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Gene Section
Mini Review

VTCN1 (V-set domain containing T cell activation inhibitor 1)

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Identity

Hugo: VTCN1
Other names: B7H4; B7-H4; B7S1; B7X; B7h.5; FLJ22418; PRO1291; RP11-229A19.4
Location: 1p13.1

DNA/RNA

Description

The VTCN1 (B7-H4) gene located in chromosome 1p13.1, consists of six exons and five introns and the coding region spans 849 bp. The mature protein is coded by the exons 3, 4, and part 5 while exons 1 and 2 encodes a signal peptide. The IgV-IgC domain, comprised of the extracellular region, is coded by exons 3, 4 and parts of 5 (Chen et al., 2003).

Transcription

B7-H4 mRNA can be detected in many tissues including placenta, kidney, liver, lung, ovary, testis and spleen. There are two transcripts of B7-H4 and both transcripts share complete homology with exons 1 to 5 in the full length B7-H4 gene. The smaller transcript of the two, generated by alternative splicing, lacks part of exon 6 (Chen et al., 2003).

Pseudogene

A possible B7-H4 pseudogene has a single exon with 94% similar nucleotide sequence identity to the cDNA of B-7H4 and is located in chromosome 20p11.1 (Chen et al., 2003).

Protein

Description

The predicted 282-amino acid B7-H4 protein contains a 2-amino acid intracellular domain, a large hydrophobic type 1 transmembrane domain and an extracellular domain (Prasad et al., 2003).

Expression

Prasad et al. (2003) showed that B7-H4 is expressed in professional antigen presenting cells. Although B7-H4 is overexpressed in several human cancers including ovary, endometrium, lung and kidney, its expression is limited in normal tissues. Shroyer et al. (2005) showed that there is a limited focal expression of B7-H4 by immunohistochemistry in several normal human tissues including fallopian tubes, endometrial glands, pancreas, larynx, lung, kidney and urinary bladder.

Localisation

B7-H4 is localized to the cell surface and cytoplasm of epithelial cells and macrophages. Expression in benign glandular cells (ductal epithelium in breast and pancreas) is localized to the apical cell surface but there is circumferential membranous localization in B7-H4 positive tumor cells.

Function

Published data shows that B7-H4 functions as a negative regulator of T cell responses and it negatively regulates the T cell immunity by the inhibition of T cell proliferation, cytokine production and cell cycle

progression. Prasad et al. (2003) reported that B7S1/B7-H4 is expressed on professional antigen presenting cells, binds to its putative receptor on activated T cells, and inhibits T cell activation and IL2 production. Sica et al. (2003) also reported that B7-H4 inhibits T cell activation and the production of both IL2 and IL10. They further showed that B7-H4 inhibits the induction of Cytolytic T Lymphocytes (CTL) in vitro and it also arrests cell cycle of T cells in G0/G1 phase.
B7-H4 may also play a role in tumor biology by providing tumors with a protective mechanism to escape from immune surveillance. Several human cancers such ovary, endometrium, breast, kidney and lung (non small cell) are known to overexpress B-7H4 and the level of B7-H4 expression in these tumors has been correlated to the number of tumor-associated and tumor-infiltrating T cells. Papkoff et al. (2005) found that overexpressed B7-H4 promotes epithelial cell transformation by protecting cells from apoptosis and a siRNA knockout of B7-H4 in tumor cell lines lead to an increased apoptosis. Kryczek et al. (2006) reported that primary ovarian tumor cells express exclusively intracellular B7-H4 protein, whereas the majority of ovarian tumor macrophages, but not tumor T cells or blood macrophages, express surface B7-H4, possibly by stimulation with tumor-associated IL6 and IL10. They also showed that B7-H4 expressing tumor macrophages suppressed HER2 specific T-cell proliferation and cytotoxicity. Further, the blocking of B7-H4 expression with specific oligonucleotides improved the tumor-associated antigen T-cell responses. They concluded that B7-H4 expressing tumor macrophages are a suppressive cell population in ovarian cancer and might prove to be a good therapeutic target.

Homology

B7-H4 shares a 24%-31% homology with other members of the B7 family and has the highest homology with B7H3 with 31% homology. (Chen et al., 2003)

Implicated in

Ovarian Cancer

Note: Chen et al. (2003) first reported the detection of B7-H4 expression in ovarian cancer but not in normal ovarian tissue. Papkoff et al. (2005) showed that B7-H4 mRNA and protein are overexpressed in human serous ovarian cancers and breast cancers with relatively little or no expression in normal tissues. Also they described that overexpression of B7-H4 in a human ovarian cancer cell line with little endogenous B7-H4 expression, increased the tumor formation in SCID mice. Shroyer et al. (2006) found that B7-H4 is highly over-expressed in primary and metastatic serous, endometrioid, and clear cell carcinomas. In contrast, B7-H4 is not expressed in most mucinous ovarian cancers. Kryczek et al. (2006) published that primary ovarian tumor cells express intracellular B7-H4, whereas a fraction of tumor macrophages expressed surface B7-H4. These authors concluded that B7-H4 expression in tumor macrophages, rather than in the ovarian tumor cells, was relevant with regard to the suppression of tumor-associated antigen-specific T cell immunity. Kim et al. (2006) showed that elevated levels of B7-H4 can be found in the serum of patients with ovarian cancer and could play a role as a biomarker in ovarian cancer. They also developed a method based on ELISA to detect B7-H4 in the serum. Diamandis (2007) reported B7-H4 expression was low in normal ovaries and in benign tumors while half of early stage and two-thirds of late stage cancers over-expressed B7-H4.

Uterine Endometrial Cancer

Note: Shroyer et al. (2007) showed that the proportion and intensity of B7-H4 staining were increased in the progression from normal, hyperplastic and malignant endometrial glandular mucosa. The proportion of B7-H4 positive tumor cells and staining intensity was also higher in high risk tumors than in low risk tumors. The proportion of B7-H4 positive tumor cells was inversely related to the number of CD3-positive and CD8-positive tumor-associated lymphocytes.

Breast Cancer

Note: Shroyer et al. (2005) showed that B7-H4 is consistently over-expressed in primary and metastatic ductal and lobular breast cancers and its expression is correlated with a negative progesterone receptor status, negative Her-2/neu status and with a history of neo-adjuvant chemotherapy. There was also a significant association between a high proportion of B7-H4 positive cells in invasive ductal carcinomas and decreased number of tumor infiltrating lymphocytes. B7-H4 immunohistochemical expression was independent of tumor grade, stage or the size of the tumors.

Non Small Cell Lung Cancer

Note: Wang et al. (2006) showed that B7-H4 is overexpressed in Non Small Cell Lung Cancer and its overexpression is negatively correlated with tumor infiltrating lymphocytes and positively associated with lymph node metastasis.

Renal Cell Cancer (RCC)

Note: Kwon et al. (2006) reported that B7-H4 was overexpressed in 59% of 259 RCC tumor specimens analyzed and that tumor cell B7-H4 expression was associated with adverse clinical and pathologic features, including constitutional symptoms, tumor necrosis, and advanced tumor size, stage, and grade. Also B7-H4 expression when coupled with B7S1 expression was associated with a poor survival from RCC. Additionally, they noted that tumor vasculature

was significantly positive for endothelial B7-H4 expression, compared with the normal adjacent renal tissue vessels.

Prostate Cancer

Note: Allison et al. (2007) published that B7x/B7-H4 is overexpressed in human prostate cancer and patients with stronger immunohistochemical B7-H4 expression had higher rates of clinical cancer recurrences and cancer specific deaths.

References

Choi IH, Zhu G, Sica GL, Strome SE, Cheville JC, Lau JS, Zhu Y, Flies DB, Tamada K, Chen L. Genomic organization and expression analysis of B7-H4, an immune inhibitory molecule of the B7 family. J Immunol 2003;171(9):4650-4654.

Prasad DV, Richards S, Mai XM, Dong C. B7S1, a novel B7 family member that negatively regulates T cell activation. Immunity 2003;18(6):863-873.

Sica GL, Choi IH, Zhu G, Tamada K, Wang SD, Tamura H, Chapoval AI, Flies DB, Bajorath J, Chen L. B7-H4, a molecule of the B7 family, negatively regulates T cell immunity. Immunity 2003;18(6):849-861.

Collins M, Ling V, Carreno BM. The B7 family of immune-regulatory ligands. Genome Biol 2005;6(6):223. (Review).

Salceda S, Tang T, Kmet M, Munteanu A, Ghosh M, Macina R, Liu W, Pilkington G, Papkoff J. The immunomodulatory protein B7-H4 is overexpressed in breast and ovarian cancers and promotes epithelial cell transformation. Exp Cell Res 2005;306(1):128-141.

Tringler B, Zhuo S, Pilkington G, Torkko KC, Singh M, Lucia MS, Heinz DE, Papkoff J, Shroyer KR. B7-H4 is highly expressed in ductal and lobular breast cancer. Clin Cancer Res 2005;11(5):1842-1848.

Bignotti E, Tassi RA, Calza S, Ravaggi A, Romani C, Rossi E, Falchetti M, Odicino FE, Pecorelli S, Santin AD. Differential gene expression profiles between tumor biopsies and short-term primary cultures of ovarian serous carcinomas: identification of novel molecular biomarkers for early diagnosis and therapy. Gynecol Oncol 2006;103(2):405-416.

Krambeck AE, Thompson RH, Dong H, Lohse CM, Park ES, Kuntz SM, Leibovich BC, Blute ML, Cheville JC, Kwon ED. B7-H4 expression in renal cell carcinoma and tumor vasculature: associations with cancer progression and survival. Proc Natl Acad Sci USA 2006;103(27):10391-10396.

Kryczek I, Wei S, Zou L, Zhu G, Mottram P, Xu H, Chen L, Zou W. Cutting edge: induction of B7-H4 on APCs through IL-10: novel suppressive mode for regulatory T cells. J Immunol 2006;177(1):40-44.

Kryczek I, Zou L, Rodriguez P, Zhu G, Wei S, Mottram P, Brumlik M, Cheng P, Curiel T, Myers L, Lackner A, Alvarez X, Ochoa A, Chen L, Zou W. B7-H4 expression identifies a novel suppressive macrophage population in human ovarian carcinoma. J Exp Med 2006;203(4):871-881.

Simon I, Zhuo S, Corral L, Diamandis EP, Sarno MJ, Wolfert RL, Kim NW. B7-H4 is a novel membrane-bound protein and a candidate serum and tissue biomarker for ovarian cancer. Cancer Res 2006;66(3):1570-1575.

Sun Y, Wang Y, Zhao J, Gu M, Giscombe R, Lefvert AK, Wang X. B7-H3 and B7-H4 expression in non-small-cell lung cancer. Lung Cancer 2006;53(2):143-151.

Tringler B, Liu W, Corral L, Torkko KC, Enomoto T, Davidson S, Lucia MS, Heinz DE, Papkoff J, Shroyer KR. B7-H4 overexpression in ovarian tumors. Gynecol Oncol 2006;100(1):44-52.

Flies DB, Chen L. The new B7s: playing a pivotal role in tumor immunity. J Immunother (1997) 2007;30(3):251-260. (Review).

Kryczek I, Wei S, Zhu G, Myers L, Mottram P, Cheng P, Chen L, Coukos G, Zou W. Relationship between B7-H4, regulatory T cells, and patient outcome in human ovarian carcinoma. Cancer Res 2007;67(18):8900-8905.

Miyatake T, Tringler B, Liu W, Liu SH, Papkoff J, Enomoto T, Torkko KC, Dehn DL, Swisher A, Shroyer KR. B7-H4 (DD-O110) is overexpressed in high risk uterine endometrioid adenocarcinomas and inversely correlated with tumor T-cell infiltration. Gynecol Oncol 2007;106(1):119-127.

Mugler KC, Singh M, Tringler B, Torkko KC, Liu W, Papkoff J, Shroyer KR. B7-H4 Expression in a Range of Breast Pathology: Correlation With Tumor T-cell Infiltration. Appl Immunohistochem Mol Morphol 2007;15(4):363-370.

Simon I, Katsaros D, Rigault de la Longrais I, Massobrio M, Scorilas A, Kim NW, Sarno MJ, Wolfert RL, Diamandis EP. B7-H4 is over-expressed in early-stage ovarian cancer and is independent of CA125 expression. Gynecol Oncol 2007;106(2):334-341.

Simon I, Liu Y, Krall KL, Urban N, Wolfert RL, Kim NW, McIntosh MW. Evaluation of the novel serum markers B7-H4, Spondin 2, and DcR3 for diagnosis and early detection of ovarian cancer. Gynecol Oncol 2007;106(1):112-118.

Zang X, Thompson RH, Al-Ahmadie HA, Serio AM, Reuter VE, Eastham JA, Scardino PT, Sharma P, Allison JP. B7-H3 and B7x are highly expressed in human prostate cancer and associated with disease spread and poor outcome. Proc Natl Acad Sci USA 2007;104(49):19458-19463.

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