Immunogenetics
DOI 10.1007/s00251-017-1015-5

REVIEW

PD-1 and cancer: molecular mechanisms and polymorphisms

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Received: 20 April 2017 / Accepted: 13 June 2017

Abstract The programmed cell death protein 1 (PD-1) is expressed by activated T cells that act as an immunoregulatory molecule, and are responsible for the negative regulation of T cell activation and peripheral tolerance. The *PD-1* gene also encodes an inhibitory cell surface receptor involved in the regulation of T cell functions during immune responses/tolerance. Beyond potent inhibitory effects on T cells, PD-1 also has a role in regulating B cell and monocyte responses. An overexpression of PD-1 has been reported to contribute to immune system avoidance in different cancers. In particular, PD-1 over-expression influences tumor-specific T cell immunity in a cancer microenvironment. Blocking the PD-1/PD-1 ligand (PD-L1) pathway could potentially augment endogenous antitumor responses. Along these lines, the use of PD-1/PD-L1 inhibitors has been applied in clinical trials against diverse forms of cancer. It was believed that antibodies targeting PD-1/PD-L1 might synergize with other treatments that enhance endogenous antitumor immunity by blocking inhibitory receptor-ligand interactions. However, in all cases, the host genetic status (as well as that of the tumor) is likely to have an impact on the expected outcomes. Various investigations have evaluated the association between PD-1 polymorphisms and the risk of various types of cancer. Frequently studied PD-1 polymorphisms, PD-1.1 (rs36084323), PD-1.3 (rs11568821), PD-1.5 (rs2227981), PD-1.9 (rs2227982), and PD-1 rs7421861, and their associations in the risk of susceptibility to different types of cancer are mentioned in this review, as are studies highlighting the significance of conducting genetic association studies in different ethnic populations.

Keywords PD-1 · Cancer · Polymorphisms · Molecular mechanisms

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Introduction

The programmed death-1 or PD-1 (CD279) protein was first isolated by the group of Ishida from a murine T cell hybridoma undergoing programmed cell death in 1992 (Ishida et al. 1992). PD-1 is a transmembrane glycoprotein type I with 50~55 kDa molecular weight and composed of 288 amino acids (Vibhakar et al. 1997). Human PD-1 proteins have 60% homology with murine PD-1 (mPD-1) (Vibhakar et al. 1997; Zhang et al. 2004). This cell surface monomer protein is an inhibitory receptor (Sharpe et al. 2007; Zhang et al. 2004) and belongs to the Ig superfamily (Francisco et al. 2010; Ishida et al. 1992; Vibhakar et al. 1997), specifically the CD28 cytotoxic T lymphocyte antigen-4 (CTLA-4) family (Jin et al. 2011). Unlike

Published online: 22 June 2017

CTLA-4, PD-1 exists as a monomer on the cell surface. Two tyrosine residues have been identified in the PD-1 cytoplasmic domain, which are supposed to play an essential role in the inhibitory function of PD-1 (Dougall et al. 2017). Moreover, inhibitory effects of PD-1 on T cells can induce cell cycle arrest. Previous studies in murine T cell hybridomas determined that there was a correlation between activation-induced apoptosis and expression of mPD-1 mRNA (Brown et al. 2003).

Human PD-L1 belongs to the B7 family (Dong et al. 1999). The PD-L1 has an important role in immune evasion by tumor cells and can enhance tumor cell growth by promoting apoptosis among antigen-specific and tumor-reactive T cells (Kashani-Sabet 2010). PD-L1 also is necessary in maintaining immune homeostasis in normal physiological condition. This ligand downregulates cytotoxic T cell activity when it binds to specific receptors on T cells and protects normal cells from collateral damage (Park et al. 2010). Thus, tumor cells expressing PD-L1 can hinder activation of new T cells (Chen et al. 2012).

This review summarizes updated concepts about the role of PD-1 pathways in adaptive immunity and discusses whether blockade of PD-1 pathways can improve immune responses, thereby develop potential utility with regard to prophylaxis and therapeutics. Moreover, by evaluating the genome-wide association studies (GWAS) and single nucleotide polymorphisms (SNPs) in human PD-1 gene, a higher risk association was demonstrated with different cancers in certain ethnic groups.

PD-1 signaling pathway

PD-1 binds to two ligands, PD-L1 (*aka* B7-H1 or CD274) and PD-L2 (*aka* B7-DC or CD273) (Duraiswamy et al. 2013; Francisco et al. 2010; McDermott and Atkins 2013; Pedoeem et al. 2014; Porichis and Kaufmann 2012; Sznol and Chen 2013). PD-L2 affinity for PD-1 is threefold higher than PD-L1; however, PD-L1 is expressed significantly on more cell types than PD-L2. Furthermore, while PD-L2 is expressed on macrophages, cultured bone marrow-derived mast cells, and dendritic cells and some subsets of B-lineage cells, PD-L1 can be expressed on both hematopoietic and non-hematopoietic cells (Ceeraz et al. 2013). Early studies showed that increasing risk of mortality due to tumor aggressiveness was associated with high tumor cell expression of PD-L1 (Ceeraz et al. 2013; Francisco et al. 2010). The role of PD-1 in downregulation of ineffective or detrimental immune responses and maintaining tolerance is critical. (Riley 2009). In fact, pathways involving PD-1 and its ligands assist successful protective immune responses, maintenance of T cell homeostasis, and self-tolerance through regulating the balance between stimulatory and inhibitory signals (Patsoukis et al. 2012b; Zamani et al. 2016).

PD-1 functions

At least two opposite roles are attributed to PD-1, beneficial and harmful. From the beneficial standpoint, this molecule has a critical role in downregulation of ineffective or detrimental immune responses and in maintaining the immunological tolerance. On the other hand, from the harmful perspective, PD-1 contributes to expansion of malignant cells by interfering with protective immune responses. Additionally, PD-L1 is commonly expressed on malignant tumor cells which can prevent proliferation of tumor-specific T cells by inducing inhibitory signals, resulting in impaired antitumor immunity (Figs. 1 and 2) (Gianchecchi et al. 2013).

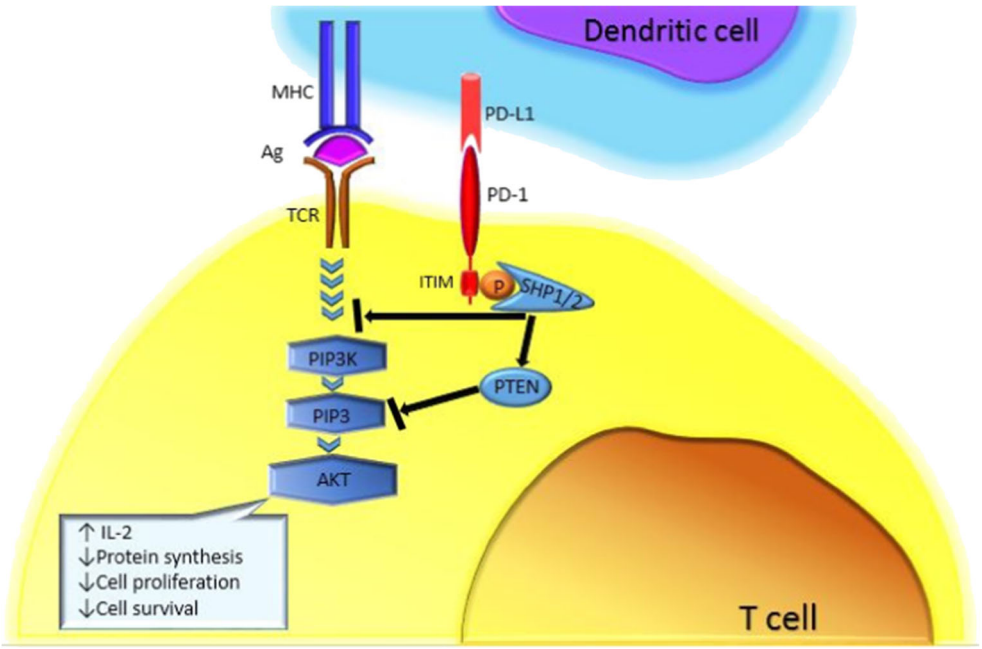

Fig. 1 PD-1 signaling pathway. Activation of the PD-1 pathway results from binding of SHP-1 and SHP-2 to immunoreceptor tyrosine-based inhibitory motif (ITIM) which can increase PTEN activity and repress T cell proliferation. Activation of PD-1 signaling can affect IL-2 release and decrease of protein synthesis. This pathway provides inhibitory signals against T cell activation

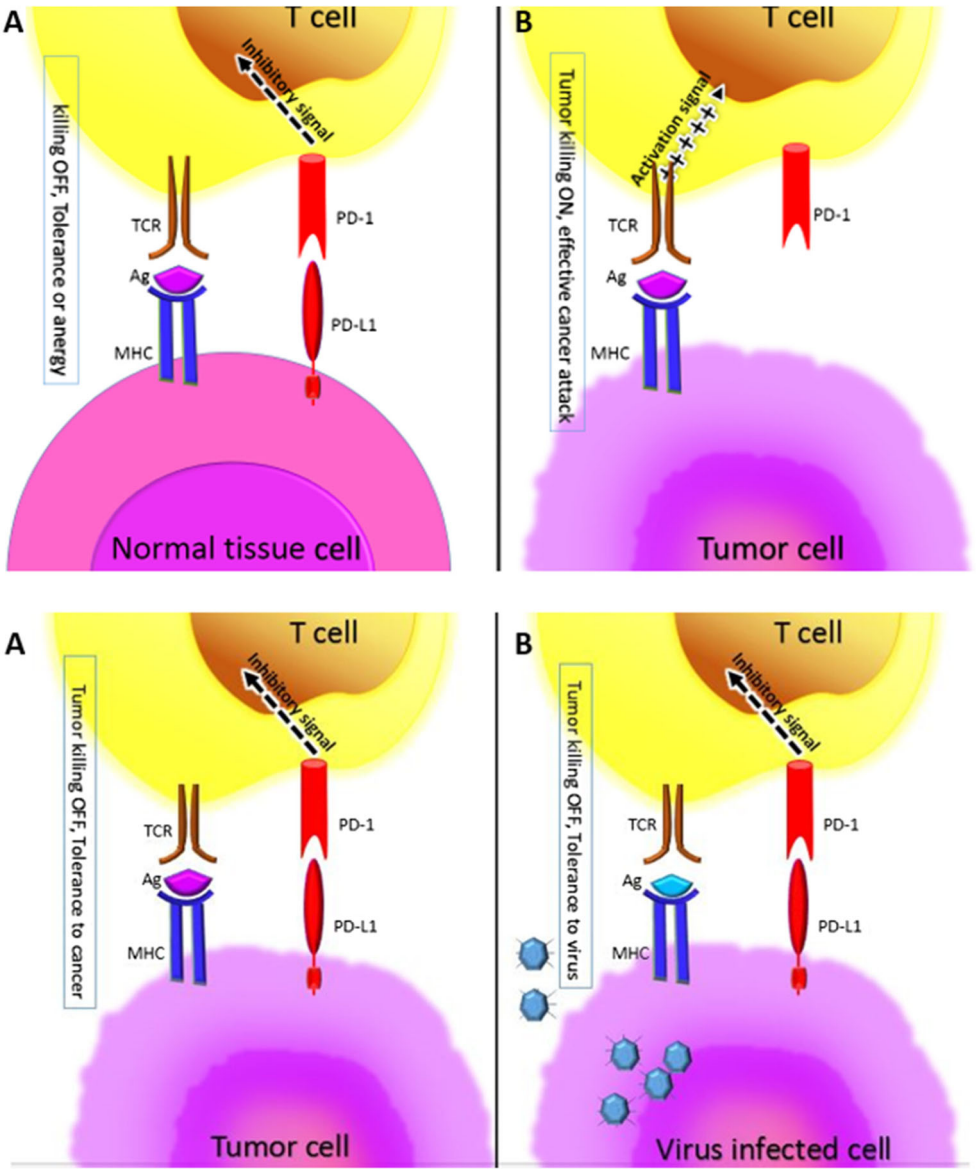

Fig. 2 *Upper panel*: PD-1 and PD-l ligation between normal tissue cells and activated T cells provides tolerance through preventing the killing activity of T cells by inducing an inhibitory signal through PD-1 (**a**). Tumor cells that lack PD-1 cannot prevent T cells from responding and therefore are subjected to death (**b**). *Lower panel*: expression of PD-L1 on the tumor (**a**) or virus-infected cells (**b**) can turn off the T cell killing activity by inducing an inhibitory signal through PD-1

PD-1 expression on immune cells

PD-1 is expressed on some immune cells, including T cells during thymic development (during T cell receptor (TCR) β rearrangement), but is also detectable on natural killer T (NKT) cells, mature $CD4^+$ and $CD8^+$ T cells, some subsets of dendritic cells, B cells, monocytes, murine thymocytes, spleen, lymph node, and bone marrow cells (Agata et al. 1996; Kobayashi et al. 2005).

PD-1 expression could be affected by some factors such as estrogen (Francisco et al. 2010), cytokines, also the tumor suppressor genes like PTEN and Lkb1, and epithelial–mesenchymal transition-related molecules (Ritprajak and Azuma 2015). The level of PD-1 mRNA in primary naive human T cells is very low within 24 h after stimulation. However, an mRNA expression peak is observed only after 48 h from stimulation with CD3/CD28-coated beads (Chemnitz et al. 2004).

The role of PD-1 in T cell adhesion

Cell recognition events occur between T cells and antigen-presenting cells (APCs), leading to T cell activation. The "stop signals" necessary for interactions between PD-1 and PD-L1 suggests that cell-cell interaction might be affected by PD-1 downstream signals (Fife et al. 2009). This hypothesis is supported by in vitro experimental works demonstrating lower T cell motility and enhanced T cell-APC contacts after antibody blockage of PD-1 or PD-L1 (Fife et al. 2009). It was also shown that PD-1 could inhibit T cell adhesion and immune synapse formation via its mediating signals (Patsoukis et al. 2012b; Zinselmeyer et al. 2013).

Based on previous researches, it seems that PD-1 plays an important role in regulating various aspects of cell adhesion, which is part of its function in the immune system. As mentioned earlier, cancer cells can evade immune responses

through expression of this membrane molecule (Pedoeem et al. 2014).

PD-1 role in regulation of T cell responses

Antigen receptor ligation can induce PD-1 expression (Agata et al. 1996; Chemnitz et al. 2004). Nuclear factor of activated T cells (NFAT) 2 binds to the promoter region of the *PDCD1* gene (coding PD-1 protein) following the T cell receptor (TCR) stimulation (Oestreich et al. 2008). Viral-specific $CD8^+$ T cells express the PD-1 transiently during infection. There are some differences in the expression pattern of this molecule between acute and chronic diseases. After elimination of acute infection, PD-1 expression decreases due to the lack of specific TCR stimulation (Barber et al. 2006; Youngblood et al. 2011). However, in chronic infections, PD-1 expression is maintained as a result of continuous TCR ligation (Blattman et al. 2009; Petrovas et al. 2007). Regulatory regions of the *PDCD1* locus are demethylated during TCR signaling, leading to active transcription. The ability of *PDCD1* locus in re-methylation will be decreased if antigen stimulation becomes continues. This phenomenon leads to an open chromatin state poised for gene expression (Youngblood et al. 2011). One of the hallmarks of T cells dysfunction is attributed to the high expression of PD-1 seen in cancer and chronic infections (Keir et al. 2008; Kim and Ahmed 2010).

The physiological role of PD-1 in lymphocyte activation

Activation of T cell requires at least two signals: the first happens when TCR recognizes specific peptide presented by major histocompatibility complex (MHC) molecule on APCs. The second signal occurs when co-stimulatory molecules ligate with their selective ligands on the APCs. Lack of any of these signals results in anergy or apoptosis, which is one of the mechanisms of immune tolerance (Mueller et al. 1989).

Besides these activating signals, some inhibitory co-stimulatory receptors also exist. CTLA-4 and the PD-1 receptors are negative co-stimulatory receptors that inhibit T cell activation by distinct mechanisms (Kornete and Piccirillo 2011; Parry et al. 2005). The balance between these positive and negative signals determines the final fate of T cell activation or peripheral tolerance (Chen 2004; Khoury and Sayegh 2004; Sharpe et al. 2007). Expression of PD-L1 has been observed on many tumor cell lines and the surface of tumor cells in patients with liver, bladder, colon, cervix, ovarian, and breast cancers (Blank et al. 2004; Brown et al. 2003; Dong et al. 2002; Wintterle et al. 2003). Expression of this molecule can be a reliable predictor of gastric carcinomas, esophageal cancers, and breast cancer (Ghebeh et al. 2006; Ohigashi et al. 2005; Wu et al. 2006). Emerging data have documented that cancer cells have been able to express ligands of negative co-stimulatory receptors to protect themselves against strong immune responses, and therefore continue to tumor growth.

PD-L1 expression on cancer cells

Studies show that PD-L1 is prevalently expressed on the APCs as well as tumor cells in numerous solid malignancies, including melanoma, squamous cell carcinoma, and carcinomas of the thyroid, brain, thymus, lung, breast, esophagus, gastrointestinal tract, colorectum, liver, pancreas, kidney, bladder, urothelium, adrenal cortex, skin, and ovary (Fay et al. 2015; Jacobs et al. 2009; Katsuya et al. 2015; Nakanishi et al. 2007; Nomi et al. 2007; Strome et al. 2003; Wilmotte et al. 2005). The role of PD-1 and PD-L1 ligation in normal physiologic conditions was discussed previously in this review. PD-L1 expression on tumor cells in the tumor microenvironment results from two mechanisms: the constitutive mechanism and induced mechanism. Both of these mechanisms are mediated by two binding sites of interferon regulatory factor 1 (IRF-1) (Lee et al. 2006). It has been shown that in BRAFV600-mutated melanoma, adaptive response of cancer cells toward immune attack culminates in PD-L1 expression. However, there is a constitutive expression of PD-L1 on tumor cells which is occurred during oncogenic processes (Khalili et al. 2012). Expression of PD-L1 rarely happens on normal tissues, but inducible expression occurs on tumor site. This issue underlies the PD-L1 pathway as a unique and different from other inhibitory pathways in immune response (Dong et al. 2002). This difference suggests that the selective expression of PD-L1 may be related to clinical outcomes in cancer patients, which provides a potential selective molecule with regard to antitumor therapy. Recent studies showed that the rate of PD-L1 expression and its correlation with tumor survival varied between tumor types; the highest and lowest PD-L1 expression levels were found in thyroid cancer and small cell neuroendocrine carcinoma, respectively (Pyo et al. 2017). Table 1 summarizes expression of PD-L1 in some of the important studies with the highest case number.

PD-1/PD-L1 blockade: pros and cons

Current clinical use of PD1/PD-L1 blockade has been supported by identification of PD-L1 (Dong et al. 1999, 2002), recognition of PD-1 as a receptor for PD-L1 (Freeman et al. 2000), and clarification of the expression, regulation, and function of the PD1/PD-L1 pathway in the human cancer microenvironment (Ahmadzadeh et al. 2009; Dong et al. 1999, 2002; Fourcade et al. 2010; Wong et al. 2007; Wu et al. 2009). Considering the clinical viewpoint, PD1/PD-L1 pathway blockade has been tested for its efficacy in a wide range of tumor types including ovarian cancer (Brahmer et al. 2012; Herbst et al. 2014), breast cancer (Brahmer et al. 2012;

Table 1 PD-L1 expression in malignancies

Cancer	Number of cases	Detection method	PD-L1 expression site	Ref
Colorectal cancer	1491	Paraffin IHC; anti-PD-L1 mAb	Significant PD-L1 expression in 37% of MMR-proficient and in 29% of MMR-deficient CRCs	(Droeser et al. 2013)
Esophageal cancer	99	Paraffin IHC, FACS; anti-PD-L1	82 patients showed positive membranous/ cytoplasmic, and 79 of them showed positive nuclear PD-L1 staining	(Konishi et al. 2004)
Gastric cancer	205	Paraffin IHC, FACS; anti-PD-L1	88 tissues were PD-L1 positive mainly in the cytoplasm and on the membrane of the tumor cells	(Jiang et al. 2014)
Pancreatic cancer	81	Paraffin IHC; anti-PD-L1	PD-L1 was shown mainly in the cytoplasm	(Wang et al. 2010)
Cervical cancer	115	Paraffin IHC; anti-B7-H1 (5H1)	PD-L1 expressed on the tumor cell membrane and throughout the tumor bed	(Karim et al. 2009)
Differentiated thyroid carcinoma	407	Paraffin IHC; anti-PD-L1 polyclonal antibody	PD-L1 expression was detected in the cytoplasm of tumor cells	(Cunha et al. 2013)
Breast cancer	636	RNAscope assay	PD-L1 mRNA expressed in 60% of breast tumor	(Schalper et al. 2014)
Ovarian cancer	70	Paraffin IHC; anti-PD-L1	NA	(Hamanishi et al. 2007)
Kidney cancer	429	Paraffin IHC; anti-PD-L1 (5H1)	PD-L1 expression was shown on both tumor cells and lymphocytes	(Thompson et al. 2007)
Liver cancer	240	Paraffin IHC; anti-PD-L1 Western blot analysis	PD-L1 was shown on the cell membrane, in the cytoplasm, or both	(Gao et al. 2009)
Oral carcinoma	45	Paraffin IHC; anti-PD-L1	NA	(Cho et al. 2011)
Nasopharyngeal carcinoma		Paraffin IHC; anti-PD-L1	PD-L1 was observed on the cell surface membrane and/or cytoplasm	(Hsu et al. 2010)
Urothelial cancer	65	Paraffin IHC; anti-PD-L1	PD-L1 was observed on the cell surface membrane and/or cytoplasm	(Nakanishi et al. 2007)
Lung cancer	109	Paraffin IHC; anti-PD-L1	PD-L1 was observed on the cell surface membrane and/or cytoplasm	(Mu et al. 2011)
Melanoma	59	Paraffin IHC; anti-PD-L1	PD-L1 was shown in the cytoplasm	(Hino et al. 2010)

Herbst et al. 2014), bladder cancer (Powles et al. 2014), colorectal cancer (Brahmer et al. 2010, 2012; Lipson et al. 2013; Topalian et al. 2012b), follicular lymphoma (Westin et al. 2014), diffuse large B cell lymphoma (Armand et al. 2013), gastric cancer (Brahmer et al. 2012), squamous cell carcinoma of the head and neck (Herbst et al. 2014), Hodgkin's lymphoma (Ansell et al. 2015), melanoma (Brahmer et al. 2010, 2012; Herbst et al. 2014; Lipson et al. 2013; Topalian et al. 2012b), non-small cell lung cancer (NSCLC) (Brahmer et al. 2010, 2012; Herbst et al. 2014; Topalian et al. 2012b), pancreatic cancer (Brahmer et al. 2012; Herbst et al. 2014), renal cell carcinoma (Brahmer et al. 2010, 2012; Herbst et al. 2014; Topalian et al. 2012b), prostate cancer (Brahmer et al. 2010; Topalian et al. 2012b), sarcoma (Herbst et al. 2014), small-cell lung cancer (Herbst et al. 2014), and uterine cancer (Herbst et al. 2014). The quality and quantity of response toward this treatment vary in different cancer types as observed in different clinical trials. Clinical trials have indicated that cancers which are favorably responsive to PD-1/PD-L1 blockade are bladder cancer (Powles et al. 2014), melanoma (Brahmer et al. 2010, 2012; Herbst et al. 2014; Lipson et al. 2013; Topalian et al. 2012b), colorectal cancer (Le et al. 2015), and hematopoietic malignancies (Ansell et al. 2015; Armand et al. 2013). Even though the circumstance of responses in antibodies to PD-1 and PD-L1 has not been carried out, levels of advantages and disadvantages in clinical trials seem to be overall consistent with each other. There is an immune-related toxicity in PD1/PD-L1 blockade but is less severe than those seen in the CTLA-4 pathway blockade (Larkin et al. 2015; Robert et al. 2015). Fatigue is the most prevalently observed side effect in PD-1/PD-L1 blockade. However, it is not usually necessary to be treated and does not limit the therapy. On the other hand, inflammatory pneumonitis has rarely been seen, which may be lethal if medical interventions are ignored immediately with immunosuppressive agents such as corticosteroids. The termination of the therapy may be mandatory in case intense exacerbations like pneumonitis or interstitial nephritis occur. Interestingly, clinical responses remain, in spite of stopping the therapy and even after application of immunosuppressive medications (Zou et al. 2016).

PD-1 polymorphism in cancer

Gene polymorphisms are natural variations in DNA sequence, gene, or chromosome that have no adverse effect for the individual and occur with fairly high frequency in the general population. Polymorphism involves one of two or more variants of a specific DNA sequence. The most ordinary type of polymorphism involves variation at a single base pair called "single nucleotide polymorphism" or SNP. Scientists are studying how SNPs in the human genome correlate with disease, drug response, and other phenotypes. Polymorphisms can also be much larger in size and involve long stretches of DNA (Snyder et al. 2015). They occur once in every 300 nucleotides on average, which means there are approximately 10 million SNPs in the human genome. SNPs can be also considered as biological markers, helping scientists to identify genes that are associated with diseases. When SNPs occur within a gene or in a regulatory region near a gene, they may play a more direct role in disease by modifying the gene function. Most SNPs are innocuous and do not have any effect on health or development. However, some variations have been established to be very essential in the study of human health. It has been reported that some SNPs have a role in individual's response to some drugs, vulnerability to environmental factors such as toxins, increased risk of developing particular diseases, and association with complex diseases such as cancer. Recent studies showed that SNPs may also have functional association with the individual's susceptibility to cancer (Ling et al. 2015).

Immunosuppressive and antitumor functions of PD-1 are thought to make it as a convincing genetic risk candidate in some of the malignancies. Investigations confirmed that PD-1 polymorphisms were associated with numerous types of cancers, including those of the colon, gastric, esophagus, breast, and liver (Haghshenas et al. 2011; Hua et al. 2011; Mojtahedi et al. 2012; Qiu et al. 2014; Savabkar et al. 2013).

This section includes the most updated and frequent PD-1 polymorphisms and their main results in cancers. It was worth considering the PD-1 functional SNPs including PD-1.1 (rs36084323), PD-1.3 (rs11568821), PD-1.5 (rs2227981), PD-1.9 (rs2227982), and PD-1 rs7421861 in different cancers. Significant relations between SNPs and cancer susceptibility in different populations examined in all genetic models are presented in Table 2.

The PD-1.1 polymorphism is located in the promoter region (−606A/G, position −538 from transcription start site). It is known that mutations in the promoter region (5′-flank) might be concerned with the transcription factor binding sites (TFBS) and motifs, as well as interrupting the activation of gene and the start of transcription (Liu et al. 2014; Zamani et al. 2015). Hence, when a polymorphism is located in the promoter region of the *PDCD-1* gene, it can likewise influence the transcription and activation of the *PD-1* gene, affecting the development of cancer and progression of human diseases. Surprisingly, the frequency of the A allele in PD-1 was higher in cases with p53 mutation, suggesting that p53 mutation is a valuable marker of aggressive disease and the mutation consequences in unresponsiveness to therapy and poor prognosis (Hua et al. 2011; Jiao et al. 2014). The PD-1.1 (G/A) polymorphisms have been assumed a risk factor for NSCLC in a Japanese population (Sasaki et al. 2014), and associated with breast cancer in a Chinese group (Hua et al. 2011).

The PD-1.3 polymorphism is located in intron 4 (+7146A/G). This SNP is a guanine (G) to adenine (A) polymorphism in the PD-1 intron was described as an enhancer-like due to the existence of four tandem repeats that contain multiple putative binding sequences of transcription factors (Mahmoudi et al. 2015; Prokunina et al. 2002). Recent studies have shown that the PD-1.3 polymorphism in this area is a regulatory SNP and indicated to be associated in vulnerability to cancers, likewise can alter the binding of the runt-related transcription factor 1 (RUNX1) and modify the transcriptional regulation and the proficiency of the PD-1 gene (Suarez-Gestal et al. 2008). Moreover, investigations show that the presence of the A allele of the PD-1.3 polymorphism disturbed the binding site for RUNX1 transcription factors and cause ruined impairing PD-1 inhibitory influence, which leads to greater lymphocyte activity. Hence, the A allele of the PD-1.3 SNP can augment the antitumor capability of immune responses and diminish the liability of cancers (Dong et al. 2016). Particularly, it has been shown that the PD-1.3 (A/G) polymorphism is associated with colon cancer in an Iranian population (Yousefi et al. 2013). However, no significant association has been achieved for breast cancer in an Iranian population (Haghshenas et al. 2011) and for hepatocellular carcinoma (HCC) in a Turkish population (Bayram et al. 2012).

The PD-1.5 polymorphism is located in exon 5 (+7785 C/T) and is a synonymous polymorphism that does not modify the final amino acid structure of the protein. Significant associations between PD-1.5 and cancers probably roots in the PD-1.5 variation linkage disequilibrium with other PD-1 gene polymorphisms that may lead to alter the PD-1 expression level. Polymorphism studies indicate that this locus is statistically associated with several cancer types such as NSCLC in Chinese (Yin et al. 2013), cervical cancer in Chinese and Swedish (Yin et al. 2013), breast cancer in Chinese, colon cancer in Iranian, gastric and digestive system cancer in Chinese and Iranian (Dong et al. 2016; Savabkar et al. 2013), and gestational trophoblastic diseases in Iranian groups (Dehaghani et al. 2009). A recent meta-analysis recommended that the PD-1.5 (rs2227981) polymorphism is associated with meaningfully decreased cancer risks; likewise, the decreased cancer risk was established in T vs. C allele for the overall population (Dong et al. 2016). The PD-1.9 polymorphism is

Table 2 PD-1 SNPs and susceptible cancers

Cancer	SNP	Effect/association	Location	Probable function	Population	Ref.
Non-small cell lung cancer	PD-L1 (A/C)	Significant	Intron 4	Unknown	Chinese	(Chen et al. 2014)
	PD-1.1 (G/A)	Significant	Promoter	Higher expression	Japan	(Sasaki et al. 2014)
	PD-1.5 (C/T)	Significant	Exon 5	Altered expression	Chinese	(Yin et al. 2014)
	PD-L1 (A/C)	Significant	Intron	Unknown	Chinese	(Ma et al. 2015)
Cervical cancer	PD-1.5 (C/T)	Significant	Exon 5	Altered expression	Chinese	(Li et al. 2016)
	PD-1.5 (C/T)	Significant	Exon 5	Altered expression	Swedish	(Ivansson et al. 2010)
Breast cancer	PD-1.3 (G/A), PD-1.5 (C/T)	Not significant	–	–	Iranian	(Haghshenas et al. 2011)
	PD-1.1 (G/A), PD-1.5 (C/T)	Not significant, significant	– –	– –	Chinese	(Hua et al. 2011)
Colon cancer	PD-1.5 (C/T)	Significant	Exon 5	Altered expression	Iranian	(Mojtahedi et al. 2012)
	PD-1 (C/T)	Not significant	–	–	Chinese	(Ge et al. 2015)
	PD-1.3 (A/G)	Significant	Intron 4	Altered expression	Iranian	(Yousefi et al. 2013)
Gastric and digestive system cancer	PD-1.5 (C/T)	Significant	Exon 5	Altered expression	Chinese	(Mamat and Arkinjan 2015)
	PD-1.5 (C/T)	Significant	Exon 5	Altered expression	Iranian	(Savabkar et al. 2013)
	PD-1.9 (C/T)	Significant	Exon 5	Altered activity	Chinese	(Tang et al. 2015)
	PD-1 rs10204525 (A/G)	No correlation	3′-UTR	–		
	PD-1 rs7421861 (T/C)	No correlation	Intron 1	–		
Hepatocellular carcinoma (HCC)	PD-1.3 (A/G)	Not significant	Intron 4	–	Turkish	(Bayram et al. 2012)
Esophageal cancer	PD-1 rs10204525 (A/G)	Significantly decreased	3′-UTR	Unknown	Chinese	(Qiu et al. 2014)
Gestational trophoblastic diseases	PD-1.5 (C/T)	Significant	Exon 5	Altered expression	Iranian	(Dehaghani et al. 2009)
Gastric cardia adenocarcinoma	rs2227982	Significant	Exon 5	Altered activity	Chinese	(Tang et al. 2015)

located in exon 5 (+7625 G/A) and therefore supposed to have a role in the splicing of the gene transcript. This is a non-synonymous SNP of PD-1, causing the amino acid substitution from valine (V) to alanine (A) during protein synthesis, which probably leads to structural and practical variations of PD-1 (Dong et al. 2016; Mamat and Arkinjan 2015). A recent study indicated a significant association between PD-1.9 (C/T) and gastric and digestive system cancers in a Chinese population (Zhou et al. 2016).

The PD-1 rs7421861 SNP is located in intron 1, where numerous regulatory elements and splicing control elements exist. A mutation in these sequences can cause interruption in the splice site, translational suppression, and even modification of the secondary structure of mRNA. Hence, the PD-1 rs7421861 SNP may induce aberrant splicing and further consequence to translational prevention (Tang et al. 2015). Recent reports revealed that PD-1 7421861 T > C was not involved in altering the risk of breast cancer and esophageal carcinoma (Tang et al. 2015). No associations have been found between cancer risks and the PD-1.9 (rs2227982) or PD-1 rs7421861 SNP in all genetic models and alleles (Dong et al. 2016). Complementary investigations revealed an association between a PD-1 rs2227982 polymorphism and reduced breast cancer risk, particularly in HER-2-positive breast cancer patients (Dong et al. 2016; Ren et al. 2016). The rs2227982 polymorphism has also been reported to increase susceptibility to gastric cardia adenocarcinoma in a Chinese population (Tang et al. 2015).

Therapeutic potentials of blocking PD-1 and its ligands in cancers

Growing evidence suggests that tumor cells can silence the immune system by expressing PD-L1 (Yang et al. 2008b). Accordingly, interactions in this way could improve the effectiveness of T cells in helping to eliminate tumors (Blank et al.

2004). On the other hand, tumor cells can suppress interleukin (IL)-2 production in T cells by expressing PD-L1 (Yang et al. 2008b). Several studies showed that targeting PD-L1 with a specific antibody could be a practical tool to interfere with tumor growth (Brahmer et al. 2012; Hamid et al. 2013b; Herbst et al. 2014; Lipson et al. 2013). Promising early clinical results demonstrated efficacy in targeting the PD-1/PD-L1 pathway in cancer immunotherapy (Topalian et al. 2012a).

One pre-clinical study showed that a blockade of PD-L1 using monoclonal antibodies led to infiltration of $CD8^+$ T cells into the tumor microenvironment and increased antitumor effects in a murine model of pancreatic cancer (Nomi et al. 2007). Antibody blocking of PD-L1 also seemed to help the tumor regression (an objective response rate of 6–17% was observed) and prolonged disease stabilization (rates of 12–41% at 24 weeks was observed) in patients with melanoma, NSCLC, and renal cell cancer (Brahmer et al. 2012). Although interfering in one specific pathway may not be the efficient and sufficient way to control tumor progression, studies in the combination therapy field have shown that simultaneously blocking of PD-1 and other inhibitory receptors achieved better effects during treatment of cancers (Pardoll 2012).

Combination of PD-L1 monoclonal antibody with gemcitabine (currently the standard chemotherapeutic agent for pancreatic cancer) shows promising synergistic antitumor effects in pancreatic cancer treatment (Nomi et al. 2007). Pharmaceutical companies are taking the advantage of PD-1 pathway capabilities for producing monoclonal PD-1 receptor or its specific ligands antibody that block the PD-1 system and prevent the immune system escaping by tumor cells (Fig. 3) (Dolan and Gupta 2014; Hamid et al. 2013a; Taube et al. 2014; Topalian et al. 2014). Pidilizumab, nivolumab, AMP-24, and lambrolizumab as PD-1 receptor antibodies, and also BMS-936559 and MPDL3280A as specific ligand antibodies (Pedoeem et al. 2014) are among these drugs. All in all, the promising results have been observed for these drugs and increased hopes for future effective treatments (Table 3).

Therapeutic prospects through PD-1 and inhibition of cell cycle

Progression of cell cycle is a narrowly and rigidly controlled procedure that relies on the expression and activation of both positive and negative regulators of the cell cycle equipment. PD-1 can block the cell cycle in the G_1 phase through interfering with these regulators (Patsoukis et al. 2012b). Cyclin-dependent kinases (CDKs) are a protein kinases family involved in regulating the cell cycle, mRNA processing, and transcription (Morgan 2007). Inhibition of CDKs (by CDK inhibitors such as p27, p21, and p15) regulates cell cycle progression (Sherr and Roberts 1999). Recent researches suggest that selective interruption in cell cycle regulation could be one of the potential targets for anti-cancer medication (Rossi et al. 2006; Williams and Stoeber 2012).

Investigations showed that PD-1 is able to inhibit proliferation of T cells by suppressing the expression of the Cdc25A-encoding gene (CDK-activating phosphatase) and upregulating that of p27 and p15 (CDK inhibitors) (Patsoukis et al. 2012b). In another study, highly purified human $CD4^+$ T cells were used to determine PD-1 signaling effects on cell cycle progression. Results showed that PD-1 signaling suppressed transcription of SKP2 and, therefore, inhibited cell cycle progression at the G_1 phase (Patsoukis et al. 2012a). SKP2 encodes a component of ubiquitin ligase SCFSkp2 which degrades p27kip1 (an inhibitor of CDK) (Carrano et al. 1999). Thus, when T cell stimulation occurs through PD-1 signaling, phosphorylation of two critical substrates of CDK is inhibited; hence, activation of CDKs is not occurred (Patsoukis et al.

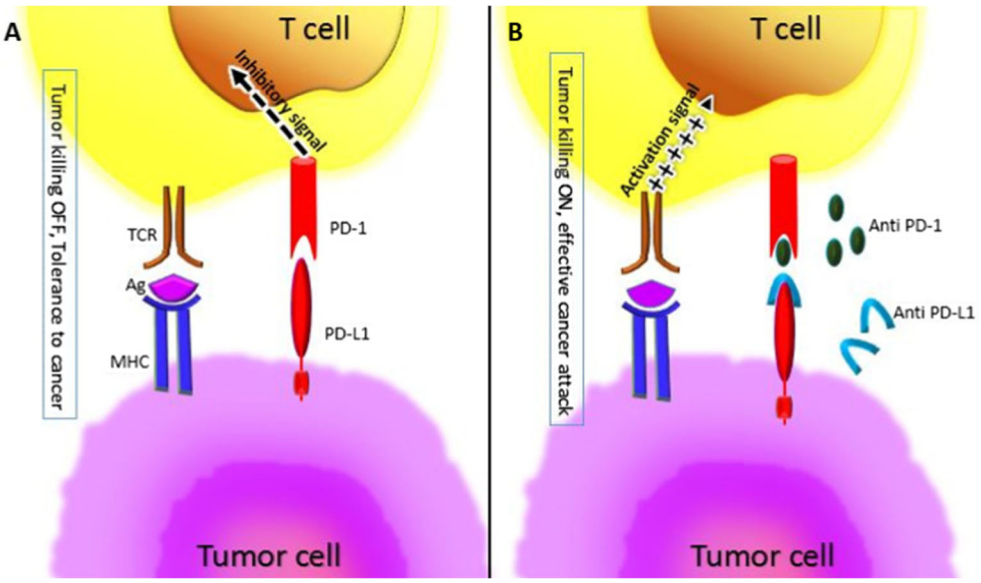

Fig. 3 Tumor cells can express PD-L1 and, therefore, silence the immune system (**a**) but, blockade of the PD-L1 pathway by monoclonal antibodies (monoclonal PD-1 receptor or its specific ligands antibody) prevents tumor from evading the immune system (**b**)

Table 3 PD-1/PD-L1 checkpoint targets in cancer immunotherapy

Drug	Target	Function	Indication	Objective response rate [a]	Ref.
Nivolumab (BMS-936558; ONO-4538; MDX-1106)	PD-1	Inhibitory receptor	Metastatic melanoma, NSCLC, RCC (renal cell carcinoma)	18% (NSCLC); 28% (melanoma); 27% (RCC)	(Brahmer et al. 2012)
Lambrolizumab (MK-3475)			NSCLC, RCC, melanoma, triple-negative breast cancer, metastatic bladder cancer, head and neck cancer	N.A.	(Carosella et al. 2015)
Pidilizumab (CT-011)			Diffuse large B cell lymphoma (DLBCL), multiple myeloma, colon cancer, acute leukemia, pancreatic and bladder cancers	70% (DLBCL)	(Carosella et al. 2015)
AMP-224			Solid tumors, cutaneous T cell lymphoma	N.A.	(Carosella et al. 2015)
BMS-936559 (MDX-1105)	PD-L1	Ligand for PD-1	NSCLC, melanoma, RCC, pancreatic, gastric, and breast cancers	10% (NSCLC); 17% (melanoma); 12% (RCC)	(Brahmer et al. 2010)
RG7446/MPDL3280			Bladder cancer, NSCLC	N.A.	(Carosella et al. 2015)
MEDI4736 (B7-H1[b])			NSCLC	N.A.	(Carosella et al. 2015)

N.A. not available

[a] Progression-free survival endpoint

[b] B7 homology 1, PD-L1

2012a). It was also demonstrated that suppression of SKP2 transcription occurred through inhibition of PI3K-Akt (phosphoinositide-3-kinase–Akt) and MEK-ERK (MEK-extracellular signal-regulated kinase) pathways (Patsoukis et al. 2012a). As known, PD-1 signaling during T cell activation can inhibit IL-2 production and, consequently, IL-2 is not able to activate the Akt signaling pathway (Francisco et al. 2009; Freeman et al. 2000; Latchman et al. 2001). Thus, PD-1 plays a selective role in Akt and MEK-ERK signaling pathways (only restored activation of MEK-ERK signaling) that leads to suppression of SKP2 transcription. PD-1 can also increase its activity by inhibiting the phosphorylation of Smad3 (a transcription factor) (Patsoukis et al. 2012a).

Increased susceptibility to tumors has been shown to arise from suppression of Smad3 expression (Han et al. 2004). Induced G1-phase arrest can occur due to apoptosis in human cancer cells (Ueno et al. 1997), contributing to antitumor effects and inhibition of cell proliferation (Li et al. 2010; Yang et al. 2008a). Another study on murine cell lines have reported that interactions between PD-1 and PD-L can lead to hindrance of cell cycle in G_0/G_1 and recruitment of SHP-2 (Latchman et al. 2001). SHP-2 is cytoplasmic tyrosine phosphatase and has a critical role in mediating cell proliferation and differentiation. Although this tyrosine phosphatase is important for transducing signal between the cell surface and the nucleus (QU 2000), regulation of cell spreading, migration, and focal adhesion is also mediated by SHP-2 (Yu et al. 1998). SHP-2 is able to promote Ras activation and play a key role as a proto-oncogene product (Matozaki et al. 2009). In addition, Latchman et al. showed that both PD-L2–PD-1 and PD-L1–PD-1 signals blocked the cell cycle progression, which led to inhibition of T cell proliferation but no increase in cell death (Latchman et al. 2001).

Conclusion and perspective

Association of gene polymorphisms in PD-1 with cancer susceptibility has drawn attentions toward implementing this molecule for anti-cancer therapy. Combining the anti-PD-1 therapeutics and current cancer treatments provides a promising era in this way. Currently available cancer therapies that can be contributing to get better results are mainly chemotherapy, cancer vaccination, irradiation, in vitro expansion of tumor-specific T cell clones, cytokine therapy, among others. In the other viewpoint, in which interferon (IFN)-α triggers unnecessary PD-1 expression resulting in diminished antitumor activity of IFN-α, combining the PD-1 blockade to this therapy compensated drawbacks of IFN-α (Terawaki et al. 2011). On the other side, combinational therapy of PD-1 and anti-CTLA-4 led to promotion in amelioration of patients with melanoma that was higher than the efficacy of each therapy alone (Wolchok et al. 2013). Currently, there is no doubt that combining the anti-PD-1 therapy with the blockade of other immune inhibitory pathways culminates in accumulated efficacy with elevated immune reaction against a tumor cell. However, reducing the adverse immune response in the patients should be noted. The most common side-effects of anti-PD-1 therapy comprise skin rash (Topalian et al. 2012b), type I diabetes (Hughes et al. 2015), myasthenia gravis (Loochtan et al. 2015), interstitial pneumonitis (Topalian et al. 2012b), and intestinal inflammation (Topalian et al. 2012b), or death in intense but rare cases. Immune system status as well as the genetic background are the most important factors to impress the final response circumstance of the patients with anti-PD-1 therapy. Furthermore, PD-1 application needs screening to obtain an optimized immune response as well as to prevent

tissue damage under specific conditions like infection. By advancements in the technologies of efficient antibody production against PD-1 as well as sufficient clinical investigations, hopefully satisfactory results in a favorable therapy for the anti-cancer immunotherapy will occur.

Acknowledgements This project was supported by a research grant from the Mashhad University of Medical Sciences.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

Agata Y, Kawasaki A, Nishimura H, Ishida Y, Tsubata T, Yagita H, Honjo T (1996) Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes. Int Immunol 8:765–772

Ahmadzadeh M, Johnson LA, Heemskerk B, Wunderlich JR, Dudley ME, White DE, Rosenberg SA (2009) Tumor antigen–specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. Blood 114:1537–1544

Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, Schuster SJ, Millenson MM, Cattry D, Freeman GJ (2015) PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 372:311–319

Armand P, Nagler A, Weller EA, Devine SM, Avigan DE, Chen Y-B, Kaminski MS, Holland HK, Winter JN, Mason JR (2013) Disabling immune tolerance by programmed death-1 blockade with pidilizumab after autologous hematopoietic stem-cell transplantation for diffuse large B-cell lymphoma: results of an international phase II trial. J Clin Oncol 31:4199–4206

Barber DL, Wherry EJ, Masopust D, Zhu B, Allison JP, Sharpe AH, Freeman GJ, Ahmed R (2006) Restoring function in exhausted CD8 T cells during chronic viral infection. Nature 439:682–687

Bayram S, Akkız H, Ülger Y, Bekar A, Akgöllü E, Yıldırım S (2012) Lack of an association of programmed cell death-1 PD1. 3 polymorphism with risk of hepatocellular carcinoma susceptibility in Turkish population: a case-control study. Gene 511:308–313

Blank C, Brown I, Peterson AC, Spiotto M, Iwai Y, Honjo T, Gajewski TF (2004) PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. Cancer Res 64:1140–1145

Blattman JN, Wherry EJ, Ha S-J, van der Most RG, Ahmed R (2009) Impact of epitope escape on PD-1 expression and CD8 T-cell exhaustion during chronic infection. J Virol 83:4386–4394

Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, Stankevich E, Pons A, Salay TM, McMiller TL (2010) Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 28:3167–3175

Brahmer JR, Tykodi SS, Chow LQ, Hwu W-J, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K (2012) Safety and activity of anti–PD-L1 antibody in patients with advanced cancer. N Engl J Med 366:2455–2465

Brown JA, Dorfman DM, Ma F-R, Sullivan EL, Munoz O, Wood CR, Greenfield EA, Freeman GJ (2003) Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol 170:1257–1266

Carosella ED, Ploussard G, LeMaoult J, Desgrandchamps F (2015) A systematic review of immunotherapy in urologic cancer: evolving roles for targeting of CTLA-4, PD-1/PD-L1, and HLA-G. Eur Urol 68:267–279

Carrano AC, Eytan E, Hershko A, Pagano M (1999) SKP2 is required for ubiquitin-mediated degradation of the CDK inhibitor p27. Nat Cell Biol 1:193–199

Ceeraz S, Nowak EC, Noelle RJ (2013) B7 family checkpoint regulators in immune regulation and disease. Trends Immunol 34:556–563

Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL (2004) 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 173:945–954

Chen DS, Irving BA, Hodi FS (2012) Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 18:6580–6587

Chen L (2004) Co-inhibitory molecules of the B7–CD28 family in the control of T-cell immunity. Nat Rev Immunol 4:336–347

Chen YB, Mu CY, Chen C, Huang JA (2014) Association between single nucleotide polymorphism of PD-L1 gene and non-small cell lung cancer susceptibility in a Chinese population. Asia Pac J Clin Oncol 10:e1–e6

Cho Y-A, Yoon H-J, Lee J-I, Hong S-P, Hong S-D (2011) Relationship between the expressions of PD-L1 and tumor-infiltrating lymphocytes in oral squamous cell carcinoma. Oral Oncol 47:1148–1153

Cunha LL, Marcello MA, Morari EC, Nonogaki S, Conte FF, Gerhard R, Soares FA, Vassallo J, Ward LS (2013) Differentiated thyroid carcinomas may elude the immune system by B7H1 upregulation. Endocr Relat Cancer 20:103–110

Dehaghani AS, Kashef MA, Ghaemenia M, Sarraf Z, Khaghanzadeh N, Fattahi MJ, Ghaderi A (2009) PDCD1, CTLA-4 and p53 gene polymorphism and susceptibility to gestational trophoblastic diseases. J Reprod Med 54:25–31

Dolan DE, Gupta S (2014) PD-1 pathway inhibitors: changing the landscape of cancer immunotherapy. Cancer control: journal of the Moffitt Cancer Center 21:231–237

Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, Roche PC, Lu J, Zhu G, Tamada K (2002) Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 8:793–800

Dong H, Zhu G, Tamada K, Chen L (1999) B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. Nat Med 5:1365–1369

Dong W, Gong M, Shi Z, Xiao J, Zhang J, Peng J (2016) Programmed cell death-1 polymorphisms decrease the cancer risk: a meta-analysis involving twelve case-control studies. PLoS One 11: e0152448

Dougall WC, Kurtulus S, Smyth MJ, Anderson AC (2017) TIGIT and CD96: new checkpoint receptor targets for cancer immunotherapy. Immunol Rev 276:112–120

Droeser RA, Hirt C, Viehl CT, Frey DM, Nebiker C, Huber X, Zlobec I, Eppenberger-Castori S, Tzankov A, Rosso R (2013) Clinical impact of programmed cell death ligand 1 expression in colorectal cancer. Eur J Cancer 49:2233–2242

Duraiswamy J, Kaluza KM, Freeman GJ, Coukos G (2013) Dual blockade of PD-1 and CTLA-4 combined with tumor vaccine effectively restores T-cell rejection function in tumors. Cancer Res 73:3591–3603

Fay AP, Signoretti S, Callea M, Teló GH, McKay RR, Song J, Carvo I, Lampron ME, Kaymakcalan MD, Poli-de-Figueiredo CE (2015) Programmed death ligand-1 expression in adrenocortical carcinoma: an exploratory biomarker study. J Immunother Cancer 3:1

Fife BT, Pauken KE, Eagar TN, Obu T, Wu J, Tang Q, Azuma M, Krummel MF, Bluestone JA (2009) Interactions between PD-1

and PD-L1 promote tolerance by blocking the TCR–induced stop signal. Nat Immunol 10:1185–1192

Fourcade J, Sun Z, Benallaoua M, Guillaume P, Luescher IF, Sander C, Kirkwood JM, Kuchroo V, Zarour HM (2010) Upregulation of Tim-3 and PD-1 expression is associated with tumor antigen-specific CD8+ T cell dysfunction in melanoma patients. J Exp Med 207: 2175–2186

Francisco LM, Sage PT, Sharpe AH (2010) The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 236:219–242

Francisco LM, Salinas VH, Brown KE, Vanguri VK, Freeman GJ, Kuchroo VK, Sharpe AH (2009) PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. J Exp Med 206:3015–3029

Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, Fitz LJ, Malenkovich N, Okazaki T, Byrne MC (2000) Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 192:1027–1034

Gao Q, Wang X-Y, Qiu S-J, Yamato I, Sho M, Nakajima Y, Zhou J, Li B-Z, Shi Y-H, Xiao Y-S (2009) Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin Cancer Res 15:971–979

Ge J, Zhu L, Zhou J, Li G, Li Y, Li S, Wu Z, Rong J, Yuan H, Liu Y (2015) Association between co-inhibitory molecule gene tagging single nucleotide polymorphisms and the risk of colorectal cancer in Chinese. J Cancer Res Clin Oncol 141:1533–1544

Ghebeh H, Mohammed S, Al-Omair A, Qattant A, Lehe C, Al-Qudaihi G, Elkum N, Alshabanah M, Amer SB, Tulbah A (2006) 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 8:190–198

Gianchecchi E, Delfino DV, Fierabracci A (2013) Recent insights into the role of the PD-1/PD-L1 pathway in immunological tolerance and autoimmunity. Autoimmun Rev 12:1091–1100

Haghshenas MR, Naeimi S, Talei A, Ghaderi A, Erfani N (2011) Program death 1 (PD1) haplotyping in patients with breast carcinoma. Mol Biol Rep 38:4205–4210

Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, Higuchi T, Yagi H, Takakura K, Minato N (2007) Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Natl Acad Sci 104:3360–3365

Hamid O, Robert C, Daud A, Hodi FS, Hwu W-J, Kefford R, Wolchok JD, Hersey P, Joseph RW, Weber JS (2013a) Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med 369:134–144

Hamid O, Sosman JA, Lawrence DP, Sullivan RJ, Ibrahim N, Kluger HM, Boasberg PD, Flaherty K, Hwu P, Ballinger M (2013b) Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic melanoma (mM). ASCO Annual Meeting Proceedings

Han S-U, Kim H-T, Seong DH, Kim Y-S, Park Y-S, Bang Y-J, Yang H-K, Kim S-J (2004) Loss of the Smad3 expression increases susceptibility to tumorigenicity in human gastric cancer. Oncogene 23:1333–1341

Herbst RS, Soria J-C, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN (2014) Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 515:563–567

Hino R, Kabashima K, Kato Y, Yagi H, Nakamura M, Honjo T, Okazaki T, Tokura Y (2010) Tumor cell expression of programmed cell death-1 ligand 1 is a prognostic factor for malignant melanoma. Cancer 116:1757–1766

Hsu M-C, Hsiao J-R, Chang K-C, Wu Y-H, Su I-J, Jin Y-T, Chang Y (2010) Increase of programmed death-1-expressing intratumoral CD8 T cells predicts a poor prognosis for nasopharyngeal carcinoma. Mod Pathol 23:1393–1403

Hua Z, Li D, Xiang G, Xu F, Jie G, Fu Z, Jie Z, Da P, Li D (2011) PD-1 polymorphisms are associated with sporadic breast cancer in Chinese Han population of Northeast China. Breast Cancer Res Treat 129:195–201

Hughes J, Vudattu N, Sznol M, Gettinger S, Kluger H, Lupsa B, Herold KC (2015) Precipitation of autoimmune diabetes with anti-PD-1 immunotherapy. Diabetes Care 38:e55–e57

Ishida Y, Agata Y, Shibahara K, Honjo T (1992) Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J 11:3887

Ivansson EL, Juko-Pecirep I, Gyllensten UB (2010) Interaction of immunological genes on chromosome 2q33 and IFNG in susceptibility to cervical cancer. Gynecol Oncol 116:544–548

Jacobs JF, Idema AJ, Bol KF, Nierkens S, Grauer OM, Wesseling P, Grotenhuis JA, Hoogerbrugge PM, de Vries IJM, Adema GJ (2009) Regulatory T cells and the PD-L1/PD-1 pathway mediate immune suppression in malignant human brain tumors. Neuro-Oncology 11:394–402

Jiang D, Xu Y-Y, Li F, Xu B, Zhang X-G (2014) The role of B7-H1 in gastric carcinoma: clinical significance and related mechanism. Med Oncol 31:1–7

Jiao Q, Liu C, Yang Z, Ding Q, Wang M, Li M, Zhu T, Qian H, Li W, Tu N (2014) Upregulated PD-1 expression is associated with the development of systemic lupus erythematosus, but not the PD-1.1 allele of the PDCD1 gene. Int J Genom 2014

Jin H-T, Ahmed R, Okazaki T (2011) Role of PD-1 in regulating T-cell immunity. Negative co-receptors and ligands. Springer

Karim R, Jordanova ES, Piersma SJ, Kenter GG, Chen L, Boer JM, Melief CJ, van der Burg SH (2009) 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 15:6341–6347

Kashani-Sabet M (2010) Tumor progression by immune evasion in melanoma. Cancer 116:1623–1625

Katsuya Y, Fujita Y, Horinouchi H, Ohe Y, Watanabe S-I, Tsuta K (2015) Immunohistochemical status of PD-L1 in thymoma and thymic carcinoma. Lung Cancer 88:154–159

Keir ME, Butte MJ, Freeman GJ, Sharpe AH (2008) PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 26:677–704

Khalili JS, Liu S, Rodríguez-Cruz TG, Whittington M, Wardell S, Liu C, Zhang M, Cooper ZA, Frederick DT, Li Y (2012) Oncogenic BRAF (V600E) promotes stromal cell-mediated immunosuppression via induction of interleukin-1 in melanoma. Clin Cancer Res 18:5329–5340

Khoury SJ, Sayegh MH (2004) The roles of the new negative T cell costimulatory pathways in regulating autoimmunity. Immunity 20: 529–538

Kim PS, Ahmed R (2010) Features of responding T cells in cancer and chronic infection. Curr Opin Immunol 22:223–230

Kobayashi M, Kawano S, Hatachi S, Kurimoto C, Okazaki T, Iwai Y, Honjo T, Tanaka Y, Minato N, Komori T (2005) Enhanced expression of programmed death-1 (PD-1)/PD-L1 in salivary glands of patients with Sjögren's syndrome. J Rheumatol 32:2156–2163

Konishi J, Yamazaki K, Azuma M, Kinoshita I, Dosaka-Akita H, Nishimura M (2004) 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 10:5094–5100

Kornete M, Piccirillo CA (2011) Critical co-stimulatory pathways in the stability of Foxp3+ T reg cell homeostasis in type I diabetes. Autoimmun Rev 11:104–111

Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P (2015) Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015:23–34

Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, Iwai Y, Long AJ, Brown JA, Nunes R (2001) PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol 2:261–268

Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D (2015) PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 372:2509–2520

Lee S-J, Jang B-C, Lee S-W, Yang Y-I, Suh S-I, Park Y-M, Oh S, Shin J-G, Yao S, Chen L (2006) Interferon regulatory factor-1 is prerequisite to the constitutive expression and IFN-γ-induced upregulation of B7-H1 (CD274). FEBS Lett 580:755–762

Li Q, Kawamura K, Ma G, Iwata F, Numasaki M, Suzuki N, Shimada H, Tagawa M (2010) Interferon-λ induces G1 phase arrest or apoptosis in oesophageal carcinoma cells and produces anti-tumour effects in combination with anti-cancer agents. Eur J Cancer 46:180–190

Li X, Jiang X, Zhang J, Jia Y (2016) Association of the programmed cell death-1 PD1. 5 C> T polymorphism with cervical cancer risk in a Chinese population. Genet Mol Res: GMR 15

Ling H, Vincent K, Pichler M, Fodde R, Berindan-Neagoe I, Slack FJ, Calin GA (2015) Junk DNA and the long non-coding RNA twist in cancer genetics. Oncogene 34:5003–5011

Lipson EJ, Sharfman WH, Drake CG, Wollner I, Taube JM, Anders RA, Xu H, Yao S, Pons A, Chen L (2013) Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. Clin Cancer Res 19:462–468

Liu C, Jiang J, Gao L, Hu X, Wang F, Shen Y, Yu G, Zhao Z, Zhang X (2014) A promoter region polymorphism in PDCD-1 gene is associated with risk of rheumatoid arthritis in the Han Chinese population of southeastern China. Int J Genom 2014

Loochtan AI, Nickolich MS, Hobson-Webb LD (2015) Myasthenia gravis associated with ipilimumab and nivolumab in the treatment of small cell lung cancer. Muscle Nerve 52:307–308

Ma Y, Liu X, Zhu J, Li W, Guo L, Han X, Song B, Cheng S, Jie L (2015) Polymorphisms of co-inhibitory molecules (CTLA-4/PD-1/PD-L1) and the risk of non-small cell lung cancer in a Chinese population. Int J Clin Exp Med 8:16585

Mahmoudi M, Rezaiemanesh A, Salmaninejad A, Harsini S, Poursani S, Bahrami T, Tahghighi F, Ziaee V, Rezaei N (2015) PDCD1 single nucleotide genes polymorphisms confer susceptibility to juvenile-onset systemic lupus erythematosus. Autoimmunity 48:488–493

Mamat U, Arkinjan M (2015) Association of programmed death-1 gene polymorphism rs2227981 with tumor: evidence from a meta analysis. Int J Clin Exp Med 8:13282

Matozaki T, Murata Y, Saito Y, Okazawa H, Ohnishi H (2009) Protein tyrosine phosphatase SHP-2: a proto-oncogene product that promotes Ras activation. Cancer Sci 100:1786–1793

McDermott DF, Atkins MB (2013) PD-1 as a potential target in cancer therapy. Cancer Med 2:662–673

Mojtahedi Z, Mohmedi M, Rahimifar S, Erfani N, Hosseini SV, Ghaderi A (2012) Programmed death-1 gene polymorphism (PD-1.5 C/T) is associated with colon cancer. Gene 508:229–232

Morgan DO (2007) The cell cycle: principles of control. New Science Press

Mu C-Y, Huang J-A, Chen Y, Chen C, Zhang X-G (2011) 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 28:682–688

Mueller DL, Jenkins M, Schwartz R (1989) Clonal expansion versus functional clonal inactivation: a costimulatory signalling pathway determines the outcome of T cell antigen receptor occupancy. Annu Rev Immunol 7:445–480

Nakanishi J, Wada Y, Matsumoto K, Azuma M, Kikuchi K, Ueda S (2007) Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. Cancer Immunol Immunother 56:1173–1182

Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, Nakamura S, Enomoto K, Yagita H, Azuma M (2007) Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res 13:2151–2157

Oestreich KJ, Yoon H, Ahmed R, Boss JM (2008) NFATc1 regulates PD-1 expression upon T cell activation. J Immunol 181:4832–4839

Ohigashi Y, Sho M, Yamada Y, Tsurui Y, Hamada K, Ikeda N, Mizuno T, Yoriki R, Kashizuka H, Yane K (2005) Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. Clin Cancer Res 11:2947–2953

Pardoll DM (2012) The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 12:252–264

Park J-J, Omiya R, Matsumura Y, Sakoda Y, Kuramasu A, Augustine MM, Yao S, Tsushima F, Narazaki H, Anand S (2010) B7-H1/CD80 interaction is required for the induction and maintenance of peripheral T-cell tolerance. Blood 116:1291–1298

Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, Linsley PS, Thompson CB, Riley JL (2005) CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 25:9543–9553

Patsoukis N, Brown J, Petkova V, Liu F, Li L, Boussiotis VA (2012a) Selective effects of PD-1 on Akt and Ras pathways regulate molecular components of the cell cycle and inhibit T cell proliferation. Sci Signal 5:ra46

Patsoukis N, Sari D, Boussiotis VA (2012b) PD-1 inhibits T cell proliferation by upregulating p27 and p15 and suppressing Cdc25A. Cell Cycle 11:4305–4309

Pedoeem A, Azoulay-Alfaguter I, Strazza M, Silverman GJ, Mor A (2014) Programmed death-1 pathway in cancer and autoimmunity. Clin Immunol 153:145–152

Petrovas C, Price DA, Mattapallil J, Ambrozak DR, Geldmacher C, Cecchinato V, Vaccari M, Tryniszewska E, Gostick E, Roederer M (2007) SIV-specific CD8+ T cells express high levels of PD1 and cytokines but have impaired proliferative capacity in acute and chronic SIVmac251 infection. Blood 110:928–936

Porichis F, Kaufmann DE (2012) Role of PD-1 in HIV pathogenesis and as target for therapy. Curr HIV/AIDS Rep 9:81–90

Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, Bellmunt J, Burris HA, Petrylak DP, Teng S-L (2014) MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 515:558–562

Prokunina L, Castillejo-López C, Öberg F, Gunnarsson I, Berg L, Magnusson V, Brookes AJ, Tentler D, Kristjansdóttir H, Gröndal G (2002) A regulatory polymorphism in PDCD1 is associated with susceptibility to systemic lupus erythematosus in humans. Nat Genet 32:666–669

Pyo J-S, Kang G, Kim JY (2017) Prognostic role of PD-L1 in malignant solid tumors: a meta-analysis. Int J Biol Markers 32:e68

Qiu H, Zheng L, Tang W, Yin P, Cheng F, Wang L (2014) Programmed death-1 (PD-1) polymorphisms in Chinese patients with esophageal cancer. Clin Biochem 47:612–617

QU CK (2000) The SHP-2 tyrosine phosphatase: signaling mechanisms and biological functions. Cell Res 10:279–288

Ren H-T, Li Y-M, Wang X-J, Kang H-F, Jin T-B, Ma X-B, Liu X-H, Wang M, Liu K, Xu P (2016) PD-1 rs2227982 polymorphism is associated with the decreased risk of breast cancer in northwest Chinese women: a hospital-based observational study. Medicine 95:e3760

Riley JL (2009) PD-1 signaling in primary T cells. Immunol Rev 229:114–125

Ritprajak P, Azuma M (2015) Intrinsic and extrinsic control of expression of the immunoregulatory molecule PD-L1 in epithelial cells and squamous cell carcinoma. Oral Oncol 51:221–228

Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M (2015) Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 372:2521–2532

Rossi AG, Sawatzky DA, Walker A, Ward C, Sheldrake TA, Riley NA, Caldicott A, Martinez-Losa M, Walker TR, Duffin R (2006) Cyclin-dependent kinase inhibitors enhance the resolution of inflammation by promoting inflammatory cell apoptosis. Nat Med 12:1056–1064

Sasaki H, Tatemaysu T, Okuda K, Moriyama S, Yano M, Fujii Y (2014) PD-1 gene promoter polymorphisms correlate with a poor prognosis in non-small cell lung cancer. Mol Clin Oncol 2:1035–1042

Savabkar S, Azimzadeh P, Chaleshi V, Mojarad EN, Aghdaei HA (2013) Programmed death-1 gene polymorphism (PD-1.5 C/T) is associated with gastric cancer. Gastroenterology and hepatology from bed to bench 6

Schalper KA, Velcheti V, Carvajal D, Wimberly H, Brown J, Pusztai L, Rimm DL (2014) In situ tumor PD-L1 mRNA expression is associated with increased TILs and better outcome in breast carcinomas. Clin Cancer Res 20:2773–2782

Sharpe AH, Wherry EJ, Ahmed R, Freeman GJ (2007) The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nat Immunol 8:239–245

Sherr CJ, Roberts JM (1999) CDK inhibitors: positive and negative regulators of G1-phase progression. Genes Dev 13:1501–1512

Snyder MW, Adey A, Kitzman JO, Shendure J (2015) Haplotype-resolved genome sequencing: experimental methods and applications. Nat Rev Genet 16:344–358

Strome SE, Dong H, Tamura H, Voss SG, Flies DB, Tamada K, Salomao D, Cheville J, Hirano F, Lin W (2003) B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res 63:6501–6505

Suarez-Gestal M, Ferreiros-Vidal I, Ortiz J, Gomez-Reino J, Gonzalez A (2008) Analysis of the functional relevance of a putative regulatory SNP of PDCD1, PD1. 3, associated with systemic lupus erythematosus. Genes Immun 9:309–315

Sznol M, Chen L (2013) Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer. Clin Cancer Res 19: 1021–1034

Tang W, Chen Y, Chen S, Sun B, Gu H, Kang M (2015) Programmed death-1 (PD-1) polymorphism is associated with gastric cardia adenocarcinoma. Int J Clin Exp Med 8:8086

Taube JM, Klein A, Brahmer JR, Xu H, Pan X, Kim JH, Chen L, Pardoll DM, Topalian SL, Anders RA (2014) Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. Clin Cancer Res 20:5064–5074

Terawaki S, Chikuma S, Shibayama S, Hayashi T, Yoshida T, Okazaki T, Honjo T (2011) IFN-α directly promotes programmed cell death-1 transcription and limits the duration of T cell-mediated immunity. J Immunol 186:2772–2779

Thompson RH, Dong H, Kwon ED (2007) Implications of B7-H1 expression in clear cell carcinoma of the kidney for prognostication and therapy. Clin Cancer Res 13:709s–715s

Topalian SL, Drake CG, Pardoll DM (2012a) Targeting the PD-1/B7-H1 (PD-L1) pathway to activate anti-tumor immunity. Curr Opin Immunol 24:207–212

Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB (2012b) Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 366:2443–2454

Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, Brahmer JR, Lawrence DP, Atkins MB, Powderly JD (2014) Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol 32:1020–1030

Ueno T, Ohtawa K, Mitsui K, Kodera Y, Hiroto M, Matsushima A, Inada Y, Nishimura H (1997) Cell cycle arrest and apoptosis of leukemia cells induced by L-asparaginase. Leukemia 11:1858–1861

Vibhakar R, Juan G, Traganos F, Darzynkiewicz Z, Finger LR (1997) Activation-induced expression of human programmed death-1 gene in T-lymphocytes. Exp Cell Res 232:25–28

Wang L, Ma Q, Chen X, Guo K, Li J, Zhang M (2010) Clinical significance of B7-H1 and B7-1 expressions in pancreatic carcinoma. World J Surg 34:1059–1065

Westin JR, Chu F, Zhang M, Fayad LE, Kwak LW, Fowler N, Romaguera J, Hagemeister F, Fanale M, Samaniego F (2014) Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial. Lancet Oncol 15:69–77

Williams GH, Stoeber K (2012) The cell cycle and cancer. J Pathol 226: 352–364

Wilmotte R, Burkhardt K, Kindler V, Belkouch M-C, Dussex G, de Tribolet N, Walker PR, Dietrich P-Y (2005) B7-homolog 1 expression by human glioma: a new mechanism of immune evasion. Neuroreport 16:1081–1085

Wintterle S, Schreiner B, Mitsdoerffer M, Schneider D, Chen L, Meyermann R, Weller M, Wiendl H (2003) Expression of the B7-related molecule B7-H1 by glioma cells a potential mechanism of immune paralysis. Cancer Res 63:7462–7467

Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, Segal NH, Ariyan CE, Gordon R-A, Reed K (2013) Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 369:122–133

Wong RM, Scotland RR, Lau RL, Wang C, Korman AJ, Kast W, Weber JS (2007) Programmed death-1 blockade enhances expansion and functional capacity of human melanoma antigen-specific CTLs. Int Immunol 19:1223–1234

Wu C, Zhu Y, Jiang J, Zhao J, Zhang X-G, Xu N (2006) Immunohistochemical localization of programmed death-1 ligand-1 (PD-L1) in gastric carcinoma and its clinical significance. Acta Histochem 108:19–24

Wu K, Kryczek I, Chen L, Zou W, Welling TH (2009) Kupffer cell suppression of CD8+ T cells in human hepatocellular carcinoma is mediated by B7-H1/programmed death-1 interactions. Cancer Res 69:8067–8075

Yang K, Zheng X-Y, Qin J, Wang Y-B, Bai Y, Mao Q-Q, Wan Q, Wu Z-M, Xie L-P (2008a) Up-regulation of p21 WAF1/Cip1 by saRNA induces G1-phase arrest and apoptosis in T24 human bladder cancer cells. Cancer Lett 265:206–214

Yang W, Chen PW, Li H, Alizadeh H, Niederkorn JY (2008b) PD-L1: PD-1 interaction contributes to the functional suppression of T-cell responses to human uveal melanoma cells in vitro. Invest Ophthalmol Vis Sci 49:2518

Yin L, Guo H, Zhao L, Wang J (2013) The programmed death-1 gene polymorphism (PD-1.5 C/T) is associated with non-small cell lung cancer risk in a Chinese Han population. Int J Clin Exp Med 7: 5832–5836

Yin L, Guo H, Zhao L, Wang J (2014) The programmed death-1 gene polymorphism (PD-1.5 C/T) is associated with non-small cell lung cancer risk in a Chinese Han population. Int J Clin Exp Med 7:5832

Youngblood B, Oestreich KJ, Ha S-J, Duraiswamy J, Akondy RS, West EE, Wei Z, Lu P, Austin JW, Riley JL (2011) Chronic virus infection enforces demethylation of the locus that encodes PD-1 in antigen-specific CD8+ T cells. Immunity 35:400–412

Yousefi AR, Karimi MH, Shamsdin SA, Mehrabani D, Hosseini SV, Erfani N, Bolandparvaz S, Bagheri K (2013) PD-1 Gene polymorphisms in Iranian patients with colorectal cancer. Lab Med 44:241–244

Yu D-H, Qu C-K, Henegariu O, Lu X, Feng G-S (1998) Protein-tyrosine phosphatase Shp-2 regulates cell spreading, migration, and focal adhesion. J Biol Chem 273:21125–21131

Zamani MR, Asbagh FA, Massoud AH, Salmaninejad A, Massoud A, Rezaei N (2015) Association between a PD-1 gene polymorphism

and antisperm antibody-related infertility in Iranian men. J Assist Reprod Genet 32:103–106

Zamani MR, Aslani S, Salmaninejad A, Javan MR, Rezaei N (2016) PD-1/PD-L and autoimmunity: a growing relationship. Cell Immunol

Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, Zhang Z-Y, Edidin MA, Nathenson SG, Almo SC (2004) Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 20:337–347

Zhou R-M, Li Y, Wang N, Huang X, Cao S-R, Shan B-E (2016) Association of programmed death-1 polymorphisms with the risk and prognosis of esophageal squamous cell carcinoma. Cancer Genet 209:365–375

Zinselmeyer BH, Heydari S, Sacristán C, Nayak D, Cammer M, Herz J, Cheng X, Davis SJ, Dustin ML, McGavern DB (2013) PD-1 promotes immune exhaustion by inducing antiviral T cell motility paralysis. J Exp Med 210:757–774

Zou W, Wolchok JD, Chen L (2016) PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: mechanisms, response biomarkers, and combinations. Sci Transl Med 8:328rv4