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26

Predictive Value of Cellular Immune Response and Tumor Biomarkers in Patients Surgically Treated for Cervical Cancer in Relation to Clinical Outcomes

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1. Introduction

Cervical carcinoma remains a leading cause of death among women in developing countries. Because recent advances in the immune pathways of gynaecologic cancers have been achieved, this field has become important in the current practice of modern oncologists.

Contemporary investigations have focused on tumor infiltrating lymphocytes, reflecting the status of the cellular immune system in different types of cervical carcinoma.

Despite complex management of cervical cancer according to the risk stratification for recurrence and local guidelines (radical hysterectomy, meaning the removal of the uterus and cervix, one third of the vagina, the parametrial tissue at the pelvic sidewall and ligature of utero-sacrals with or without lymphadenectomy, followed by adjuvant radio and chemotherapy), up to 40% of patients still develop relapse of their cancer.

Since the immune response towards cervical cancer is thought to be important in either clearing or controlling the viral infection, the evaluation of local cellular immune response seems to be critical for the classification of patients according to their risk for the therapeutic decision and also may potentially indicate new adjuvant treatment strategies including immunotherapy. Moreover, new predictive biomarkers (including tumor proliferation and tumor invasion markers) are essential to identify patients with high risk of relapse and to optimize disease management.

Research on both intra- and peritumoral infiltration of immune cells has lead to a better understanding and management of cervical cancer, especially in recognition of new predictive biomarkers. Also, the evaluation of local cellular immune response in cervical cancer with or without relapse may indicate new strategies in order to improve survival.

Nowadays, promising vaccines to prevent the development of *Human Papillomavirus* (HPV)-induced cervical carcinoma are already distributed all over the world.

In addition to the scientific world interest in understanding the mechanisms of mucosal HPV carcinogenesis in the less susceptible organs, the findings indicate that HPV type 16 and 18 vaccines could also potentially protect HPV-vaccinated persons against cancers, including the following: anus, vagina, vulva, penis, oral cavity and oropharynx.

There has been recently a great interest in understanding the role of host's immune response in the natural history of HPV and in particular anti-viral cell mediated immunity. Several studies have shown that altered cell mediated immunity is strongly associated with increased HPV infection and cervical cancer. Persistent infection with HPV oncogenic types is the most important event in the progression to cervical precancerous lesions and cervical cancer.

Several immune cells subtypes are strongly involved in the cellular immune response after exposure to a non-self antigen including mononuclear phagocytes, natural killer (NK) cells, polymorph nuclear leukocytes and biochemical factors such as complement system.

Immune effector system involves essential processes as innate or adaptive that occurs in sequences after the exposure to a non-self antigen. After antigen ingestion, activation of NK cells allows the recognition of the processed by specific T-cells which play a central role in cellular immune response. On the other hand, B-cells control and regulate the humoral immune response.

It is now widely accepted that disease is caused by infection with high risk HPV types which may or may not be associated with clinically apparent lesion. Woman who cannot clear the viral infection became persistent HPV carriers and constitute the high risk group for progression to cervical cancer.

Current studies have suggested that immunological defects are associated with higher prevalence and persistence of HPV infection, especially in individuals with *Human Immunodeficience Virus* (HIV) infection. In addition, some evidences have found that other mechanisms than immunosuppression such as interactions between HIV and HPV viral genes may influence the increased risk of neoplasia and invasive cancer (Moscicki, 2000; Scott, 2000).

The anti-viral effects of cellular immunity have been hampered by several factors including (i) gene transcription patterns of HPV, (ii) inadequate interpretation, (iii) assessment of HPV type specificity.

Conversely, the lesions caused by HPV infection are generally localized to squamous epithelial sites. HPV has learned to evade the host's immunity through years of co-evolution, with the consequence that the immune response induced by HPV after natural infection, aiming to clear or control an incident infection with oncogenic HPV types, is, therefore, attenuated (Goncalves & Donadi, 2004; Hatch, 1999; Piersma, 2007; Scott, 2001; Stoler, 2010).

2. Epidemiology

The leading cause for human cervical cancer is still represented by HPV infection, a common sexually transmitted disease. While the risk for acquiring HPV infection is directly

linked to the number and behavior of sexual partners, most infections have a benign clinical course and resolve spontaneously. However, up to 10% of women became persistent HPV carriers and constitute the high risk group for progression to cervical carcinoma (Goncalves & Donadi, 2004; Scott, 2001).

It is widely recognized that HPV types with specific oncogenic risk include HPV type 16, HPV type 18, HPV type 31, HPV type 33, HPV type 35, HPV type 45, HPV type 51, HPV type 52, HPV type 58, HPV type 59, 66 and 68.

Based on its rarity, recurrent respiratory papillomatosis (RRP) recognized as one potential manifestation of HPV infection in the airways, gives only unsatisfactory reports.

Of notice is that for some locations the cases are in men (penile cancer) or both in men or women (anal cancer and cancers of the oropharynx and oral cavity) needs to be further examined.

3. Screening and diagnosis

The most common screening method used to detect high grade squamous intraepithelial lesions (HSIL) is conventional cervical cytology, followed by colposcopy and directed biopsy. Furthermore, the PAP-test continues to have an unclear meaning.

Thus, approximately 1/1000 of women will develop cervical carcinoma.

The findings gained during the last years on persistent high risk HPV types in women developing cervical carcinoma have provided the basis for evaluation of the clinical utility of testing for cancer-associated HPV types (Ancuta, 2009; Goncalves & Donadi, 2004; Scott, 2001).

International guidelines recommend screening in women aged 25-50 years every three years and in women aged 51-60 years every five years. Women older than 60 years of age are not the subject for screening.

Women who are both vaccinated and test negative for HPV are typically characterized by a low risk for emergent cervical disease. In addition, they can be safely reassured for a long time prior to their next screening assessment. In contrast, women who are HPV positive could undergo cytological testing and follow well-established protocols for clinical assessment.

It is widely accepted that the evaluation of cervical cancer should include a clinical staging system, as well as an imaging and biological assessment. Chest X-ray, intravenous urography, cystoscopy and proctoscopy, lymphangiography, CT scan, CT directed lymph node aspiration, magnetic resonance imaging (MRI), positive emission tomography (PET) scan, blood count, serum chemistry profile and urine analysis are allowable techniques for documenting the extent of tumor spread (Goncalves & Donadi, 2004; Scott, 2001).

4. Management

The case for beginning to introduce HPV testing as the primary screening test for women aged over 30 years is now overwhelming. Different cross-sectional studies have already demonstrated a far higher sensitivity for detecting cervical intraepithelial neoplasia grade 2 (CIN2) or grade 3 (CIN3) than cytology (HPV sensitivity over 95%, cytology sensitivity between 55% and 75%), even if a lower specificity was proposed.

The variables that can potentially interfere with HPV infection comprise the following (Stoler, 2010):

- Cervical anatomy and the location of the squamo-columnar junction;
- The nature and size of the biopsy specimen;
- The location of the biopsy;
- The number of biopsies;
- The colposcopic appearance;
- The orientation on embedding;
- The depth and the quality of the histologic sections;
- The criteria used for interpretation;
- The inter-observer variation amongs pathologists.

Colposcopy has the sensitivity for the detection of neoplastic disease in the range of 60 to 70% in the management of women presenting with abnormal cervical cytology and those with lesions of intraepithelial disease. However, its sensitivity may be increased into range of more than 90% when employed together with exfoliative cytology or HPV-DNA testing or both. Therefore, all HPV positive women should be referred for colposcopic evaluation.

HPV-testing strategy is the preferred management option for women with an equivocal cytology derived from a liquid-based PAP sample.

Women who are ASC-US HPV positive are best managed by colposcopic technique.

Treatment options classically include surgery, radiotherapy and chemotherapy, while modern approach is also based on immunotherapy.

Immunotherapy represents the manipulation of immunologic processes, namely biologic therapy, or the application of biologic response modifiers (BRMs). It is nowadays widely recognized that the biologic therapy may have immunologic effects and can act through multiple mechanisms such as:

- to increase the number of effector cells;
- to decrease host's suppressor immunologic mechanisms;
- to make the tumor cells more susceptible to damage by immunologic activity;
- to improve the host's tolerance to radiotherapy or chemotherapy (Goncalves & Donadi, 2004; Nedergaard, 2007; Nedergaard, 2008; Scott, 2001).

4.1 Passive immunotherapy

Passive immunotherapy techniques have been used in some melanoma and renal carcinoma patients resulting in objective responses. Because the lymphokine-activated killer cells (LAK) plus interleukin-2 (IL-2) technique is associated with significant toxicity, variations of these methods need further studied (Monie, 2007; Scott,, 1997; Scott, 2001; Wang, 1999).

4.2 Passive humoral immunotherapy

The passive humoral immunotherapy technique allows *in vitro* detection of monoclonal anti-tumor antibodies directed against a variety of human cancers (Goncalves & Donadi, 2004; Monie, 2007; Scott, 2001).

4.3 Active specific immunotherapy

Active specific immunotherapy has been used to induce therapeutic cellular immunity by using intact tumor cells, defined tumor antigens, and immunostimulants. Moreover, autochtonous tumor cells genetically modified to produce immunostimulatory molecules are being evaluated in clinical trials (Monie, 2007; Norris, 1990; Scott, 2001).

Granulocyte-macrophage colony stimulating factor (GM-CSF) or interleukin-2 co-stimulatory molecules such as B7-1 and allogeneic class I MHC molecules are commonly used (Monie, 2007; Scott, 2001).

4.4 Allogeneic tumor cells

This procedure may be performed in patients with acute lymohoblastic and acute myeloblastic leukemia. Irradiated allogeneic tumor cells and bacille Calmette-Guerin vaccine (BCG) are used (Monie, 2007; Scott, 2001).

4.5 Defined tumor antigen based vaccines

More recently, approaches using defined tumor antigen based vaccines are among the most promising techniques. Prolonged remissions have been observed because a defined end-point is available. There is enough evidence that antigens derived from genes that have mutated during tumor development and antigens that have a normal sequence but are not expressed in the tumor have been demonstrated as a target of specific T-cells grown from cervical cancer patients (Monie, 2007; Norris, 1990; Scott, 2001).

5. Immunological aspects in cervical cancer

Immunological aspects of cervical cancer are still of interest, tumor specific immune response being one of the most promising fields in cervical cancer research. As HPV is the etiological agent of a family of diseases that cause more cancer death in women worldwide than any other form of cancer, the goal of the newer trials is to identify novel strategies for cervical cancer immunotherapy (Monie, 2007; Scott, 2001).

HPV types 16 and 18 represent probably the most prevalent oncogenic types found in cancerous cervical tissues, accounting for up to 80% of the cervical cancer cases. Moreover, the risk of progression to cervical carcinoma is higher for HPV types 16 and 18 than for other known types of HPV (Ancuta, 2009; Goncalves & Donadi, 2004; Scott, 2001).

However, most adult women will completely recover from their HPV infection, with a reported clearance rate of 30% at 6 months and 50% at 12 months. Therefore, a persistent infection with HPV may be defined as the continued detection of viral DNA of the same HPV type for at least 12 months.

After transmission by sexual contact, it has been demonstrated that the virus does not cause viraemia or systemic infection and remains located in the epithelial cells of cervical mucosa.

It is well known that the virus adaptation to the differentiation of the superficial cells is an essential process to evade the host's immunity. Besides, HPV by itself is not cytolytic for the keratinocytes. The squamous epithelium undergoes a programmed cell death and

descuamation. HPV infects basal layer of the epithelium that mature vertically to the superficial surface of it; therefore, the viruses are released only in the most superficial layers of the squamous epithelium into the cervical lumen (Goncalves & Donadi, 2004; Scott, 2001).

Usually, the entire process from infection to viral release is less than three weeks. The natural keratinocytes death is not accompanied by inflammation and, therefore, viral proteins are not visible to the host immune system.

Most of women with early invasive cervical cancer are asymptomatic. In such cases, cervical smears may be effective in detecting early stage disease. On the other hand, advanced cervical cancer displays two primary pathways of extension: (i) local expansion and (ii) lymphatic or hematogenous dissemination.

It is actually known that mononuclear cells commonly infiltrate cervical tissue in different types of carcinoma, particularly in intra-tumoral sites, supporting the immune response against tumor. Previous studies have already shown the importance of local immune cell response in patient stratification according to the risk of disease recurrence after treatment. Moreover, three different cell subsets including TCD3+, BCD20+ and CD45+ leucocytes have been extensively studied among women with or without recurrence of their cancer after the surgery (Ancuta, 2009). Higher densities infiltrates are thought to be associated with a better clinical outcome. In addition, it seems that there is a relationship between different types of immune cells and survival: high density of cells is frequently observed in connection with free survival (Ancuta, 2009). The strongest discriminatory potential was attributed to densities of CD3+ in both intra- and peritumoral tissue; besides, according to a multiple regression model, CD3+ seems to be considered a potent prognostic factor for relapse (Ancuta, 2009). Nevertheless, no predictive biomarker is still validated for the use in clinical practice (Ancuta, 2009).

5.1 The innate immune system

The innate immune system generates non-specific protection against non-self antigens and does not intensify following repetitive infection events, while the aim of adaptive immunity is to induce cell mediated immune response by providing pathogen specific immunological memory.

Inflammation is a complex process that involves the recruitment of macrophages, neutrophils, dendritic cells and the release of cytokines and complement components. Dendritic cells activated by local cell injuries take up and process microbial agents while migrating to the draining lymph nodes, where they become antigen presenting cells and interact with T helper lymphocytes. Moreover, they are able to activated differentiation of T cytotoxic lymphocytes that allows rapid and strong response directed against the pathogen infected cells able to kill the pathogen (effector T-cells) and a fraction of the T cytotoxic and T helper cells becomes T memory cells (Arany, 1995; Arany & Tyring, 1996; de Gruijl, 1998; Goncalves & Donadi, 2004; Scott, 2001; Moscicki, 2000).

On the other hand, T helper lymphocytes activate the humoral immune response, which results in the production of specific antibodies against viral infection. In addition, these cells activate the differentiation of B lymphocytes into plasma cells that will neutralize the virus by binding to the viral capside proteins and other plasma cells that are able to synthetize

and to secrete antibodies which maintain a protective level of antibodies long time after the first contact with the virus (al-Saleh, 1998; Bell, 1995; de Gruijl, 1998; Goncalves & Donadi, 2004; Scott, 2001).

B memory cells will provide rapid and amplified antibody response after re-infection with the same pathogen.

HPV is a double stranded DNA virus that contains 8000 base pairs. There is strong evidence that two key regions have been described in HPV:

- the early region which contains eight genes (E1 to E8), involved in the viral DNA replication function (E1 and E8), transcription control (E2 and E8) and cellular transformation (E5, E6 and E7);
- the late region, with two genes (L1-L2), which code for the capsid proteins.

Viral DNA replication remains located mainly in the basal cells of the epithelium's proliferative cells, whereby most individuals eliminate the HPV 12 to 24 months after the diagnosis.

On the other hand, the oncogenic viral types are associated with high grade squamous intraepithelial lesions and it is known that the host's humoral and cellular immune system can explain the latency of HPV infection. Also, the responses to cytokine action during carcinogenic and non-carcinogenic processes are evidence of the role of immunological control in tumoral progression or progress of lesions associated with HPV infection (Ancuta, 2009; Bethwaite, 1996; Crowley-Nowick , 2000; Scott, 2001).

The interaction between these mechanisms is responsible for malignant transformation in women with HPV infection:

- one of these involves a modification of the AP1 transcription factor, endogenous synthesis of anti-viral interferon beta;
- the other involves the interaction between INK4A and transforming activity of E6.

Modern data support the fact that epithelial cells appear to play much more complex roles in cell mediated immune response than a mechanical barrier.

Cervical keratinocytes constitutively secrete pro-inflammatory cytokines, growth factors and chemokines. Main cytokines which promote anti-viral effects are represented by transforming growth factor beta (TGF-β), tumor necrosis factor alpha (TNF-α) and beta (TNF-β) and interferon (IFN), respectively. Several cytokines such as IFN-α, IFN-β, TNF-α and TGF-β which are essentially produced by epithelial cells, display significant anti-viral and anti-proliferative effects.

Additionally, a promising mechanism by which TGF-β, TNF-α and the IFNs are able to inhibit the *in vitro* proliferation of both HPV-transformed keratinocytes and expression of HPV genes including the early genes E6 and E7 has been advanced (Crowley-Nowick, 2000; Scott, 2001).

It has been demonstrated that E7 interacts with the tumor suppressing retinoblastoma gene protein, while E6 has been shown to be critical in cancer development by enhancing protein p53 degradation through ubiquitin-mediated proteolysis via a mechanism requiring E6-

associated protein. Thus, all these data highlighted once more the notion that E6 and E7 proteins appear to have essential role in malignancy (Youde, 2000; Scott, 2001).

Varied results of the potential for HPV-infected cells to escape immune response, accompanied by the growth inhibitory effects of cytokines, are highly depending on experimental findings.

TGF-β1 provides a good example of growth inhibitory effect in either HPV type 16 or HPV 18 transformed cells. Studies investigating the role of exogenous effects of TGF-β1 showed that the TGF-β1 induce growth inhibition in HPV 16 immortalized human keratinocyte cell line may be accompanied by suppression of steady-state levels of RNA down-regulation of the genes c-*myc*, suggesting a mechanistic association between TGF-β up-regulation and HPV-infected cells. The same researches also reported that over-expression of TGF-β1 treatment of HPV 16 immortalized cells results in proliferation enhancing bcl-2 and NFkB genes (Goncalves & Donadi, 2004; Scott, 2001).

HPV infected cells are grown in a medium that stimulates early stages of tumor progression; therefore, TGF-β appears to stimulate cells growth. The effect is seen only in HPV infected cells, but not in HPV negative ones, favoring increased expression of epidermal growth factor receptor and its ligand. These examples suggest that HPV infected cells may escape early, even before malignant transformations occurs.

The evaluation of the growth inhibitory effects of TNF-α in HPV infected cells has revealed that TNF-α appears to have an anti-proliferative effect on HPV 16 infected cells. The characterization of this growth inhibitory effect has lead to the suggestion that it involves growth arrest in G0-G1 phase.

As recently reviewed by certain authors, a growth-stimulatory effect involving an amphiregulin-mediated autocrine loop has been demonstrated for both IL-10 and TNF-α in some HPV 16 or 18 infected epithelial cells. They finally concluded that it could provide an early escape from growth inhibition in HPV-immortalized cells. In addition to the anti-proliferative effect, IFNs have also been investigated.

It seems that IFN-α inhibits the proliferation of HPV 16 infected cells at lower dose as compared to those needed to inhibit the growth of normal keratinocytes. It has also been shown that IFN-α inhibits E7 protein expression without interfering with transcription, suggesting that the inhibition of proliferation is mediated through E7 protein but not E6 protein expression. Moreover, the authors have concluded that IFNs may be virus-type specific or cell-line specific. A direct potential anti-viral role for IFNs in HPV-infected cells was therefore identified (Hatch & Fu, 1999; Nakagawa, 2000; Scott, 2001; Wang, 1999).

Interestingly, neither IFN-α and IFN-γ have been shown to reduce the transcription of E6 and E7 genes in a HPV 16 transformed keratinocyte line (HPK-1A) (Kleine, 1995; Lee, 1999; Scott, 2001). More recent work indicates that IFN-β reduces the transcription of both E6 and E7 genes in HPV 16 transfected keratinocyte-line (HPK-1A). Besides, there is actually strong evidence that malignant transformation is accompanied by the loss of responsiveness to the inhibitory properties of cytokines. TGF-β, for example, may play roles in checking the HPV gene transcription in non-tumorigenic HPV 16 immortalized cell type lines and malignant transformation could involve partial resistance to it (Nakagawa, 2000; Scott, M, 2001; Stoler, 2010).

The hypothesis that the resistance to the growth-inhibitory effects of several cytokines may occur in HPV-immortalized cells even prior to malignancy is actually proposed. The authors suggested that chronic inflammation has led to a selective advantage for abnormal cells *in vivo* by synthesis of pro-inflammatory cytokines. They concluded that a possible escape of cytokine mediated growth inhibition in HPV infected cells was identified.

The studies described above suggest the possibility that HPV infected cells may evade the growth inhibitory effects of cytokines by modulating the production of cytokines and other mechanisms. For example, they have more recently demonstrated that a correlation between increased tumorigenicity, significantly decreased expression of TNFα receptors and resistance to TNF-mediated inhibition of proliferation was observed. The studies concluded that type I and type II receptors levels in serum of patients with HPV 16 or 18 cervical carcinoma were significantly increased (Bontkes, 1999; Scott, 2001).

The characterization of this effect has led to the suggestion that soluble type I and type II TNF-α receptors may facilitate the growth of lesions in the HPV infected epithelium. As a further example, a possible mechanism by which HPV infected cells may escape the anti-proliferative cytokines effect, that conversion of non-tumorigenic He La fibroblast hybrids to malignant cells is accompanied by the ability of TNF-α to suppress HPV 18 gene transcription, suggesting a mechanistic association between loss of TNF-α sensitivity and alterations in the composition of the activator protein 1 complex.

HPV 16 E7 inactivates the induction of the IFN-α inductible genes by blocking the translocation of p48, the DNA binding part of the IFN stimulated gene factor 3 transcription complex, to the molecules upon IFN-α stimulation. The characterization of this cytokines role, except IFN-γ, in keratinocyte growth regulation in HPV infected cells has led to the observation that these may play autocrine roles in HPV infection (Goncalves & Donadi, 2004; Kleine, 1995; Lee, 1999; Norris, 1990; Scott, 2001; Symington & Santos, 1990).

5.2 Adaptive cell mediated immunity

The findings provide preliminary evidence for an association between two phases (recognition and effector), focusing on the cells involved and membrane bound molecules that mediate the immune response.

5.2.1 Recognition phase

Several studies have addressed the potential role of Langerhans cells in HPV lesions which may contribute to persistence of the infection. For example, S100+cells (antibodies) are significantly reduced in SIL compared to normal cervical epithelium, whereas CD1+ (antibodies) cells are not. As recently reviewed, cytokines with some contribution from Langerhans cells appear to be crucial mediators of the recognition phase. It seems that IL-1β, IL-1α, TNF-α and IL-10 are involved in Langerhans cells migration, acting as promoters or inhibitors of these cells.

Several investigators have described a possible association between HPV infection and deficits in production of these cytokines, based on findings of reduced IL-1α, IL-1β, TNF-α and GM-CSF and cervical carcinoma lines.

Besides, there is a relationship between diminished production of certain cytokines and persistent HPV infection. For example, TNF-α expression was highly expressed in low-grade squamous intraepithelial lesions (LSIL) biopsy specimens as compared to HSIL specimens. These abnormalities may contribute, along with local other immune processes, to an altered antigen-presentation to T cells in pre-invasive cervical lesions. Thus, abnormal immune responses suggest the possibility that HPV may evade immune-surveillance (Bethwaite, 1996; Goncalves & Donadi, 2004; Scott, 2001).

5.2.2 Effector phase

5.2.2.1 T-cell responses to HPV infection

Different analyses have suggested the potential role of T helper lymphocytes in providing protection against the persistence of HPV infection by measuring T-cell proliferative responses (Ancuta, 2009). It seems that more frequent responses to HPV 16 antigens E6 and E7 gene products were observed in subjects who had developed SIL compared to those who were cytologically normal, indicating that these antigens are important in SIL prevention.

In a similar study focused on HPV 16 proteins other than E6 and E7 (HPV 16 E2, HPV 16 E5, HPV 16 L1), T-cell proliferative responses to HPV 16 showed no association with disease outcome.

Moreover, results from certain trials have been equally confused by several factors including differences in subject populations, antigens (making the interpretation of T-cell helper response to HPV infection difficult) and the activities of T helper cells themselves (these are involved in production of auto-antibodies by B lymphocytes).

Other researchers have shown that responses to HPV 16 E5 proteins are more frequently observed in subjects with progressing LSIL than subjects without LSIL and those with HSIL. The results revealed that these responses may be correlated with clearance of HPV infection than with resolution of SIL.

Since T helper lymphocytes have important roles in aiding the development of cytotoxic lymphocytes, a possible association between these cells and clearance of virus may not be accurate reflections of a correlation between T helper cells responses and the HPV infection (Arany, 1995; Bethwaite, 1996; Dolei, 1999; Goncalves & Donadi, 2004; Nakagawa, 2000; Scott, 2001).

5.2.2.2 Research on CTL-mediated killing

Few studies have demonstrated the presence of activated CTL in SIL. CD8+CTL are known to be responsible for recognizing and killing HPV infection and SIL. One such study has reported that subjects with positive responses to E6 or E7 peptide can lead to the regression of tumors expressing E6 or E7; additionally, this regression is mediated by TCD8+, MHC class-I-CTL. Also, HPV E6 and/or E7 specific CTL were observed in patients with cervical carcinoma. Moreover, it has been demonstrated that CTLs were not only be capable of leasing HLA-matched, but also identified HPV specific CTL in lymph nodes and cervical cancer. Across sectional analysis of HPV16 E6 and/or E7-specific CTL showed that these were lower in women with HPV 16 infection who have developed SIL than in women with HPV 16 infection who had not developed SIL.

Lack of CTL response to the HPV 16 E6 protein is more frequently observed in subjects with persistent HPV infection, suggesting that CTL response to E6 was correlated with viral clearance. However, additional studies are necessary for defining the role of CTL in the regression of SIL.

Some researchers reported positive tetramer responses to HPV 16 E7 by isolating T lymphocytes specific for HPV, but the interpretation is difficult since the development of cervical cancer was not prevented (Bethwaite, 1996; Nakagawa, 2000; Scott, 2001; Sheu, 1999).

5.2.2.3 Studies of antigenic epitopes in HPV infection

There is little information about antigenic epitopes of HPV using mouse model systems and human systems, respectively. Nevertheless, certain research papers focusing on CTL epitopes of HPV 16 E6 and E7 proteins have identified five common HLA types; also, the immunological response of nine of these potential epitopes for HLA-2.1 was demonstrated. For example, E6 (29-38), E7 (11-20), E7 (82-90) and E7 (86-93) were identified using HLA-2.1. Immunogenicity of three of the four peptides [E7 (11-20), E7 (82-90) and E7 (86-93)] was confirmed by using CTL induction of peripheral blood mononuclear cells (PBMCs) from humans *in vitro*. The fourth of these peptides (CTL4) has been observed in SIL and cervical cancer (de Gruijl , 1998; Youde, 2000; Scott, 1999; Scott, 2001; Wang, 1999).

5.2.2.4 MHC class II restricted antigen presentation in the effector phase

A couple of recent studies have concluded that transcription of class II MHC molecules may be due to interferon gamma treatment of HPV 16 or 18 immortalized keratinocytes. They have demonstrated that HLA-DR epithelial cells, T-cells and Langerhans cells may participate in immune reactions by down-regulating HLA-DR due to interferon gamma secretion by activated T cells.

The hypothesis that up-regulation of HLA-DR expression was absent in cutaneous warts was suggested based on differences between cutaneous and mucosal anti-HPV immune responses. Also, other authors have reported that expression of HLA-DR is associated with HSIL and HPV may evade immune responses by blocking up-regulation of MHC class II expression. In addition, impaired up-regulation of this antigen in patients with genital condylomas responded to interferon treatment compared to those who did not; a possible causal link between high E7 expression in the non-responders and the lower inducibility of HLA-DR expression was identified (Crowley-Nowick, 2000; de Gruijl, 1998; Goncalves & Donadi, 2004; Youde, 2000; Scott, 2001; Wang, 1999).

5.2.2.5 MHC class I restricted antigen presentation in the effector phase

While normal keratinocytes constitutively express MHC class I molecules, HPV-infected tissues also commonly express high MHC class I levels as suggested by one report. Besides, these keratinocytes are susceptible to class I mediated lysis by alloantigen-primed CTL.

In a recent analysis, loss of MHC class I expression have been reported in cutaneous warts, although only partial loss of expression was seen in condylomas. In addition, studies using specimens from cervical cancers biopsies have reported a drastic reduction in MHC class I expression.

Finally, many investigators have described a possible correlation between loss of MHC class I in cervical cancer biopsy specimens and tumor type, disease stage and HPV 16 or 18 types. They concluded that loss or down-regulation if MHC class I expression is associated with more frequent disease recurrences.

Another research group has demonstrated that expression of the transporter associated with antigen presentation (TAP-1) is also associated with recurrence of the disease, suggesting that HPV may evade immune-surveillance by down-regulating TAP-1. As well, loss or down–regulation of MHC class I expression is critical for CTL-mediated killing (Bethwaite, 1996; Crowley-Nowick, 2000; de Gruijl, 1998; Youde, 2000; Scott, 2001; Wang, 1999).

5.3 Regulation of T cell immune responses

5.3.1 Chemokines and adhesion molecules

Another area of interest is the recruitment of activated lymphocytes at the sites of inflammation, defining immune processes that involve both chemokines and membrane bound adhesion molecules.

Several studies have described a close association between IL-8 production and the recruitment of neutrophils and T cells, while other have reported that malignant transformation of cervical keratinocytes is associated with higher IL-8 levels, especially when stimulated by IL-1 or TNF-α. In addition, T cells synthesis and secretion of IFN-γ may be accompanied by high IL-8 levels, stimulating, in turn, cellular immune responses.

Certain novel papers on malignant transformation have also mentioned higher IL-8 levels in women with histologic evidence of HPV infection, whereas the levels of RANTES (Regulated on Activation Normal T Expressed Secreted Factor) and MIP-1α (Macrophage Inflammatory Protein-1 alpha) are confounded. On the other hand, some approaches suggest that IL-8 synthesis in HPV 16 or 18 immortalized cell lines was significantly diminished.

Cervical keratinocytes are capable of producing MCP-1 (Macrophage Chemo-attractant Protein 1) and HPV 18+ HeLa cells transfected without the vector containing cDNA for MCP-1 lead to rapidly growing tumors. Some recent data suggest that ICAM-1 (Intercellular Adhesion Molecule-1) and its ligand, LFA-1 (Leukocyte Function Associated Antigen 1), seems to be important in adhesion processes by involving specific antigen recognition and CTL mediated killing.

Advanced researches have proposed the hypothesis that the adhesion process is accompanied by increased expression of ICAM-1 as a result of TNF-α and IFN-γ contribution. In addition, small clusters of LFA-1 positive T cells were found in the lower half of the epithelium surrounding ICAM-1 positive keratinocytes. Furthermore, the communication between T cells and keratinocytes is believed to be supported by the ICAM-1 overlapped with HLA-DR expression as bystanders of the adhesion process.

Whereas old data support the observation that impaired expression may play a role in the progression of the malignant process, the role of adhesion molecules in cervical cancer was recently up-dated (Bethwaite, 1996; Bell, 1995; Dolei, 1999; Monnier-Benoit, 2006; Scott, 2001; Wang, 1999).

5.3.2 Cytokines regulating T-cell responses

In the last years, many articles have reviewed the classification of activated T-helper cells aiming to understand humoral and cellular immune responses in cervical cancer (Ancuta, 2009).

A larger number of cells with particular focus on Th1 and Th2 cytokines production may play a role in local immune response. The classification include IFN-γ, TNF-α and IL-2 producing T helper type 1 cells which stimulate cellular immune response and IL-4, IL-5, IL-10 and IL-13 producing T helper type 2 cells, which in turn stimulate humoral immune response.

The observation that Th1-Th2 paradigm may play a role in HPV infection has support from several studies. Th1 cytokines such as IFN-γ and IL-2 may also be important in the natural history of HPV infection (Mosmann & Sad; 1996; Scott, 1999; Scott, 2001).

Moreover, immunohistochemmical analysis has been proposed by many researchers to study cervical cancer biopsy specimens; they compared immunohistological studies of cervical carcinoma with results from normal cervical epithelium demonstrating fewer Th1 cells (IL-2+) and higher density of Th2 cells (IL-4+).

The authors have suggested that the IL-2 synthesis may be related to HPV type 16 *in vitro* stimulation. For example, the lowest IL-2 levels were demonstrated in women with cervical cancer, while the highest levels of IL-2 were reported in cytologically normal HPV women. Besides, there is strong evidence that MHC class I and/or MHC class II molecules down-regulation may decrease immune recognition of HPV-associated tumors through modulating IL-10 production (Bethwaite, 1996; Dolei, 1999; Goncalves & Donadi, 2004; Monnier-Benoit, 2006; Wang, 1999).

5.4 Clearance of HPV infection and clinical implications

As emphasize by some authors, HPV may evade local immune response by limiting the extent of viral antigens to immunologic recognition.

Three potential mechanisms for HPV immune-surveillance were actually proposed, including:

- E7 protein may inhibit local immune response by blocking the antigen presenting function of dendritic cells from the epithelium in cervical tissue;
- an effective immune response against the HPV infected cells in the basal epithelium, where the E6 and E7 early genes are expressed; capsid encoding genes delayed expression may be the consequence of the inhibition promoted by a codon usage still remain exploratory, but this scenario is still exploratory;
- lack of CTL response to the HPV infected cells: keratinocytes may be less susceptible to class I mediated lysis by alloantigen-primed CTL (Bethwaite, 1996; Dolei, 1999; Goncalves & Donadi, 2004; Palefsky, 1999; Scott, 2001; Wang, 1999)

6. Prophylactic HPV vaccines

Multiple studies indicate there are several challenges and uncertainties that need to be resolved before HPV vaccination. In addition, socio-cultural factors will affect the

acceptability of the HPV vaccine in high risk developing countries. Patients must acquire more information for accepting HPV vaccination. After considering the evidence, the clinicians come to a unanimous decision that such information might include the need for prevention and applicable information concerning where to acquire and how to fund HPV vaccination.

Two prophylactic HPV vaccines, namely Cervarix^{R} and Gardasil^{R} (Silgard), have been already approved; they are directed against and contain virus-like particles (VLPs) specific for two of the most important oncogenic HPV types 16 and 18. In addition, Gardasil^{R} is a quadrivalent vaccine that also includes VLPs for HPV 6 and 11, the most common HPV types found in up to 90% of genital warts (Harper, 2009; Kitcher, 2008). These vaccines offer protection for 70% of cancers, but also for about 90% of HPV type 16/18 associated CIN (Kitcher, 2008).

Although the immunogenic properties of the prophylactic HPV vaccines give the possibility of long term protection for women in a wide range of years, the vaccination seems to be most advantageous in preadolescent girl (Kitcher, 2008). It is widely recognized that the above mentioned prophylactic vaccines are able to induce high titers of neutralizing antibodies; however, Cervarix^{R} is responsible for significantly higher titers of antibodies than Gardasil^{R} (Harper, 2009).

With regard to baseline seropositivity, increased memory B cell response is commonly reported in women who were both seronegative and PCR negative for oncogenic HPV types 16 and 18 at the time of vaccination (Harper, 2009). Also, several studies showed that adolescents mounted an antibody response that was significantly higher compared to the seronegative old women (Harper, 2009). Because the meaning of loss of antibody titers is unclear, long term studies are necessary to prove the efficacy for the HPV vaccines.

In general, both Gardasil^{R} and Cervarix^{R} are safe for the majority subjects who received vaccines. The most commonly reported adverse events were pain, erythema, swelling, myalgias, arthralgias, headaches and gastrointestinal symptoms. In the mean time, no serious adverse events (hospitalization, disability, death) have been reported (Harper, 2009).

Special consideration should be made about vaccine administration in pregnancy; three therapeutic scenarios are defined, as follows:

- the vaccination during pregnancy is not allowed;
- if one dose of vaccine has been received before pregnancy, all three administration should be taken after delivery;
- if two doses have been received before pregnancy, the last dose could be administrated in postpartum period (Harper, 2009).

No scientific evidence supports the interruption of a pregnancy because of the partial vaccine administration; additionally, there is no formal contraindication to vaccination during lactation (Harper, 2009).

7. Conclusions

Developments in the technology of measuring HPV antibody response in serum specimens would facilitate directions for further research in the prevention, control and management

in cervical cancer and might encourage additional clinical trials research on HPV infection and cervical carcinoma that need to be widely disseminated to the clinicians and women by updating screening and management protocol.

The current perception of HPV persistency is not fully understand by many physicians and researchers. Therefore, viral persistency will be taken into account in an organized context in screening programs.

Because of the very high efficacy shown by HPV vaccines, the cytology-based screening programs will be less efficient and potentially rates of over-diagnosis and over-treatment of indefinite lesions will multiply.

Transition time to redefine screening protocols including a later age at the beginning and less frequent screening visits is thus essential.

In addition to HPV-based screening programs, many issues are not fully comprehend, requiring a lot of educations: triage of cytological pre-invasive lesions, follow-up after treatment of SIL, detection of p16, detection of HPV mRNA, prophylactic vaccination against HPV infection.

Baseline assessment of women with cervical carcinoma with and without relapse is critical in order to identify association with classical negative prognostic factors including tumor size and grading, histological type, clinical stage FIGO and lymph node invasion.

The assessment of local cellular immune response seem to be critical for stratifying patients according to their risk, for the therapeutic option; moreover, understanding of local immune response in cervical carcinoma may potentially guide new adjuvant treatment strategies including immunotherapy.

Several studies have already demonstrated that tumor-infiltrating lymphocytes (composition, distribution, cell count) reflect the status of the cellular immune system in patients with cervical cancer. Different immune cell subsets, especially T-cells subpopulation, were assessed in tissue specimens from different types of cervical carcinoma; despite some controversial data, the majority of researchers have indicated that tumor infiltration by immune cells are associated with improved clinical outcome in cancer patients, especially in cervical cancer.

To identify the immune cells of interest, the specific antigens expressed on cell surface could be detected by immunohistochemistry, using corresponding antibodies. There is some evidence that immunohistochemistry assessment in women experiencing recurrence of their cervical cancers has revealed low densities of immune cells infiltrating the tumor.

There is actually enough evidence to promote the hypothesis that local cellular immune response is essential for guiding further cancer evolution and prognosis. However, larger cohort studies based on extended analysis of several immune cells are critical for the validation of prognostic biomarkers in cervical cancer.

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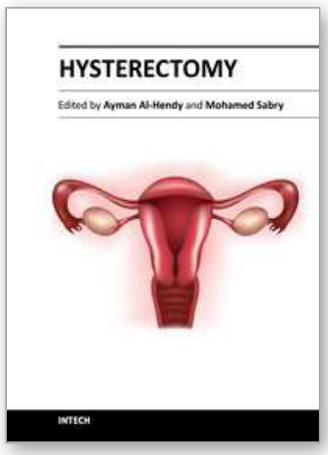

Hysterectomy
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This book is intended for the general and family practitioners, as well as for gynecologists, specialists in gynecological surgery, general surgeons, urologists and all other surgical specialists that perform procedures in or around the female pelvis, in addition to intensives and all other specialities and health care professionals who care for women before, during or after hysterectomy. The aim of this book is to review the recent achievements of the research community regarding the field of gynecologic surgery and hysterectomy as well as highlight future directions and where this field is heading. While no single volume can adequately cover the diversity of issues and facets in relation to such a common and important procedure such as hysterectomy, this book will attempt to address the pivotal topics especially in regards to safety, risk management as well as pre- and post-operative care.

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