OncoImmunology 1:7, 1194-1196; October 2012; © 2012 Landes Bioscience

Cancer testis antigens
A new paradigm for cancer therapy

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Keywords: cancer testis antigens, SPAG9, biomarkers, immunotherapy, cancer vaccines

Abbreviations: SPAG9, sperm-associated antigen 9; CT, cancer testis; JNK, c-Jun N-terminal kinase; CTLA4, cytotoxic T-lymphocyte antigen 4

Cancer immunotherapy is a promising field with limited success, also due to lack of tumor-specific targets. In our attempt of exploring novel biomarkers and immunotherapeutic targets against cancer, we have discovered a novel cancer testis antigen, SPAG9, in cancers of different histological origin and demonstrated its potential role in oncogenesis.

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries.[1] The clinical management of cancer encompasses various aspects, including prevention, detection and treatment. Most cancers become clinically manifest only when they have already invaded the surrounding tissues or have metastasized. At this stage, the therapeutic options are limited, include aggressive chemotherapy (e.g., with cytotoxic agents such as paclitaxel), hormonal therapy (e.g., with tamoxifen), targeted therapy (e.g., imatinib) and immunotherapy. Cancer immunotherapy has an edge over other classical treatment modalities in that it is less prone than conventional drugs to severe side effects.

Cancer immunotherapy is a highly-targeted approach and encompasses any strategy that directs the components of the innate and adaptive immune system against cancer. Cancer immunotherapy can provide durable clinical responses even against the most challenging cancers. Nonetheless the translation of immunological knowledge "from bench to bedside" has been limited due to the poor availability of ideal candidate targets on cancer cells. In this regard, a unique class of antigens known as cancer testis (CT) antigens, which are specifically expressed in the normal testis and show aberrant expression in various malignancies, is the focus of an intense wave of research, both as putative biomarkers and for their potential to constitute convenient targets for immunotherapeutic strategies (**Fig. 1**).[2] CT antigens are the most prominent exception of tumor-associated antigens as, despite constituting self molecules, they are physiologically expressed only in immunoprivileged tissues (such as the testis) and should therefore not induce tolerance. This underlines the potential value of these antigens, as compared with others, as efficient inducers of antitumor immune responses. In this context, a report recently published in *Nature Medicine* states, "Wiping out cells expressing CT antigens should theoretically cause 'no side effects,' no off-target effects on normal tissues, none at all."[3] This supports the contention that there is growing need to explore the development of anticancer vaccines, implementing antigens that are—alone or in combination—indispensable for tumor cells. Such novel strategies will establish a basis for the design of future therapeutic regimens for a better clinical care of cancer patients.

We have recently discovered a novel CT antigen, sperm-associated antigen 9 (SPAG9), which is involved in c-Jun N-terminal kinase (JNK)-signaling and functions as a scaffold protein for JNKs, thus playing an important role in cell survival, proliferation, apoptosis and tumor development.[4] Recently, SPAG9 was detected in epithelial ovarian cancer (90%), breast cancer (88%), cervical cancer (82%), renal cell cancer (88%) and colorectal cancer (74%) patients.[5-7] Apart from being expressed in a majority of cancers, SPAG9 is also found to be associated with cellular proliferation, migration and invasiveness of cancer cells. Testis is considered as an immunopriviledged organ due to lack of Class I MHC expression on the surface of germ cells. Therefore, testis-specific proteins that are also expressed by cancerous tissues have the potential to stimulate cellular as well as humoral immune responses in cancer patients. Supporting this notion, our findings demonstrated that SPAG9 can elicit humoral immune responses in a majority of epithelial ovarian cancer (67%), breast cancer (80%), cervical cancer (80%), renal cell carcinoma (77%) and colorectal cancer (74%) patients.[5-7] Antibodies against SPAG9 represent a less-invasive method of cancer detection and might serve as a biomarker for these malignancies. Our future studies aim at exploring the

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Submitted: 05/07/12; Accepted: 05/08/12
http://dx.doi.org/10.4161/onci.20686

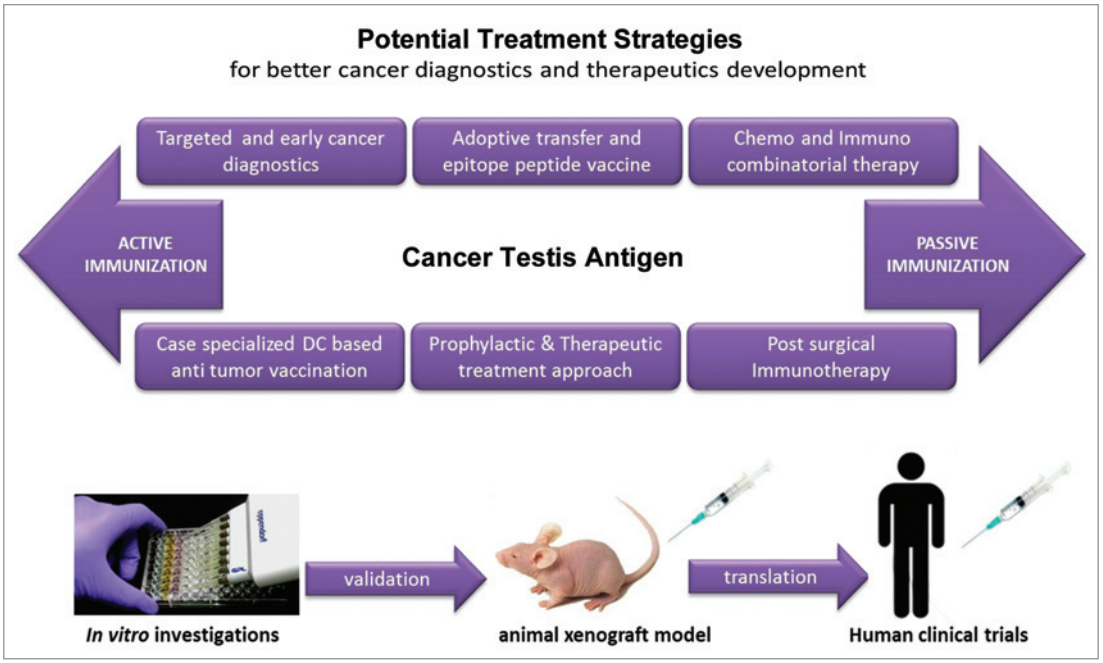

Figure 1. Schematic representation of the importance of cancer testis (CT) antigens in cancer diagnostics and immunotherapy. CT antigens are a unique class of proteins that is highly exclusively expressed in the testis and in a wide variety of tumors. CT antigens can evoke an immune response in cancer patients and may serve as diagnostic tools and therapeutic targets. CT antigens are being explored as candidates for the development of novel, optimized anticancer therapies.

immunotherapeutic potential of SPAG9 as a target for antigen-based antitumor vaccines, T-cell/B-cell epitope peptide vaccines, dendritic cell (DC)-based vaccines, monoclonal antibodies and monoclonal antibody-conjugated warheads.

The efficacy of cancer vaccines depends on the ability of the vaccine to break immunological tolerance, overcome immunosuppression and either activate antigen-specific cytotoxic T cells with robust effector functions or generate efficient antibodies against cancer-specific antigens. Clinical trials based on strategies targeting two well characterized CT antigens have shown limited success in cancer patients. In this regard, two parallel Phase II studies, using heterologous prime-boost vaccination with rV-NY-ESO-1 and rF-NY-ESO-1 reported clinical benefit for patients affected by melanoma and ovarian cancer at high risk for relapse.[8] Recently discovered strategies for vaccine development are passive immunization through adoptive T-cell transfer, active immunization through vaccination, and the blockage of co-inhibitory signaling of tumor-specific T cells (for instance, by means of anti-CTLA4 or anti-PD1 antibodies). Recent clinical trials in patients with metastatic breast and ovarian cancer reported benefits for the administration of the MUC-1/CEA/TRICOM poxviral-based vaccine in patients who had limited tumor burden prior chemotherapy.[9] These immunotherapies can be combined with each other, with various forms of immunomodulation, as well as with classical anticancer therapies, to counteract negative regulation of immune response. In this context, an important vaccine that has been shown to provide survival benefit in metastatic castration-resistant prostate cancer patients is PSA-Tricom (Prostvac), which has now been approved by the US Food and Drug Administration. Further clinical trials using combination of PSA-Tricom and anti-CTLA4 antibodies (ipilimumab) are also underway to improve the immune outcome.[10]

In conclusion, additional antigens should be explored for the development of novel immunotherapeutic strategies that maximize immune responses against cancer. Among multiple tumor-associated antigens, SPAG9 represents a promising candidate owing to its expression pattern and immunogenicity in cancers of different origins. Additional large scale studies are warranted to explore the immunotherapeutic potential of SPAG9 in cancer patients.

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