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Detection of cancer/testis antigens as a diagnostic tool in routine pathology practice

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Most of the studies on cancer/testis (CT) antigens performed to date have focused on their potential value as targets for immunotherapy. Several recent studies, however, revealed that CT antigens might represent useful tools for diagnostic pathology, in particular for the identification of squamous cell carcinoma and related pre-malignant lesions, as well as specific types of sarcoma.

Cancer/testis (CT) antigens are exclusively or predominantly expressed by fetal and adult germ cells, but not (or at a minimal level) by normal somatic tissues. Moreover, several types of cancers aberrantly express CT antigens, often eliciting humoral and/or cell-mediated immune responses. For this reason, CT antigens are considered attractive targets for the development of therapeutic anticancer vaccines.[1] Of more than 100 CT antigens described so far (source CTDatabase, http://www.cta.lncc.br/), those that are encoded on chromosome X (CT-X) are the most CT-restricted and most immunogenic in cancer patients. Among CT-X antigens, melanoma antigen family A-3 (MAGEA3) and cancer/testis antigen 1B (CTAG1B, best known as NY-ESO-1) have been specifically targeted by immunotherapeutic interventions in many completed and ongoing clinical trials.[1]

The restricted expression of CT-X antigens in malignant lesions, but not in normal somatic tissues, suggest that they also could provide a useful diagnostic tool in routine pathological assessments. The immunohistochemical detection of CT antigens could potentially be useful at least in 2 different diagnostic settings:[1] as a biomarker to distinguish benign lesions from their malignant counterparts, and[2] as a biomarker to discriminate between morphologically similar tumors. These 2 diagnostic applications of CT antigens were the subject of several recent publications from us[2,3] and others.[4,5]

A good biomarker for distinguishing benign from malignant lesions must be expressed by a high percentage of cases of the tumor and at both early and late disease stages. Moreover, if the biomarker is expressed early during malignant transformation, it could have the additional value of identifying pre-malignant, often referred to by pathologists as "dysplastic," lesions. Based on these criteria, CT antigens would constitute poor biomarkers for most neoplasms, as individual CT antigens are usually expressed in < 40% of most tumor types (and in a significantly lower percentage of so-called "CT-poor" tumors). Moreover, early-stage primary cancers are expected to express CT antigens at a lower frequency than metastatic lesions of the same type.[1] Nonetheless, we recently found CT-X antigens to be potentially useful in the pathological diagnosis of squamous cell carcinoma (SCC) and its precursor lesions, specifically in the esophagus[2] and the head and neck region.[3] Among digestive tract carcinomas, we found esophageal SCCs to have the highest frequency of CT-X expression, with 62% of cases expressing at least one of eight CT-X antigens tested, i.e., MAGEA3, NY-ESO-1, G antigen (GAGE), MAGEC1 (also known as CT7), MAGEC2 (also known as CT10), CT45A1, sarcoma antigen 1 (SAGE1), and nuclear RNA export factor 2 (NXF2). Furthermore, 82% (18/22) of histologically dysplastic esophageal lesions were immunoreactive for an antibody cocktail detecting 6 distinct CT-X antigens, indicating that CT-X antigens are frequently expressed in pre-invasive early squamous malignancy (**Fig. 1**). Similar findings were obtained for SCCs of the head and neck, as 66% of such resected tumors expressed at least one CT-X antigen. Dysplastic squamous lesions of the head and neck, however, expressed CT-X antigens much less frequently than their esophageal counterparts (8/65, 12%), indicating that most low-to-moderate dysplastic lesions of the head and neck region are presumably benign. Since the morphological diagnosis of squamous dysplasia at both these anatomical sites is subjective and a significant inter-observer variation has been observed among pathologists, our findings suggest that CT-X expression can be a useful and objective tool for diagnosing early squamous malignancies.

The second possible diagnostic utility of CT-X antigens is in the differential diagnosis of tumor types that are morphologically similar. Such a diagnostic

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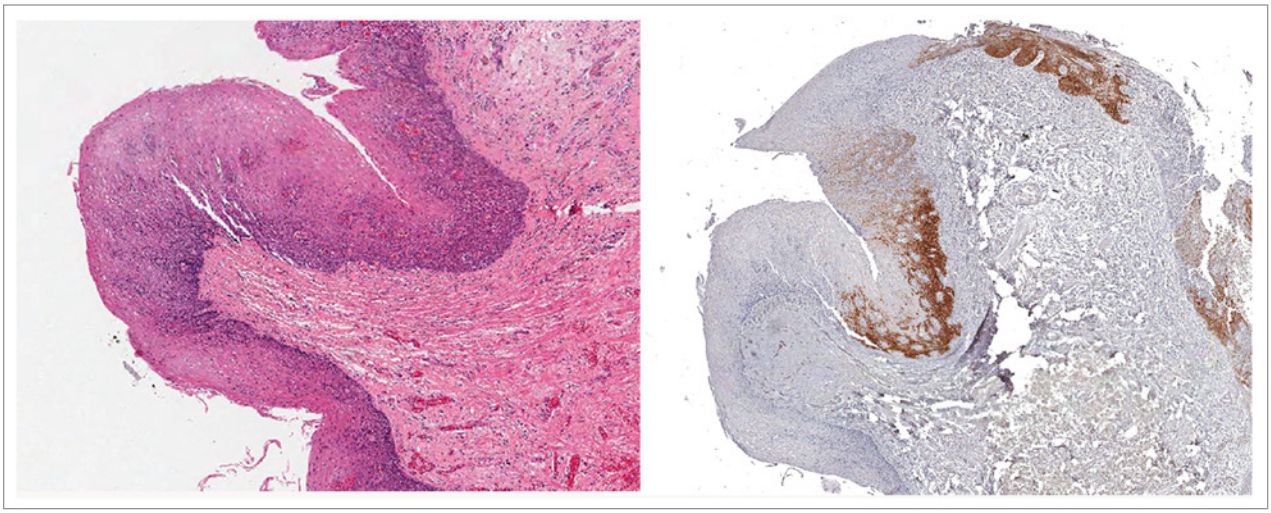

Figure 1. Squamous dysplasia in an esophageal biopsy. Routine hematoxylin and eosin (H&E) staining shows the maturation of squamous cells toward the surface, but the expansion of the neoplastic clone is not evident *(left)*. The immunohistochemical detection of cancer/testis antigens encoded on chromosome X (CT-X antigens) with a specific antibody cocktail identifies neoplastic cells in a patchy distribution and intervening residual benign squamous epithelium *(right)*.

potential of CT-X antigens, specifically NY-ESO-1, was recent confirmed by studies on synovial sarcoma and liposarcoma.[5-7] NY-ESO-1 was previously found to be expressed by 80% of synovial sarcomas.[8] Unlike the heterogeneous expression pattern that is often observed for CT antigens in other tumors, most synovial sarcomas express NY-ESO-1 to high levels and diffusely, a desirable feature for a diagnostic biomarker. These findings were confirmed by a recent and comprehensive study by Lai et al., in which NY-ESO-1 was found to be expressed by ~85% of synovial sarcomas but rarely (< 5%) by other sarcomas.[5,9] The authors concluded that the immunohistochemical detection of NY-ESO-1 could be a valuable confirmatory test for synovial sarcoma.

Similar results were obtained by Hemminger et al., who analyzed the expression of NY-ESO-1 in myxoid and round cell liposarcoma.[4,6] In this study, almost all (36/38, 95%) cases of myxoid and round cell liposarcoma expressed NY-ESO-1, the vast majority of which (34/36, 94%) exhibiting a strong and diffuse expression pattern. In contrast, other sarcomas (with the exception of synovial sarcoma) appear to express NY-ESO-1 very rarely: in 0/100 cases in one study[4] and in 10/367 in another.[5] These findings led Hemminger and colleagues to propose NY-ESO-1 as a sensitive and specific biomarker for diagnosing myxoid and round cell lipocarcoma.[6]

In summary, although they have mostly been studied in the context of anticancer immunotherapy, CT-X antigens have recently been shown to constitute useful immunohistochemical biomarkers for the diagnosis of SCC and specific types of sarcoma. The diagnostic potential of CT-X antigens should be further explored.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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