ARTICULO DE REVISION

Update on the Pathogenesis and Immunotherapy of Esophageal Squamous Cell Carcinoma

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RESUMEN

El carcinoma de células escamosas de esófago (CCEE) es el subitpo histólogico predominante de cáncer esofágico, y se caracteriza por su alta mortalidad y diferencias geográficas en cuanto a su incidencia. A pesar de que se ha dedicado mucha investigación en esta área, aún no se conoce la causa exacta de esta neoplasia. Nuestro entendimiento de la patogénesis, epidemiología y comportamiento del CCEE continúa en desarrollo con los avances en el campo de la biología molecular. Algunos de estos avances incluyen la investigación en la etiopatogénesis (virus -como el papilomavirus humano-, y genes susceptibles a cáncer), genes relacionados a tumores (oncogenes, genes supresores de tumores), así como nuevas formas de inmunoterapia neoadyuvante para el tratamiento de esta neoplasia.

PALABRAS CLAVE: Carcinoma esofágico, células escamosas, HIV, oncogenes, inmunoterapia.

SUMMARY

The esophageal squamous cell carcinoma (ESCC) is the prevailing histology subtype of esophageal cancer and is distinguished by its high mortality and its geographic differences in regards to its incidence. The exact cause of this neoplasia is still unknown in spite of all the research made in this area. Our understanding about pathogenesis, epidemiology and behaviour of the ESCC is still in progress thanks to the advances on the field of molecular biology. Some of these advances include the research of etiopathogenesis (virus, as the human papillomavirus, and the genes susceptible to cancer), genes associated with tumors (oncogenes, tumor suppressor genes), as well as new forms of neoadjuvant immunotherapy for the treatment of this neoplasia.

KEY WORDS: Esophagus carcinoma, squamous cells, HIV, oncogenes, immunotherapy.

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INTRODUCTION

Cancer of the esophagus exists in 2 main forms with different etiological and pathological characteristics, squamous cell carcinoma (SCC) and adenocarcinoma (ADC) (1). Regardless of the cell type (squamous or adenocarcinoma), esophageal carcinoma is an uncommon but agressive malignancy that usually presents in a locally advanced stage (2). Esophageal squamous cell carcinoma (ESCC) is the predominant histological subtype of esophageal cancer and is characterized by poor prognosis and a wide incidence variation in different geographical regions (3, 4).

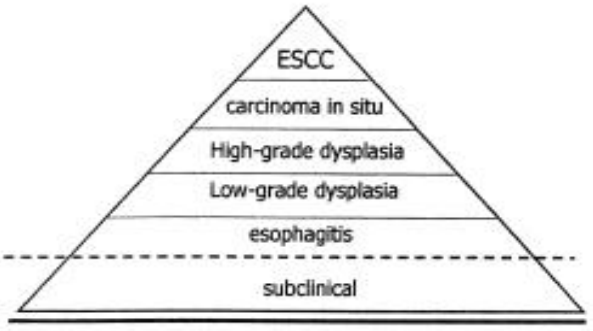

Fig 1. Esophageal squamous cell carcinoma Natural History. ESCC constitutes the final stage of a sequence of histopathological changes that involves esophagitis, atrophy, mild to severe dysplasia, carcinoma in situ and finally, invasive cancer.

I. PATHOGENESIS

Human papillomavirus

A possible role for Human papillomavirus (HPVs) in ESCC has been suspected since the infection of this DNA virus in the epithelium plays a crucial role in the development of cervical SCC (5, 6). However, the role of HPV in the pathogenesis of esophageal SCC is still conflicting, with regional susceptibility differences among populations around the world (7). Studies mainly from China, were the initial association was found (8), report HPV to be present in relatively high percentages of ESCC cases (9-15). A different picture seems to occur in several European countries, were studies failed to detect HPV in ESCC (16-22). A rare involvement of HPV in ESCC has been reported in Belgium (23) and Brazil (24). In Japan HPV may be absent (25) or infrequent, and what is more surprising HPV has been found even in DNA from non-cancerous esophageal mucosa (26). I recently reported absence of HPV in a group of samples from Papua Guinea (27) and a a few cases from Peru, assessed by three different high sensitive PCR based detection systems (28, 29, 30).

Tumor suppressor genes (p53, pRB)

Genetic changes associated with the development of ESCC include mutation of the p53 gene, disruption of cell-cycle control in G1 by several mechanisms, including alterations in the retinoblastoma protein (RB), activation of oncogenes, and inactivation of several tumor suppressor genes. HPV early genes, E6 and E7, are important in cancer development functioning as transforming genes. E6 protein binds to and promotes degradation of the tumor suppressor protein, p53, while E7 protein complexes and inactivates the RB protein; together, they disrupt cell cycle regulation (31, 32). Genetic changes associated with the development of ESCC include mutation of the p53 gene and disruption of cell-cycle control by several mechanisms (including alterations of RB). ESCC constitutes the final stage of a sequence of histopathological changes that involves esophagitis, atrophy, mild to severe dysplasia, carcinoma in situ and finally, invasive cancer (Fig 1). Focal accumulation of p53 protein mutations in esophagitis areas at the margins of tumors have been observed (33). Mutations of the p53 gene are also involved in the pathogenesis of adenocarcinomas in Barrett's esophagus. Assessment of p53 mutations status may be clinically important as a parameter for the definition of risk groups after potentially curative resections (34).

Overexpression and p53 mutations occurs frequently in both HPV negative and HPV positive ESCC lesions (35). Overexpression of p53 and loss of pRB is considered abnormal (36). RB expression can be even found in high frecuencies in ESCC (higher than p53)(37-39). Immunohistochemically determined loss of RB protein expression may indicate loss of heterozygosity of the RB gene (40).

Amplification of several other oncogenes have been detected in esophageal squamous cell carcinomas (41). The alterations observed in tumor suppressor genes or oncogenes in the esophagus can be, in any case, due to exposure to other carcinogens, such as aflatoxin B1, benzopyrene produced by fungi and bacteria, and nitrosamines caused by cigarette smoking (42, 43). Chronic mucosal irritation due to hot beverage drinking has been also considered as an etiological factor (44, 45). Smoking, alcohol consumption, and low fruit and vegetable consumption have been recently reported as risk factors for ESCC in a multicenter population-based case-control study (46), pointing out the impact of lifestyle in the pathogenesis of this neoplasia.

II. IMMUNOTHERAPY

Immune response against tumors

Local infiltration of T-cells, B-cells and macrophages has been found to be a useful prognostic factor for 5-year survival in esophageal SCC cases without preoperative radiotherapy, chemotherapy or immunotherapy, indicating that this local immunocyte infiltration, in and around the cancer stroma, is a manifestation of the host defense against cancer (47). In fact immunosuppression, which is associated with a variety of tumors, most commonly lymphoma, may also lead to the development of squamous cell carcinoma of the esophagus (48).

T cells are critical mediators of tumor immunity. T lymphocytes can recognize specific antigens on human tumors (not displayed on the surface of normal cells), these "tumor rejection antigens" are peptides of tumor-cell proteins presented to T cells by MHC class I molecules. The anti-tumor response is unable to spontaneously eliminate an established tumor, either because the tumor-specific antigens are not

immunogenic enough, or because tumor cells can escape recognition and killing by cytotoxic T cells (Fig. 2). The aim of tumor immunotherapy is to enhance and augment such T cell response.

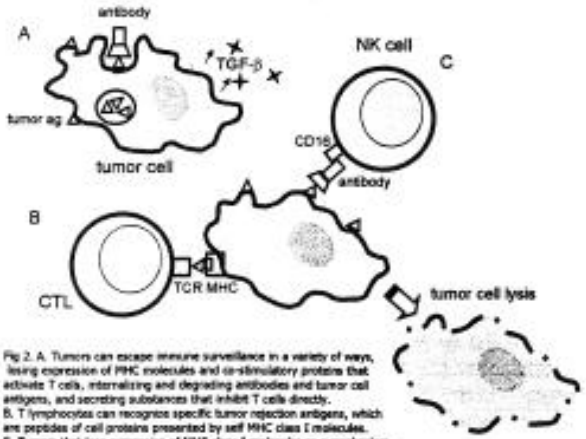

Fig 2. A. Tumors can escape immune surveillance in a variety of ways, losing expression of MHC molecules and co-stimulatory proteins that activate T cells, internalizing and degrading antibodies and tumor cell antigens, and secreting substances that inhibit T cells directly. B. T lymphocytes can recognize specific tumor rejection antigens, which are peptides of cell proteins presented by self MHC class I molecules. C. Tumors that lose expression of MHC class I molecules as a mechanism of escape are more susceptible to NK cell killing. Tumor-specific antibodies might be able to direct the lysis of the tumor cells by NK cells.

Use of activated lymphocytes stimulated with tumor-pulsed dendritic cells (to enhance the cytotoxity of the activated lymphocytes) showed disappearance of skin metastatsis of ESCC and might be useful for local treatment or postoperative adjuvant therapy (49).

Interleukin-2 (IL-2) is a T-cell growth factor, it mediates the in vivo expansion of T-cells with specific immunological functions as well as expand non-Major Histocompatability Complex (MHC) restricted lymphokine activated killer (LAK) cells. Administration of IL-2 could mediate the regression of established human cancer like metastatic melanomas, metastatic kidney cancers and B-cell lymphomas (50). In fact, use of IL-2 preoperative as neoadjuvant immunochemotherapy for locally advanced esophageal cancer may cause significant tumor regression in both size and shape (with clear surgical margins and absence of metastasis) (51).

Clinically significant tumor regression of solid metastatic lesions from esophageal cancer has been achieved through the use of locoregional adoptive immunotherapy (AIT). Locoregional administration (either endoscopically injected into primary tumor site or directly injected into metastatic lymph nodes) of autologous lymphocytes stimulated with autologous tumor cells and IL-2 in vitro, could achieve tumor regression in a considerable percentage of patients with advanced and recurrent esophageal cancer, with moderate and tolerable toxicity (52-54). It may be benefitial especially as postoperative adjuvant therapy in esophageal cancer (55). These studies suggest that CTLs rather than LAK cells are needed to achieve the tumor regression. However, tumors that lose expression of MHC class I molecules as a mechanism of escape from immune surveillance are more susceptible to killing by natural killer cells (NK) (Fig 2C).

Furthermore, various cancers, including human esophageal carcinomas express Fas ligand (FasL) and can kill lymphoid cells (tumor-infiltrating lymphocytes (TIL) by Fas-mediated apoptosis, thereby contributing to the immune privilege of the tumor (56). Another approach involves the use of cis-dichlorodiammineplatinum (CDDP) as a Fas inducer to make esophageal tumors susceptible to Fas antigen and LAK cytotoxic effector cells (57).

Tumor-specific antibodies might be able to direct the lysis of the tumor cells by NK cells via their Fc receptors (Fig 2B). The use of a monoclonal antibody of murine origin (KIS1) shown to react specifically with an antigen of human squamous cell carcinoma (SCC) had the problem of inducing the generation of human anti-mouse antibody (HAMA). The use of the KIS1 F(ab')2 fragment, i.e. the part of the antibody that interacts with its antigen, may not only overcome this difficulty, but has been shown to be superior to intact KIS1. Furthermore, it may be clinically useful for radioimmunodetection followed by tumor targeting therapy for patients with SCC of the esophagus (58).

The oncolytic herpes simplex-1 virus (NV1066), is a virus that has been engineered to infect and lyse tumor cells selectively. Due to its oncolytic activity in vitro and in vivo, which can be tracked endoscopically as it expresses the gene for green fluorescent protein (GFP), may be a useful therapy against esophageal cancer (59).

Recent progress in gene technology has identified some cancer-rejection genes and peptides such as MAGE, MART, etc. Effective HPV vaccines constitute our most promising weapon in the battle against cervical cancer (60), nevertheless its usefulness would be debatable as we previously discussed that the role of this virus in ESCC is controversial. Since the clinical efficacy of HLA class I-restricted peptide vaccines is still poor, many researchers are mainly administering immuno-cell therapies. As the number of clinicals trials of cancer-specific immunotherapy for esophageal carcinomas continues to increase, we hope that new apects on the way of how to use the immune response to attack this neoplasia will be enlighted.

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