review

The immunoinhibitory B7-H1 molecule as a potential target in cancer: Killing many birds with one stone

Sehar Afreen, Said Dermime *

Immunology and Innovative Cell Therapy Unit, Biomedical Research Facility, Research Center, King Fahad Specialist Hospital Dammam, PO Box 15215, 31444 Dammam, Saudi Arabia

* Corresponding author. Address: Biomedical Research Facility, Research Center, King Fahad Specialist Hospital Dammamm, MBC-074, Bldg 100, Office 31, PO Box 15215, 31444 Dammam, Saudi Arabia. Tel.: +966 3 8442222x7099 (Office), +966 562763375 (Home). said.dermime@kfsh.med.sa, · sdermime@hotmail.com · Accepted for publication 6 September 2013

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Over expression of B7-H1 (also named PDL-1 or CD 274) molecule in cancer has been linked to worse prognosis and resistance to anti-cancer therapies in several malignancies. In this review, we update on the expression of B7-H1 molecule in solid and hematological malignancies. We also describe the possible mechanisms by which this molecule inhibits/downregulates the immune response to cancer cells. Finally, we highlight current and future potential therapeutic strategies that can be further developed to target this molecule.

The immune system can identify and control nascent tumor cells through a process named cancer immunosurveillance.[1] This process has been the subject of studies in both animal models and cancer patients. However, cancer immunotherapy has so far only shown modest clinical benefits for patients with cancer. This is due to the fact that the immune system can promote tumor progression through chronic inflammation, immunoselection of poorly immunogenic variants, and by suppressing antitumor immunity.[1,2] B7 homolog 1 (B7-H1), also known as programmed death ligand-1 (PDL-1) or CD274, is an inhibitory molecule of T cells that has been implicated in the protection of tumor cells from immune attack.[3] B7-H1 expression, and its association with clinicopathological, prognostic and immunological factors, has been reported in several human malignancies including breast,[4–9] ovarian,[8–11] cervical,[12] oral,[13–15] head and neck,[16,17] brain,[18–22] lung,[8,9,23–25] nasopharyngeal,[26,27] esophageal,[28,29] gastric,[30] liver,[31–36] colorectal,[8,9,37,38] pancreatic,[39–44] renal,[45–50] urothelial,[51–53] skin,[9,54–57] and blood cancers.[8,58–70] Overexpression of this molecule has been linked to worse prognosis and resistance to anti-cancer therapies in many of these malignancies (Table S1). The B7-H1 molecule binds to its receptor, programmed death 1 (PD-1) on tumor specific T cells, which leads to their apoptosis, and thus shields the tumor cells from lysis by activated T cells.[71] Cancer cells also release immunosuppressive cytokines such as transforming growth factor beta (TGF-β), Interferon gamma (IFN-γ), and Fas ligand that upregulate B7-H1 expression and further aid the tumor cells to elude immune responses.[72] Further, blocking of B7-H1 or its receptor PD-1 with monoclonal antibodies has been demonstrated to trigger anti-tumor immune responses, and enhance the effectiveness of anti-cancer immunotherapy.[73] Targeting this molecule can therefore lead to a major breakthrough in cancer treatment. This review illustrates the expression and pathological correlations of the B7-H1 molecule in human cancers, its role in carcinogenesis, and its possible therapeutic targeting strategies to enhance the anti-tumor immune response in malignancies.

EXPRESSION OF B7-H1 IN HUMAN CANCERS

B7-H1 expression in solid tumors

Lung cancer

The B7-H1 expression was first demonstrated by Konishi et al.[24] in 2004 in frozen tissue specimens

of 52 (100%) patients with non small cell lung carcinomas (NSCLC). Both adenocarcinomas and squamous cell carcinomas expressed this molecule. The expression was observed both in the membrane and the cytoplasm of tumor cells in a scattered fashion. However, its expression was not associated with the clinicopathological factors or the survival of the patients. The density of tumor-infiltrating lymphocytes (TILs) was inversely correlated to the B7-H1 positive tumor sites in five patients. Later, Mu et al. (2011)[25] reported the expression of B7-H1 in 58 of 109 (53%) paraffin-embedded specimens of NSCLC patients. B7-H1 positive cells were significantly abundant in adenocarcinomas than in squamous cell carcinomas of the lung. The expression was correlated with survival of less than three years after lobectomy.[25]

Very recently, Boland et al.[23] demonstrated expression in 42 of 214 (20%) paraffin-embedded specimens of squamous NSCLC patients. B7-H1 in the tumors was predominantly expressed in the cell membrane and minimally in the cytoplasm. The expression, however, was not significantly correlated with the clinical outcomes.[23] Further studies, preferably on frozen specimens are required to confirm the lower expression of B7-H1 in squamous NSCLC.

Gastric carcinoma

B7-H1 expression in gastric carcinoma patients was reported by Wu et al. (2006).[30] The expression was detected in paraffin-embedded sections of 43 of 102 (42%) gastric carcinoma patients. The expression was significantly associated with tumor size, tumor depth invasion, lymph node metastasis, and reduced survival. B7-H1 was shown to be a significant prognostic factor[30] in gastric carcinoma patients.

Hepatocellular carcinoma (HCC)

In 2009, Gao et al.[32] studied B7-H1 expression in paraffin-embedded specimens of 204 hepatocellular carcinoma (HCC) subjects. Intratumoral B7-H1 expression was an independent prognostic factor for disease free survival. Relapse risk was two times more likely for B7-H1 positive patients after resection surgery compared with B7-H1 negative subjects. B7-H1 positive patients had significantly poor disease free survival and overall survival than B7-H1 negative patients. B7-H1 positive subjects had more tumors with vascular invasion. The expression was positively correlated with Forkhead box P3 (Foxp3) positive regulatory TILs (Tregs).[32] an immunoregulatory T cell population known to downregulate the immune response in cancer.

In parallel with the Gao et al. study, Wu et al.[35] reported elevated B7-H1 expression in 35 of 71 (49%) HCC cases. Patients with elevated B7-H1 expression had significantly poor survival compared with low expression subjects.[35]

In 2011, Geng et al.[33] studied B7-H1 expression in 60 HCC cases. Elevated B7-H1 mRNA and protein expression levels were detected in all HCC samples. The expression was positively correlated with the upregulation of Interleukin-10 (IL-10) in tumor cells,[33] an immunoregulatory cytokine known to downregulate the immune response in cancer. In parallel with this study, Wang et al.[34] reported B7-H1 expression in 24 of 26 (93%) frozen HCC tissue samples. The B7-H1 expression was significantly associated with the earlier tumor stage. However, no significant correlation was found between B7-H1 expression and the tumor grade.[34]

Recently, Chen et al.[31] demonstrated high grade B7-H1 expression in 29 of 63 (46%) HCC cases. The expression was detected in both the membrane and cytoplasm of the tumor cells. High B7-H1 expression was significantly associated with the infiltration of tumor-associated macrophages,[31] a cell population known to downregulate the immune response in cancer.

Intrahepatic Cholangiocarcinoma (ICC)

Intrahepatic cholangiocarcinoma (ICC) is a primary malignancy of liver that arises from the bile duct epithelium. It is the second most common cancer of the liver after HCC.[36] Ye et al.[36] reported B7-H1 expression in paraffin-embedded specimens from 31 of 31 (100%) ICC patients. B7-H1 expression was significantly higher in ICC cells than in the adjacent tissue. Elevated B7-H1 expression was associated with poor histological differentiation and advanced tumor-nodal-metastatic (TNM) stage. The density of CD8+ TILs (a cytotoxic T cell population known to eliminate cancer cells) was inversely correlated with intratumoral B7-H1 expression. Apoptotic CD4+ and CD8+ TILs count was higher in the cases with elevated B7-H1 expression compared with the cases of lower expression. The difference, however, did not reach statistical significance.[36]

Colon cancer

Overexpression of B7-H1 molecule has been implicated in the immune escape of several human malignancies, including colorectal carcinoma.[9,37,38] Dong et al.[9] were the first to detect the B7-H1 presence via immunohistochemical analysis in 10 of 19 (53%) frozen samples of colon cancer patients.

In 2005, Xiao et al.[38] detected B7-H1 molecule in TILs via *in situ* hybridization on paraffin-embedded colorectal carcinoma samples. Significantly more elevated expression levels of this molecule were observed in the tumor cells than in TILs. Metastasis of colorectal carcinoma was correlated with an increase in the expression level of B7-H1 in both tumor cells and TILs. Moreover, the expression in TILs was significantly associated with the degree and depth of tumor invasion. The study concluded that B7-H1 overexpression could be involved in the apoptosis of TILs in colorectal carcinoma patients and thus promote immune escape of tumor cells.[38]

Hua et al.[37] reported high B7-H1 expression in 15 of 33 (45%) cases of colorectal carcinoma. There was a significant inverse correlation between B7-H1 expression and CD3+ TILs density in the tumor nest and the tumor stroma. The densities of CD4+/Foxp3+ and CD8+/Foxp3+ Tregs in B7-H1 high group were significantly higher than those of the B7-H1 low group. Other clinicopathological factors were not determined.[37]

Pancreatic cancer

The B7-H1 expression was demonstrated in pancreatic cancer patients for the first time by Nomi et al. in 2007.[43] The expression was detected in 20 of 51 (39%) frozen tumor samples. The B7-H1 status was determined to be a significant independent prognostic factor. B7-H1 positive patients had significantly worse survival rates compared with B7-H1 negative patients. B7-H1 expression had a significant inverse correlation with CD4+ TILs and CD8+ TILs. However, no significant correlation was found between B7-H1 and tumor, nodal, metastatic statuses, and pathologic stage.[43]

Geng et al.[40] reported B7-H1 expression in paraffin-embedded tumor samples of 40 pancreatic cancer patients. The expression was predominantly observed in the cytoplasm of tumor cells. B7-H1 expression was significantly higher in pancreatic carcinoma tissues than in the normal tissue. Positive B7-H1 status was significantly associated with advanced tumor stage and poor tumor differentiation. However, the expression did not correlate with the size of the tumor. A positive correlation was demonstrated between intratumoral B7-H1 overexpression and IL-10 level at both the mRNA and protein levels.[40]

Loos et al.[42] also demonstrated B7-H1 expression in paraffin-embedded tumor samples. B7-H1 expression was detected in pancreatic cancer cells, tumor-surrounding tubular complexes, pancreatic islet cells, TILs, and endothelial cells. The expression in pancreatic cancer cells was significantly correlated with postoperative survival. B7-H1 positive status was also associated with the increased prevalence of Foxp3+ TILs Tregs compared to B7-H1 negative tumors. However, it did not reach statistical significance ($P = 0.06$).[42]

Later in 2009, Huang et al.[41] also reported elevated expression levels of B7-H1 in tissues of 60.5% patients with pancreatic carcinoma. No significant expression was observed in normal samples. B7-H1 positive status was significantly associated with IL-10 level in tumor tissues. Similarly, Chen et al.[39] determined B7-H1 expression in 18 of 40 (45%) pancreatic cancer patients. B7-H1 expression was significantly correlated with advanced tumor stage, and was demonstrated to be an independent poor prognostic factor.[39]

A year later, Wang et al.[44] reported significantly higher B7-H1 expression in pancreatic carcinoma tissues than in normal samples. B7-H1 expression was significantly correlated with tumor pathological grade, and it was a prognostic indicator of poor disease-specific survival. All of these studies indicate a possible role of B7-H1 in immune escape of pancreatic cancer cells.[44]

Ovarian cancer

B7-H1 has been implicated in the immune evasion of various tumors, including ovarian cancer.[8–11] In 2007, Hamanishi et al.[11] investigated the expression of B7-H1 in paraffin-embedded specimens of 70 ovarian cancer patients. Their study revealed that elevated B7-H1 expression levels were associated with poor prognosis. The overall survival rate of five years in high B7-H1 expression patients was significantly worse than in those who had a lower B7-H1 expression. Moreover, the progression-free survival rate of high expression patients was significantly lower compared to patients with lower expressions of this molecule. Multivariate analysis concluded that B7-H1 was an independent poor prognostic factor for both progression-free and overall survival of ovarian cancer patients.[11]

Breast cancer

Breast cancer is the leading cause of cancer related deaths in women.[74,75] The first study demonstrating the presence of B7-H1 molecule expression in breast cancer patients was documented by Ghebeh et al. (2006).[4] The correlation of this molecule with the clinicopathological status of the malignancy was investigated in frozen tumor samples of 44 breast cancer patients.[4] B7-H1 expression (membranous and/or cytoplasmic) was detected in the tumor cells and/or

TILs of 50% of breast cancer patients. The expression was totally absent in healthy tissue areas of the affected breast. B7-H1 expression was found to be significantly correlated with bad prognostic factors including large tumor size, histology grade III tumors, negative estrogen receptors, negative progesterone receptors, and human epidermal growth factor receptor 2 (Her2/neu) negative status.[4] A year later, these findings were further confirmed by the same group in their follow-up study of 69 breast cancer patients.[5] B7-H1 expression was also demonstrated to be associated with the proliferative potential of the tumor cells.[5] The B7-H1 expression was significantly correlated with the Ki-67 proliferative marker and a high mitotic index. Most tumor cells simultaneously revealed expression of B7-H1 and nuclear expression of Ki-67.[5] Moreover, the association of B7-H1 positive TILs with Foxp3+ Tregs in the tumor microenvironment was investigated by Ghebeh et al. (2008).[6] B7-H1 expression in TILs within the tumor environment was significantly correlated with the presence of Foxp3+ Tregs[6] In their subsequent investigation in 2010, Ghebeh et al.,[7] demonstrated that doxorubicin was able to downregulate the B7-H1 cell surface expression and to upregulate its nuclear expression in breast cancer cells. Blockade of B7-H1 via small interfering ribonucleic acid (siRNA) led to significantly enhanced apoptosis in 90% of the breast cancer cells. Furthermore, Akt pathway inhibition and doxorubicin treatment synergistically lowered both the cell surface and nuclear expression of B7-H1 molecule in the tumor cells.[7] These studies therefore suggest that immunotherapeutic targeting of PD-L1/PD-1 pathway in breast cancer patients in conjunction with the available therapeutic modalities can facilitate the effectiveness of other anti-tumor treatment strategies.[76]

Cervical carcinoma

Cervical cancer is the second most common malignancy reported in women (after breast cancer) around the globe.[77–81] In 2009, Karim et al.[12] reported intratumoral B7-H1 cell surface expression in paraffin-embedded sections of 22 of 115 (19%) cervical cancer patients. The expression was significantly associated with increased intraepithelial infiltration by Foxp3+ T cells ($P = 0.022$). However, it did not correlate with the survival of the patients.[12] This lower percentage of B7-H1 positive cervical cancer patients and its negative correlation with survival can be attributed to the fact that 51 patients in the study had already received post-operative radiotherapy. Further studies on frozen specimens and untreated patients are required to investigate the correlation of B7-H1 expression with the prognostic factors of the disease.

Squamous cell carcinomas of the head and neck (SCCHN)

Head and neck carcinomas account for 5% of all cancers, and over 90% of them are squamous cell carcinomas.[82] In 2003, Strome et al.[17] demonstrated B7-H1 expression in 16/24 (66%) frozen tumor samples of squamous cell carcinomas of the head and neck (SCCHN) patients. Both intracytoplasmic and membrane expressions were observed. Clinical and prognostic correlations were not determined in this study.[17] Later in 2013, Lyford-Pike et al.[16] reported B7-H1 expression in 14/20 (70%) paraffin-embedded specimens of human papilloma virus-associated head and neck squamous cell carcinomas (HPV-SCCHN). Cell surface expression was observed in cancer cells at the tumor periphery and CD68+ tumor-associated macrophages. However, the clinical and prognostic correlations were not determined.[16]

B7-H1 expression in oral squamous cell carcinomas (OSCC) was studied by Malaspina et al.[14] and Cho et al.[13] In 2011, Malaspina et al.[14] reported expression in 38/39 (97%) frozen tumor samples of OSCC patients. B7-H1 expression was highly expressed in CD14+ TILs.[14] In a similar study, Cho et al.[13] demonstrated expression in 39 of 45 (87%) paraffin-embedded specimens of OSCC subjects. The expression was both membranous and cytoplasmic in the tumor cells. Tumor-associated fibroblasts were also found to be positive for B7-H1 expression in 18 of 45 (40%) patients. Its expression by the tumor cells did not affect the survival of OSCC patients. However, it was significantly correlated with less differentiated OSCC cells. A decrease in the number of TILs in the tumor environment was also correlated with the expression of B7-H1. However, the B7-H1+ tumor-associated fibroblasts had no impact on the clinical parameters of the patients.[13]

Nasopharyngeal carcinoma (NPC)

NPC is the third most common malignancy of East Asia with the incidence of 15–50 cases per 100,000 population.[83] B7-H1 expression has been investigated in nasopharyngeal carcinomas (NPCs).[26,27] In 2008, Zhang et al.[27] reported expression in 40 of 59 (68%) NPC patients. The expression was significantly correlated with advanced tumor stage and lymphatic metastasis.[27] Later, Hsu et al.[26] demonstrated expression in paraffin-embedded tumor samples of NPC patients. However, the expression was not associated with the clinical outcomes of the patients. This

might be due to the fact that all 28 patients involved in the study had already completed curative chemo/radiotherapy.[26] Further studies of untreated patients are required to confirm the clinicopathological significance of B7-H1 in NPCs.

Esophageal cancer

Esophageal cancers are the seventh leading cause of cancer related mortalities in the US, with a five-year survival rate of merely 17%.[84] In 2005, Ohigashi et al.[29] reported B7-H1 expression in 18 of 41 (44%) frozen specimens of squamous esophageal cancer patients. The expression was observed both in the membrane and the cytoplasm of the tumor cells. The overall survival of B7-H1 positive patients was significantly worse than that of B7-H1 negative patients. B7-H1 status was a highly significant independent prognostic factor.[29]

B7-H1 expression has also been reported in Barrett's carcinoma (adenocarcinoma of the distal esophagus).[28] Barrett's carcinoma is one of the most aggressive malignancies and arises from intestinal metaplasia.[28] In 2011, Loos et al.[28] demonstrated B7-H1 expression in paraffin-embedded specimens of 74 of 101 (73%) Barrett's carcinoma patients. It was abundantly expressed in the tumor and the TILs cell membrane and cytoplasm. Elevated intratumoral B7-H1 expression was significantly associated with advanced tumor size and invasiveness, as well as increased risk of mortality from cancer. A high expression of B7-H1 was also associated with a twofold lower median prevalence of TILs (0.32 versus 0.67). However, the correlation was not statistically significant ($P = 0.06$).[28]

Urothelial cancer

Urothelial cancer is the second most common malignancy of the genitourinary tract.[85] The disease is the second most common cause of deaths related to genitourinary tumors.[85]

In 2007, Inman et al.[52] reported B7-H1 expression in paraffin-embedded specimens of 79 of 280 (28%) urothelial cancer patients. The expression was detected in the plasma membrane of the tumor cells. B7-H1 was significantly associated with advanced grade tumors. The expression of B7-H1 was also a significant determinant of the status of tumor stage progression.[52]

In the same year, Nakanishi et al.[53] demonstrated B7-H1 expression in the frozen tumor samples of patients with urothelial cancer. Focal pattern expression was detected in the membrane and the cytoplasm of cancer cells. B7-H1 was significantly correlated with the tumor grade, and was notably associated with primary tumor classification. Elevated B7-H1 expression was significantly associated with poor survival compared with low grade B7-H1 expression. Postoperative tumor recurrence was also significantly associated with higher B7-H1 expression.[53]

In 2008, Boorjian et al.[51] detected B7-H1 expression in 39 of 314 (12%) paraffin-embedded tumor samples. Predominant membrane and occasional cytoplasmic expression were observed in the tumor cells. The expression was significantly related to advanced disease stage at cystectomy. Considerably elevated B7-H1 expression was observed in tumors with greater number of PD-1 positive TILs. The expression was a significant predictor of mortality after cystectomy. Subjects with organ confined B7-H1 positive tumors were three times more likely to die after cystectomy than B7-H1 negative patients.[51]

Later, Wang et al.[86] reported B7-H1 expression in 36 of 50 (72%) paraffin-embedded tumor samples. B7-H1 expression was significantly associated with the tumor grade and the clinical stage of the disease. B7-H1 positive patients had significantly poorer survival than B7-H1 negative subjects. Furthermore, the expression of B7-H1 molecule was demonstrated to be an independent prognostic factor of urothelial cancer of the bladder.[86]

Renal cell carcinoma (RCC)

Renal cell carcinoma (RCC) is the thirteenth most common cancer worldwide.[87] The disease is usually asymptomatic during early stage but is highly metastatic. In 2004, Thompson et al.[47] reported B7-H1 expression in 130 of 196 (66%) frozen RCC samples. Expression was detected both in tumor cells and TILs. High intratumoral B7-H1 expression was significantly associated with adverse pathological features that included higher nuclear grade, regional lymph node involvement, histological tumor necrosis, and distant metastasis. Patients with elevated B7-H1 expression levels (either in TILs or tumors) were 4.5 times more likely to die from RCC than patients who had lower B7-H1 expression.[47]

In 2005, the same group investigated B7-H1 expression in 17 of 26 (65%) frozen metastatic RCC tumor samples.[48] Expression was detected in tumor cells and TILs. High B7-H1 expression (in tumors and/or TILs) was significantly associated with increased risk of death.[48]

In their 2006 study, Thompson et al. demonstrated B7-H1 expression in 73 of 306 (24%) paraffin-embedded RCC tumor samples.[49] B7-H1 expression was significantly associated with adverse

pathological features including advanced tumor-nodal-metastatic (TNM) stage, increase in tumor size, high nuclear grade, and coagulative tumor necrosis. B7-H1 positive patients were four times more likely to die from RCC than B7-H1 negative patients. The expression was significantly associated with metastatic progression.[49]

The following year, Krambeck et al.[46] reported on the expression of B7-H1 in 70 of 298 (24%) paraffin-embedded specimens of RCC. B7-H1 positive patients were four times more likely to die from RCC than B7-H1 negative patients. The expression was independently associated with death from RCC.[46]

Wilms' tumor (nephroblastoma)

Wilms' tumor or nephroblastoma is the second most common renal malignancy of childhood.[88] In 2008, Routh et al.[89] demonstrated B7-H1 expression in 11 of 81 (14%) paraffin-embedded Wilms' tumor specimens. Intratumoral B7-H1 expression was associated with a threefold increased risk of recurrence. However, this association did not reach statistical significance ($P = 0.057$). Nonetheless, patients with B7-H1 positive favorable tumor histology were at significantly increased risk of disease recurrence ($P = 0.027$) than subjects with B7-H1 negative favorable tumor histology.[89]

Melanoma

Melanoma is the deadliest malignancy among skin cancers. It is responsible for 50,000 deaths each year worldwide, and its incidence is still rising.[90] Advanced stage patients have a median survival of one year only. The available treatments prolong the lives of patients but do not completely cure the disease.[90,91]

In 2010, Hino et al.[55] reported high B7-H1 expression in 34 of 59 (58%) paraffin embedded melanoma specimens. Tumor thickness was significantly higher in the high expression group than in the lower expression group. Advanced tumor stage had significantly more elevated B7-H1 expression than in those with less advanced tumors. Patients with lymph node metastasis had a significantly higher B7-H1 expression than patients without lymph node metastasis. Patients with high B7-H1 expression also had significantly lower overall survival than the lower expression patient group, thus indicating that B7-H1 expression was an independent predictor of overall survival.[55]

Similarly, Gadiot et al.[54] reported B7-H1 expression in paraffin-embedded specimens of 63 melanoma patients. Higher frequency of B7-H1 positive staining was detected in satellite metastases (25%), and in in-transit metastases (40%). B7-H1 expression was shown to increase with disease progression.[54]

Recently, Taube et al.[56] demonstrated B7-H1 expression in 57 of 150 (38%) paraffin-embedded melanoma patients. The study found 98% of B7-H1 positive samples were highly associated with TILs compared to 28% of the B7-H1 negative cases. B7-H1 expression was significantly associated with inflammatory infiltrates. Clinicopathological factors, including tumor thickness and TNM stage, were not associated with B7-H1 expression. Further, B7-H1 expression in metastatic melanoma patients correlated with significantly improved survival. This result can, however, be misleading because 43% of the metastatic melanoma patients involved in the study had already received systemic immunotherapy, including high dose interleukin-2 (IL-2), IFN-α, anti-PD-1 monoclonal antibody/vaccine, or combinations of these agents.[56] Further studies (preferably on frozen samples) of untreated patients are required to investigate the possible role of B7-H1 in the immune escape of melanoma cells and in the overall survival of melanoma patients.

Brain tumors

Brain tumors account for 2% of all the malignancies.[19] The most common brain tumors are meningiomas and gliomas.[19] In 2003, Wintterle et al.[21] reported B7-H1 expression in glioma patients. The expression was detected in 10 of 10 (100%) frozen tumor samples of glioma patients. More than 50% of the cells in 50–90% of the tumor samples expressed B7-H1.[21] Two years later, Wilmotte et al.[20] demonstrated B7-H1 expression in 46 of 54 (85%) frozen glioma samples. Significantly intense B7-H1 staining, with more than 30% positively stained cells, was detected in 18 of 33 samples of high grade anaplastic astrocytoma and glioblastoma compared with diffuse astrocytoma and oligodendroglioma samples. B7-H1 expression was therefore correlated with tumor grade.[20]

In 2009, Yao et al.[22] detected B7-H1 expression in 36 of 48 (75%) frozen glioma samples. The expression was significantly higher in advanced grade gliomas than in low grade tumors. Intratumoral B7-H1 expression was negatively correlated with the number of cytotoxic CD8+ T cells.[22] Similarly, Jacobs et al.[19] reported B7-H1 expression in 51of 83 (61%) paraffin-embedded brain tumor samples (meningiomas, gliomas, adenomas and schwanomas). Later, Avril et al.[18] demonstrated B7-H1 expression in 10 of 20 (50%) paraffin-embedded tumor samples. However, the clinicopathological correlations of B7-H1 were not determined in these studies.[18]

Thymic neoplasms (thymomas)

Thymomas are tumors that originate from the thymus, and have a worse prognosis at advanced stages.[92] B7-H1 expression in thymomas was detected by Brown et al. (2003).[8] Ten out of 15 (67%) samples of benign thymoma, 11 of 11 (100%) samples of invasive thymoma, and 7 of 8 (88%) samples of thymic carcinomas were B7-H1 positive. Overall, 82% of the total 34 samples showed B7-H1 expression. Clinicopathological correlations were not determined.[8]

B7-H1 expression in hematological malignancies

Lymphomas

Lymphomas are the malignancies of B/T lymphocytes. Lymphomas account for 55.6% of all blood cancers.[93] B7-H1 expression has been reported in the following lymphomas:

Peripheral T cell lymphoma (PTCL). Peripheral T cell lymphoma (PTCL) is the most common form of T cell lymphoma, and is aggressive. It is a sub-type of non-Hodgkin's lymphoma (NHL).[94] In 2003, Brown et al.[8] detected B7-H1 via immunohistochemical analysis of 7 of 11 (64%) samples of PTCL. In 2009, Wilcox et al.[59] reported B7-H1 expression in 22 of 144 (15%) PTCL samples using immunohistochemical analysis. The expression was detected in tumor cells and monocytes. However, the clinicopathological associations of B7-H1 were not determined in these studies.

Cutaneous T cell lymphoma (CTCL). Cutaneous T cell lymphoma (CTCL) is a subtype of NHL that presents in the skin.[95] In 2009, Wilcox et al.[59] demonstrated B7-H1 expression in 3 of 11 (27%) paraffin-embedded specimens of CTCL. The expression was detected in tumor cells and monocytes. The clinicopathological associations of B7-H1 were not determined.[59]

Adult T-cell lymphoma (ATL). Adult T-cell lymphoma (ATL) is a rare but highly aggressive subtype of NHL.[96] In 2009, Kozako et al.[58] demonstrated increased B7-H1 expression in 5 of 23 (22%) cases of ATL patients. B7-H1 expression was detected in CD4+/CD25+ T cells. No expression was observed in *de novo* ATL patients. However, more than 10% CD4+/CD25+ T cells of the 22% ATL patients showed the expression one year after diagnosis. No clinicopathological correlations of B7-H1 were investigated.[58]

Diffuse large B cell lymphomas (DLBLC). Diffuse large B cell lymphomas (DLBLC) is the most common type of NHL among adults,[97] and is aggressive. It has an annual incidence of seven to eight cases per year.[97] In 2011, Andorsky et al.[98] reported B7-H1 expression in 9 of 33 (27%) frozen samples via immunohistochemical analysis. Clinicopathological significance of B7-H1 was not determined in this study.[98]

Leukemia

Leukemia is the eleventh most common cause of cancer-related deaths worldwide.[99] The expression of the B7-H1 molecule and its clinicopathological correlations have been studied in both acute and chronic leukemias.[60–68] In 2006, Salih et al.[60] reported B7-H1 expression in a cohort of patients with acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL) and chronic lymphoblastic leukemia (CLL). Overall, 17 of 30 (57%) cases were B7-H1 positive.[60]

A year later, Li et al.[61] investigated B7-H1 expression in 59 AML/ALL patients. The expression was significantly high in relapsed patients, and newly diagnosed patients had lower levels of B7-H1 expression than normal controls. Furthermore, the expression was significantly higher in non-complete remission patients after therapy than in patients with complete remission. B7-H1 was correlated with response to therapy.[61] The following year, Chen et al.[62] reported B7-H1 expression in 25 of 60 (42%) AML/ALL patients. Significantly higher expression was detected in relapsed AML patients than in the newly diagnosed subjects. B7-H1 positive AML subjects had significantly reduced survival compared to B7-H1 negative subjects. B7-H1 proved to be an independent prognostic factor. Immunotherapeutic efficacy was significantly reduced in B7-H1 positive patients than in B7-H1 negative subjects. Moreover, B7-H1 was significantly upregulated in patients following immunotherapy.[62]

In 2009, Ge et al.[64] detected B7-H1 expression in 42 of 42 (100%) AML patients. More than 5% of AML cells were B7-H1 positive in 18 of 42 (43%) of leukemia samples. The expression was significantly higher in the leukemic cells of AML patients than in the bone marrow mononuclear cells of healthy volunteers.[64] In 2010, Berthon et al.[65] reported high B7-H1 expression in 14 of 79 (18%) of AML patients. Spontaneous expression was significantly increased in 5 of 9 (56%) of relapsed patients.[65]

In 2012, Sun et al.[67] studied B7-H1 expression in 50 AML patients. The expression was lower in *de novo* AML patients than in the healthy volunteers. However, it was highest in the relapsed patients. B7-H1 expression before therapy was significantly higher in non-cytogenetic remission patients than in

patients in complete remission. B7-H1 gene expression was therefore correlated with response to therapy.[67] In the same year, Li et al.[63] studied B7-H1 expression in 74 AML/ALL patients. The expression was significantly higher in non-complete remission patients after therapy compared with patients in complete remission. B7-H1 gene expression was correlated with response to therapy.[63]

Grzywnowicz et al.[68] demonstrated B7-H1 expression in 44 of 44 (100%) of CLL patients. B7-H1 expression was significantly higher in CLL patients than in the peripheral blood/bone marrow mononuclear cells of healthy volunteers. The expression was significantly higher in tyrosine kinase zeta-associated protein (ZAP-70) positive subjects compared with ZAP-70 negative patients.[68] These studies suggest a possible role of B7-H1 in the immune escape of leukemic cells and its association with response to therapy.

Multiple myeloma (MM)

Multiple myeloma (MM) is the second most common hematological malignancy in the western world after NHL, and accounts for 10% of all blood cancers.[100] In 2007, Liu et al.[72] detected B7-H1 expression in a majority of 82 MM patients. The expression was significantly higher in plasma cells in MM patients than in non-MM subjects. Very recently, Tamura et al.[70] reported B7-H1 expression in 10 of 40 (25%) MM cases. The expression was significantly associated with increased serum lactate dehydrogenase levels and the percentage of myeloma cells in the bone marrow. Furthermore, the expression of B7-H1 tended to be higher in advanced stage patients. However, its association did not reach statistical significance. B7-H1 expression was upregulated in patients who relapsed or became resistant to anti-MM therapy.[70]

MECHANISM OF B7-H1 MEDIATED TUMOR CELL IMMUNE RESISTANCE

B7-H1 is a member of the B7 family of immunoregulatory molecules.[4,101] It is a surface glycoprotein known to be expressed on conventional CD4+ and CD8+ T cells, dendritic cells (DCs), macrophages, B cells, Tregs, epithelial cells, endothelial cells, immune privileged sites such maternal-fetal barrier,[4,101] and on a majority of tumor cells (Table S1). Both co-stimulatory and co-inhibitory characteristics of B7-H1 molecule have been reported.[102–104] The inhibitory behavior of B7-H1 molecule is attributed to its binding with a co-inhibitory receptor, PD-1, also known as CD 279.[9,105] PD-1 is expressed on Tregs, B cells, antigen-activated CD4+ and CD8+ T cells, natural killer (NK) cells, and frequently on TILs.[106] In contrast, the stimulatory role of B7-H1 has been ascribed to its binding with yet unidentified, co-stimulatory non-PD-1 receptors.[9,103]

Classical mechanism of adaptive immune response activation

Dendritic cells (DCs) are the most pivotal of antigen presenting cells (APCs) that initiate immune responses.[107] Immature DCs express major histocompatibility complex class-II (MHC-II) and other co-stimulatory molecules, and reside in non-lymphoid tissues.[108] DCs upregulate MHC-II molecules on their cell surfaces and migrate to the lymphoid tissues upon stimulation with foreign invaders or other danger-associated molecules. At this stage, they may encounter naïve T cells.[108] Activation of naïve CD4+ T helper cells requires the linkage of the T cell receptor (TCR) with antigen loaded MHC-class II complex on mature DCs, while the activation of CD8+ cytotoxic T lymphocytes (CTLs) requires the binding of the TCR with antigen-loaded major histocompatibility complex class-I (MHC-class I) complex on APCs.[109] This is known as Signal 1.[109] Following Signal 1, another co-stimulatory signal is required for the T cells to induce an effective immune response and thereafter the induction of apoptosis in the target cell.[110] CD28 is the principal co-stimulatory receptor expressed on both CD4+ T helper and CD8+ CTLs.[110,111] Successful simultaneous generation of Signal 1 and binding of CD28 to their co-stimulatory ligands, B7-1 (also known as CD80) or B7-2 (also known as CD86), on DCs/APCs generates Signal 2.[112] This second signal stimulates T cells by reducing the threshold of TCR signaling, which is accomplished by the formation of immunological synapse, triggering IL-2 production and upregulation of Bcl-X2 anti-apoptotic protein which protects T cells from apoptosis.[113,114] Subsequent proliferation of T cells and their secretion of cytokines and cytolytic molecules, such as perforin and granzyme, cause tumor/target cell death[112] (Fig. 1A).

B7-H1 upregulation and dampening of immune responses

Absence of Signal 2 renders T cells anergic.[114] Persistent antigen presentation leads to upregulation of PD-1 on T cells, which is followed by the expression of B7-H1 on APCs in the local tissue.[115] Subsequent B7-H1/PD-1 interaction inhibits TCR signaling by recruiting the Src homology region 2 domain containing phosphatases 1 and 2 (SHP-1, SHP-2).[116] These

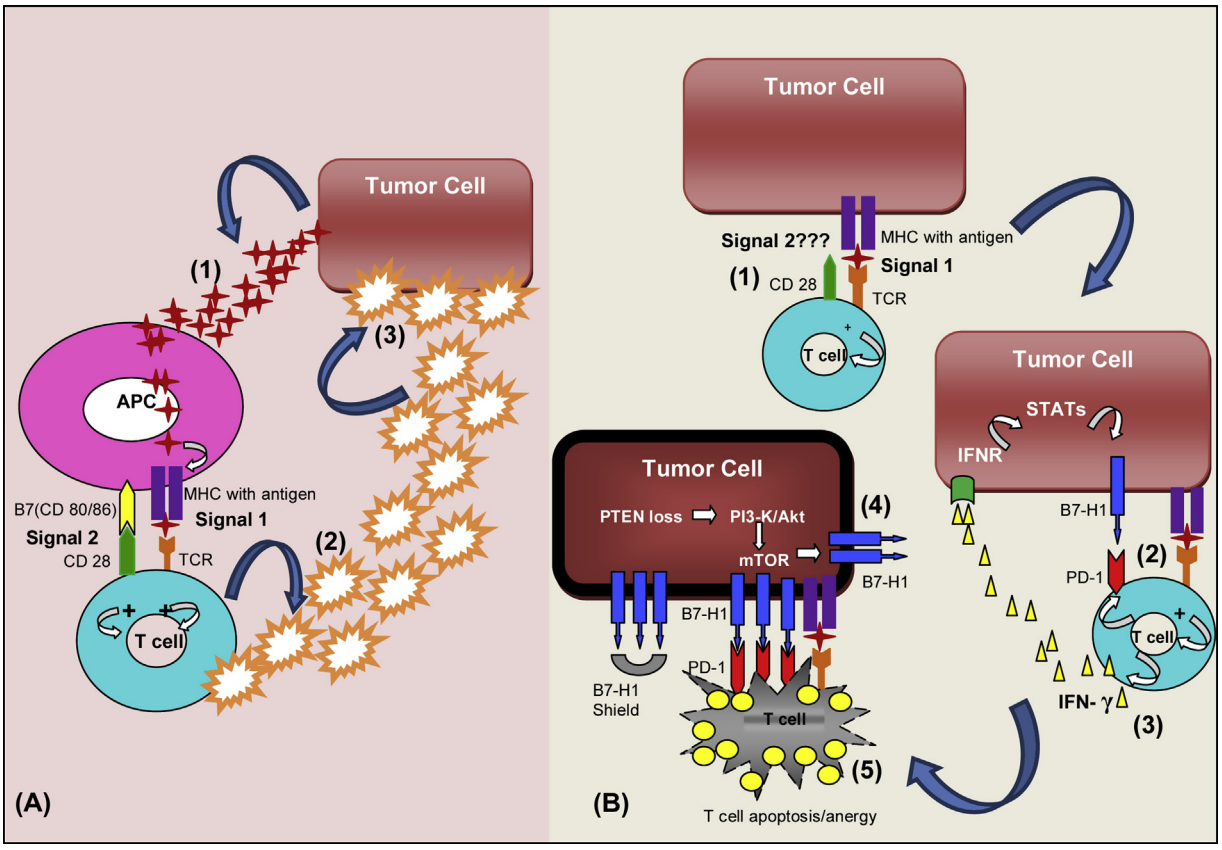

Fig. 1. Comparison of the effective classical immune response against tumor-derived antigens versus the tumoral B7-H1 mediated immune escape. (A) Classical immune response against tumor-derived antigens and tumor cell lysis. (1) Tumor antigens released by the tumor cells are captured by antigen presenting cells (APCs) and processed to small peptides for their presentation by the major histocompatibility complex (MHC) molecule. The T cell is activated through linkage of T cell receptor (TCR) with MHC-antigen complex (Signal 1).[109] A co-stimulatory signal (Signal 2: B7/CD28 interaction) is also required to initiate an effective anti-tumor immune response by the T cells. (2) This causes the T cells to release cytotoxic compounds (such as granzymes/perforin) that attack (3) and disrupt the plasma membrane of tumor cells, causing tumor cell death/lysis.[112–117] (B) Failure of T cell to launch an effective anti-tumor immune response. (1) Absence of Signal 2 leads to prolonged antigen presentation.[114,115] (2) Consistent presentation of the antigen causes upregulation of PD-1 on T cells followed by the (3) release of inflammatory cytokines, activation of signal transducer and activator of transcription (STATs) pathways and subsequent upregulation of B7-H1 on the tumor cells. (4) Loss of phosphatase and tensin homolog (PTEN) activates the phosphatidylinositide 3-kinase/Akt (PI3-K/Akt) and mammalian target of rapamycin (mTOR) pathways which also lead to the upregulation of B7-H1 on the tumor cells. (5) B7-H1 and PD-1 over expression and their interaction cause T cell exhaustion/anergy and/or apoptosis, thus enabling the tumor cells to effectively evade the immune system[113–119].

enzymes mediate a stop signal, and thus limit the interaction of APCs/DCs with T cells.[117] This overexpression and interaction of inhibitory molecules causes exhaustion and/or apoptosis of T cells by impairing their metabolism, inhibiting the release of Bcl-X2 anti-apoptotic protein,[113,114] impairing effector cytokine production (such as IL-2 and IFN- γ) and T cell proliferation.[115,118,119] The B7-H1/PD-1 axis has also been demonstrated to increase the number of Foxp3+ Tregs in the local tissue environment,[120] which further inhibits the immune response by contributing to the suppression of production of effector cytokines and proliferation of effector T cells.[121,122] It has been demonstrated that B7−/− mice are deprived of the ability to produce Tregs.[6,123] Blockade of B7-H1 has been shown to prevent Treg-mediated immune regulation,[124] indicating the crucial role of B7-H1 in the generation and immunoregulatory function of Tregs. Moreover, Amarnath et al.[125] have shown that B7-H1/PD-1 interaction is also responsible for converting human T helper 1 (Th1) cells to Tregs *in vivo*, and prevents the onset of human to mouse xenogeneic graft versus host disease (xGVHD). Blockade of the B7-H1/PD-1 pathway or inhibition of SHP-1/SHP-2 was shown to restore Th1 differentiation and to induce xGVHD.[125]

It has been observed that tumor sites are often loaded with TILs.[126] Logically, this should aid the immune system in the clearance of tumor cells. Indeed, in ovarian[127] and gastric cancer[128] patients, the infiltration of T cells, myeloid DCs, and NKs has been associated with a better prognosis. However, this factor has also been associated with a poor prognosis in

B7-H1 positive RCC patients.[129] Furthermore, the B7-H1 positive status is linked to tumor metastasis and increased risk of mortality in RCC subjects.[49,129] B7-H1 expression could thus be responsible for the association of TILs with poor prognosis as tumor cells might exploit the B7-H1 expression to overcome anti-tumor immune responses mediated by TILs.[126]

Mechanisms of B7-H1 upregulation by tumor cells

The expression of B7-H1 by tumor cells depends on two kinds of mechanisms: innate and adaptive immune resistance.[130] Innate resistance corresponds to B7-H1 upregulation by oncogenic signaling pathways in the tumor cells.[130] For example, phosphatase and tensin homolog (PTEN) loss in breast cancer cells[131] and gliomas[132] activates phosphatidylinositide 3-kinase/Akt (PI3K/Akt) and phosphatidylinositide 3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathways which subsequently result in B7-H1 overexpression. Likewise, anaplastic lymphokinase signaling in lymphomas and lung cancer upregulates B7-H1 via signal transducer and activator of transcription 3 (STAT 3) signaling.[133] Toll-like receptor 4 has also been reported to upregulate B7-H1 expression on macrophages by lysophosphatidylserine-dependent signal transducer and activator of transcription 1 (STAT 1) signaling mechanism[134,135] (Fig. 1B).

Adaptive immune resistance refers to the exploitation of PD-1 ligand; B7-H1 by tumor cells to evade endogenous immune response.[130] B7-H1 is normally expressed to protect a tissue from immune attack. However, cancer cells exploit it to protect themselves from cytolysis.[130] The adaptive immune resistance of tumor cells can be ascribed to the observation that B7-H1 expression is often induced by interferons, mainly IFN-γ.[136–138] Although IFN-γ is known for its role in the defense against viral infections, it has been shown to upregulate B7-H1 expression in non-lymphoid tissues.[139,140] IFN-γ plays an immunosuppressive role by inducing the expression of the transcription factor, interferon regulatory factor 1 (IRF-1). IRF-1 then binds to the promoter region of B7-H1 gene and leads to its expression[141] (Fig. 1B). B7-H1 upregulation has been observed at inflammatory sites in the encephalomyelitis model,[142] and in muscle biopsies from inflammatory myopathy patients.[143] Recently, Taube et al.[56] have reported a significant correlation of B7-H1 expression in melanoma cells with IFN-γ expression in the tumor microenvironment. Thus, the benefit of IFN-γ in the autoimmune setting, and its role in tumor immune tolerance might be attributed in part to the upregulation of B7-H1 at inflammatory sites, which subverts immune responses by B7-H1/PD-1 interaction.

TARGETING THE B7-H1 MOLECULE

B7-H1 blockade by anti-B7-H1 monoclonal antibody and soluble recombinant peptide

Antibodies that target tumor cell-associated B7-H1 block its engagement with the PD-1 receptor on T cells. This allows CTLs to launch an effective immune response against the B7-H1 positive tumor cells.[130,144] Moreover, anti-B7-H1 monoclonal antibodies (mAbs) could likely lead to tumor cell death by the NK cell mediated-antibody dependent cell cytotoxicity (ADCC) pathway.[145] In this pathway, the Fc receptor of NK cells binds with the Fc domain of the tumor cell bound anti-B7-H1 mAb, resulting in tumor cell lysis through the production of effector cytokines (such as IFN-γ, IL-2) and cytotoxic granules[145] (Table 1).

Very recently, Brahmer et al.[146] examined the safety and efficacy of BMS-936559, a human B7-H1 specific IgG4 mAb in a Phase I clinical trial. The study involved 207 patients with cancers that included melanoma, RCC, NSCLC, ovarian, pancreatic, gastric and breast cancers in advanced stages. Objective responses were reported in 2 of 17 RCC, 5 of 49 NSCLC, 9 of 52 melanoma, and 1 of 17 ovarian cancer patients. No response was observed in any of the patients with B7-H1 negative tumors; however, 6–17% of the patients showed durable tumor regressions. Prolonged disease stabilization was observed in 12–41% of the patients with advanced melanoma, and with RCC and NSCLC patients at six months' follow-up. Importantly, none of the patients developed pneumonitis and the rate of treatment-related grade 3–4 adverse events were 9%.[146] Conversely, 3% cases of pneumonitis and 14% grade 3–4 adverse events were reported on an anti-PD1 clinical trial by Topalian et al.[147] This could be partly explained by the fact that B7-H1 blockade spares B7-DC, a molecule which is expressed only in a minority of human cancers.[145] B7-DC blockade in mice has been reported to excessively increase T helper cell 2 (Th2) immune response, exacerbating inflammation of respiratory tract.[148] Hyperactivation of Th2 cells is also associated with increased production of interleukin 4 (IL-4) which is known to dampen Th1 immune response.[145,148,149] B7-DC sparing could thus prevent the onset of severe toxic inflammation, lower the occurrence of anti-B7-H1 mAb-related adverse events, and prevent a decline in Th1 activity against the tumor cells.

Table 1. Suggested potential therapeutic strategies that inhibit B7-H1 expression in tumors.

Agent/ intervention	Pathway targeted/mechanism	Effect on tumor microenvironment	Reference
Anti-B7-H1 mAb	ADCC	B7-H1/PD-1 interaction blockade; prevents regulatory T cell recruitment and CTL apoptosis, induces tumor regression and prolongs disease stabilization in patients with advanced cancers	Hirano et al. (2005)[73], Brahmer et al. (2012)[146]
Sinomenine	Unknown	Prevents induction of B7-H1 surface expression in TECs	Chen et al. (2005)[104]
Triptolide	Inhibits NF-κB transcription	Prevents induction of B7-H1 surface expression	Chen et al. (2006)[174], Liang et al. (2008)[153]
Honokiol	Inhibits PI3K/mTOR pathway	Downregulates B7-H1 surface expression; decreases number of regulatory T cells	Crane et al. (2009)[132]
Nimesulide	Unknown COX-2/PGE2 independent pathway	Prevents induction of B7-H1 surface expression; induces tumor cell apoptosis and inhibits tumor cell proliferation	Liang et al. (2009)[191]
sPD-1-CH50	Binds to B7-H1 and blocks its interaction with PD-1	Increases cytotoxic activity of macrophages and CTLs against B7-H1 positive tumor cells	Qiu et al. (2009)[150]
Doxorubicin	Akt dependent pathway dominant in nucleus, and unknown Akt independent pathway dominant in cell surface	Downregulates cell surface B7-H1 expression by translocation to the nucleus	Ghebeh et al. (2010)[7]
siRNAs	B7-H1 cell surface knockdown B7-H1 nuclear knockdown	Enhances effector functions and proliferation of CD4 and CD8 positive human T cells Significantly enhances doxorubicin mediated tumor cell apoptosis	Hobo et al. (2010,2013)[193,194], Iwamura et al. (2012)[192], Ghebeh et al. (2010)[7]

Abbreviations: Anti-B7-H1 mAb = Anti-B7-H1 monoclonal antibody; ADCC = Antibody Dependent Cell-Mediated Cytotoxicity pathway; CTL = Cytotoxic T lymphocyte; TECs = Renal tubular epithelial cells; NF-κB = Nuclear factor-kappa light chain enhancer of activated B cells; PI3K/mTOR = Phosphatidylinositide 3-kinase/mammalian target of rapamycin pathway; COX-2/PGE2 = Cyclooxygenase 2/Prostaglandin- E2 pathway; sPD-1-CH50 = Soluble programmed death 1 recombinant peptide with CH50 fibronectin domain; siRNAs = Small interfering RNA.

A recombinant peptide, soluble programmed death 1 in conjunction with CH50 fibronectin domain (sPD-1-CH50) is known to bind to B7-H1 and inhibit its interaction with the PD-1 in a murine hepatoma model.[150] This strategy has been shown to enhance the recruitment and cytotoxic activity of T cells/macrophages against B7-H1 positive tumor cells and to increase the production of effector T cell cytokines (Table 1). The sPD-1-CH50 treatment was also shown to inhibit the growth and metastasis of the tumor cells *in vivo*.[150] Blockade of B7-H1 by anti-B7-H1 mAbs and sPD-1-CH50 therefore has a potential therapeutic significance for the inhibition of growth and invasion of tumors, as well as the acceleration of anti-tumor immunity.

B7-H1 suppression by chemotherapeutic drugs

Chemotherapeutic drugs are designed to treat cancers by inducing apoptosis and inhibiting proliferation of tumor cells.[151] They include anthracyclines (e.g. doxorubicin, danorubicin), alkaloids (e.g. doxetaxcel, sinonemine), alkylating agents (e.g. cisplatin), and pyrimidine antagonist (e.g. arabinofuranosyl cytidine; Ara-C). However, these drugs may also have immunomodulatory properties.[7,152,153] Doxorubicin, an anthracycline-based drug used in the treatment of breast cancer,[154] and childhood soft tissue sarcomas and lymphomas,[155,156] is reported to stimulate the production of cytokines,[157] CTL[158] and NK cell immune responses,[157] enhance differentiation of macrophages,[159] and downregulate cell surface B7-H1 expression in breast cancer cells.[7] Nevertheless, doxorubicin upregulates B7-H1 nuclear expression via Akt dependent pathway in tumor cells which renders them anti-apoptotic.[7] This is because nuclear translocation of B7-H1 molecule can permit its interaction with the apoptotic machinery of the tumor cell.[7] Administration of doxorubicin in conjunction with siRNA-mediated B7-H1 knockdown has been shown to augment doxorubicin-mediated tumor cell apoptosis.[7]

A combination of chemotherapy with B7-H1 targeting can therefore be beneficial in overcoming

drug-mediated immune resistance of tumor cells and enhancing anti-tumor immunity.

Sinomenine, an alkaloid extracted from a Chinese medicinal plant *Sinomenium acutum*,[160] is well known in the Far East for the treatment of rheumatoid arthritis,[160–162] autoimmune nephritis,[163,164] renal allograft rejection,[165] and hepatitis.[165] Sinomenine has been widely recognized for its immunosuppressive and anti-inflammatory properties,[104] and has recently been demonstrated to possess anti-tumoral properties as well.[104] Sinomenine-mediated downregulation of B7-H1 mRNA and protein expression of IFN-γ and tumor necrosis factor alpha (TNF-α) treated renal tubular epithelial cells (TECs) has been reported by Chen et al.[104] TECs with B7-H1 overexpression were seen to inhibit cytotoxic cytokine production by T cells in TEC: T cell co-cultures, and sinomenine treatments resulted in significantly enhanced effector cytokine production by the T cells (Table 1). The drug could thus be a feasible option for the treatment of RCC.[104]

Triptolide, an oxygenated diterpene compound extracted from a Chinese medicinal herb, *Tripterygium wilfordii*, has been widely used in the Far East for the treatment of autoimmune diseases such as rheumatoid arthritis, and tumors.[166,167] Triptolide has been shown to induce tumor cell apoptosis both *in vitro* and *in vivo*[168–170] (Table 1). Moreover, remission rates of 87% in granulocytic leukemia and 71% in mononucleocytic leukemia have been reported in Triptolide clinical trials in China.[171] The anti-tumor property of this compound has been ascribed to its ability to activate caspase-3 and caspase-8,[172] and render tumor cells more susceptible to topoisomerase inhibitors[173] (Table 1). Triptolide enhances doxorubicin-mediated apoptosis of tumor cells,[168] and downregulates B7-H1 expression in TNF-α regulated TECs by decreasing transcription of nuclear factor-kappa light chain enhancer of activated B cells (NF-κB).[174] B7-H1 inhibition by triptolide could thus partly explain its anti-tumoral behavior.

Honokiol, a natural dietary product extracted from the seed cones of *Magnolia grandiflora*, attenuates tumor growth in breast,[175,176] gastric,[177,178] colon,[179,180] pancreatic,[181] and skin cancers.[182] Honokiol inhibits transcription of NF-κB[175] and the (PI3K/mTOR) pathway,[176] both of which are implicated in the upregulation of B7-H1 expression[174] (Table 1). Indeed, honokiol has been demonstrated to downregulate B7-H1 expression in PTEN deficient glioma, breast, and prostate cancer cells.[132] Honokiol can therefore be an appealing therapeutic option in overcoming cancer cell immune resistance.

Cyclooxygenase 2 (COX-2) is an enzyme which catalyses the conversion of arachidonic acid to prostaglandins (PG-E2).[183] Over expression of COX-2 has been implicated in inflammation and reported in a number of human cancers including lung, breast, skin, prostate and colon cancers.[183] Nimesulide is a selective COX-2 inhibitor, and is known to inhibit proliferation of tumor cells and induce tumor cell apoptosis *in vitro*,[184,185] as well as prevent metastasis *in vivo*.[186–188] Nonetheless, it has been suggested that COX-2 independent mechanisms are involved in nimesulide-mediated anti-tumor responses.[189–191] Liang et al.[191] reported the downregulation of B7-H1 expression in IFN-γ treated human breast cancer cells. They showed that COX-2 inhibitors other than nimesulide (NS-398 and meloxican) fail to inhibit B7-H1 expression. Furthermore, addition of PG-E2 to IFN-γ treated breast cancer cells did not inhibit nimesulide-mediated B7-H1 downregulation, which indicated that COX-2/PG-E2 independent mechanisms might be involved[191] (Table 1). Inhibition of B7-H1 by nimesulide can therefore be a potential therapeutic strategy to boost anti-tumor immune responses.

Tumor specific B7-H1 gene silencing by siRNA

siRNA-mediated gene silencing in conjunction with adoptive T cell therapy using tumor specific T cells provide an opportunity to specifically target tumor cells[192] (Table 1). Iwamura et al.[192] reported on the generation of CD8+ T cell clones which recognize a tumor antigen specific MAGE-A4-derived peptide. TCR-α and β genes from these CD8+ T cell clones were isolated and transduced retrovirally into human T cells, which expressed B7-H1 upon stimulation with the MAG-A4 positive tumor antigen. In this, the siRNA-mediated knockdown of the B7-H1 molecule is shown to augment the cytotoxic activity of the tumor specific T cells.[192]

DC-based vaccines are being explored to boost immunity in patients with chronic viral infections and cancer. However, limited clinical benefits have been observed, suggesting the need to improve the potency of DC-based vaccines.[193] Hobo et al.[194] investigated enhanced cytotoxic cytokine production (IFN-γ, IL-2, IL-5, TNF-α) by minor histocompatibility antigen (MiHA)-specific CD8+ T cells and memory cells of relapsed leukemia patients upon stimulation with siRNA-mediated B7-H1 knockdown DCs in T cell: DC co-culture experiments. This strategy also augmented the production of granzyme B by antigen experienced CTLs and increased their proliferative capacity.[194] In their recent study, Hobo et al.[193] demonstrated the development of enhanced clinical grade

DC vaccine by lipidoid nanoparticle-mediated transfection of DCs with B7-H1 siRNA. The B7-H1 silenced DCs effectively enhanced *ex vivo* antigen-specific CD8+ T cell responses from transplanted leukemia and lymphoma patients.[193]

B7-H1 siRNA treatment of breast cancer cells has also been shown to enhance doxorubicin-mediated apoptosis by knocking down nuclear B7-H1 expression.[7] [See Section 4: Targeting the B7-H1 molecule]. These findings suggest that siRNA-mediated silencing of B7-H1 gene can be utilized to boost anti-tumor immunity in conjunction with tumor-specific adoptive T cell therapy and chemotherapy to augment the efficacy of anti-tumor vaccines.

CONCLUSION

Cancer cells exploit the co-inhibitory B7-H1 molecule to evade the immune system. Overexpression of B7-H1 molecule has been linked to worse prognosis and poor response to anti-cancer therapeutic strategies in several human malignancies. Targeting B7-H1 expression can open the inhibitory gate and render many tumor cell types susceptible to lysis/apoptosis, therefore killing many birds with one stone. This strategy may improve the efficacy of standard available cancer treatments.

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

SA collected the review data and wrote the manuscript. SD designed the structure of the review, directly supervised the review process, participated in writing, and critically reviewed the manuscript. Both authors read and approved the final manuscript.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.hemonc.2013.09.005.

REFERENCES

1. Dermime S, Gilham DE, Shaw DM, Davidson EJ, Meziane el-K, Armstrong A, et al.. Vaccine and antibody-directed T cell tumour immunotherapy. Biochim Biophys Acta 2004;1704(1):11–35.
2. Vesely MD, Schreiber RD. Cancer immunoediting: antigens, mechanisms, and implications to cancer immunotherapy. Ann N Y Acad Sci 2013;1284:1–5.
3. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S A 2002;99(19):12293–7.
4. Ghebeh H, Mohammed S, Al-Omair A, Qattan A, Lehe C, Al-Qudaihi G, et al.. The B7-H1 (PD-L1) T lymphocyte-inhibitory molecule is expressed in breast cancer patients with infiltrating ductal carcinoma: correlation with important high-risk prognostic factors. Neoplasia 2006;8(3):190–8.
5. Ghebeh H, Tulbah A, Mohammed S, Elkum N, Bin Amer SM, Al-Tweigeri T, et al.. Expression of B7-H1 in breast cancer patients is strongly associated with high proliferative Ki-67-expressing tumor cells. Int J Cancer 2007;121(4):751–8.
6. Ghebeh H, Barhoush E, Tulbah A, Elkum N, Al-Tweigeri T, Dermime S. FOXP3+ Tregs and B7-H1+/PD-1+ T lymphocytes co-infiltrate the tumor tissues of high-risk breast cancer patients: implication for immunotherapy. BMC Cancer 2008;23(8):57.
7. Ghebeh H, Lehe C, Barhoush E, Al-Romaih K, Tulbah A, Al-Alwan M, et al.. Doxorubicin down-regulates cell surface B7-H1 expression and up-regulates its nuclear expression in breast cancer cells: role of B7-H1 as an anti-apoptotic molecule. Breast Cancer Res 2010;12(4):R48.
8. Brown JA, Dorfman DM, Ma FR, Sullivan EL, Munoz O, Wood CR, et al.. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol 2003;170(3):1257–66.
9. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al.. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8(8):793–800.
10. Curiel TJ, Wei S, Dong H, Alvarez X, Cheng P, Mottram P, et al.. Blockade of B7-H1 improves myeloid dendritic cell-mediated antitumor immunity. Nat Med 2003;9(5):562–7.
11. Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al.. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Natl Acad Sci U S A 2007;104(9):3360–5.
12. Karim R, Jordanova ES, Piersma SJ, Kenter GG, Chen L, Boer JM, et al.. Tumor-expressed B7-H1 and B7-DC in relation to PD-1+ T-cell infiltration and survival of patients with cervical carcinoma. Clin Cancer Res 2009;15(20):6341–7.
13. Cho YA, Yoon HJ, Lee JI, Hong SP, Hong SD. Relationship between the expressions of PD-L1 and tumor-infiltrating lymphocytes in oral squamous cell carcinoma. Oral Oncol 2011;47(12):1148–53.
14. Malaspina TS, Gasparoto TH, Costa MR, de Melo EF, Ikoma Jr MR, Damante JH, et al.. Enhanced programmed death 1 (PD-1) and PD-1 ligand (PD-L1) expression in patients with actinic cheilitis and oral squamous cell carcinoma. Cancer Immunol Immunother 2011;60(7):965–74.
15. Tsushima F, Tanaka K, Otsuki N, Youngnak P, Iwai H, Omura K, et al.. Predominant expression of B7-H1 and its immunoregulatory roles in oral squamous cell carcinoma. Oral Oncol 2006;42(3):268–74.
16. Lyford-Pike S, Peng S, Young GD, Taube JM, Westra WH, Akpeng B, et al.. Evidence for a role of the PD-1:PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma. Cancer Res 2013;73(6):1733–41.
17. Strome SE, Dong H, Tamura H, Voss SG, Flies DB, Tamada K, et al.. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res 2003;63(19):6501–5.
18. Avril T, Saikali S, Vauleon E, Jary A, Hamlat A, De Tayrac M, et al.. Distinct effects of human glioblastoma immunoregulatory molecules programmed cell death ligand-1 (PDL-1) and indoleamine 2,3-dioxygenase (IDO) on tumour-specific T cell functions. J Neuroimmunol 2010;225(1–2):22–33.
19. Jacobs JF, Idema AJ, Bol KF, Nierkens S, Grauer OM, Wesseling P, et al.. Regulatory T cells and the PD-L1/PD-1 pathway mediate immune suppression in malignant human brain tumors. Neuro Oncol 2009;11(4):394–402.
20. Wilmotte R, Burkhardt K, Kindler V, Belkouch MC, Dussex G, Tribolet N, et al.. B7-homolog 1 expression by human glioma: a new mechanism of immune evasion. Neuroreport 2005;16(10):1081–5.
21. Wintterle S, Schreiner B, Mitsdoerffer M, Schneider D, Chen L, Meyermann R, et al.. Expression of the B7-related molecule B7-H1 by glioma cells: a potential mechanism of immune paralysis. Cancer Res 2003;63(21):7462–7.
22. Yao Y, Tao R, Wang X, Wang Y, Mao Y, Zhou LF. B7-H1 is correlated with malignancy-grade gliomas but is not expressed exclusively on tumor stem-like cells. Neuro Oncol 2009;11(6):757–66.
23. Boland JM, Kwon ED, Harrington SM, Wampfler JA, Tang H, Yang P, et al.. Tumor B7-H1 and B7-H3

expression in squamous cell carcinoma of the lung. Clin Lung Cancer 2013;14(2):157–63.
24. Konishi J, Yamazaki K, Azuma M, Kinoshita I, Dosaka-Akita H, Nishimura M. B7-H1 expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. Clin Cancer Res 2004;10(15):5094–100.
25. Mu CY, Huang JA, Chen Y, Chen C, Zhang XG. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. Med Oncol 2011;28(3):682–8.
26. Hsu MC, Hsiao JR, Chang KC, Wu YH, Su IJ, Jin YT, et al.. Increase of programmed death-1-expressing intratumoral CD8 T cells predicts a poor prognosis for nasopharyngeal carcinoma. Mod Pathol 2010;23(10):1393–403.
27. Zhang F, Liu Z, Cui Y, Wang G, Cao P. The clinical significance of the expression of costimulatory molecule PD-L1 in nasopharyngeal carcinoma. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2008;22(9):408–10 [in Chinese].
28. Loos M, Langer R, Schuster T, Gertler R, Walch A, Rauser S, et al.. Clinical significance of the costimulatory molecule B7-H1 in Barrett carcinoma. Ann Thorac Surg 2011;91(4):1025–31.
29. Ohigashi Y, Sho M, Yamada Y, Tsurui Y, Hamada K, Ikeda N, et al.. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. Clin Cancer Res 2005;11(8):2947–53.
30. Wu C, Zhu Y, Jiang J, Zhao J, Zhang XG, Xu N. Immunohistochemical localization of programmed death-1 ligand-1 (PD-L1) in gastric carcinoma and its clinical significance. Acta Histochem 2006;108(1):19–24.
31. Chen J, Li G, Meng H, Fan Y, Song Y, Wang S, et al.. Upregulation of B7-H1 expression is associated with macrophage infiltration in hepatocellular carcinomas. Cancer Immunol Immunother 2012;61(1):101–8.
32. Gao Q, Wang XY, Qiu SJ, Yamato I, Sho M, Nakajima Y, et al.. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin Cancer Res 2009;15(3):971–9.
33. Geng L, Deng J, Jiang G, Song P, Wang Z, Jiang Z, et al.. B7-H1 up-regulated expression in human hepatocellular carcinoma tissue: correlation with tumor interleukin-10 levels. Hepatogastroenterology 2011;58(107–108):960–4.
34. Wang BJ, Bao JJ, Wang JZ, Wang Y, Jiang M, Xing MY, et al.. Immunostaining of PD-1/PD-Ls in liver tissues of patients with hepatitis and hepatocellular carcinoma. World J Gastroenterol 2011;17(28):3322–9.
35. Wu K, Kryczek I, Chen L, Zou W, Welling TH. Kupffer cell suppression of CD8+ T cells in human hepatocellular carcinoma is mediated by B7-H1/programmed death-1 interactions. Cancer Res 2009;69(20):8067–75.
36. Ye Y, Zhou L, Xie X, Jiang G, Xie H, Zheng S. Interaction of B7-H1 on intrahepatic cholangiocarcinoma cells with PD-1 on tumor-infiltrating T cells as a mechanism of immune evasion. J Surg Oncol 2009;100(6):500–4.
37. Hua D, Sun J, Mao Y, Chen LJ, Wu YY, Zhang XG. B7-H1 expression is associated with expansion of regulatory T cells in colorectal carcinoma. World J Gastroenterol 2012;18(9):971–8.
38. Xiao JX, Bai PS, Lai BC, Li L, Zhu J, Wang YL. B7 molecule mRNA expression in colorectal carcinoma. World J Gastroenterol 2005;11(36):5655–8.
39. Chen XL, Yuan SX, Chen C, Mao YX, Xu G, Wang XY. Expression of B7-H1 protein in human pancreatic carcinoma tissues and its clinical significance. Ai Zheng 2009;28(12):1328–32 [in Chinese].
40. Geng L, Huang D, Liu J, Qian Y, Deng J, Li D, et al.. B7-H1 up-regulated expression in human pancreatic carcinoma tissue associates with tumor progression. J Cancer Res Clin Oncol 2008;134(9):1021–7.
41. Huang DS, Liu JW, Geng L, Jiang GP, Shen GL, Yao WF. Role of B7-H1 in pancreatic carcinoma immune evasion. Zhonghua Wai Ke Za Zhi 2009;47(4):282–5.
42. Loos M, Giese NA, Kleeff J, Giese T, Gaida MM, Bergmann F, et al.. Clinical significance and regulation of the costimulatory molecule B7-H1 in pancreatic cancer. Cancer Lett 2008;268(1):98–109.
43. Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al.. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res 2007;13(7):2151–7.
44. Wang L, Ma Q, Chen X, Guo K, Li J, Zhang M. Clinical significance of B7-H1 and B7-1 expressions in pancreatic carcinoma. World J Surg 2010;34(5):1059–65.
45. Blank C, Kuball J, Voelkl S, Wiendl H, Becker B, Walter B, et al.. Blockade of PD-L1 (B7-H1) augments human tumor-specific T cell responses in vitro. Int J Cancer 2006;119(2):317–27.
46. Krambeck AE, Dong H, Thompson RH, Kuntz SM, Lohse CM, Leibovich BC, et al.. Survivin and B7-H1 are collaborative predictors of survival and represent potential therapeutic targets for patients with renal cell carcinoma. Clin Cancer Res 2007;13(6):1749–56.
47. Thompson RH, Gillett MD, Cheville JC, Lohse CM, Dong H, Webster WS, et al.. Costimulatory B7-H1 in renal cell carcinoma patients: indicator of tumor aggressiveness and potential therapeutic target. Proc Natl Acad Sci U S A 2004;101(49):17174–9.
48. Thompson RH, Gillett MD, Cheville JC, Lohse CM, Dong H, Webster WS, et al.. Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. Cancer 2005;104(10):2084–91.
49. Thompson RH, Kuntz SM, Leibovich BC, Dong H, Lohse CM, Webster WS, et al.. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer Res 2006;66(7):3381–5.
50. Thompson RH, Dong H, Kwon ED. Implications of B7-H1 expression in clear cell carcinoma of the kidney for prognostication and therapy. Clin Cancer Res 2007;13(2 Pt 2):709s–15s.
51. Boorjian SA, Sheinin Y, Crispen PL, Farmer SA, Lohse CM, Kuntz SM, et al.. T-cell coregulatory molecule expression in urothelial cell carcinoma: clinicopathologic correlations and association with survival. Clin Cancer Res 2008;14(15):4800–8.
52. Inman BA, Sebo TJ, Frigola X, Dong H, Bergstralh EJ, Frank I, et al.. PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression. Cancer 2007;109(8):1499–505.
53. Nakanishi J, Wada Y, Matsumoto K, Azuma M, Kikuchi K, Ueda S. Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. Cancer Immunol Immunother 2007;56(8):1173–82.
54. Gadiot J, Hooijkaas AI, Kaiser AD, van Tinteren H, van Boven H, Blank C. Overall survival and PD-L1 expression in metastasized malignant melanoma. Cancer 2011;117(10):2192–201.
55. Hino R, Kabashima K, Kato Y, Yagi H, Nakamura M, Honjo T, et al.. Tumor cell expression of programmed cell death-1 ligand 1 is a prognostic factor for malignant melanoma. Cancer 2010;116(7):1757–66.
56. Taube JM, Anders RA, Young GD, Xu H, Sharma R, McMiller TL, et al.. Colocalization of inflammatory response with B7-H1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. Sci Transl Med 2012;4(127):127ra37.
57. Li H, Wang C, Guo G, Gao C, Wu Y, Chen Y. The characteristic expression of B7-associated proteins in Langerhans cell sarcoma. Acta Histochem 2012;114(7):733–43.
58. Kozako T, Yoshimitsu M, Fujiwara H, Masamoto I, Horai S, White Y, et al.. PD-1/PD-L1 expression in human T-cell leukemia virus type 1 carriers and adult T-cell leukemia/lymphoma patients. Leukemia 2009;23(2):375–82.
59. Wilcox RA, Feldman AL, Wada DA, Yang ZZ, Comfere NI, Dong H, et al.. B7-H1 (PD-L1, CD274) suppresses host immunity in T-cell lymphoproliferative disorders. Blood 2009;114(10):2149–58.
60. Salih HR, Wintterle S, Krusch M, Kroner A, Huang YH, Chen L, et al.. The role of leukemia-derived B7-H1 (PD-L1) in tumor-T-cell interactions in humans. Exp Hematol 2006;34(7):888–94.
61. Li X, Wang YF, Ge W, Li ZJ, Yu Z, Li YT, et al.. Real-time quantitative PCR detecting B7-H1 gene expression in leukemia cells and its clinical implications. Zhonghua Xue Ye Xue Za Zhi 2007;28(12):837–40 [in Chinese].
62. Chen X, Liu S, Wang L, Zhang W, Ji Y, Ma X. Clinical significance of B7-H1 (PD-L1) expression in human acute leukemia. Cancer Biol Ther 2008;7(5):622–7.
63. Li X, Sun WJ, Xu Y, Li ZJ, Yu Z, Deng SH, et al.. Expression of B7-H1 gene in leukemia cells and its clinical significance. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2012;20(3):541–4, in Chinese].
64. Ge W, Ma X, Li X, Wang Y, Li C, Meng H, et al.. B7-H1 up-regulation on dendritic-like leukemia cells suppresses T cell immune function through modulation of IL-10/IL-12 production and generation of Treg cells. Leuk Res 2009;33(7):948–57.
65. Berthon C, Driss V, Liu J, Kuranda K, Leleu X, Jouy N, et al.. In acute myeloid leukemia, B7-H1 (PD-L1) protection of blasts from cytotoxic T cells is induced by TLR ligands and interferon-gamma and can be reversed using MEK inhibitors. Cancer Immunol Immunother 2010;59(12):1839–49.
66. Norde WJ, Maas F, Hobo W, Korman A, Quigley M, Kester MG, et al.. PD-1/PD-L1 interactions contribute to functional T-cell impairment in patients who relapse with cancer after allogeneic stem cell transplantation. Cancer Res 2011;71(15):5111–22.
67. Sun WJ, Li X. B7-H1, a prognostic factor for patient's response to therapy of acute myeloid leukemia. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2012;20(6):1332–5.
68. Grzywnowicz M, Zaleska J, Mertens D, Tomczak W, Wlasiuk P, Kosior K, et al.. Programmed death-1 and its ligand are novel immunotolerant molecules expressed on leukemic B cells in chronic lymphocytic leukemia. PLoS ONE 2012;7(4):e35178.
69. Hallett WH, Jing W, Drobyski WR, Johnson BD. Immunosuppressive effects of multiple myeloma are overcome by PD-L1 blockade. Biol Blood Marrow Transplant 2011;17(8):1133–45.
70. Tamura H, Ishibashi M, Yamashita T, Tanosaki S, Okuyama N, Kondo A, et al.. Marrow stromal cells induce B7-H1 expression on myeloma cells, generating aggressive characteristics in multiple myeloma. Leukemia 2013;27(2):464–72.
71. Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother 2005;54(4):307–14.
72. Liu J, Hamrouni A, Wolowiec D, Coiteux V, Kuliczkowski K, Hetuin D, et al.. Plasma cells from multiple myeloma patients express B7-H1 (PD-L1) and increase expression after stimulation with IFN-{gamma} and TLR ligands via a MyD88-, TRAF6-, and MEK-dependent pathway. Blood 2007;110(1):296–304.
73. Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al.. Blockade of B7-H1 and PD-1 by

monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res 2005;65(3):1089–96.
74. Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, et al.. Cancer statistics, 2004. CA Cancer J Clin 2004;54(1):8–29.
75. Breast Cancer Facts and Figures 2003–2004. American Cancer Society. Available at: <http://www.cancer.org/acs/groups/content/@nho/documents/document/caff2003brfpwsecuredpdf.pdf>; 2004 [accessed 05/06, 2013].
76. Hasan A, Ghebeh H, Lehe C, Ahmad R, Dermime S. Therapeutic targeting of B7-H1 in breast cancer. Expert Opin Ther Targets 2011;15(10):1211–25.
77. zur Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. Nat Rev Cancer 2002;2(5):342–50.
78. Bosch FX, Manos MM, Muñoz N, Sherman M, Jansen AM, Peto J, et al.. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. J Natl Cancer Inst 1995;87(11):796–802.
79. Nakagawa M, Stites DP, Patel S, Farhat S, Scott M, Hills NK, et al.. Persistence of human papillomavirus type 16 infection is associated with lack of cytotoxic T lymphocyte response to the E6 antigens. J Infect Dis 2000;182(2):595–8.
80. Welters MJ, de Jong A, van den Eeden SJ, van der Hulst JM, Kwappenberg KM, Hassane S, et al.. Frequent display of human papillomavirus type 16 E6-specific memory t-Helper cells in the healthy population as witness of previous viral encounter. Cancer Res 2003;63(3):636–41.
81. de Jong A, van Poelgeest MI, van der Hulst JM, Drijfhout JW, Fleuren GJ, Melief CJ, et al.. Human papillomavirus type 16-positive cervical cancer is associated with impaired CD4+ T-cell immunity against early antigens E2 and E6. Cancer Res 2004;64(15):5449–55.
82. Peyrade F, Cupissol D, Geoffrois L, Rolland F, Borel C, Ciais C, et al.. Systemic treatment and medical management of metastatic squamous cell carcinoma of the head and neck: review of the literature and proposal for management changes. Oral Oncol 2013;49(6):482–91.
83. Li Y, Shi X, Rong X, Peng Y, Tang Y. Neurosurgery and prognosis in patients with radiation-induced brain injury after nasopharyngeal carcinoma radiotherapy: a follow-up study. Radiat Oncol 2013;11(8):88.
84. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60(5):277–300.
85. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57(1):43–66.
86. Wang Y, Zhuang Q, Zhou S, Hu Z, Lan R. Costimulatory molecule B7-H1 on the immune escape of bladder cancer and its clinical significance. J Huazhong Univ Sci Technolog Med Sci 2009;29(1):77–9.
87. Wettersten HI, Weiss RH. Potential biofluid markers and treatment targets for renal cell carcinoma. Nat Rev Urol 2013;10(6):336–44.
88. Green DM, D'Angio GJ, Beckwith JB, Breslow NE, Grundy PE, Ritchey ML, et al.. Wilms tumor. CA Cancer J Clin 1996;46(1):46–63.
89. Routh JC, Ashley RA, Sebo TJ, Lohse CM, Husmann DA, Kramer SA, et al.. B7-H1 expression in Wilms tumor: correlation with tumor biology and disease recurrence. J Urol 2008;179(5):1954–9 [discussion 1959–60].
90. Slipicevic A, Herlyn M. Narrowing the knowledge gaps for melanoma. Ups J Med Sci 2012;117(2):237–43.
91. Tsao H, Atkins MB, Sober AJ. Management of cutaneous melanoma. N Engl J Med 2004;351(10):998–1012.
92. Thomas CR, Wright CD, Loehrer PJ. Thymoma: state of the art. J Clin Oncol 1999;17(7):2280–9.
93. Howlader N, Noone A, Krapcho M, Neyman N, Aminou R, Altekruse S, et al. SEER cancer statistics review, 1975–2009. Available at: <http://seer.cancer.gov/csr/1975_2010/>; 2009 [accessed 04/17, 2013].
94. Kumar V, Robbins SL. Robbins basic pathology. 8th ed. Philadelphia: Saunders/Elsevier; 2007.
95. Delfino C, Grandi V, Pileri A, Rupoli S, Quaglino P, Alterini R, et al.. Combination treatment in CTCL: the current role of bexarotene. G Ital Dermatol Venereol 2012;147(6):573–80.
96. Yodoi J, Takatsuki K, Masuda T. Letter: two cases of T-cell chronic lymphocytic leukemia in Japan. N Engl J Med 1974;290(10):572–3.
97. Tamás L, Sári E, Répássy G, Szabó P, Bagdi E, Krenács L, et al.. Spontaneous remission in localized diffuse large B-cell lymphoma. Pathol Oncol Res 2011;17(3):779–84.
98. Andorsky DJ, Yamada RE, Said J, Pinkus GS, Betting DJ, Timmerman JM. Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumor-associated T cells. Clin Cancer Res 2011;17(13):4232–44.
99. Mathers CD, Boschi-Pinto C, Lopez AD, Murray CJL. Cancer incidence, mortality and survival by site for 14 regions of the world. Available at: http://www.who.int/healthinfo/paper13.pdf>; 2001 [accessed 04/21/2013].
100. Collins CD. Problems monitoring response in multiple myeloma. Cancer Imaging 2005;5(Spec No. A):S119–26.
101. Kuipers H, Muskens F, Willart M, Hijdra D, van Assema FB, Coyle AJ, et al.. Contribution of the PD-1 ligands/PD-1 signaling pathway to dendritic cell-mediated CD4+ T cell activation. Eur J Immunol 2006;36(9):2472–82.
102. Nakazawa A, Dotan I, Brimnes J, Allez M, Shao L, Tsushima F, et al.. The expression and function of costimulatory molecules B7H and B7-H1 on colonic epithelial cells. Gastroenterology 2004;126(5):1347–57.
103. Yadav D, Sarvetnick N. Costimulation and pancreatic autoimmunity: the PD-1/PD-L conundrum. Rev Diabet Stud 2006;3(1):6–10.
104. Chen Y, Li J, Zhang J, Zhao T, Zou L, Tang Y, et al.. Sinomenine inhibits B7-H1 and B7-DC expression on human renal tubular epithelial cells. Int Immunopharmacol 2005;5(9):1446–57.
105. Hori J, Wang M, Miyashita M, Tanemoto K, Takahashi H, Takemori T, et al.. B7-H1-induced apoptosis as a mechanism of immune privilege of corneal allografts. J Immunol 2006;177(9):5928–35.
106. Raimondi G, Shufesky WJ, Tokita D, Morelli AE, Thomson AW. Regulated compartmentalization of programmed cell death-1 discriminates CD4+CD25+ resting regulatory T cells from activated T cells. J Immunol 2006;176(5):2808–16.
107. Bell D, Chomarat P, Broyles D, Netto G, Harb GM, Lebecque S, et al.. In breast carcinoma tissue, immature dendritic cells reside within the tumor, whereas mature dendritic cells are located in peritumoral areas. J Exp Med 1999;190(10):1417–26.
108. Lutz MB, Kurts C. Induction of peripheral CD4+ T-cell tolerance and CD8+ T-cell cross-tolerance by dendritic cells. Eur J Immunol 2009;39(9):2325–30.
109. Inman BA, Frigola X, Dong H, Kwon ED. Costimulation, coinhibition and cancer. Curr Cancer Drug Targets 2007;7(1):15–30.
110. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515–48.
111. Lenschow DJ, Walunas TL, Bluestone JA. CD28/B7 system of T cell costimulation. Annu Rev Immunol 1996;14:233–58.
112. Dermime S, Aljurf MD. Current advances, problems and prospects for vaccine-based immunotherapy in follicular non-Hodgkin's lymphoma. Leuk Lymphoma 2005;46(4):497–507.
113. Salomon B, Bluestone JA. Complexities of CD28/B7: CTLA-4 costimulatory pathways in autoimmunity and transplantation. Annu Rev Immunol 2001;19:225–52.
114. Foell J, Hewes B, Mittler RS. T cell costimulatory and inhibitory receptors as therapeutic targets for inducing anti-tumor immunity. Curr Cancer Drug Targets 2007;7(1):55–70.
115. Hofmeyer KA, Jeon H, Zang X. The PD-1/PD-L1 (B7-H1) pathway in chronic infection-induced cytotoxic T lymphocyte exhaustion. J Biomed Biotechnol 2011;2011:451694.
116. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173(2):945–54.
117. Fife BT, Pauken KE, Eagar TN, Obu T, Wu J, Tang Q, et al.. Interactions between PD-1 and PD-L1 promote tolerance by blocking the TCR-induced stop signal. Nat Immunol 2009;10(11):1185–92.
118. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al.. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192(7):1027–34.
119. Carter L, Fouser LA, Jussif J, Fitz L, Deng B, Wood CR, et al.. PD-1:PD-L inhibitory pathway affects both CD4(+) and CD8(+) T cells and is overcome by IL-2. Eur J Immunol 2002;32(3):634–43.
120. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. Science 2003;299(5609):1057–61.
121. Ng WF, Duggan PJ, Ponchel F, Matarese G, Lombardi G, Edwards AD, et al.. Human CD4(+)CD25(+) cells: a naturally occurring population of regulatory T cells. Blood 2001;98(9):2736–44.
122. Thornton AM, Shevach EM. CD4+CD25+ immunoregulatory T cells suppress polyclonal T cell activation in vitro by inhibiting interleukin 2 production. J Exp Med 1998;188(2):287–96.
123. Liang S, Alard P, Zhao Y, Parnell S, Clark SL, Kosiewicz MM. Conversion of CD4+ CD25- cells into CD4+ CD25+ regulatory T cells in vivo requires B7 costimulation, but not the thymus. J Exp Med 2005;201(1):127–37.
124. Kitazawa Y, Fujino M, Wang Q, Kimura H, Azuma M, Kubo M, et al.. Involvement of the programmed death-1/programmed death-1 ligand pathway in CD4+CD25+ regulatory T-cell activity to suppress alloimmune responses. Transplantation 2007;83(6):774–82.
125. Amarnath S, Mangus CW, Wang JC, Wei F, He A, Kapoor V, et al.. The PDL1–PD1 axis converts human TH1 cells into regulatory T cells. Sci Transl Med 2011;3(111):111ra120.
126. Dong H, Chen X. Immunoregulatory role of B7-H1 in chronicity of inflammatory responses. Cell Mol Immunol 2006;3(3):179–87.
127. Zhang L, Conejo-Garcia JR, Katsaros D, Gimotty PA, Massobrio M, Regnani G, et al.. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. N Engl J Med 2003;348(3):203–13.
128. Ishigami S, Natsugoe S, Tokuda K, Nakajo A, Xiangming C, Iwashige H, et al.. Clinical impact of intratumoral natural killer cell and dendritic cell infiltration in gastric cancer. Cancer Lett 2000;159(1):103–8.
129. Webster WS, Lohse CM, Thompson RH, Dong H, Frigola X, Dicks DL, et al.. Mononuclear cell infiltration in clear-cell renal cell carcinoma independently predicts patient survival. Cancer 2006;107(1):46–53.
130. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12(4):252–64.
131. Crane CA, Panner A, Murray JC, Wilson SP, Xu H, Chen L, et al.. PI(3) kinase is associated with a

mechanism of immunoresistance in breast and prostate cancer. Oncogene 2009;28(2):306–12.
132. Crane C, Panner A, Pieper RO, Arbiser J, Parsa AT. Honokiol-mediated inhibition of PI3K/mTOR pathway: a potential strategy to overcome immunoresistance in glioma, breast, and prostate carcinoma without impacting T cell function. J Immunother 2009;32(6):585–92.
133. Marzec M, Zhang Q, Goradia A, Raghunath PN, Liu X, Paessler M, et al.. Oncogenic kinase NPM/ALK induces through STAT3 expression of immunosuppressive protein CD274 (PD-L1, B7-H1). Proc Natl Acad Sci U S A 2008;105(52):20852–7.
134. Yamazaki T, Akiba H, Iwai H, Matsuda H, Aoki M, Tanno Y, et al.. Expression of programmed death 1 ligands by murine T cells and APC. J Immunol 2002;169(10):5538–45.
135. Loke P, Allison JP. PD-L1 and PD-L2 are differentially regulated by Th1 and Th2 cells. Proc Natl Acad Sci U S A 2003;100(9):5336–41.
136. Kim J, Myers AC, Chen L, Pardoll DM, Truong-Tran QA, Lane AP, et al.. Constitutive and inducible expression of b7 family of ligands by human airway epithelial cells. Am J Respir Cell Mol Biol 2005;33(3):280–9.
137. Lee SK, Seo SH, Kim BS, Kim CD, Lee JH, Kang JS, et al.. IFN-gamma regulates the expression of B7-H1 in dermal fibroblast cells. J Dermatol Sci 2005;40(2):95–103.
138. Wilke CM, Wei S, Wang L, Kryczek I, Kao J, Zou W. Dual biological effects of the cytokines interleukin-10 and interferon-γ. Cancer Immunol Immunother 2011;60(11):1529–41.
139. Oelke M, Moehrle U, Chen JL, Behringer D, Cerundolo V, Lindemann A, et al.. Generation and purification of CD8+ melan-A-specific cytotoxic T lymphocytes for adoptive transfer in tumor immunotherapy. Clin Cancer Res 2000;6(5):1997–2005.
140. Carreno BM, Collins M. BTLA: a new inhibitory receptor with a B7-like ligand. Trends Immunol 2003;24(10):524–7.
141. Lee SJ, Jang BC, Lee SW, Yang YI, Suh SI, Park YM, et al.. Interferon regulatory factor-1 is prerequisite to the constitutive expression and IFN-gamma-induced upregulation of B7-H1 (CD274). FEBS Lett 2006;580(3):755–62.
142. Saint-Ruf C, Ungewiss K, Groettrup M, Bruno L, Fehling HJ, von Boehmer H. Analysis and expression of a cloned pre-T cell receptor gene. Science. 1994. 266: 1208–1212. J Immunol 2009;182(9):5165–9.
143. Wiendl H, Mitsdoerffer M, Schneider D, Chen L, Lochmüller H, Melms A, et al.. Human muscle cells express a B7-related molecule, B7-H1, with strong negative immune regulatory potential: a novel mechanism of counterbalancing the immune attack in idiopathic inflammatory myopathies. FASEB J 2003;17(13):1892–4.
144. Mellman I, Nelson WJ. Coordinated protein sorting, targeting and distribution in polarized cells. Nat Rev Mol Cell Biol 2008;9(11):833–45.
145. Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy-inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18(24):6580–7.
146. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al.. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366(26):2455–65.
147. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al.. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366(26):2443–54.
148. Akbari O, Stock P, Singh AK, Lombardi V, Lee WL, Freeman GJ, et al.. PD-L1 and PD-L2 modulate airway inflammation and iNKT-cell-dependent airway hyperreactivity in opposing directions. Mucosal Immunol 2010;3(1):81–91.
149. Huber S, Hoffmann R, Muskens F, Voehringer D. Alternatively activated macrophages inhibit T-cell proliferation by Stat6-dependent expression of PD-L2. Blood 2010;116(17):3311–20.
150. Qiu H, Liu S, Xie C, Long J, Feng Z. Regulating immunity and inhibiting tumor growth by the recombinant peptide sPD-1-CH50. Anticancer Res 2009;29(12):5089–94.
151. Martínez-Lacaci I, García Morales P, Soto JL, Saceda M. Tumour cells resistance in cancer therapy. Clin Transl Oncol 2007;9(1):13–20.
152. Apetoh L, Mignot G, Panaretakis T, Kroemer G, Zitvogel L. Immunogenicity of anthracyclines: moving towards more personalized medicine. Trends Mol Med 2008;14(4):141–51.
153. Liang M, Fu J. Triptolide inhibits interferon-gamma-induced programmed death-1-ligand 1 surface expression in breast cancer cells. Cancer Lett 2008;270(2):337–41.
154. Early Breast Cancer Trialist's Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005 May 14–20;365(9472):1687–717.
155. Fermé C, Eghbali H, Meerwaldt JH, Rieux C, Bosq J, Berger F, et al.. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med 2007;357(19):1916–27.
156. Tsukasaki K, Utsunomiya A, Fukuda H, Shibata T, Fukushima T, Takatsuka Y, et al.. VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group Study JCOG9801. J Clin Oncol 2007;25(34):5458–64.
157. Ehrke MJ, Ryoyama K, Cohen SA. Cellular basis for adriamycin-induced augmentation of cell-mediated cytotoxicity in culture. Cancer Res 1984;44(6):2497–504.
158. Maccubbin DL, Wing KR, Mace KF, Ho RL, Ehrke MJ, Mihich E. Adriamycin-induced modulation of host defenses in tumor-bearing mice. Cancer Res 1992;52(13):3572–6.
159. Haskill JS. Adriamycin-activated macrophages as tumor growth inhibitors. Cancer Res 1981;41(10):3852–6.
160. Yamasaki H. Pharmacology of sinomenine, an anti-rheumatic alkaloid from *Sinomenium acutum*. Acta Med Okayama 1976;30(1):1–20.
161. Liu L, Riese J, Resch K, Kaever V. Impairment of macrophage eicosanoid and nitric oxide production by an alkaloid from *Sinomenium acutum*. Arzneimittelforschung 1994;44(11):1223–6.
162. Liu L, Buchner E, Beitze D, Schmidt-Weber CB, Kaever V, Emmrich F, et al.. Amelioration of rat experimental arthritides by treatment with the alkaloid sinomenine. Int J Immunopharmacol 1996;18(10):529–43.
163. Dai YB, Liu HX, Zao LI. Immunosuppressive effect of Sinomenine on ICAM-1 expression in rat renal allograft rejection. Mod J Integr Tradit Chin West Med 2003;12:1358–61.
164. Yang P, Yang L, Luo Z. Effects of Sinomenine on T lymphocyte subsets in rat renal allograft transplantation model. J Clin Urol 2003;10:620–2.
165. Kondo Y, Takano F, Yoshida K, Hojo H. Protection by sinomenine against endotoxin-induced fulminant hepatitis in galactosamine-sensitized mice. Biochem Pharmacol 1994;48(5):1050–2.
166. Peng A, Gu Y, Lin SY. Herbal treatment for renal diseases. Ann Acad Med Singapore 2005;34(1):44–51.
167. Yao H, Zhou J, Li D, Wu N, Bader A, Höxtermann S, et al.. FK506 enhances triptolide-induced down-regulation of cyclooxygenase-2, inducible nitric oxide synthase as well as their products PGE2 and NO in TNF-alpha-stimulated synovial fibroblasts from rheumatoid arthritic patients. Eur J Med Res 2005;10(3):110–6.
168. Chang WT, Kang JJ, Lee KY, Wei K, Anderson E, Gotmare S, et al.. Triptolide and chemotherapy cooperate in tumor cell apoptosis. A role for the p53 pathway. J Biol Chem 2001;276(3):2221–7.
169. Jiang XH, Wong BC, Lin MC, Zhu GH, Kung HF, Jiang SH, et al.. Functional p53 is required for triptolide-induced apoptosis and AP-1 and nuclear factor-kappaB activation in gastric cancer cells. Oncogene 2001;20(55):8009–18.
170. Tengchaisri T, Chawengkirttikul R, Rachaphaew N, Reutrakul V, Sangsuwan R, Sirisinha S. Antitumor activity of triptolide against cholangiocarcinoma growth in vitro and in hamsters. Cancer Lett 1998;133(2):169–75.
171. Lee KY, Chang W, Qiu D, Kao PN, Rosen GD. PG490 (triptolide) cooperates with tumor necrosis factor-alpha to induce apoptosis in tumor cells. J Biol Chem 1999;274(19):13451–5.
172. Frese S, Pirnia F, Miescher D, Krajewski S, Borner MM, Reed JC, et al.. PG490-mediated sensitization of lung cancer cells to Apo2L/TRAIL-induced apoptosis requires activation of ERK2. Oncogene 2003;22(35):5427–35.
173. Fidler JM, Li K, Chung C, Wei K, Ross JA, Gao M, et al.. PG490-88, a derivative of triptolide, causes tumor regression and sensitizes tumors to chemotherapy. Mol Cancer Ther 2003;2(9):855–62.
174. Chen Y, Zhang J, Li J, Zhao T, Zou L, Tang Y, et al.. Triptolide inhibits B7-H1 expression on proinflammatory factor activated renal tubular epithelial cells by decreasing NF-kappaB transcription. Mol Immunol 2006;43(8):1088–98.
175. Singh T, Katiyar SK. Honokiol, a phytochemical from *Magnolia* spp., inhibits breast cancer cell migration by targeting nitric oxide and cyclooxygenase-2. Int J Oncol 2011;38(3):769–76.
176. Liu H, Zang C, Emde A, Planas-Silva MD, Rosche M, Kühnl A, et al.. Anti-tumor effect of honokiol alone and in combination with other anticancer agents in breast cancer. Eur J Pharmacol 2008;591(1–3):43–51.
177. Liu SH, Wang KB, Lan KH, Lee WJ, Pan HC, Wu SM, et al.. Calpain/SHP-1 interaction by honokiol dampening peritoneal dissemination of gastric cancer in nu/nu mice. PLoS ONE 2012;7(8):e43711.
178. Sheu ML, Liu SH, Lan KH. Honokiol induces calpain-mediated glucose-regulated protein-94 cleavage and apoptosis in human gastric cancer cells and reduces tumor growth. PLoS ONE 2007;2(10):e1096.
179. Ponnurangam S, Mammen JM, Ramalingam S, He Z, Zhang Y, Umar S, et al.. Honokiol in combination with radiation targets notch signaling to inhibit colon cancer stem cells. Mol Cancer Ther 2012;11(4):963–72.
180. He Z, Subramaniam D, Ramalingam S, Dhar A, Postier RG, Umar S, et al.. Honokiol radiosensitizes colorectal cancer cells: enhanced activity in cells with mismatch repair defects. Am J Physiol Gastrointest Liver Physiol 2011;301(5):G929–37.
181. Arora S, Bhardwaj A, Srivastava SK, Singh S, McClellan S, Wang B, et al.. Honokiol arrests cell cycle, induces apoptosis, and potentiates the cytotoxic effect of gemcitabine in human pancreatic cancer cells. PLoS ONE 2011;6(6):e21573.
182. Guillermo RF, Chilampalli C, Zhang X, Zeman D, Fahmy H, Dwivedi C. Time and dose–response effects of honokiol on UVB-induced skin cancer development. Drug Discov Ther 2012;6(3):140–6.
183. Subbaramaiah K, Dannenberg AJ. Cyclooxygenase 2: a molecular target for cancer prevention and treatment. Trends Pharmacol Sci 2003;24(2):96–102.
184. Foderà D, D'Alessandro N, Cusimano A, Poma P, Notarbartolo M, Lampiasi N, et al.. Induction of apoptosis and inhibition of cell growth in human hepatocellular carcinoma cells by COX-2 inhibitors. Ann N Y Acad Sci 2004;1028:440–9.

185. Hida T, Kozaki K, Muramatsu H, Masuda A, Shimizu S, Mitsudomi T, et al.. Cyclooxygenase-2 inhibitor induces apoptosis and enhances cytotoxicity of various anticancer agents in non-small cell lung cancer cell lines. Clin Cancer Res 2000;6(5):2006–11.
186. Fukutake M, Nakatsugi S, Isoi T, Takahashi M, Ohta T, Mamiya S, et al.. Suppressive effects of nimesulide, a selective inhibitor of cyclooxygenase-2, on azoxymethane-induced colon carcinogenesis in mice. Carcinogenesis 1998;19(11):1939–42.
187. Nam KT, Hahm KB, Oh SY, Yeo M, Han SU, Ahn B, et al.. The selective cyclooxygenase-2 inhibitor nimesulide prevents Helicobacter pylori-associated gastric cancer development in a mouse model. Clin Cancer Res 2004;10(23):8105–13.
188. Shaik MS, Chatterjee A, Singh M. Effect of a selective cyclooxygenase-2 inhibitor, nimesulide, on the growth of lung tumors and their expression of cyclooxygenase-2 and peroxisome proliferator-activated receptor-gamma. Clin Cancer Res 2004;10(4):1521–9.
189. Deasy BM, O'Sullivan-Coyne G, O'Donovan TR, McKenna SL, O'Sullivan GC. Cyclooxygenase-2 inhibitors demonstrate anti-proliferative effects in oesophageal cancer cells by prostaglandin E(2)-independent mechanisms. Cancer Lett 2007;256(2):246–58.
190. Han S, Roman J. COX-2 inhibitors suppress lung cancer cell growth by inducing p21 via COX-2 independent signals. Lung Cancer 2006;51(3):283–96.
191. Liang M, Yang H, Fu J. Nimesulide inhibits IFN-gamma-induced programmed death-1-ligand 1 surface expression in breast cancer cells by COX-2 and PGE2 independent mechanisms. Cancer Lett 2009;276(1):47–52.
192. Iwamura K, Kato T, Miyahara Y, Naota H, Mineno J, Ikeda H, et al.. SiRNA-mediated silencing of PD-1 ligands enhances tumor-specific human T-cell effector functions. Gene Ther 2012;19(10):959–66.
193. Hobo W, Novobrantseva TI, Fredrix H, Wong J, Milstein S, Epstein-Barash H, et al.. Improving dendritic cell vaccine immunogenicity by silencing PD-1 ligands using siRNA-lipid nanoparticles combined with antigen mRNA electroporation. Cancer Immunol Immunother 2013;62(2):285–97.
194. Hobo W, Maas F, Adisty N, de Witte T, Schaap N, van der Voort R, et al.. SiRNA silencing of PD-L1 and PD-L2 on dendritic cells augments expansion and function of minor histocompatibility antigen-specific CD8+ T cells. Blood 2010;116(22):4501–11.

GLOSSARY

B7-H1: B7 homolog 1
PDL-1: programmed death ligand-1
PD-1: PD -1
TGF-β: transforming growth factor beta
IFN-γ: interferon gamma
NSCLC: non small cell lung carcinomas
TILs: tumor infiltrating lymphocytes
HCC: hepatocellular carcinoma
Foxp3: Forkhead box P3
IL: interleukin
ICC: intrahepatic cholangiocarcinoma
TNM: tumor-nodal-metastatic stage
Tregs: regulatory T cells
Her2/neu: human epidermal growth factor receptor 2
siRNA: small interfering RNA
HPV: human papilloma virus
CTLs: cytotoxic T lymphocytes
SCCHN: squamous cell carcinomas of the head and neck
OSCC: oral squamous cell carcinomas
NPC: nasopharyngeal carcinoma
RCC: renal cell carcinoma
PTCL: peripheral T cell lymphoma
NHL: non-Hodgkin's lymphoma
CTCL: cutaneous T cell lymphoma
ATL: adult T-cell lymphoma
DLBLC: diffuse large B cell lymphomas
AML: acute myeloid leukemia
CML: chronic myeloid leukemia
ALL: acute lymphatic leukemia
CLL: chronic lymphatic leukemia
ZAP-70: tyrosine kinase zeta-associated protein
MM: multiple myeloma
DCs: dendritic cells
APCs: antigen presenting cells
MHC-II: major histocompatibility complex class II
TCR: T cell receptor
MHC-class I: major histocompatibility complex class I
SHP-1/ SHP-2: Src homology region 2 domain containing phosphatase 1/2
Th 1: T helper 1 cells
xGVHD: xenogeneic graft versus host disease
NKs: natural killer cells
PTEN: phosphatase and tensin homolog
PI3K: phosphatidylinositide 3-kinase
mTOR: mammalian target of rapamycin
STAT: signal transducer and activator of transcription
anti-B7-H1 mAb: anti-B7-H1 monoclonal antibody
ADCC: antibody dependent cell cytotoxicity
Th 2: T helper 2 cells
sPD-1-CH50: soluble programmed death 1 recombinant peptide in conjunction with CH50 fibronectin domain
TNF-α: tumor necrosis factor alpha
TECs: renal tubular epithelial cells
NF-κB: nuclear factor-kappa light chain enhancer of activated B cells
COX-2: cyclooxygenase 2
PG-E2: prostaglandin E2
MiHA: minor histocompatibility antigen