B7-H4 Expression as a Predictive Biomarker in Human Cervical Cancer Immunotherapy

Mini Review

Idowu Temitayo

Department of Microbiology and Immunology, Inje University college of Medicine, Busan, South Korea.

Abstract

Over the years Immunotherapy has evolved as a beneficial method in the treatment of cancer through the blockade of immune checkpoint molecules which are up regulated on activated lymphocytes, antigen presenting cells (APC`s) and on tumor cells to down regulate immune cell effector functions. B7-H4, which has been shown to be expressed on cervical cancer, is also associated with the poor prognosis of cervical cancer patients. Blockade of this ligand expressed on cervical cancers can be a novel target for molecular targeted immunotherapy against cervical cancer, which is known as the second most diagnosed malignancy among female worldwide.

Keywords: Immunotherapy; Checkpoint Molecules; Cervical Cancer.

Introduction

According to the International Federation of Gynecology and Obstetrics (FIGO), cervical cancer is described as the second most common diagnosed malignancy in females worldwide [1]. Treatment options for patients with cervical cancer includes, surgery, radiation therapy, chemoradiationand chemotherapy, however, these treatment options are dependent on various factors like, the patients age, cancer stage, type of cervical cancer, the patients desire to have children among others [2, 3].

B7 family members and their receptors which plays a vital role in the maintenance of self-tolerance and regulation of innate and adaptive immunity in tumor bearing hosts [4] has also been shown to be powerful inhibitors of antigen specific response [5]. B7-H4, a B7 family whose receptor is yet to be identified is widely expressed on cervical cancers and various gynecological cancers [6]. B7-H4 functions through the inhibition of T cell proliferation, cell cycle arrest and cytokine production [7-9]. Blockade of this inhibitory response by specific monoclonal antibody as described by various *in vitro* and *in vivo* assays enhances T cell effector functions [10].

Summary of latest researches

Huang et al., and Liu et al. described that B7-H4 expression correlates with poor prognosis for cervical cancer patients. Huang et al detected B7-H4 expression on 71 (69.6%) out of 102 cervical cancer specimen by immunohistochemical detection and showed that there was no significant correlation between the expression of B7-H4 and patients age, FIGO stage, histological type or lymph node status, very similar to studies by Liu et al [11, 12]. Also, Wang et al. described that B7-H4 expression was detected in 31 out of 67 (46%) cases of cervical cancer. They showed that upon immunoflourescent staining CD4+ T, CD8+ T and FOXP3+ T cell infiltration were detected in cervical cancer tissue. There were more infiltrating CD8+ T and FOXP3+ T cells than infiltrating CD4+ T cells, but there was no significant difference in the number of infiltrating CD4+ T and FOXP3+ T cells between B7-H4 and negative cases, However, the average number of infiltrating CD8+ T cells and their IFN-y production was significantly lower in B7-H4 positive cases compared to negative cases, there result was similar to that of the works of Bedoya et al [13]. Further *in vitro* studies showed that B7-H4 inhibits the proliferation of CD4+ and CD8+ T cells, however it promotes the production of IL10 and TGF-B1 and also Tregs., Wang et al., concluded that B7-H4 plays an important role in depressing the anti-tumor immunity of cervical cancer microenvironment [14].

Recently, Huang et al., described that B7-H4 is overexpressed on cervical cancer and there expression is associated with cancer stage and tumor size as described by the International Federation of Gynecology and Obstetrics (FIGO) but not associated with age,

Idowu Temitayo (2016) B7-H4 Expression as a Predictive Biomarker in Human Cervical Cancer Immunotherapy. *Int J Cancer Stud Res*. 5(2), 96-97.

96

histological types and differentiation and lymph nodes metastasis. They also described that B7-H4 expression negatively correlates with IL2 production and a conclusion that B7-H4 among other markers may be a useful biomarker in patients with cervical cancer for predicting immunotherapeutic treatment methods [11].

Commentary

Clinical implications

o   B7-H4 is expressed on a wide range of cervical cancer.
o   B7-H4 expression on cervical cancer doesn't correlate with Age, histological types or lymph node metastasis but rather cancer stage and tumor size.
o   B7-H4 up regulation is one of the major mechanisms possessed by cervical cancer to escape immunity through T cell inhibition and the production of IL10 and TGF-B1and T regs.

In summary, based on new reports, it can be deducted that B7-H4 is overexpressed in human cervical cancers and it correlates with patients' age and cancer stage but not age, histological types or lymph node metastasis. B7-H4 expression inhibits both CD8^{+} and CD4^{+} T cells and it is further associated with low numbers of infiltrating CD8^{+} T cells and IFN-g production.In conclusion, B7-H4 plays an important role in suppressing anti-tumor immunity in the microenvironment of cervical cancer and it may be a suitable biomarker target for cervical cancer immunotherapy.

Acknowledgment

References

[1].   Parkin DM, Bray F, Ferlay J, Pisani P (2001) Estimating the world cancer burden: Globocan 2000. Int J Cancer 94(2): 153–156.
[2].   World Health Organization (2006) Comprehensive cervical cancer control: a guide to essential practice (2 edn). Geneva.
[3].   Petignat Patrick, Roy Michel (2007) Diagnosis and management of cervical cancer. BMJ 335(7623):765-768.
[4].   Fauci JM, Straughn JM Jr, Ferrone S, Buchsbaum DJ (2012) A review of B7-H3 and B7-H4 immune molecules and their role in ovarian cancer. Gynecol Oncol 127(2): 420-425.
[5].   Zou W, Chen L (2008) Inhibitory B7- family molecules in the tumour microenvironment. Nature Rev Immunol 8(6): 467–477.
[6].   JB Smith, C Stashwick, DJ Powell Jr (2014) B7-H4 as a potential target for immunotherapy for gynecologic cancers: A closer look Gynecol Oncol, 134(1): 181–189.
[7].   Sica GL, Choi IH, Zhu G, Tamada K, Wang SD, Tamura H, et al., (2003) B7-H4, a molecule of the B7 family, negatively regulates T cell immunity. Immunity 18(6): 849 861.
[8].   Prasad DV, Richards S, Mai XM, Dong C (2003) B7S1, a novel B7 family member that negatively regulates T cell activation.Immunity 18(6): 863 873.
[9].   Zang X, Loke P, Kim J, Murphy K, Waitz R, Allison JP (2003) B7x: a widely expressed B7 family member that inhibits T cell activation. Proc Natl Acad Sci USA 100(18): 10388-10392.
[10]. Qian Y, Shen L, Xu C, Wu Z, Brockmeyer NH, Altmeyer P, et al., (2011) "Development of a novel monoclonal antibody to B7-H4: characterization and biological activity". Eur J Med Res 16(7): 295–302.
[11]. Huang C, Zhou L, Chang X, Pang X, Zhang H, Zhang S (2016) B7-H3, B7-H4, Foxp3 and IL-2 expression in cervical cancer: Associations with patient outcome and clinical significance. Oncol Rep 35(4): 2183-2190.
[12]. Liu W, Shibata K, Koya Y, Kajiyama H, Senga T, Yamashita M, et al., (2014) B7-H4 overexpression correlates with a poor prognosis for cervical cancer patients. Mol Clin Oncol 2 (2): 219–225.
[13]. Bedoya AM, Jaramillo R, Baena A, Castaño J, Olaya N, Zea AH, et al., (2013) Location and density of immune cells in precursor lesions and cervical cancer Cancer Microenviron 6 (1): 69–77.
[14]. Xin Wang, Tingting Wang, Man Xu, Ling Xiao, Yi Luo, Wenlian Huang, et al., (2014) B7-H4 overexpression impairs the immune response of T cells in human cervical carcinomas. Hum Immunol. 75(12): 1203–1209.

Idowu Temitayo (2016) B7-H4 Expression as a Predictive Biomarker in Human Cervical Cancer Immunotherapy. *Int J Cancer Stud Res*. 5(2), 96-97.

97