Cellular Therapy and Transplantation (CTT). Vol. 8, No. 2, 2019
doi: 10.18620/ctt-1866-8836-2019-8-2-8-16
Submitted: 21 January 2019, accepted: 15 March 2019

PD-1 receptor on immune cells, its expression and potential role in cancer therapy

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Citation: Elezov DS, Kudryavtsev IV. PD-1 receptor on immune cells, its expression and potential role in cancer therapy. Cell Ther Transplant 2019; 8(2): 8-16.

Summary

PD-1 is among key receptors conveying an inhibitory signal to T cells. Over last decade, PD-1 and its ligand PD-L1 draw much attention, due to high efficiency of therapy with PD-1/PD-L1 inhibitors in a number of malignant disorders. In this review article, we aimed to summarize current data on the PD-1 receptor expression in different immune cell subpopulations, like as its potential role in cellular antitumor response. Along with molecular structure and receptor-ligand interactions, the main attention is drawn to special features of PD-1 expression on the CD8+ T cell population which plays a key role in antitumor immune response. Some common changes of PD-1 expression levels during the cell activation and differentiation are considered, mainly, for the CD8+ T cells. Moreover, we discuss PD-1 expression on the surface of regulatory T cells, NK cells, invariant NKT cells, myeloid suppressor cells which may play an important role for anticancer immune response. When performing current therapy with PD-1/PD-L1 inhibitors, the mentioned populations may influence development of resistance to this mode of immune treatment. Therefore, a number of recent studies are directed for studying the PD-1/PD-L1 involvement into the immune regulation and to test prospects of their usage as biomarkers for clinical immune checkpoint therapy.

Keywords

PD-1, PD-L1, expression, T cells, antitumor therapy, checkpoint inhibitors.

Introduction

Over last decade, the issue of PD-1 and PD-1 ligand (PD-L1) is being actively studied due to attempted clinical usage of their inhibitors in cancer treatment. In particular, PD-1 inhibitory drugs (e.g., nivolumab) have elicited good response in Hodgkin's disease patients [1] if also applied in the setting of hematopoietic stem cell transplantation (HSCT). Activation of antitumor T cell populations is considered the main reason for success in anti-PD-1 treatment. However, only a part of patients are responding to the PD-1 inhibitors, thus suggesting individual differences of PD-1/PD-L1 regulation. These patient-specific differences should be better described at the levels of PD-1 production, PD-1/PD-L1 binding, and resulting stimulation of anticancer immunity in distinct clinical disorders. Hence, the immune regulation mechanisms of PD-1 and other immune checkpoint molecules are still poorly understood in many aspects. We tried to summarize the latest data on PD-1 receptor immunology and its potential role in the development of antitumor response.

CD8+ T cells present the key effector population of antitumor adaptive immune response. A lot of positive and negative factors are known to participate in their regulation. At the present time, the so-called "double-signal" model is used to describe a TCR-mediated recognition by naïve T lymphocyte of MHC/antigen on antigen-presenting cell. This recognition event results either into activation of T cells, or its anergy.

To achieve effective activation of antigen-specific T lymphocytes, a signal from the TcR/MHC complex should be accomplished by additional antigen-independent (or costimulatory) signal from other receptors on the responding T cells. However, certain factors may down-regulate the T cell activation. These suppressive effects are performed *via* appropriate receptors on T cells (e.g. PD-L1 and PD-L2) functioning as immune checkpoints [2]. Under normal conditions, this inhibitory mechanism prevents excessive activation of T cell populations, e.g., adverse autoimmune reactions, thus maintaining a peripheral immune tolerance [3]. The opposite task, i.e., promotion of T cell-mediated antitumor activity requires inhibition of the PD-1 receptors, performed by specific anti-PD-1 monoclonal antibodies now proposed for clinical use.

Hence, special attention is drawn to these costimulatory and coinhibitory interactions, since appropriate pathways are involved in immune escape of malignant tissues or virus-infected cells, as well as in development of autoimmune reactions [4]. The costimulatory and inhibitory receptors are not limited to naïve T cells, being also active in regulatory, effector and memory T cells. The most studied costimulatory pathway includes CD80(B7-1)/CD86(B7-2) receptors on the surface of antigen-presenting cells that interact with CD28 Ig-like molecules on T lymphocytes. There are both costimulatory receptors (CD28, ICOS), and inhibitory molecules (CTLA-4, PD-1, BTLA) on lymphocytes (Fig. 1).

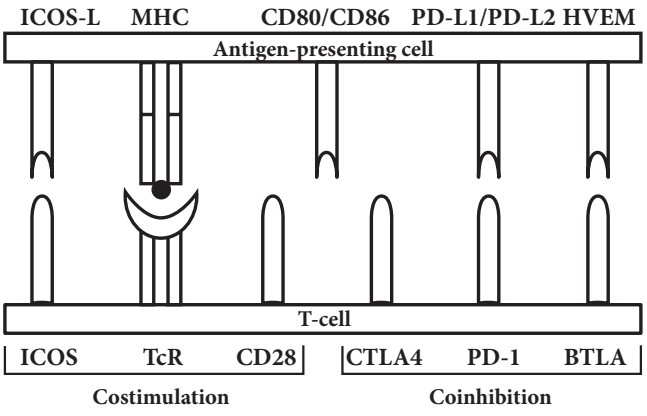

Figure 1. Main molecules and interactions during T cell activation. CD28 family receptors and their ligands on the membranes of T lymphocytes (bottom) during their contacts with ligand molecules on the antigen-presenting cells (top)

PD-1 molecule is a member of CD28 family, but, like as its main ligand (PD-L1), it is considered a separate player at these signal pathways participating in T cell activation. Initial therapeutic interest was connected with an opportunity to augment the immune response *via* the costimulatory signal receptors. However, with discovery of immune checkpoints, the research was focused on these inhibitory molecules thus providing impressive results in therapy of some malignant diseases and a Nobel Prize 2018 for J. P. Allison (studies in PD-1/PD-L1) and T. Honjo (discovery of CTLA4 receptor). The both inhibitory receptors are involved into APC-T cell interactions (Fig. 2). The targeted CTLA-4 inhibition by Ipilimumab was initially used for antitumor immune therapy, proving its efficiency in melanoma and other epithelial carcinomas. Monoclonal antibodies to PD-L1 were developed later, and numerous clinical trials have shown its efficiency in some malignancies, especially, Hodgkin lymphoma and melanoma, thus giving some promise for usage of PD-1/PD-L1 inhibitors in clinical oncology [5].

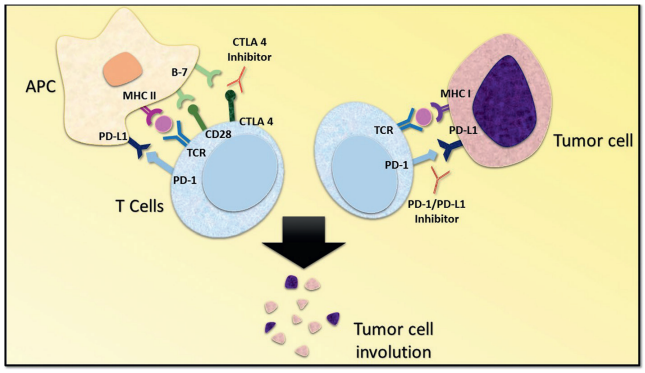

Figure 2. Mechanism of CTLA 4 and PD-1/PD-L1 inhibition. The activation of T cells is mediated by the interaction of T cell receptor and the CD28 receptor with class II major histocompatibility complex and B7 costimulatory molecule. The interaction of CTLA-4 with B7 molecule delivers an inhibitory signal, effectively checked by CTLA-4 inhibitors. The negative regulation of T cells resulting from PD-1/PD-L1 interaction between T cells and tumor cells is prevented by PD-1/PD-L1 inhibitors (Chae et al., 2018) [5]

PD-1: molecular structure

The *Programmed Death-1* receptor (PD-1, CD279) is expressed on the surface membrane of some immune cell populations. As many other membrane receptors, PD-1 is a transmembrane protein (type 1) from the immunoglobulin superfamily, with extracellular IgV domain. PD-1 is broadly represented on different leukocyte populations and it can be detected on T, B, NK, and natural killer T cells (NKT cells), as well as on monocytes, dendritic cells, thymocytes. The protein consists of 288 amino acids and includes an Ig-variable domain, a "stem" of ca. 20 amino acids, as well as transmembrane and cytoplasmic domains. The latter includes tyrosine-based inhibitory signal motifs (ITIM), a similar tyrosine-based switch motif (ITSM). PD-1 is encoded by the *Pdcd1* gene mapped at the chromosome 2 in humans

(in mice, at chromosome 1). *Pdcd1* contains 5 protein-coding exons, i.e.: exon 1 encodes signal sequence; exon 2 for the IgV domain; exon3, for transmembrane domain; exons 4 and 5 encode cytoplasmic domain with ITIM- and ITSM motifs. Four additional protein variants may exist, due to alternative mRNA splicing. The soluble PD-1 form is encoded by the *Pdcd1* variant with missed exon 3 [6]. The *Pdcd1* transcription is regulated by several transcription factors, i.e., NFATc1 [7], IRF9 [8], FoxO1 [9], Notch signaling [10]. T-bet and Blimp-1 factors are known to inhibit PD-1 expression [11, 12].

PD-1 ligands: PD-L1 and PD-L2

PD-1 is able to bind some specific ligands, i.e., PD-L1 (B7-H1, CD274), or PD-L2 (B7-DC, CD273). These inhibitory molecules are necessary for induction of immunological tolerance and suppression of excessive tissue damage in the inflammatory foci in peripheral tissues, and, probably, escape of tumor cells from immune surveillance. Affinity of PD-L2 for PD-1 is 2 to 6-fold higher than PD-L1/PD-1 binding [13]. However, most studies deal with PD1/PDL1 interactions that are primarily caused by broad PD-1 distribution and ability of its expression on various hematopoietic cells and other tissues. On the contrary, PD-L2 expression is mostly limited by dendritic cells, macrophages and lung cells. PD-1 ligands exhibit additional receptors. PD-L1 interacts with B7-1 (CD80) and participates in transduction of inhibitory signal [14]. Hence, B7-1 represents a common ligand for the three receptor types: CD28, CTLA-4, PD-L1 (Fig. 3). Moreover, PD-L2 may bind the RGMB (Repulsive Guidance Molecule B) expressed on lung macrophages, and on alveolar epithelium, thus participating in maintenance of local immune tolerance [15].

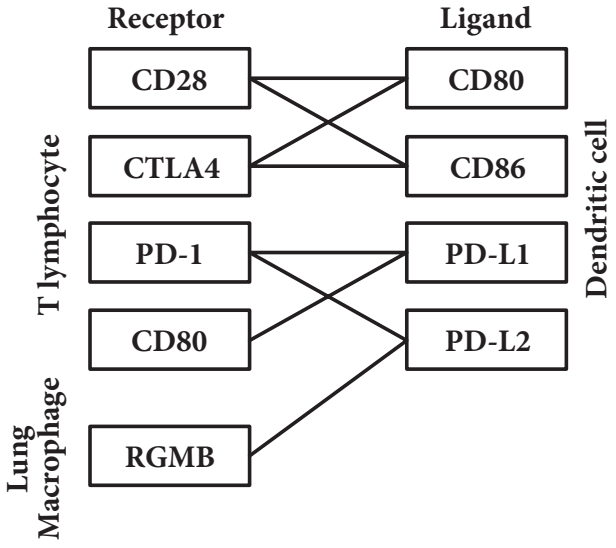

Figure 3. Main molecular interactions connected with PD-1 pathway

Methodology of PD-1/PD-L1 detection in tumor samples

There are some conventional laboratory methods of PD-1/PDL-1 diagnostics and appropriate semi-quantitative assays based on detection of specific protein or mRNAs. Immunohistochemical (IHC) testing has some problems with different quality of biopsies as well with cutoff values. Despite of these issues, several IHS commercial systems are now used and intercompared. Moreover, detection of soluble PD-L1 (sPD-L1) is feasible in blood sera of the patients with solid cancer, showing some correlation with response to PD-1 inhibitors [16].

In general, however, the PD-1 receptors and their ligands in tissue samples are detected by immunohistochemical techniques at single-cell level, as it was performed by Zaya et al. [17]. The workers studied expression of PD-1/PD-1L in different specimens of malignant tissue from the patients with nodal peripheral T-cell lymphomas. The slices from formalin-fixed paraffin-embedded blocks were used for immunostaining, and the ratios of antigen-positive cells were scored at 0 to 4. Their quite heterogenous results for different lymphoma types have shown great complexity of PD-1/PDL1 expression which, probably, may impact on clinical response to PD-1 and PD-1L inhibitors.

To study systemic malignancies (e.g., leukemias), or to assess leukocyte populations, flow cytometric methods may be applied as it was performed by Zhang et al. [18]. The authors studied PD-1 expression on the surface of CD4+, CD8+ lymphocytes and PDL-1 on the monocytes of cervical cancer patients. Such approach may be also applied to the patients with myelo- and lymphoproliferative disorders in case of appropriate trials with PD-1 inhibitors.

FISH techniques allow of determining PDL-1 gene copy numbers in malignant cells, i.e. specific gene amplification in the cells of interest. As shown with lung cancer specimens, this parameter seems to correlate with PDL-1 protein expression, as well as overall survival of the patients [19].

PD-1 expression and functioning of T cells

PD-1 is an antagonist of signals coming from the T cell receptor. Therefore, its expression research has aroused great practical interest. PD-1 expression on T cells is a consequence of cell activation, showing a distinct kinetics. Along with TcR/antigen contact, it may be induced by cytokines with common γ-chain, e.g., IL-2, IL-7, IL-15 [20], IFNα [8], and, to lesser degree, with IL-21.

PD-1 is absent or low on the surface of resting T cells. However, its expression levels are drastically increasing within several hours after stimulation [21]. E.g., the PD-1 levels on T helpers from peripheral blood showed a four-fold increase as soon as 24 h after their *in vitro* exposure to standard cell stimulants (PMA or ionomycin) [22]. Experiments with *in vitro* activation of murine lymph node lymphocytes

have shown PD-1 expression detectable in 1/3 of the CD4+ и CD8+ cells having been activated for 24 hours [23]. PD-1 expression level in T and B cells from mouse spleen was also increased following stimulation with anti-CD3 antibodies, or ConA and anti-IgM antibodies [24]. Differential effects are shown for distinct agents, e.g., bacterial LPS or dexamethasone did not affect PD-1 levels, whereas PMA/ionomycin caused an increase of this receptor on the surface of murine T and B lymphocytes. Hence, the inhibitory effects of PD-1 may be exhibited as soon as upon their early activation.

When studying the inhibitory effects of PD-1 upon T cell functions, an association was revealed between the rate of signal, resulting from the ligand-receptor interactions, and ability of cells for cytokine production, proliferation and cytotoxic activities in response to antigenic stimulation [25]. E.g., the PD-1 stimulation did not exert sufficient effects upon IFNγ and β-chemokine production, associated with full inhibition of IL-2 and TNFα secretion.

Meanwhile, the cytotoxic T cells that expressed PD-1 at very high rates, were able to trigger a reaction cascade switching the *in vitro* apoptosis [26]. Introduction of antibodies to PD-1 into the cell cultures promoted apoptosis only in the cell populations with PD-1^{high}++CD3+CD8+ phenotype, without any sufficient effect upon cytotoxic T cells expressing PD-1 at low density.

A similar trend was noted for the virus-specific T cells, when the PD-1/PD ligand interaction was followed by apoptosis, but not effector attack towards virus-infected cells. When studying chronic virus choriomeningitis in mice, blockage of PD-1/PD-L1 pathway during early activation of naïve T cells resulted into stronger effects of cytotoxic T cells against the virus-infected cells [27]. Exponential clonal T cell expansion was also observed, with TcR re-expression within 2 weeks and accumulation of antigen-specific cells able to express cytotoxic properties. [28]. In case of PD-L1 pathway blockade, a population of hyperactivated proinflammatory TCR^{high}CD8+ T cells, able to exhibit and augment antitumor immune response along with probable autoimmune lesions in the model of mice lymphoma [28, 29].

PD-1 expression on T cells depends on their differentiation state

Normally, PD-1 is detected on ca. 10% of peripheral T cells, with similar rates for CD4+ and CD8+ T lymphocytes [30]. PD-1 expression levels sufficiently differ at distinct stages of T cell differentiation and besides show some special features for the high- and low-PD1 populations. E.g., when assaying PD-1 expression on peripheral cytotoxic T cells from healthy donors, this receptor was revealed on 40-80% memory T cells, being absent on naïve cells [31,32]. Among mature cytotoxic cells, PD-1 was revealed on 60% of the memory effector cells with CD45RA–CCR7–, whereas this value did not exceed 25% for the central memory cells. Higher expression of mRNAs for CD28 and CD27 costimulators and inhibitory CTLA-4 receptors, as well as homing-mediating chemokine receptors CXCR6, CXCR4 и CCR5, and Granzyme K were characteristic for the PD-1hi cells. If compared with PD-1-negative cytotoxic T cells, the low KIR «killer cell Ig-like receptors» expression, as well as low Granulysin and Granzyme B expression were revealed in the given population. Notably, presence of PD-1 on the cell surface was associated with decreased levels of mRNAs for cell adhesion molecules, i.e., CD11b, CD11c and CD56 [31].

Surface phenotypic analysis of PD-1^{hi} and PD-1^{low} CD8+ memory T cell populations has shown that CD127 expression is higher at the PD-1^{hi} cell surface whereas more perforin was revealed in the granules of PD-1^{low} cells. Moreover, the PD-1 positivity was accompanied by increased CD95/Fas levels and decreased anti-apoptotic factor Bcl-2, if compared to the PD-1-negative cells [33].

Worth of note, the PD-1 expression is sometimes used as an additional marker of T cell differentiation. E.g., the phenotype of central memory T cells could be described as CCR7+CD27+CD28+CD45RA–CD57–KLRG1–PD1– cells. In the course of further differentiation into the effector memory cells, they acquire CCR7–CD27+/–CD28+/–CD45RA–CD57+/–KLRG1+/–PD1+ profile, whereas differentiated TEMRA effector cells are described as CCR7–CD27–CD28–CD45RA+CD57+KLRG1+PD1+/– subpopulation [34]. This approach allows to consider PD-1, along with CD57 and KLRG1, as markers of late differentiation T lymphocyte aging.

PD-1 expression in different subpopulations of immune cells

Regulatory T cells

The PD-1/PD-L1 interactions are highly important for differentiation of naïve T cells towards induced regulatory cells (iTregs) and for their functional support [35, 36]. E.g., the TGFβ-mediated transition from naïve T cells to Tregs proceeded much more efficient in contact with PD-L1 than in absence of this ligand. Also it was shown for Th1 polarization towards Tregs [37]. Moreover, the contacts between PD-1 on regulatory T cells and PD-L1 on cytotoxic T cells are quite necessary for suppressory effect of CD8+ T cells, as shown for the virus-specific immune response [38]. After blockade of PD-1, but not PD-L1 separately on murine Treg cells *in vitro*, a decreased suppressor activity of this population was observed with respect to cytotoxic T cell proliferation and IFNγ production. Such features of PD-1/PD-L1 signaling towards Tregs may be considered as a special mechanism causing insufficiency of, e.g., antitumor immune response, in case of excessive PD-L1 production by malignant cells [39].

NK cells

PD-1 expression shows some specific features in natural killer (NK) cell populations. When studying CMV-seropositive donors and patients with ovarian cancer, the PD-1 receptor was highly expressed on CD56^{dim}, but not on CD56^{bright} blood lymphocytes with mature NK phenotype (NKG2A–KIR+CD57+) [39]. The PD-1-specific mRNA expression was also higher in CD56^{dim} than in CD56^{bright} NK cells, and the specific protein was detected in all NK cells by means of confocal microscopy [41]. PD-1 expression on NK cells was also shown in other cancers, e.g. Kaposi sarcoma myeloma

and gastrointestinal cancers [42, 43, 44]. Studying the effects of PD-1/PD-L1 blockage in various *in vitro* systems and murine cancer models has demonstrated a significance of this signal pathway for inhibition of NK cell functions, as well as their recovery in case of its blockade [45, 46]. However, real significance of the PD1/PDL1 pathway in antitumor immune response, and in particular, antitumor activity against malignant cells with acquired MHC-1 loss is not clear so far. Therefore, the NK activation mechanisms when using PD-1/PD-L1 inhibitors remain unclear and deserve further studies. E.g., one may suggest induced PD-L1 expression by tumor cells in response to IFNγ secretion by NK cell, with subsequent attraction of PD-1+ T cells and Tregs expansion [46].

Invariant NKT cells (iNKT)

PD-1/PD-L1 signaling is important for invariant NKT cells both in cancer and chronic viral diseases. E.g., peripheral iNKT cells in patients with non-small-cell lung cancer expressed PD-1 at sufficiently higher levels than in healthy donors [47]. *In vitro* stimulation of iNKT cells by α-galactosyl ceramide caused increased PD-1 expression, whereas PD-1/PD-L1 blockage prevented anergy of this population and induced Th1-cytokines, thus leading to NK cell activation [47, 48, 49].

Myeloid suppressor cells (MDSC)

MDSC population is able to inhibit T and NK cell activity, thus being considered as a suppressor population. The MDSC level and PD-1 expression are increased under permanent antigenic stimulation. E.g., the patients with chronic hepatitis B exhibited higher levels of MDSC (CD14+HLA-DR$^{-/low}$) in peripheral blood, as well as PD-1 expression on these cells. The suppressor effects of this population against cytotoxic T cells could be caused by the PD-1-induced IL-10 production [50]. In mice with mammary tumors, a largely increased PD-1 expression was revealed in tumor-infiltrating MDSCs (CD11b+Gr1+), when compared to expression in bone marrow and spleen. Moreover, the PD-1+ MDSC population showed higher proliferation rates than the PD-1-negative MDSCs [51]. MDSCs may influence the efficiency of anticancer immune therapy with PD-1/PD-L1 inhibitors [52], and contents of this population may be regarded as a potential prognostic marker in this treatment mode [53].

PD-1 expression on T cells in malignant diseases

The inhibitors of PD-1/PD-L1 have yielded impressive results in clinics when treating several cancer diseases, despite still unclear immunological effects produced by these agents. However, efficiency of such therapeutic option proved to be maximal in cancer with high mutation burden, or in tumors with very high expression of PD-L1. In general, the rate of PD-L1 expression in tumors is limited to 20 per cent of cases, but the therapeutic effects are not limited by only absence or presence of PD-L1 or PD-1 expression on malignant cells or tumor-associated lymphocytes [54]. In recent years, clinical research is directed towards combined anticancer therapy including PD-1/PD-L1 inhibitors, in order to improve clinical outcomes [55].

PD-L1, a natural PD-1 ligand, was subject to a number of studies in the field of cancer therapy. PD-L1 expression is normally absent in benign tissues, but it is observed in malignant cells. Increased PD-L1 expression seems to be induced by IFNγ, a physiological response limiting the inflammation area and preventing tissue damage [56, 57]. Cancer cells and their microenvironment may develop PD-L1 expression, due to attraction of lymphocytes, i.e., IFNγ-producing T cells. In melanoma patients, the melanocytes are grouped around PD-1+ tumor-infiltrating lymphocytes [58]. The T cells expressing PD-1 (and, probably, B7-1) seem to become dysfunctional when binding PD-L1, and they lose their effector abilities, thus leading to escape of tumor cells from immune surveillance, causing the so-called adaptive resistance [59].

Current predictive diagnostics of the PD-1/PD-L1 blocker efficiency is based on this presumption, by determining PD-L1 expression in malignant tissue by means of immunohistochemistry. More recently, a number of works suggest low efficiency of this index as a marker of therapeutic response [60]. Moreover, a constitutively high PD-L1 expression is found in some cancers which does not depend on presence of tumor-infiltrating lymphocytes, e.g., in Hodgkin lymphoma [61, 62]. Hence, the patients with PD-L1 negative tumors can still respond to immune checkpoint blockade, however a subgroup of PD-L1+ patients still do not respond, as shown for some common solid cancers [63].

PD-1 expression is increased on the surface of T cells in the wide range of oncological diseases [64, 65]. Expression of this molecule in melanoma was sufficiently higher on the tumor-infiltrating CD4+ and CD8+ T cells as compared to normal blood cells and tissues. Antigen-specific T cells showed the same feature. PD1-positive intratumor CD8+ T cells were characterized by the so-called "exhausted" phenotype: they expressed CTLA-4, showed low cytokine production in response to PMA/ionomycin, but being mostly positive for HLA-DR and CD127-negative [65].

In breast cancer, PD-1 expression in tumor-infiltrating CD8+ T cells was also increased. However, the intratumor T cells had different phenotype and functional properties, i.e, TIM-3 and 2B4 proved to be more expressed on CD8+ T cells from melanoma patients, whereas CD8+ T cells from breast cancer patients retained their degranulation ability, IFNγ, TNFα and IL-2 production, and could be therefore regarded as functional cell population [66]. Similar situation is noted for other malignant diseases including oncohematological diseases, e.g AML [67]. Hence, an increased PD-1-expression on CD8+ T cells could not be considered a common feature of cellular dysfunction which may develop in response to a variety of microenvironmental factors in distinct tumor types.

Hence, PD-1 expression in T lymphocytes, being induced by many biologically active factors, is the least reliable predictor of clinical response to PD-1 inhibitors. So far, the major predictive markers for checkpoint inhibitor response include PD-L1 expression, and indirect markers, such as high tumor mutational burden, microsatellite instability, CD8 infiltrates etc. [63].

Conclusion

PD-1 is an inhibitory receptor of cellular immune response expressed on different immune cell populations. There are sufficient features of PD-1 expression and regulation of anti-tumor response, being dependent on PD-1 ligands (PDL-1), costimulatory molecules and target tumor antigens.

We have considered some features of PD-1 expression in normal cells and malignancies which show great variability when studied in experimental models and under clinical conditions. This functional heterogeneity may explain wide variability of individual response in clinical studies of PD-1 inhibitors in different human malignancies. Further search for more reliable and immediate laboratory predictors of response to PD-1 inhibitors deserve future studies.

Conflict of interest

No conflict of interests is declared.

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Рецептор PD-1 на иммунных клетках, его экспрессия и потенциальная роль в противоопухолевой терапии

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Резюме

В последнее десятилетие к PD-1 и его лиганду PD-L1 приковано большое внимание в связи с высокой эффективностью терапии ряда опухолевых заболеваний блокаторами PD-1/PD-L1. В рамках данного обзора обобщены данные по экспрессии рецептора PD-1 на различных популяциях Т-клеток и его потенциальной роли в противоопухолевом иммунном ответе.

Кроме общего описания молекулярной структуры и межмолекулярных взаимодействий, основное внимание в обзоре уделено особенностям экспрессии PD-1 на популяции CD8+ Т-клеток, которая играет центральную роль в противоопухолевом иммунном ответе. Общие закономерности изменений уровня экспрессии PD-1 в ходе процессов клеточной активации и дифференцировки были рассмотрены в основном относительно этой клеточной популяции. Экспрессия PD-1 отмечается также на поверхности Т-регуляторных, NK-, инвариантных NKT-, миелоидных супрессорных клеток, что, вероятно, имеет важную роль в ходе противоопухолевого иммунного ответа, и имело отражение в данном обзоре. При проведении терапии ингибиторами PD-1/PD-L1 вышеперечисленные популяции могут влиять на формировании резистентности к данному виду терапии. В связи с этим, многие современные исследования направлены на выяснение их вовлеченности в процесс иммунорегуляции и возможности использования их в качестве биомаркеров оценки эффективности терапии ингибиторами иммунных контрольных точек.

Ключевые слова

PD-1, PD-L1, экспрессия, Т-клетки, противоопухолевая терапия, ингибиторы иммунных контрольных точек.