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Potential therapeutic vaccine strategies and relevance of the immune system in uterine cervical cancer

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Summary

The interaction of HPV with the immune system has been studied, but the results are still inconclusive for several reasons. Until now, we have not been able to understand the mechanisms of immune system regulation in the uterine cervix. HPV infection does not unleash an inflammatory response, and consequently an efficient and specific immune response against the virus. Moreover, an understanding of HPV infection and local immune response is indispensable for the development of new bioactive drugs and therapies for patients with both non invasive and invasive tumors, mainly for patients that do not present regression with radiotherapy or chemotherapy or in whom the tumors are surgically unresectable. The aim of this review is to provide support in understanding potential mechanisms used by the immune system to destroy neoplastic cells, comparing the immunotherapy used in cancer and discussing the possibility of developing new drugs based on these mechanisms of action.

Key words: Neoplasia; Cancer; Uterine cervical cancer; Immunotherapy; Human papillomavirus; Interferon; Cellular therapy; Immune system.

Introduction

Uterine cervical cancer is the second most common malignant neoplasm among women and, according to the World Health Organization, it is responsible for 300,000 deaths per year around the world. Its occurrence is only exceeded by skin cancer [1]. However, these situations could be lower, given that uterine cervical cancer could be avoided through detection and treatment of preneoplastic lesions [2].

Epidemiological and laboratory evidence has indicated that human papillomavirus (HPV) can be detected in 85 to 100% of the patients diagnosed with this type of neoplasm [3, 4].

The infection occurs more frequently in young women, particularly in those who start to be sexually active before the age of 18 years, and in those who smoke, are pregnant and have multiple sexual partners [5, 6]. Murta et al. demonstrated in cytologically normal patients that the prevalence of infection declines with increasing age [3, 7] and that, among women who present cytological alterations due to HPV, the percentage regression reaches around 85% of the cases [7, 8]. This same group, studying women with cytological alterations due to HPV, concluded that these lesions could continue to be present for a mean period of four years, in around 13% of the cases. Nonetheless, the risk factors that are thought to promote persistence of this infection need to be better studied [7].

HPV belongs to the family *Papovaviridae*. It is an epitheliotropic DNA virus that is sexually transmitted and causes approximately 30 million new infections every year. It is present in the lower genital tract of around 10% of women.

This family of viruses possesses tropism for keratinocytes, thereby inducing papillomas as part of its normal life cycle [9]. It is composed of around 100 described subtypes and infects a large variety of organisms in a species-specific manner. Although the majority of the types induce benign papillomas, there are some types that are classified as presenting high risk and which contribute towards the development of anogenital cancer. Some examples of these are HPV 16, 18, 45 and 56, which may give rise to malignant transformation by infecting epithelial cells [4].

Many cases of cervical cancer begin in the transformation zone, a region between the endocervix and ectocervix [10]. The first stage in malignant development is cervical intraepithelial neoplasia (CIN), in which the neoplastic cells have not yet invaded the basal membrane and are premalignant. These precursor lesions can be classified histologically into different grades (CIN I, II and III), according to the extent of the lesion [11]. CIN can regress, persist or progress to invasive cancer, and the latter occurs in varying proportions, ranging from 3% to 30% of the cases, depending on the conditions.

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Immunological characteristics of the female reproductive tract

The immune system of the female reproductive tract behaves in a site-specific manner, i.e., the response may be different depending on the location and the degree of sterility [12-14]. This hypothesis has also been supported by functional studies using the model of *Chlamydia trachomatis,* which have indicated different T-lymphocyte patterns in the upper and lower tracts during the course of infections [13].

The upper genital tract has both an innate immune response [15] and an acquired immune response [16]. These responses keep the tract in a predominantly aseptic state and rapidly protect the reproductive organs from pathogens, thereby maintaining the function and integrity of the tissues. For this, there needs to be fine-tuning for the immune system, between the response to pathogens and either tolerance to semen or a semi-allogeneic concept. However, a large number of scientific studies will still be needed for the characteristics of the immune response in the uterine cervix to be elucidated.

Immune response to HPV

Several components of the innate and adaptive responses are mobilized for recognizing infections caused by HPV and eliminating the cells infected by the virus. The first line of defense consists of the innate immune response, which takes place in the epidermis and in the epithelium of the mucosa [17]. This can be considered to be the non-specific resistance to infection that occurs when the pathogens first come up against the immune system.

The innate immunity to HPV is mediated by several mechanisms, including induction of interferon (IFN) and activation of macrophages and natural killer cells. However, some infections caused by HPV are not rapidly eliminated by the immunity of the mucosa, and chronic expression of this virus at low levels may induce tolerance to the infected epithelium [18]. Several studies have demonstrated that HPV interacts with the immune system [19-21] but, despite this, it is capable of evading or inactivating the acquired immune response [22]. There are various hypotheses for such evasion mechanisms: first, the virus does not have a blood dissemination phase; second, it does not cause lysis of keratinocytes and therefore does not induce an inflammatory response; and third, production and release of the virus takes place in the differentiated squamous cells that are distant from the cytokines and immunocompetent cells of the submucosa.

Inflammation

Inflammatory response has a central role in innate immunity, and it is stimulated by cytokines such as IL-1 and TNF-α, which may be synthesized by keratinocytes after some type of injury has been suffered [23]. These two cytokines stimulate changes in the adhesion molecules and capillary permeability, release of other cytokines (chemokines) and also negative regulation of E6 and E7 expression in keratinocytes [24]. Acute inflammatory response leads to elimination of the infection and repair of the damaged tissue, and is responsible for triggering acquired immunity. On the other hand, the chronic inflammation that occurs when the infection persists for a long time has been considered to be one of the risk factors that could trigger various human cancers [25].

One characteristic of HPV infection is the absence of inflammatory response. Recent studies have suggested that some gene products from HPV may directly block the activity of the inflammatory mediators. The E6 protein of HPV 16 inhibits the expression of IL-18, which is proinflammatory [26], and competitively bonds with the receptor for this cytokine [27]. This same protein in the virus also bonds with the receptor for TNF-α and protects the cells from the induction of apoptosis [28].

Even though HPV infection does not readily induce an acute immune response, the expression and release of specific proinflammatory cytokines such as IL-1, TNF-α, IL-12, IL-10 and TGF-β becomes increased during the CIN III stage and in cases of invasive cervical cancer [29-31]. On the other hand, contrary to these findings, cervical carcinoma cells and cells immortalized by HPV *in vitro* present reduced quantities of proinflammatory cytokines [32, 33]. What this clearly demonstrates is that the microenvironment is fundamentally important for the release of these factors.

Macrophages

One important component of the innate immune response is the phagocytic cells. The recruitment of polymorphonuclear leukocytes (PMNs) and monocytes to the infection site is mediated by the release of cytokines and chemokines from the infected tissue. Several studies have reported that macrophages are present in increased quantities in infections caused by HPV or CIN [34, 35] and in cervical carcinoma cases [36]. Moreover, these cells are present in both the epithelium and stroma, and are capable of killing cells that have been transformed by HPV-16 [37]. Corroborating this idea, papillomas that present regression have significant infiltrates of macrophages that stain positively for TNF-α, thus correlating with the apoptosis of the infected epithelial cells [38].

Natural killer (NK) cells

NK cells are a subpopulation of lymphocytes that recognize and destroy damaged and infected cells in a non-specific manner. They may be activated by means of treatment with cytokines, to produce lymphokine-activated NK cells (LAK). The mechanism for the action of these cells basically takes place through the release of cytotoxic granules on

the surface of the target cells, thereby inducing apoptosis of these cells. In addition, through synthesizing TNF-α and IFN-γ, the inflammation is increased and other components of the immune response are activated.

Even though the lysis caused by NK cells is deficient in patients who have pre-cancerous lesions or cancer induced by HPV [39], this cell lineage is found in the CIN stroma [40]. However, epithelial cells immortalized by HPV-16 and lineages of cervical carcinoma cells are relatively resistant to NK cells, but sensitive to lysis by LAK cells [41, 42]. Data from the literature have also demonstrated that the E6 and E7 proteins of HPV-16 inhibit the ability of NK cells to synthesize IFN-γ using *in vitro* tests [27]. These data indicate that one of the possible mechanisms for controlling HPV infection could be by means of an efficient response from NK cells.

Cytokines

Cytokines are glycoproteins that are released from cells to act through autocrine, paracrine or endocrine mechanisms. The first studies on these molecules began in the 1950s and reached a peak in the 1980s with the molecular cloning of these peptides. Today, it is known that several different cell types have the capacity to synthesize and release these proteins, ranging from immune response cells to central nervous system cells such as microglia. The way these molecules act is through bonding to specific receptors in the target cell, thereby triggering several intracellular signaling pathways that may result in activation or inactivation of different genes. The participation of cytokines goes from modulation of hematopoiesis as far as activation or inhibition of growth and differentiation of specific cells, and control over the mechanisms for the natural immunity and inflammatory response. Cytokines were originally classified as those of the Th1 pattern, of which the most important ones are IL-2, IL-12, IFN-γ and TNF-α (responsible for activating the cell immune response), and those of the Th2 pattern, for example IL-4, IL-10 and TGF-β (responsible for activating the humoral immune response). Recently, a further classification emerged: the Th3 type, characterized by the presence of IFN-γ and IL-10. This pattern appears to be involved in the induction of tolerance.

Regression of HPV infection has been associated with an immune response mediated by cytokines of the Th1 pattern [19, 38]. In contrast, the development of CIN is mediated by a cytokine secretion pattern of the Th2 type, with a reduced IL-12/IL-10 ratio [43] and increased quantities of the cytokines that are considered to be immunosuppressors, such as TGF-b and IL-10 [34, 29, 44]. Topical immunomodulators such as imiquimod, which is utilized in clinically treating HPV infection, act by inducing the secretion of cytokines of the Th1 pattern, such as TNF-α, IFN-γ and IL-12 in the monocytes and macrophages. These cytokines are responsible for increasing the cell-mediated immune response [45].

Adaptive immunity

In a simple way, the adaptive immune response could be defined as an immune response that involves the participation of cellular types with highly specific antigen receptors. However, this specific response starts only with an unspecific recognition of these antigens by antigen presenting cells (APCs), that thereafter catching and processing present peptides by MHC class II, activating auxiliary T lymphocytes (CD4+); or in the case of intracellular antigens, e.g., virus or tumor antigens, the processing results in a presentation by MHC class I molecules, thus activating cytotoxic T lymphocytes (CD8+).

The antigen presenting process is extremely complex and involves membrane molecules, soluble mediators and intracellular ways of activation such as APC as much as T lymphocytes.

Dendritic cells

The dendritic cells (DCs) originate from hematopoietic stem cells within the bone marrow and under physiological conditions differentiate into immature dendritic cells that circulate via blood to peripheral tissues. DCs are recognized as the most powerful antigen presenting cells (APCs) for priming both cytotoxic (CD8+) and helper (CD4+) T cells. Following an encounter with antigens the immature DCs initiate their maturation process and during this phase the cells increase their migratory capacity to the regional lymph nodes to activate T lymphocytes.

The coordination that the DCs exert between the innate and adaptive immunity is indispensable to an induction of an effective response against tumors. However, several steps are necessary to develop an effective immune response able to eliminate the tumor cells. DCs have to recognize tumor molecules, to internalize and process these antigens, to migrate to lymph nodes, and then to present the tumor antigen to T-cells to induce a cellular response. However, the immune system often fails, presumably due to alterations in the aforementioned mechanisms [46].

In patients with head and neck squamous cell carcinoma, as well as in patients with metastatic disease in breast, colorectal, gastric, lung, cervix, endometrial and renal cell carcinoma the number of blood DCs were altered [47-49]. Similarly, in primary tumors including breast, colorectal, gastric, esophageal, thyroid and bladder transitional cell carcinoma it appeared that DCs were not recruited [50-52]. These and additional data [51, 53] are clinically relevant as they are associated with a significantly poorer prognosis in patients with several types of cancer.

Several studies have suggested that DC dysfunction was indeed a systemic process and supported the notion that soluble factors derived from tumors affect DC. Several reports have now confirmed that by releasing IL-10, IL-6, M-

CSF, vascular endothelial growth factor (VEGF), gangliosides and prostanoids, tumors can prevent DC differentiation and function *in vitro* and *in vivo* [54-59].

Due to the capacity of the development of cellular vaccine based in dendritic cells, they are actually used in several situations, including tumors induced by HPV. In mice with a C3 sarcoma (tumor expressing HPV16 E7) vaccination with immature DC pulsed with an MHC restricted HPV16 E7 class I peptide and eradication of tumors occurred in 80% of mice [60]. Both immature and mature autologous DC primed with antigens derived from synthetic tumor antigen peptides or tumor lysate from a variety of tumors have been shown to mediate major anti-tumor responses in humans, including cervical cancer [61].

Unfortunately, no consensus exists with respect to the key issues such as the loading method for optimum immune responses and of activating/maturation of the DC phenotype, as well as optimum route of DC administration, DC dosage schedule and DC dose.

T lymphocytes

Clues to the nature of the cellular immune response to HPV infection have come from immunohistologic studies comparing spontaneously regressing and non regressing genital warts and from recent advances in HPV vaccines.

Regressing genital warts present a large infiltrate of T-cells (both CD4+ and CD8+) and macrophages in wart stroma and epithelium, infiltrating lymphocytes express activation markers, and the cytokine milieu is dominated by proinflammatory cytokines such as IL-12, TNF-alpha and IFN-gamma. Moreover non-regressing genital warts are characterized by a lack of immune cells at the site of infection: the few intraepithelial lymphocytes are CD8+ cells, and mononuclear cells are present mainly in the stroma [62].

Immunity against HPV16 E6 and E7 oncoproteins has been tested by stimulation of peripheral blood mononuclear cells (PBMC) obtained from patients infected by HPV. To assess HPV-specific cytotoxic T-lymphocyte (CTL) activity, PBMC from HPV-16 patients were stimulated with recombinant protein, defined minimal peptide-epitopes or with recombinant adenovirus expressing HPV 16 E6 and E7 infected PHA blasts for 7-21 days. In some studies, CTL reactivity against both HPV 16 E6 and E7 was predominantly found in patients that cleared infection [63, 64]. Other studies, especially in patients with persistent infections or progressive disease, displayed CTL reactivity [65, 66].

Recently, new insights have emerged with the new vaccines with HPV peptides. Vaccination of cervical cancer patients resulted in the detection of an occasional vaccine-induced T-cell response against HPV [67, 68]. The advances of the new vaccines will clarify some important aspects of immune response to HPV necessary to improve the vaccines.

Interferons

These are a family of cytokines that have important functions in the immune system [69]. Type I IFNs, which include IFN-α and β, are produced by epithelial cells and contribute towards the first line of antiviral defense by inhibiting proliferation and inducing apoptosis of the cells that are infected by the virus [70]. On the other hand, type II IFN (IFN-γ) is produced by activated T cells and NK cells, and is an important modulator of immune function. Both types of IFN inhibit the expression of mRNA from the E6 and E7 proteins in immortalized HPV cells [71, 72]. Even though both types reduce the expression of the genes for HPV, the most effective is type II (IFN-γ). This family of cytokines has been used for treating HPV infections. However, the efficacy of the therapy has been inconsistent, given that some patients respond effectively [73], while others respond only partially.

Recent studies have demonstrated that the E6 and E7 proteins of HPV-16 and 18 have a close relationship with the synthesis of these cytokines and with tumor progression. E6 and E7 are capable of specifically inhibiting the expression and signaling of IFNs [74, 75], thereby allowing the virus to escape from the normal antiviral response [76]. These proteins are positively regulated during the progression of CIN [77], while there is a reduction in the levels of IFN-β and γ in these patients [43, 78, 79]. Although some of these studies have been carried out *in vitro,* this observation is compatible with the clinical studies [80], since patients who express high levels of E7 in the tissue are more resistant to treatment with IFN, while patients with low levels of E7 are sensitive. Together, these results indicate that the expression of high levels of the E6 and E7 proteins negatively regulates the expression and signaling of the IFN, thereby directly influencing the efficacy of immunotherapy using IFN.

Immunotherapy

Tumor treatment using the immune system as a tool is a very old dream within science. It may have begun in the 19th century, when surgeons and other scientists in Europe and the United States started to observe tumor regression that was associated with parallel resolution of erysipelas.

Since then, studies on the immune system have advanced significantly, and today the first steps towards manipulating this system in our favor have been taken. Several types of immunotherapy have been developed for the possible treatment of such neoplasia. Some of them involve immunostimulant therapy, antibodies, cytokines or cell therapies (Table 1). From the point of view of application, some methods have not gone beyond *in vitro* tests, while others have been and are being tested on animals. Just a few have gone into the phase of clinical trials on humans.

Table 1. — *Principal clinical applications of immunotherapy in different types of tumors*.

Immunotherapy	Clinical applications	References
Immunostimulants		
BCG	Melanoma, vesicular tumors	81, 82
Levamisole	Melanoma, carcinoma e of the uterin cervix, colorectal tumors	83, 84
Antibodies		
Chimeric monoclonal antibodies	Non-Hodgkin's lymphoma	85, 86
Humanized monoclonal antibodies	Metastatic breast cancer, leukemia, lymphoma	87
Cytokines		
IL-2	Renal carcinomas, melanoma, tumors of the central nervous system, hematological tumors, tumors of the head and neck	88-94
IL-12	Experimental phase in animals; use in humans has been prohibited by the FDA, because of deaths related to its use	95
IL-6	Advanced solid tumors and renal tumors	96, 97
IL-4	Renal and pulmonary tumors, melanoma	98-100
IFN	Hematological tumors, melanoma, renal tumors, Kaposi's sarcoma, tumors of the vulva and vagina, tumors of the ovaries	101
Cellular therapies		
Adoptive transfer of T-lymphocytes	Leukemia	102, 103
Peptide vaccination for act in T-lymphocytes	Myeloid leukemia, Melanoma	104, 105
Therapy using dendritic cells	Melanoma, prostate tumors, renal tumors, cervical cancer	106-110
Peptides		
Virus-like particles (VLPs)	Tumors induced by HPV (human papilloma virus)	111-113

As mentioned above, the oldest attempts to treat tumors using immunotherapy were by means of immunostimulant therapy. Treatments for cancer patients using bacteria and their products go back to the end of the 19th century when William B. Coley started to treat cancer patients using the supernatant from cultures of Micrococcus pyogenes and Serratia marcescens. This vaccine became known as Coley's mixed bacterial vaccine (MBV).

A variety of immunostimulants and immunomodulators have now been utilized in clinical and preclinical studies. Particular attention has been given to contact allergens, bacillus Calmette-Guérin (BCG), muramyl dipeptide, Corynebacterium parvum, and levamisole. The use of 6-mercaptopurine, doxorubicin, cisplatin and even cyclophosphamide can be cited. In large doses, the last is utilized for inhibiting the responses of T and B lymphocytes, but at low doses it eliminates suppressor cells and acts as an immunostimulant.

The utilization of antibodies in therapy against neoplasia has also been envisaged for around two decades. More specifically, monoclonal antibodies (mAbs) have been developed for different types of tumors. The problem of administering antibodies that were developed in mice has been overcome through molecular biology, with their transformation into chimeric humanized antibodies. Today, the main problem is how to characterize an appropriate target antigen for each type of neoplasm. However, for the vast majority of neoplasms, science has not yet been able to characterize these tumor proteins.

Much has been done and learned through clinical investigations utilizing cytokines as the therapy. The application that has been most published, although it is not the most effective one, is the use of IL-2 in renal tumors and melanomas. For other cytokines, experimental and basic investigation studies have been conducted with a view to their utilization. However, one of the difficulties is that the experimental models utilized, in the same way as for other diseases, are in most cases models using homozygotic animals, which definitely does not occur with patients. Thus, the treatment schemes, doses and immunological responses vary from patient to patient, and sometimes the results are completely different from those found in animals. Another limiting factor in developing these protocols for humans is that the ethical precepts only permit treatment for patients who are already in a terminal phase, with tumors that are unlikely to regress. This limits studies on other types of tumors and at phases in which the response could be better characterized and with better results. Despite these obstacles, therapy using cytokines has emerged as a promising method, particularly when allied with other types of immunotherapy.

One of the great expectations in science regarding tumor treatment relates to the utilization of IFN, since this is the first human cytokine found to be effective as a treatment for tumors. Immunotherapy using IFN-α has been employed for treating multiple myeloma, chronic myeloid leukemia, non-Hodgkin's lymphomas, renal carcinoma, epidermoid cervical cancer, head and neck tumors and melanomas, and also for treating CIN.

Although it is recognized in the literature that IFN-α modulates the growth and differentiation of tumor cells and affects cell communication and intracellular signaling, the mechanisms through which tumor regression takes place have not been completely elucidated. Our research group has clinical studies under development along these lines, investigating which immune response cells are involved in tumor regression and what their mechanism of action is. Other points to be elucidated are the treatment schemes and the optimum doses for each type of tumor.

Nonetheless, it is known that the immune system does not act just as a mechanism for inducing tumor regression. It is a fully coordinated response that involves a range of actions from the activation of antigen-presenting cells (dendritic cells) to the activation of T-helper and cytotoxic lymphocytes and NK cells. Therapy using IFN-alpha only involves one line of action, which is possibly the activation of natural killer cells and cytotoxic lymphocytes, but we

believe that the activation of T-helper lymphocytes has fundamental importance in obtaining a much more effective antitumoral response.

As seen, immunological studies gained impetus from the middle of last century onwards. Nevertheless, many mechanisms still remain to be elucidated in order to be able to effectively manipulate this system, so that the objective of eliminating and/or preventing the emergence of tumors can be achieved by using the immune system as the tool.

Despite all these attempts to manipulate the immune system in our favor, much remains to be done. As discussed above, the desired drug must activate several cellular types of the innate and adaptative immune response; a potential drug for these are the cytokines. In a special review the most promising are alpha, beta and gamma interferons, and in spite of the results with the three types in a separate way [74], they are unique cytokines that could activate the immune system in several ways. With regard to developing antitumor drugs, a great leap forward for the pharmaceutical industry would be to develop a drug similar to interferon that would conserve in its structure the molecular and biological characteristics that are common to the three main types of IFN (alpha, beta and gamma). One way would be to exclude from the molecule the portion that could be responsible for the side-effects of these cytokines, which are extremely similar. This idealized drug could activate the principal receptors for these cytokines all at once and, at the same time, induce apoptosis and modify the high rate of mitosis in the tumor cells, but also, activate cells of the immune system, like macrophages, dendritic cells, T-helper and cytotoxic lymphocytes which could specifically destroy metastatic cells. Another extremely interesting point could be to develop this ideal drug – abolishing the structure of the sequence of the three interferons which could be responsible for the adverse effects that are actually very similar in patients treated with these drugs, as thrombocytopenia, leukopenia, fatigue and psychiatric disorders, and that are actually the main restriction in clinical practice [114-116]. Until such time, we will continue to study and investigate the possible antitumoral mechanisms in the immune system to improve the existing protocols and develop new therapies.

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