Japanese Dental Science Review (2014) 50, 91—99

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Review Article

Cancer/testis antigens: A prospective reagent as diagnostic and immunotherapeutic targets for squamous cell carcinoma of the head and neck

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Received 31 January 2014; received in revised form 28 May 2014; accepted 13 June 2014

KEYWORDS
Cancer/testis antigen;
SEREX;
Antibody response;
Squamous cell carcinoma of the head and neck

Summary Numerous tumor antigens have so far been identified from various tumors using the serological identification of antigens by recombinant expression cloning (SEREX) method. Among them, cancer/testis (CT) antigens are considered promising target molecules for immunotherapy for patients with various cancers. We performed several SEREX analyses of various cancers to identify CT antigens, including gastric adenocarcinoma, lung adenocarcinoma, and colon cancer, and consequently identified additional CT antigens, such as XAGE-1, CCDC62-2, GKAP1, and TEKT5. However, although SEREX analysis of squamous cell carcinoma of the head and neck (HNSCC) has been performed several times, only a few CT or HNSCC specific antigens have yet been isolated. Compared with other tumors, a small number of studies have been reported on the antigen proteins specific to HNSCC. We here reported the expression of selected CT antigens and their immunogenicity in patients with HNSCC. The results obtained suggested that CCDC62-2, GKAP1, and TEKT5 are immunogenic in HNSCC and also demonstrated their potencies as diagnostic markers for patients with HNSCC in combination with other CT antigens such as NY-ESO-1, MAGE-A3, and MAGE-A4.

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http://dx.doi.org/10.1016/j.jdsr.2014.06.001
1882-7616

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1. Introduction

The incidence of squamous cell carcinoma of the head and neck (HNSCC) is more than 20,000 new cases per year in Japan and ~500,000 cases annually worldwide. Surgical resection is commonly performed followed by combined chemotherapy or radiotherapy. However, the 5-year survival rates of patients with this cancer have remained at approximately 50% for the past 2 decades, in spite of advances in surgical procedures as well as various combinations of chemotherapeutic agents [1,2]. Therefore, the development of new therapeutics and their integration into current forms of therapy remain a major goal for the future. Recent progresses in tumor immunology based on the molecular identification of tumor antigens may allow immunotherapy to become another promising treatment to improve the outcomes of patients with HNSCC. Following the introduction of the T cell epitope cloning technique by Boon et al. [3], numerous antigens coding for immunogenic sequences have been identified in different tumor types, including MAGE families in malignant melanoma [4] and NY-ESO-1 in esophageal cancer [5]. Cancer/testis (CT) antigens have become promising targets for the diagnosis of and immunotherapy for patients with various tumors because of their unique expression patterns [6]. Compared with other tumors, a small number of studies have been reported on the antigen proteins specific to HNSCC [7,8]. We here reported the expression of selected CT antigens and their immunogenicity in patients with HNSCC.

2. CT antigens

The defining characteristics of CT antigens are high levels of expression in male germ cells such as spermatogonial stem cells, spermatogonia, spermatocytes, spermatids, and spermatozoa during spermatogenesis in the testis, and lack of expression in normal tissues [9]. The expression of CT antigens has also been reported in the ovary and placenta [10,11]. The genes of CT antigens are activated and aberrantly expressed in a wide range of different tumor types and have been shown to be antigenic in tumor-bearing patients [12]. CT antigens are now classified as X-CT and non-X-CT based on whether the gene is located on the X chromosome (Table 1). X-CT antigens are often organized in well-defined clusters to constitute multigene families [13,14]. However, genes encoding non-X-CT antigens are distributed throughout the genome and are mostly single-copy genes. Since different CT antigens are expressed during different stages of spermatogenesis (Fig. 1), their function may be versatile, *e.g.* the regulation of mitotic cycling in spermatogonia, an association with the meiotic cycle in spermatocytes, and finalizing acrosome maturation in sperm.

Table 1 List of known CT antigens and CT antigen families.

CT antigen	No. of genes	Chromosome
MAGE-A	11	Xq28
BAGE	5	13
GAGE	8	Xp11.4-11.2
SSX	9	Xp11.2
NY-ESO-1/LAGE-1	2	Xq28
SCP1	1	1p13
CT7/MAGE-C1	1	Xq26-27
CT8/HOM-TES-85	1	Xq24
CT10	1	Xq27
cTAGE	5	18p11
XAGE-1	5	Xp11.21-22
OY-TES-1	1	12p13.31
AKAP3	1	12p13.3
CCDC62-2	1	12q24.31
GKAP1	1	9q21.32
TEKT5	1	16p13.13

More than 110 genes or gene families coding for CT antigens have been identified to date by several methodologies [15], such as T-cell epitope cloning, serological identification of antigens by recombinant expression cloning (SEREX), representational difference analysis (RDA), DNA