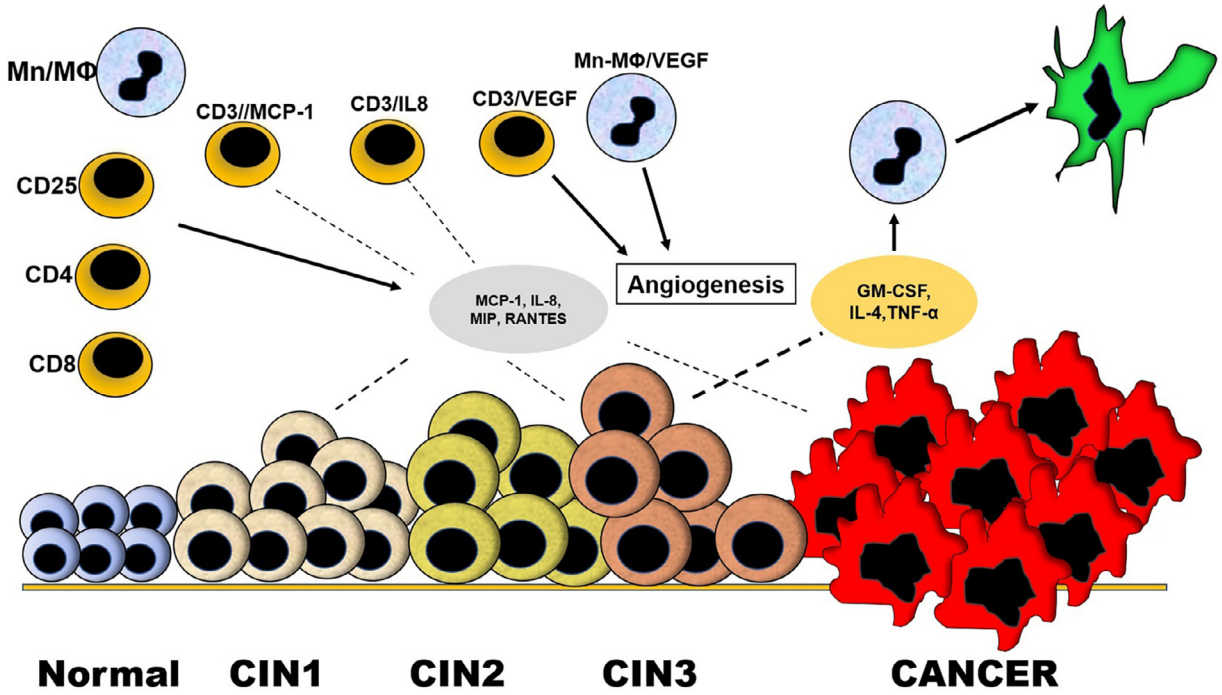

Fig. 2. Infiltration of leukocytes into the neoplastic cervical tissues. During cervical dysplasia, cytokines capable of attracting leukocytes (chemokines) and inducing leukocyte infiltration can be produced. These infiltrating cells can be mononuclear cells with phenotypes of CD8, CD4, CD25 and monocytes/macrophages (Mn/MΦ). Some of the infiltrating cells may be producers of MCP-1 and IL-8 (CD3/MCP-1, CD3/IL-8) and contribute to the overall production of these chemokines during the neoplasia. Other infiltrating cells can produce vascular endothelial growth factor (CD3/VEGF, Mn/MΦ/VEGF) and contribute to angiogenesis facilitating the dysplasia progression. In situ production of granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-4 and TNF-α by cervical tissue during the cervical dysplasia can induce differentiation of monocytes/macrophages into dendritic cells, relevant cells against HPV infection, the main inducer of cervical dysplasia.

of the pathogenesis of CIN and cervical cancer. Tumors commonly are infiltrated by leukocytes. The immune cell infiltration into the cancer tissue included increased numbers of monocyte/macrophages, helper T cells (CD4+), and CD25+ lymphocytes compared to benign tissue [128]. Chemokines are cytokines which induce chemotaxis on many cell types which play a crucial role in inflammatory processes and in tumor associated angiogenesis, as well as in tumor progression. The production of attractants for leukocytes such as MCP-1, IL-8 and macrophage inflammatory proteins (MIP) has been identified in tumor tissues of patients with different neoplasms [129, 130]. In this regard, increased expressions of MCP-1 and IL-8 in CIN were observed accompanied by increment of lymphocyte infiltration co-expressing CD3/MCP-1 and CD3/IL-8. CD3/MCP-1 cell percentage was found decreased and CD3/IL-8 percentage increased according to the CIN evolution, suggesting tumor progression [131]. MCP-1 and IL-8 positive lymphocytes may potentially contribute to the overall concentration of chemokines produced during cervical dysplasia and enhance leukocyte attraction.

The inflammatory microenvironment has been linked to the progression of cervical neoplasia. Th17 lymphocyte subtype produces the anti-inflammatory cytokine IL-17 that can be involved in the progression of these neoplasms. It has been shown that CCL20 is related to the decreased of Th17 lymphocytes in cervical neoplasia suggesting a role of this molecule in the neoplasm progression [132]. In addition, the expression of CCL20 is directly linked to the expression of dendritic cells. Thus, viral proteins such as E6 and E7 from HPV that can decrease the expression of CCL20, decrease the presence of dendritic cells in cervical neoplasia and therefore are important factors in tumor progression [133]. However, the expression of chemokines such as CXCL9/10/11 is highly correlated with high expression of dendritic cell subtypes (CD141/BDCA3$^+$cDC1) in squamous cell carcinoma primary tumors [134].

The association of angiogenesis and leukocyte infiltration in CIN has also been reported. Increased expression of vascular endothelial growth factor (VEGF) co-expressed in lymphocytes (CD3/VEGF) and in monocyte-macrophages was observed related to the progression of CIN. A significant increment of CD3/VEGF lymphocytes was found in CIN3 and monocyte-macrophages expressing VEGF in CIN2 and 3 [112]. The expression of VEGF in lymphocytes and monocytes/macrophages is suggestive of VEGF production by these leukocytes and may play an important role in the induction of angiogenesis by these cells. In this regard, angiogenesis is a complex process that plays an important role in the development of many types of cancer. The role of angiogenesis in cervical neoplasia is related to HPV- inhibition of p53 and stabilization of hypoxia-inducible factor-1α. Both mechanisms are able to increase expression of VEGF [135]. Activation of VEGF promotes endothelial cell proliferation and migration, favoring formation of new blood vessels and increasing permeability of existing blood vessels [135]. Associated with those findings, increased micro vessel density was reported in CIN3 and cervical cancer [136, 137] (Fig. 2).

Cytokines can act *in situ* to induce differentiation of infiltrating mononuclear leukocytes to dendritic cells. In this regard, mononuclear cells obtained from patients with low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL) and cervical cancer showed different grade of differentiation to dendritic cells according to the extent of cervical lesions (high percentage in HSIL and low percentage in LSIL) when they are stimulated by granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-4 and TNF-α [138]. The existence of dendritic cells in the cervical tissue together with the differentiation of monocytes/macrophages to dendritic cells may be relevant in the *in situ* and systemic response against HPV infection, the main inducer of cervical dysplasia [139]. Therapeutic attempts have been made to alter presence and function of infiltrating leukocytes in the cervix neoplasm. In this regard, intralesional IFN-α 2b treatment in patients with CIN 2/3 resulted with a reduction in CD4+ and CD8+ *T* lymphocyte infiltration [140] (Fig. 2).

Immune therapy

In general, cervical cancer (CC) immune therapy can be divided into four groups: immune checkpoint blockade, adoptive cell transfer therapy, cytokine treatment and therapeutic vaccines. Cancer cells can escape from the immune balance by provoking an immune-suppressive state and tumor growth. Checkpoint blockades aim to break microenvironment immune suppression. Programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte antigen-4 (CLTA-4) are the most promising immune checkpoints targeted in CC [141, 142]. The expression levels of PD-1/PD-L1 and CTLA-4 are high in CC, and dendritic cells and T cells express high levels of PD-1 and PDL1 in CIN samples [143, 144]. Blockade of PD-1/PD-L1 interrupted immune suppression in CC, by increasing subset of T cells, CD8+FoxP3+CD25+*T* cells and decreasing immune-suppressive Tregs cells [145]. In addition, the combination of PD-1/PD-L1 and CTLA-4 may enhance the therapeutic efficiency [146].

Antigen- specific T cell immunotherapy could be used to attack tumor evasion and may have many potential benefits. Thus, by optimizing dendritic cells maturation and adding appropriate cytokines, it is possible to obtain oncoproteins E6 and E7-specific T cells [147]. Chimeric antigen receptor T cells have been used in CC cells and achieved positive results [148]. Autologous cytokine-induced killer cell transfusion in CC patients improved immune function and life quality [149].

Cytokine therapies have been used for cancer treatment. Their specific functions in CC are not clear. However, IL-2 and IL-6 confer protection to CC cells against apoptosis [150, 151]. Immunoactive TNF- α and immunosuppressive IL-10 are associated with CC susceptibility [152].

Various therapeutic vaccines are being developed, including DNA, RNA and peptide vaccines. All of these vaccine types exerted antitumor effects through activating the T cell response, especially CD8+ cells [153, 154]. Several clinical trials have indicated that therapeutic vaccines plus immune checkpoint inhibitors or radiotherapy together induced an immune response in premalignant lesions and CC [155].

Conclusions

The *in-situ* upregulation of cytokines in the cervical tissue plays a very important role in the progression or in the reduction of cervical neoplasia. These cytokines can generally be expressed in conjunction with other cytokines and their interaction can be linked to a result regarding the evolution of cervical neoplasia. Neoplastic tissue can produce chemokines that induce the infiltration of leukocytes, which can produce various types of cytokines that modulate the neoplasm progression. Factors such as HPV infection can interact with the immune response and influence the progression of the neoplasm. Knowledge of the effects of each cytokine during cervical dysplasia is important for the therapeutic use of these molecules.

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Declaration of Competing Interest

The authors declare no competing interest.

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