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STEAP-1: A Potential Biomarker, Promising Target?

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Abstract

STEAP1 is one of six-transmembrane epithelial antigen of prostate (STEAP) highly expressed in human prostate cancer and is up-regulated in multiple cancers, including bladder, colon, breast, Ewing and lung cancers. Immunohistochemical analysis demonstrates significant STEAP1 expression at the intercellular communication between adjacent cells suggesting that this antigen must be a channel, or a transport protein indicating its potential role in tumor cell intercellular communication increasing the potential of STEAP1 as a diagnostic, prognostic, prophylactic and/or therapeutic target for new immunotherapeutic strategies. In prostate cancer, overexpression relates adenocarcinoma and prostatic intraepithelial neoplasia scores suggest that STEAP1 could be involved in tumor initiation and progression and may be of clinical usefulness in early disease diagnosis. Also, STEAP1 can serve as a biomarker of worse prognosis because of its association with higher Gleason score, seminal vesicle invasion, biochemical recurrence, and worse outcome. Therapeutically, STEAP1 is one of a few prostate cancer antigens that meet the appropriate criteria and represent an attractive target for antibody cancer therapy. It can be a target of anti-tumor CD8, or serve as a tool for vaccination as shown by xenograft models and phases I/II studies. STEAP1 could also serve as a new marker of tumor angiogenesis in lung cancer, indicate for occult residual tumor cells in patients with Ewing Sarcoma and also be used as a cell surface antigen for the development of breast cancer immunotherapy. The standardization of its evaluation as well as the validation through randomized trials would be necessary.

Keywords: STEAP1; Prostate cancer; Biomarker; Immunotherapy

Introduction

The human 6-transmembrane epithelial antigen of prostate (STEAP) family comprises four proteins specific to mammals with metalloreductases activity showing their importance in metal metabolism. They participate in a several biologic processes, such as molecular transport in the endocytic and exocytic pathways and control of cell proliferation and apoptosis [1].

STEAP1 was the first member of the STEAP family to be identified as a prostate-specific cell-surface antigen over-expressed in human prostate cancer and also expressed in several human cancer cell lines obtained from breast, pancreas, genitourinary tract , gastrointestinal tract, ovary, cervix, ewing sarcoma, and lung with little or no expression in vital organs [2]. STEAP1 protein presents a molecular topology of six transmembrane domains with intracellular N- and C- terminals and three extracellular and two intracellular loops. This protein is composed by 339 amino acids with a molecular weight of 36 KDa, and it is localized on chromosome 7q21, a region close to the telomeric sequences.

Immunohistochemical analysis of clinical specimens demonstrates significant STEAP1 expression at the intercellular communication between adjacent cells suggesting that this antigen must be a channel, or a transport protein indicating its potential role in tumor cell intercellular communication increasing the potential of STEAP1 as a diagnostic, prognostic, prophylactic and/or therapeutic target for new immunotherapeutic strategies [3,4].

In this short communication, we bring the current knowledge about STEAP1 as a new biomarker and a new therapeutic target especially in prostate cancer, lung cancer and other solid cancers with the therapeutic progress.

STEAP1 in prostate cancer: A model of knowledge development

Considering the incidence and the mortality of prostate cancer and some of the limitations of the PSA test as a marker of this disease, we believe that it is important to study novel putative biomarkers in prostate cancer (PCa). Although it is well characterized that STEAP1 is overexpressed in PCa, and normal prostatic tissues preferentially located on the plasma membrane of epithelial cells, particularly on cell-cell junctions, and to a lesser extend dispersed on the cytoplasm [5]. This overexpression relates adenocarcinoma and prostatic intraepithelial neoplasia scores suggest that STEAP1 could be involved in tumor initiation and progression and may be of clinical usefulness in early disease diagnosis [6]. STEAP1 can serve as a biomarker of worse prognosis because of its association with higher Gleason score, seminal vesicle invasion, biochemical recurrence, and worse outcome (metastasis or PCa-specific death) [6,7].

Biologic regulation of STEAP1 is unusually complicated in PCa and does not seem to involve epigenetic mechanisms. Paradoxically, STEAP1 expression can be androgen-stimulated, androgen-repressed, or androgen-independent in pre-clinical PCa models [6-8]. On the basis of its upregulation in several contexts, STEAP1 has been the focus of multiple antibody development programs for therapy.

Prostate cancer is the most common malignancy affecting men and is the second-leading cause of cancer death [9], the only targeted therapy that proved efficacy in its metastatic form in term of overall survival is cell-based immunotherapy by sipuleucel-T [10]. This high

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costs associated with *in vitro* loading of autologous antigen presenting cells fostered attempts to develop vaccination approaches relying on *in vivo* loading of antigen presenting cells (APCs) as STEAP1 with antigen and immune stimulants (other active immunotherapy approaches by vaccination or monoclonal antibodies). Among these approaches vaccination, the use of a STEAP1 epitope (262-270) knowed as an antigenic peptide capable of started effective anti-tumor T-cell responses that can be used to develop immunotherapy specific in prostatic cancer [11]. A prostate-cancer vaccine called CV9103 containing self-adjuvanted mRNA encoding the STEAP1 is shown well tolerated and immunogenic in a phase I/IIa study including 44 patients with advanced castration-resistant prostate-cancer [11]. Active Immunization using recombinant DNA and modified vaccinia virus Ankara (MVA) vectors delivering STEAP1 antigens is a promising approach for prevention and/or treatment of prostate cancer [12].

STEAP-1 is one of a few prostate cancer antigens that meet the appropriate criteria and represent an attractive target for antibody cancer therapy based on its strong and homogeneous expression of in prostatic cancer specimens, together with its restricted expression in normal tissues [13]. Two unique mAbs specific to the extracelluar epitopes of STEAP-1 showed antitumor efficacy by inhibiting STEAP-1-induced intercellular communication in a dose-dependent manner and by inhibiting the growth of different xenograft tumor models [13]. This successful generation has allowed the subsequent development of antibody drug conjugates (ADCs) anti-STEAP1 by combination of a humanized IgG1 anti-STEAP1 conventional antibody to a potent antimitotic auristatin drug, monomethyl auristatin E (MMAE) using ThioMab antibody technology [14]. The goal is to adjust the overall structure for better tissue distribution. An ADC DSTP3086S contains the humanized igG1 anti-STEAP1 monoclonal antibody linked to the potent anti-mitotic agent MMAE has a tolerable safety profile and shows evidence of anti-tumor activity [15].

STEAP1 is a new marker highly expressed at all phases of prostate cancer including nodes and bone metastases. This property can give it the status of a predictive marker of the effectiveness of bone targeted therapies widely used in prostate cancer. So, zoledronic acid strongly decreased cell viability and lowered *STEAP* gene expression [16].

STEAP1 in lung cancer: A new marker of tumor angiogenesis

STEAP1 could also serve as a new marker of tumor angiogenesis in lung cancer. Zhuang et al. reported the molecular profiles obtained after sequencing of healthy and tumour lung tissue. For their study, the authors used a novel technique for isolation and purification of endothelial cells by enzymatic techniques associated with electromagnetic sorting. After RNA extraction, amplification, and sequencing (microarray, RNA-seq, RT-PCR), the authors have identified on tumor endothelial cells 122 genes encoding for angiogenic factors, transmembrane proteins, and metalloproteases Further detailed expression profiling of STEAP1 on 82 lung cancer patients confirmed STEAP1 as a novel target in the tumour vasculature. The authors conclude that cell-surface tumour endothelial expression of STEAP1 will facilitate the pre-clinical validation with therapeutic antibodies and vaccine development. Further work is needed to characterize their functions and their roles in the endothelial biology and angiogenesis in the lung Functional analysis of STEAP1 using siRNA silencing implicates a role in endothelial cell migration and tube formation [17].

STEAP1 in other cancers

STEAP1 is strongly overexpressed in many solids cancers including breast, bladder carcinoma and colon cancer as well as Ewing's sarcoma [2]. Ewing's sarcoma (ES) is a highly aggressive bone or soft-tissue cancer mostly affecting children and young adolescents in which biological markers are very limited [18]. STEAP1 messenger RNA (mRNA) circulates in peripheral blood of cancer patients [19] and its detection in bone marrow is indicative for occult residual tumor cells in patients with ES [20]. Moreover, STEAP1 was found to be a bona fide marker for human mesenchymal stem cells [21] lending support to the hypothesis of a mesenchymal origin of ES [22].

STEAP1 overexpression increases the invasive properties and intracellular levels of reactive oxygen species (ROS) of ES cells [23]. For all of these reasons, Grunewald et al investigated the value of STEAP1 as an immunohistological marker for outcome prediction of patients with ES [24]. They provide evidence that high membranous STEAP1 expression is associated with improved overall survival (OS). Moreover, high membranous STEAP1 immunoreactivity showed a trend toward a better histological tumor response to chemotherapy and, conversely, STEAP1-silenced ES cells were more resistant to chemotherapy *in vitro*. These data unravel a hitherto unanticipated role of STEAP1 as a promising independent biomarker for outcome prediction of ES.

However, the findings are not conclusive, as still other studies show an association High STEAP1 mRNA expression, cancer metastasis and short survival [20]. One possibility is that the effects of STEAP1 expression might differ depending on the cancer cell types or populations indicating the existence of specific subgroups of patients, some of which might benefit from adapted therapy regimens for treatment of Ewing's sarcoma [24]. Paradoxically in colorectal cancers, patients with high STEAP1 expression would have favorable clinical outcomes [25]. STEAP1 had a more significant association with clinical outcome in elderly patients and in patients with late stage cancers, late T values, and early N values. This indicated that the prognostic role might differ among patients with specific clinicopathological characteristics. The underlying mechanism whereby STEAP1 promotes circulating tumor cell formation and favorable prognosis needs further investigation [25].

Alike prostate cancer in men, breast cancer is the most common cancer type in women. STEAP1 is over-expressed in human breast cancer cases, and in normal breast tissue adjacent to breast tumors, where it is localized in the cell membrane of epithelial cells and in fibroblasts suggests that, like in prostate, STEAP1 can also be used as a cell surface antigen for the development of breast cancer immunotherapy [26]. There was no difference in the STEAP1 mRNA expression between infiltrative ductal carcinoma and normal epithelial tissue adjacent to these tumors, suggesting that an increase in STEAP1 may anticipate tumor development or invasiveness [26]. 17b-Estradiol seems to be the only known regulator of STEAP1 expression in breast cancer. This hormone downregulates STEAP1 expression both *in vivo* in rat mammary glands and *in vitro* in MCF-7 breast cancer cells [26].

Suppression of ovarian function recognized as therapeutic standard for pre-menopausal patients may increase STEAP1 expression. This increase may be useful as a target for T-cell-based immunotherapy. The balance between the beneficial effects of castration, and the consequences arising from the resulting increase in STEAP1 levels, which may promote cell proliferation [27], should be addressed in future studies. However, as STEAP1 expression correlates negatively with ER, it is more likely that STEAP1 may become a useful target for tumor immunotherapy in ER-negative tumors.

Immunotherapy for renal cell and bladder cancer is one of the most promising therapeutic approaches. STEAP is over expressed in

urological cancers and specific helper T lymphocytes were induced to recognize the naturally processed peptide epitopes (STEAP102-116 and STEAP192-206) arising from STEAP expressing tumor cells. Theses epitopes are attractive helper T lymphocyte that can elicit effective antitumor T-cell responses against STEAP expressing urological tumors. These observations may allow the translation of T-cell based immunotherapy into clinical use to eradicate RCC and bladder cancer [28].

In conclusion, STEAP1 can serve as a potential immunotherapeutic target as well as a biomarker, emphasizing its clinical relevance in many cancers especially in prostate adenocarcinoma. The standardization of its evaluation as well as the validation through randomized trials would be necessary.

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