Drug Resistance Updates 43 (2019) 10–28

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

YY1 regulates cancer cell immune resistance by modulating PD-L1 expression

Emily Hays, Benjamin Bonavida*

Department of Microbiology, Immunology and Molecular Genetics, David Geffen School of Medicine, University of California, Los Angeles, CA, 90095, United States

ARTICLE INFO

Keywords:
YY1
PD-L1
Crosstalks
Signaling
Therapy

ABSTRACT

Recent advances in the treatment of various cancers have resulted in the adaptation of several novel immunotherapeutic strategies. Notably, the recent intervention through immune checkpoint inhibitors has resulted in significant clinical responses and prolongation of survival in patients with several therapy-resistant cancers (melanoma, lung, bladder, etc.). This intervention was mediated by various antibodies directed against inhibitory receptors expressed on cytotoxic T-cells or against corresponding ligands expressed on tumor cells and other cells in the tumor microenvironment (TME). However, the clinical responses were only observed in a subset of the treated patients; it was not clear why the remaining patients did not respond to checkpoint inhibitor therapies. One hypothesis stated that the levels of PD-L1 expression correlated with poor clinical responses to cell-mediated anti-tumor immunotherapy. Hence, exploring the underlying mechanisms that regulate PD-L1 expression on tumor cells is one approach to target such mechanisms to reduce PD-L1 expression and, therefore, sensitize the resistant tumor cells to respond to PD-1/PD-L1 antibody treatments. Various investigations revealed that the overexpression of the transcription factor Yin Yang 1 (YY1) in most cancers is involved in the regulation of tumor cells' resistance to cell-mediated immunotherapies. We, therefore, hypothesized that the role of YY1 in cancer immune resistance may be correlated with PD-L1 overexpression on cancer cells. This hypothesis was investigated and analysis of the reported literature revealed that several signaling crosstalk pathways exist between the regulations of both YY1 and PD-L1 expressions. Such pathways include p53, miR34a, STAT3, NF-kB, PI3K/AKT/mTOR, c-Myc, and COX-2. Noteworthy, many clinical and pre-clinical drugs have been utilized to target these above pathways in various cancers independent of their roles in the regulation of PD-L1 expression. Therefore, the direct inhibition of YY1 and/or the use of the above targeted drugs in combination with checkpoint inhibitors should result in enhancing the cell-mediated anti-tumor cell response and also reverse the resistance observed with the use of checkpoint inhibitors alone.

1. Introduction

Cancer cells harbor various mutations that allow for enhanced proliferation and survival beyond that of normal cells. Cancer cells escape the host's cellular regulatory systems and immune systems, leading to uncontrolled growth, metastasis, and death. Cancers vary in their types of mutations they carry and the underlying mechanisms by which they cause the disease in the host. Thus, various therapeutic modalities have been developed for different cancers, including (1) chemotherapy, which among various mechanisms of action also kills cells by damaging DNA and inhibiting mitosis (Weaver and Cleveland, 2005; Gonen and Assaraf, 2012; Wijdeven et al., 2016; Mudduluru et al., 2016; Zhitomirsky and Assaraf, 2016; Alam, 2018), (2) radiotherapy, which uses high energy rays to destroy cancer cells in a targeted area (Krause et al., 2017), and (3) immunotherapies, which enhance the host immune system's attack on malignant cells (Zhang and Chen, 2018). However, a plethora of mechanisms of chemoresistance frequently emerge which markedly limit the efficacy of chemotherapy, hence the burning need for novel modalities to overcome antitumor drug resistance (Livney and Assaraf, 2013; Li et al., 2016; Bar-Zeev et al., 2017). Likewise, several mechanisms have been found that underlie resistance to immunotherapies (Rieth and Subramanian, 2018;

Abbreviations: AID, activation-induced deaminase; c-Myc, cellular Myc; COX-2, cyclooxygenase-2; HDACs, histone deacetylases; IGF-1, insulin-like growth factor-1; IFNγ, interferon gamma; IL, interleukin; LAG3, lymphocyte activation gene 3; mTOR, mammalian target of rapamycin; miRs, microRNAs; NF-κB, nuclear factor Kappa-light-chain-enhancer of activated B cells; PTEN, phosphatase and tensin homolog; PI3K, phosphoinositide 3-kinase; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death receptor ligand 1; Akt, protein kinase B; TGFβ, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; YY1, Yin Yang 1

* Corresponding author.
E-mail address: bbonavida@mednet.ucla.edu (B. Bonavida).

https://doi.org/10.1016/j.drup.2019.04.001
Received 12 March 2019; Received in revised form 3 April 2019; Accepted 5 April 2019

Draghi et al., 2019) and several strategies have been reported to reverse immune resistance (Bonavida and Chouaib, 2017).

The immune system plays several roles in protecting the host from cancer via various mechanisms. These include preventing virus-induced tumors, preventing an inflammatory environment conducive to tumorigenesis, and identifying cells that have escaped tumor-suppressor mechanisms and targeting them for cell death before they can become malignant (Vesely et al., 2011; D'Souza et al., 2019). Both innate and adaptive immunities play a role in preventing tumorigenesis. Innate immune cell populations such as natural killer cells, natural killer T-cells, and γδ T-cells can interact with cancer cells and dendritic cells. Macrophages can also respond to damage-associated molecular patterns caused by tumor-derived DNA (Woo et al., 2015). Additionally, adaptive immune components such as T-cells can mount cytotoxic immune responses against cancer cells and prevent malignancy (Vesely et al., 2011; Farhood et al., 2019). Thus, several types of immunotherapies have been developed to enhance host immune responses. Some examples include antibody therapy, in which antibodies are generated against cancer antigens or receptors and cell-mediated T-cell therapy, which involves the induction of tumor-specific T-cells or ex vivo genetic modification of T-cells to enhance specific antitumor activities (Vesely et al., 2011; Liu and Guo, 2018; Paucek et al., 2019).

However, cancer development can still occur under conducive conditions. Despite the many defenses the host immune system harbors, cancer cells can circumvent host immunity through various mechanisms to cause tumorigenesis and malignancy. For example, genetic mutations in cancer cells often lead to uncontrolled proliferation and poor expression of cancer-associated antigens. These cancer antigens can be presented to T-cells on major histocompatibility class I molecules (MHC1); however, cancer cells downregulate MHC I molecules to silence antigen presentation and escape T-cell cytotoxicity. Cancer cells have also been shown to upregulate anti-apoptotic proteins to resist cell killing as well as proteins involved in growth pathways to enhance their survival and resistance to therapies (Vesely et al., 2011; Carrington et al., 2017).

Cancer cells evade the immune response by creating a tumor microenvironment (TME) in which immune cell effector functions are inhibited and repressed (Quail and Joyce, 2013; Chen et al., 2015b). Tumor cells develop defects in antigen presentation processes or upregulate ligands that disarm cytotoxic T-cells in order to escape the adaptive immune system. A mechanism through which this occurs is via upregulation of ligands for checkpoint proteins expressed on the surface of cytotoxic T-cells, such as PD-1. The checkpoint PD-1 receptor on T-cells, when signaled by its ligand, PD-L1, leads to T-cell anergy and naturally serves as a mechanism for preventing immune overstimulation (Zou et al., 2016). PD-L1 is not expressed at high levels on most human cells under normal conditions, but PD-L1 is highly expressed on the cellular surface of various human cancers (Chen and Han, 2015). Ligation of PD-L1 on tumor cells and the PD-1 receptor on T-cells leads to inhibition of T-cell effector functions, such as T-cell-mediated killing of cancer cells.

Recent advances in cancer immune therapies have led to the development of FDA-approved anti-PD-1 and anti-PD-L1 antibodies that have been shown to be effective in a subset of patients with cancers, such as melanoma, lung, and bladder, as well as in patients with advanced unresponsive tumors (Chen and Han, 2015). However, these antibodies are not always effective in all patients with overexpressed PD-L1 positive cancers, as therapy resistance was reported in up to 60% of patients treated (O'Donnell et al., 2017). Therefore, there is still a need for more effective single and combination immune therapies. For instance, targeting the mechanisms by which PD-L1 is upregulated in cancer cells is one approach to enhance antitumor immunity. However, the mechanisms by which tumor cells upregulate PD-L1 expression are not fully understood.

The transcription factor, YY1, has been identified as a master regulator of many pathways involved in cell growth, survival, epithelial to mesenchymal transition (EMT), metastasis, resistance to chemotherapy, etc. Hence, many cancers have been shown to overexpress YY1 and correlate with poor outcomes (Bonavida and Kaufhold, 2015; Shi et al., 2015; Khachigian, 2018). We, therefore, hypothesized that YY1 may play a role in the regulation of PD-L1 via crosstalks among the signaling pathways. This review provides evidence demonstrating that YY1 regulates PD-L1 expression via several mechanisms, including (a) p53 and miR34a, (b) cytokines and growth factors IL6, IL17, TGFβ, IFNγ, (c) PTEN/PI3K/AKT/mTOR signaling pathways, (d) c-Myc, as well as (e) COX-2. Thus, one mechanism by whichYY1 regulates tumor resistance to cytotoxic immune functions is through the regulation of PD-L1 expression on tumor cells. In this chapter, we review (1) The role of YY1 in cancer and its regulation of immune resistance, (2) The role of PD-L1 expression in cancer and its resistance to cytotoxic anti-tumor activities, (3) The delineation of several signaling crosstalk pathways in which YY1 regulates the expression of PDL1, both directly and indirectly, and (4) The clinical implications and the exploration of the crosstalk signaling pathways for new targeted therapies to reverse tumor cell immune resistance.

2. YY1: general properties

Several recent reviews on YY1 have described in detail the various functional roles of YY1 in cancer (Agarwal and Theodorescu, 2017; Wang et al., 2017a). In the present review, the focus will be on the relationship between the expression of YY1 and PD-L1. Therefore, we will briefly discuss below the main highlights of YY1 that are relevant to the topic of this review.

2.1. Gene structure and amino acid sequence

YY1 is a zinc-finger transcription factor and member of the Polycomb Group protein family. Polycomb Group proteins are epigenetic regulators of transcription and are involved in stem-cell identity, differentiation and disease (Di croce and Helin, 2013). Using fluorescent in situ hybridization (FISH) analysis, YY1 was mapped to the telomere region of human chromosome 14 at segment q32.2 (Yao et al., 1998; Weintraub et al., 2017). Within the YY1 gene, there are four C2H2-type zinc-finger motifs, which mediate its DNA binding. YY1 is a 414 amino acid protein with 5 exons and a predicted molecular mass of 44 kDa. However, SDS-polyacrylamide gel analysis has shown a molecular mass of 68 kDa due to the structure of the protein (Galvin and Shi, 1997; Kaufhold et al., 2017). Analysis of the YY1 DNA sequence revealed the promoter to be a sequence of 54 bp-long sequence located downstream of the transcriptional start site (Yao et al., 1998; Mandal et al., 2017). There are two domains which mediate its activity as a transcriptional repressor or activator. The C-terminal domain is responsible for transcriptional repression, while the N-terminus domain is responsible for transcriptional activation (Nguyen et al., 2004; Weintraub et al., 2017). In addition to these two domains, there is also a glycine/alanine rich region (amino acids 161–204), a glycine/lysine rich region (amino acids 181–204), a histidine cluster (amino acids 70–80) and a spacer region (amino acids 205–299) (Fig. 1A and B). The glycine/alanine region is essential for transcriptional transactivation, while the glycine/lysine region is important for repressor activity (Bushmeyer et al., 1995; Yang et al., 1996; Weintraub et al., 2017). Deletion of the histidine and spacer regions indicated their roles in the rescuing ability of cells, while the spacer deletion reduced the ability of YY1 to interact with Hdm2 and regulate p53 (Sui et al., 2004; Khachigian, 2018). The amino acids 200–226 within the spacer region have been defined as the REPO (Recruitment of Polycomb) domain for its role in coordinating polycomb protein interactions with DNA (Wilkinson et al., 2010).

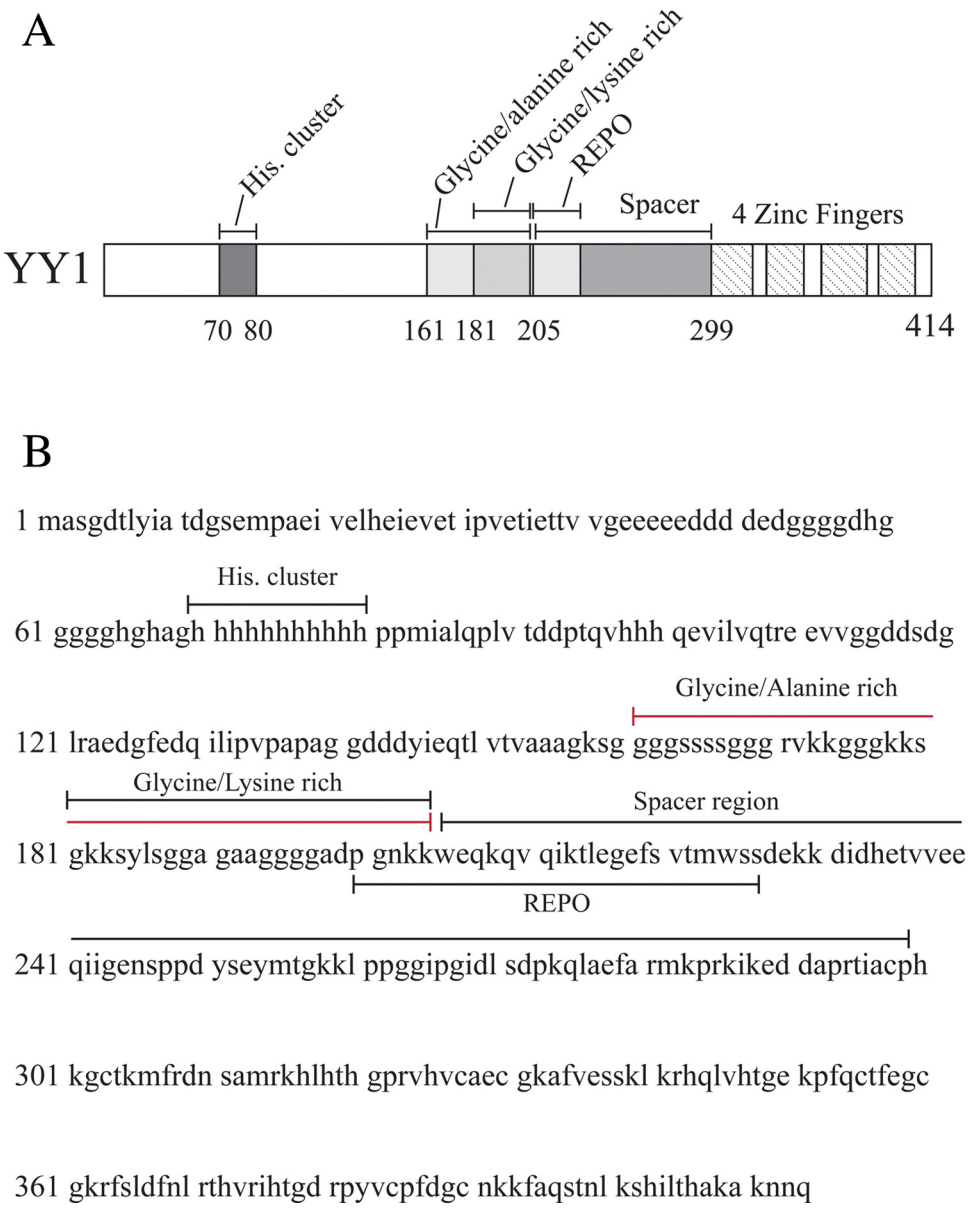

Fig. 1. A: YY1 Gene Structure. The various domains and their location within the YY1 gene are represented in this diagram. Histidine cluster: amino acids 70–80, glycine/alanine rich region: amino acids 161–204, glycine/lysine rich region: amino acids 181–204, spacer region: amino acids 205–299, REPO (Recruitment of Polycomb): amino acids 200–226. **B**: Annotated YY1 Amino Acid Sequence. This diagram represents the 414 human YY1 amino acid sequence and the various domains. Histidine cluster: amino acids 70–80, glycine/alanine rich region: amino acids 161–204, glycine/lysine rich region: amino acids 181–204, spacer region: amino acids 205–299, REPO (Recruitment of Polycomb): amino acids 200–226. Sequence from https://www.ncbi.nlm.nih.gov/protein/3915889#sequence_P25490.2.

2.2. YY1 expression and function during development

Several studies have shown that YY1 plays a fundamental role in various stages of embryogenesis. Mouse embryos with inactivating YY1 mutations were examined at various gestational stages to determine the role of YY1 during embryogenesis. The homozygous mutated YY1 allele caused lethality at the peri-implantation stage, while heterozygosity for the mutant allele caused developmental retardation (Donohoe et al., 1999; Wang et al., 2018c; Gabriele et al., 2017). These findings suggest a role of YY1 in embryonic stem cell development.YY1 has been shown to play a role in cardiac morphogenesis and heart development during embryogenesis (Beketaev et al., 2015) and regulate cardiac α-actin gene expression (Chen and Schwartz, 1997; Gregoire et al., 2017). Thus, YY1 is an essential transcription factor for functional embryogenesis.

YY1 is also essential in several stages of development, including X inactivation (Jeon and Lee, 2011), neural development (Morgan et al., 2004; Knauss et al., 2018), muscle development (Jin et al., 2016), intestinal development (Kumar et al., 2016), and lung development (Boucherat et al., 2015).

YY1 has been identified as a negative regulator of muscle miR expression in myogenesis; in this respect, miR-29 is an important miR involved in myogenesis. The miR-29a has been shown to induce vascular smooth muscle cell differentiation from embryonic stem cells by negatively regulating YY1 (Jin et al., 2016). YY1 collaborates with Rybp, a myogenesis regulator, and NF-kB to silence miR-29 and negatively regulate myogenesis (Wang et al., 2008; Zhou et al., 2012). YY1 silences miR-29 by recruiting Ezh2 and HDAC1 after being activated by NF-kB (Wang et al., 2007; Zhang et al., 2016a). Other mRNAs involved in muscle development also interact with YY1. The miR-1 interacts with YY1 through a negative feedback loop to regulate myogenic differentiation and injury-induced muscle regeneration (Zhou et al., 2012).

YY1 plays a key role in intestinal development. YY1 acts as a positive regulator of the homeobox protein Hoxa5, a gene which is crucial to mouse gut and lung organogenesis (Bérubé-Simard et al., 2014). YY1 regulates intestinal villus development (Kumar et al., 2016) and contributes to intestinal development via regulation of mitochondrial gene expression (Cunningham et al., 2007; Perekatt et al., 2014; Park et al., 2017). YY1 is also crucial for lung development and regulates tracheal cartilage formation, cell differentiation, lung branching, and airway dilation (Boucherat et al., 2015). YY1 has also been shown to negatively regulate lung cancer cell proliferation via regulation of Sox2ot (Zhang

et al., 2017).

Through its networks with a vast array of proteins and other epigenetic factors, YY1 plays an important role in various developmental processes. Neural, muscular, intestinal and lung development all rely on YY1 for some form of regulation. Without adequate regulation of YY1, these processes are impaired or inhibited.

2.3. Expression of YY1

2.3.1. In various human tissues and cancers

YY1 is expressed in various human tissues at different levels and has been found to be inadequately regulated in malignant tissues. Using a variety of human tissue samples, a full length YY1 cDNA probe was used to detect mRNA expression levels in healthy and cancerous tissues (Chinnappan et al., 2009; Bonavida and Kaufhold, 2015). There were at least six YY1 mRNA isoforms detected ubiquitously in normal adult and fetal tissues, but over-expression of two specific isoforms, 7.5 and 2.9 kb in size, were detected in gastrointestinal and other cancer cells. Thus, YY1 may play a role in development or progression of gastrointestinal cancer. High YY1 expression in some cancerous tissues is associated with poor outcomes. In an osteosarcoma study, ten different osteosarcoma samples were analyzed using immunohistochemistry and RT-PCR to determine the levels of YY1 expression compared to normal bone samples (de Nigris et al., 2006, 2012). YY1 had very low expression levels or was almost absent in normal tissues, compared to osteosarcoma tissues which had significantly higher levels of YY1 expression. Overexpression of YY1 in osteosarcoma patients was found to be associated with metastasis and poor outcome (de Nigris et al., 2011). In another study, cervical cancer specimens from 30 patients were analyzed for YY1 expression and correlated with pathogenesis (Wang et al., 2018b). Increased YY1 expression was strongly associated with malignancy of the cervix and the progression of cervical squamous cell carcinoma (CSCC). However, in some cancers, high YY1 expression can be associated with more favorable outcomes. In a study of 26 follicular lymphoma patient biopsies, high YY1 expression was found to be strongly associated with longer patient survival ($p < .01$) (Naidoo et al., 2011; Sandison et al., 2013).

Overall, YY1 is primarily overexpressed and seldom under-expressed in many cancers. Table 1 summarizes the relationship between YY1 expression and different forms of cancer.

2.3.2. In immune cells

YY1 is involved in the regulation of several developmental immune processes. YY1 is involved in the development of B cells by regulating VDJ recombination of the immunoglobulin heavy-chain locus and the progenitor-B-to-precursor-B-cell transition (Liu et al., 2007; Kleiman et al., 2016; Banerjee et al., 2016). YY1 also regulates B-cell development by facilitating the nuclear translocation of the enzyme Activation-induced Deaminase (AID), which is essential for class-switch recombination and somatic hypermutation (Zaprazna and Atchison, 2012).

YY1 is also involved in the regulation of, and differentiation of, T-cells. The differentiation of T-regulatory cells, which is essential to the regulation of the immune system, is directly inhibited by YY1 through the transcriptional repression of Foxp3 (Hwang et al., 2016). YY1 also transcriptionally regulates cytokines, such as IL-2, IL-5, IL-6, IL- 8, IL-17, CCL4, IFN-γ (Table 3). The roles of these cytokines vary across the immune system and can have beneficial or adverse effects in different diseases.

Some cell checkpoint receptors are transcriptionally activated by YY1, such as PD-1, LAG3, and Tim3, which can contribute to T-cell exhaustion and disease progression (Balkhi et al., 2018). YY1 is also essential for the invariant natural killer T (NKT) cell development and asserts its regulation through transcriptionally activating the Plzf gene promoter (Ou et al., 2018). Invariant NKT cells are associated with a variety of other immune functions and the lack of these lymphocytes is associated with poor patient outcomes in several cancers (Motohashi et al., 2011). YY1 also contributes to tumor cell resistance to FasL-induced apoptosis by downregulating Fas expression (Garbán and Bonavida, 2001; Pothoulakis et al., 2017). Additionally, inhibition of YY1 and upregulation of DR5 expression sensitizes cells to TRAIL apoptosis (Bonavida, 2015). In the following sections, the specific mechanisms in which YY1 transcriptionally regulates other proteins involved in cancer development and progression will be discussed.

Table 1
YY1 Expression in Cancer. The cancer YY1 is abnormally expressed in (first column), high or low expression (second column), prognostic significance (third column).

Cancer Type	Level of YY1 expression compared to normal tissues	Prognostic effect based on expression level
Osteosarcoma	High de Nigris et al., 2006	Poor de Nigris et al., 2011
Cervical	High Wang et al., 2018b	Poor Wang et al., 2018b
Follicular Lymphoma	High Naidoo et al., 2011	Good Naidoo et al., 2011
Pancreatic	High Liu et al., 2018	Good Zhang et al., 2014
Lung	High Hou et al., 2010	Poor Xu et al., 2013
Prostate	High Seligson et al., 2005	Poor Seligson et al., 2005
Ovarian	High Berchuck et al., 2005	Good Matsumura et al., 2009
Colon	High Chinnappan et al., 2009	Poor Zhang et al., 2013a
Gastric	High Kang et al., 2014	Poor Kang et al., 2014
Bladder	High Sanchez-Carbayo et al., 2006	Poor Sanchez-Carbayo et al., 2006
Breast	High Curtis et al., 2012	None Curtis et al., 2012
Multiple Myeloma	High Huerta-Yepez et al., 2014	Poor Huerta-Yepez et al., 2008

2.4. YY1: transcriptional regulation

2.4.1. Factors that trigger YY1 expression

Several factors have been shown to trigger or activate YY1, such as IGF-1 (Flanagan, 1995; Blättler et al., 2012) and TNF-α (Huerta-Yepez et al., 2006; Iwai et al., 2018). In quiescent NIH3T3 cells, YY1 expression was rapidly stimulated by the addition of IGF-1 (Flanagan, 1995). Further studies of this interaction have shown YY1 and IGF-1 to be positively correlated in human brain tumors and to play a role in brain gliomatogenesis and meningioma development (Baritaki et al., 2009). YY1 is also stimulated by TNF-α. Treatment of prostate cancer cells with TNF- α resulted in increased YY1 expression and down-regulated Fas expression, while the blockage of TNF- α resulted in decreased YY1 expression and upregulated Fas expression (Huerta-Yepez et al., 2006; Iwai et al., 2018). This study not only revealed an important activator of YY1, but it also suggested a role of YY1 in FasL-induced apoptosis resistance in cancer cells. Additionally, C/EBPβ was found to increase YY1 activity by mutating a single promoter binding site within the HPV11 gene, indicating a regulatory role of YY1 in HPV disease types (Ralph et al., 2006; Wang et al., 2018b).

In lymphocytes, YY1 was stimulated by the addition of Morphine and activated transcription of mu opioid receptor genes (Li et al., 2008; Zaprazna et al., 2017), which are important in various immune functions (Roy et al., 1998; Pentland et al., 2018). In a human CD4 T-cell line, lysoPC, a lysolecithin involved in atherogenesis and inflammation (Kume and Gimbrone, 1994; Heriansyah et al., 2019), also stimulated the expression of YY1 in a concentration-dependent manner (Hara et al., 2008; Yuan et al., 2017). Various factors stimulate YY1

expression and, thus, provide insights as to how YY1 may be regulated.

2.4.2. Transcriptional and post-transcriptional regulators of YY1

Transcription of the YY1 protein is regulated by the transcription factor NF-kB and auto-regulated by itself. In the regulation of skeletal muscle differentiation, NF-κB directly binds to the YY1 promoter through its p50/p65 heterodimer complex and stimulates YY1 gene expression (Wang et al., 2007; Zhang et al., 2018c). In human B cell lines, NF-kB also binds to YY1 through its Rel-B component at the hs4 enhancer region of the Igh gene, forming a complex that may play a role in the anti-apoptotic response (Sepulveda et al., 2004; Morozzi et al., 2017). RelB association with YY1 also promotes the regulation of IFN-β expression, which is important in the anti-viral response (Siednienko et al., 2011). YY1 is also auto-regulated through its own DNA-binding sites within the first intron (Do Kim et al., 2009; Khachigian, 2018). Once YY1 levels reach a certain threshold, the transcription factor begins to negatively regulate its own locus.

Several types of post-transcriptional modifications of the mature YY1 protein can result in the increase or decrease of its DNA-binding capacity, stability, and transcriptional activity. These mechanisms include acetylation (Yao et al., 2001; Wang et al., 2016a), poly(ADP-ribosyl)ation (Oei and Shi, 2001), *O*-linked *N*-acetylglucosaminylation (*O*-GlcNAcylation) (Hiromura et al., 2003), *S*-nitrosation (Hongo et al., 2005; Bonavida and Garban, 2015), methylation (Zhang et al., 2016b), and sumoylation, which also stabilizes YY1 (Deng et al., 2007).

Translocation of transcription factors to the nucleus is essential for transcriptional regulation. Several types of stimuli can induce YY1 translocation to the nucleus, such as the Toll Like Receptor 3 ligand, polyriboinosinic:polyribocytidylic acid (TLR3 poly(I:C)) (Siednienko et al., 2011), Fas, tumor necrosis factor, and etoposide treatment (Krippner-Heidenreich et al., 2005), as well as actin polymerization in pulmonary vascular smooth muscle cells (Favot et al., 2005). Subcellular localization of YY1 is also dependent on the cell cycle and DNA synthesis activity within the cell (Palko et al., 2004; Wu et al., 2018). Thus, confinement of YY1 to the cytoplasm can be a modality of repressive regulation of the transcription factor (Ficzycz et al., 2001; Wu et al., 2018). The subcellular localization of YY1 is important in its transcriptional regulation and is dependent on several signals and the stage of the cell cycle.

2.4.3. Phosphorylation and activity

YY1 can be post-transcriptionally regulated by phosphorylation at its tyrosine, threonine, and serine amino acid residues. Phosphorylation is an important layer of regulation for the DNA-binding capacity of YY1 (Becker et al., 1994; Rizkallah and Hurt, 2009; Daraiseh et al., 2018; Wang and Goff, 2015). Several kinases phosphorylate YY1, such as Plk1 (Sandison et al., 2013), TOPK/PBK (Rizkallah et al., 2015), c-Abl kinase (Daraiseh et al., 2018), casein kinase II alpha (CK2α) (Riman et al., 2012), Aurora kinase B (Kassardjian et al., 2012), and Aurora kinase A (Alexander and Rizkallah, 2017). Phosphorylation of YY1 by a variety of kinases regulates its transcriptional activity, influences its stability, and thus serves as an additional level of post-transcriptional YY1 regulation.

2.4.4. Role of micro RNAs (miRs) in the regulation of YY1

There have been many micro RNAs (miRs) found to be involved in the negative regulation of YY1. Many of the miRs regulate YY1 through negative feedback loops. Some of these miRs and their effects on YY1 are summarized in Table 2A.

Studies are ongoing to find several more miRs involved in YY1 repression and negative feedback. These mechanisms of regulation are involved in many disease types. Therefore, more research on YY1 and miRs may lead to new treatments and therapies. A summary of the known YY1 regulatory activators and repressors is shown in Table 2B .

2.5. YY1 as a transcription factor

Due to the ubiquitous nature of YY1, this transcription factor is involved in many regulatory mechanisms in various processes and pathways in the body. Thus, every factor influenced by YY1 cannot be discussed in this review and has been reviewed elsewhere (Agarwal and Theodorescu, 2017; Wang et al., 2006). However, a summary of some of the factors and pathways influenced by YY1 are shown in Table 3. The results of these interactions often have effects in both the pathogenesis of cancer and modulation of the anti-cancer immune processes.

3. PD-L1: general properties

3.1. Gene structure

The PD-L1 protein is encoded by the CD274 gene and is expressed in T-cells, B-cells and several types of tumor cells. PD-L1 is a transmembrane protein that interacts with the PD-1 receptor expressed on T-cells in order to inhibit T-cell activation and cytokine production (Lin et al., 2008; Kythreotou et al., 2018; Zak et al., 2017). The gene has 7 exons and is located in the genome on chromosome 9 at location 9p24 (Shi et al., 2013). It is part of the immunoglobulin superfamily and has an Ig-like V-type domain and an Ig-like C2-type domain (Dong et al., 1999; Berger and Pu, 2018). There are 3 main sections of the gene identified through BLAST, which correspond to the extracellular domain, helical domain, and cytoplasmic domain of the protein. The seven exons correspond to the 5′ UTR, signal sequence, IgV-like domain, IgC-like domain, transmembrane domain, intracellular domain, and 3′ UTR, respectively (Shi et al., 2013)

3.2. Amino acid sequence

The amino acid sequence is 290 amino acids in length. The Ig-like V-type domain ranges from amino acids 26–131, while the Ig-like C2-type domain ranges from amino acids 132–234 and the signal peptide ranges from amino acids 1–22 (Dong et al., 1999). The extracellular domain corresponds to amino acids 26–238, while the transmembrane domain corresponds to amino acids 240–260 and the cytoplasmic domain corresponds to amino acids 261-290. The amino acid sequence is shown below with the annotated domain locations (Fig. 2).

3.3. Expression and function

3.3.1. In tissues

PD-L1 is normally expressed in non-lymphoid tissues in the body. It is highly expressed in the heart, skeletal muscle, placenta, and lung (Dong et al., 1999; Torabi et al., 2017). PD-L1 is upregulated in the target organs of tissue-specific autoimmune diseases, suggesting a role for PD-L1 in tissue-directed inflammatory responses (Liang et al., 2003; Lanzolla et al., 2019). Tissue-expressed PD-L1 mediates peripheral T-cell tolerance and autoimmunity by binding to PD-1 on T-cells and inhibiting pathogenic self-reactive CD4+ T-cells and the resulting cytokine production (Keir et al., 2006; Bommarito et al., 2017). In addition to regulating effector T-cell responses, PD-1 and PD-L1 interaction also plays a role in the early fate decisions of CD8 T-cells (Goldberg et al., 2007; Sen et al., 2016).

3.3.2. In cancer

Several cancers exhibit an upregulation of PD-L1 expression to provide protection from cell death by cytotoxic T-cells and to maintain an immunosuppressive tumor microenvironment (Topalian et al., 2012). By upregulating PD-L1, tumor cells block T-cell functions and antitumor responses (Topalian et al., 2012). This leads to enhanced tumorigenesis and invasiveness of cancer cells (Iwai et al., 2002; Fabrizio et al., 2018). The presence of tumor cells with upregulated PD-L1 correlates with poor prognosis in patients with several types of

Table 2A
Role of MiRs in the Regulation of YY1. Name of the MiR (first column), effect on YY1 (second column), the disease or process which this interaction affects (third column), reference (fourth column).

Micro RNA	Effect on YY1	Involved Process	Reference
MiR-29	Repression	Skeletal myogenesis and rhabdomyosarcoma	(Wang et al., 2008)
MiR-29a	Repression	AKT pathway in Adenocarcinoma	(Zhang et al., 2018c)
MiR-7	Repression	Colorectal cancer	(Zhang et al., 2013a)
MiR-181	Repression	Cervical cancer	(Zhou et al., 2015)
MiR-381	Repression	Ovarian cancer	(Xia et al., 2016)
MiR-205	Repression	Gastric cancer	(Yin et al., 2014)
MiR-1	Repression	Skeletal myogenesis	(Lu et al., 2012)
MiR-141-3p	Repression	Papillary thyroid cancer	(Fang et al., 2018)
MiR-186	Repression	Prostate cancer	(Lu et al., 2017)
MiR-34a	Repression	P53 network	(Chen et al., 2010)
MiR-34c	Repression	Myoblast proliferation	(Wang et al., 2017c)
MiR-34 family	Repression	Gastric carcinogenesis	(Wang et al., 2014)
MiR-147b	Repression	Cardiovascular disease	(Yue et al., 2018)
MiR-215	Repression	Colon cancer	(Chen et al., 2016)
MiR-584	Repression	Gastric cancer	(Zheng et al., 2017)
MiR-30a	Repression	Pancreatic cancer	(Yang et al., 2017)

Table 2B
Regulators of YY1 Expression. The regulator of YY1 (first column), negative or positive regulation (second column), reference (third column).

Regulatory Factor of YY1	Type of Regulation on YY1	Reference
Fas	Positive	(Krippner-Heidenreich et al., 2005)
TLR3 (Poly(I:C))	Positive	(Siednienko et al., 2011)
O-GlcNAcylation	Positive	(Hiromura et al., 2003)
IGF-1	Positive	(Flanagan, 1995; Baritaki et al., 2009)
TNF-α	Positive	(Huerta-Yepez et al., 2006)
Morphine	Positive	(Li et al., 2008)
LysoPC	Positive	(Hara et al., 2008)
C/EBPBeta	Positive	(Ralph et al., 2006)
FGF-2	Positive	(Santiago et al., 2001)
FGF-21	Positive	(Ji et al., 2015)
NF-kB	Positive	(Wang et al., 2007; Sepulveda et al., 2004)
Aurora kinases	Negative	(Kassardjian et al., 2012; Alexander and Rizkallah, 2017)
TOPK/PBK	Negative	(Rizkallah et al., 2015)
Nitric Oxide	Negative	(Hongo et al., 2005)
YY1	Negative	(Do Kim et al., 2009)
p300	Negative	(Yao et al., 2001)
PCAF	Negative	(Yao et al., 2001)
HDAC1	Negative	(Yao et al., 2001)
HDAC2	Negative	(Yao et al., 2001)
Poly(ADP-ribose) Polymerase	Negative	(Oei and Shi, 2001)
Actin Polymerization	Negative	(Favot et al., 2005)
PIASy	Negative	(Deng et al., 2007)
SET7/9	Negative	(Zhang et al., 2016b)
Plk1	Negative	(Sandison et al., 2013)
c-Abl kinase	Negative	(Daraiseh et al., 2018)
CK2alpha	Negative	(Riman et al., 2012)
Prohibitin	Negative	(Joshi et al., 2007)

cancer, such as ovarian cancer (Hamanishi et al., 2007), urothelial cell carcinoma of the bladder (Boorjian et al., 2008), hepatocellular carcinoma (Gao et al., 2009), malignant melanoma (Spranger et al., 2013), inflammatory and non-inflammatory breast cancers (Bertucci et al., 2015), non-small-cell lung cancer (NSCLC) (D'incecco et al., 2015), and renal cell carcinoma (RCC) (Iacovelli et al., 2016). There are currently antibody therapies with both anti-PD-1 and anti-PD-L1 antibodies available for cancer patients. In an analysis of 20 trials carried out in metastatic melanoma (MM), NSCLC, and RCC patients receiving anti-PD-1/PD-L1 antibodies, the summary objective response rates for MM patients were 45% and 27% in PD-L1 positive and negative patients, respectively (Gandini et al., 2016). In NSCLC patients, the summary objective response rates were 29% and 11% in PD-L1 positive and negative patients, respectively. RCC patients did not show any significant difference between PD-L1 positive and negative status. Overall, this study concluded that PD-L1 expression is significantly associated with mortality and response to antibody treatment in MM and NSCLC patients. In another study, NSCLC patients who expressed PD-L1 on at least 50% of tumor cells treated with a monoclonal antibody against PD-1 were compared to patients treated with chemotherapy (Reck et al., 2016). Patients treated with the drug Pembrolizumab, an anti-PD-1 antibody, had significantly longer progression-free survival and overall survival and fewer adverse events than patients treated with platinum-based chemotherapy. Therefore, antibodies against PD-1 can be more effective than chemotherapy for NSCLC patients. Antibody therapies against PD-1/PD-L1 have also been shown to be effective in patients with gastric cancer (Muro et al., 2016), metastatic breast cancer (Dirix et al., 2016), RCC (Motzer et al., 2015).

Although immune checkpoint antibodies have had positive responses in many PD-L1 positive patients, these antibodies are not always effective, as resistance was reported in up to 60% of patients treated (O'Donnell et al., 2017). Thus, many new therapeutic targets and combination therapies are being explored. Although PD-L1 expression on tumor cells is correlated with a better response to checkpoint inhibitor antibodies, two recent studies have shown that PD-L1 on host myeloid cells is the primary target for the PD-1/PD-L1 checkpoint inhibitors and that tumor expression of PD-L1 is essentially irrelevant in the checkpoint inhibitor mechanism (Lin et al., 2018b; Tang et al., 2018). Thus, tumor expression of PD-L1 may only be a biomarker for therapeutic responses to the PD-1/PD-L1 checkpoint blockade. In addition to the PD-1 and PD-L1 checkpoint inhibitors, other drugs that may block regulatory pathways which enhance cytotoxic T-cell activity are under development. Some of these drugs are aimed to block LAG3, TIM3 or HAVCR2, VISTA or C10orf54, and TIGIT (Gotwals et al., 2017). There are also new therapies that are engineered to up-regulate pathways that stimulate T-cell function and inhibit immunosuppressive metabolites and cytokines (Gotwals et al., 2017). The combination of different therapeutic approaches is highly needed to generate more effective treatments for cancer patients.

3.4. Regulation of PD-L1 expression

PD-L1 is upregulated on dendritic cells, vascular endothelial cells, and tumor cells in response to inflammatory cytokines, such as IFN-γ (Wilke et al., 2011; Wang et al., 2017b). There are many signaling pathways involved in the activation and regulation of PD-L1 expression and are listed in Table 4. Also, there are many more miRs involved in

Table 3
Processes and factors influenced by YY1. The factor influenced by YY1 (first column), positive or negative regulation (second column), type of regulation (third column), brief description of the effect of the interaction (fourth column), reference (fifth column).

Factor or process influenced by YY1	Positive or Negative regulation	Level of Regulation of factor	Effect of interaction	Reference
PTEN	Negative	Transcriptional	Resistance to apoptosis by CTL and cytotoxic drugs	(Reddy et al., 2012)
Snail	Positive	Transcriptional	Increased epithelial-mesenchymal transitions	(Palmer et al., 2009)
AID nuclear translocation, AID mediated mutations	Positive	Post- translational physical interaction	Regulation of class switch recombination and somatic hypermutation	(Zaprazna and Atchison, 2012; Zaprazna et al., 2017)
COX-2	Positive	Transcriptional	Increased inflammatory response to LPS	(Joo et al., 2007)
p53	Negative	Post- translational physical interaction	Repression of p53 tumor suppressor leading to cancer progression	(Sui et al., 2004)
PKB/AKT phosphorylation	Positive	Post- translational physical interaction	Increased breast cancer cell survival and proliferation	(Zhang et al., 2016a)
MMP10	Negative	Transcriptional	Suppressed invasion and metastasis of pancreatic cancer cells	(Zhang et al., 2014)
CCL4 chemokine	Positive	Transcriptional	Overexpression of CCL4 in pulmonary disease	(Rangel-Santiago et al., 2016)
MYCT1	Negative	Transcriptional	Leads to laryngeal tumorigenesis and cancer progression	(Qu et al., 2017)
c-Myc	Negative	Transcriptional	Leads to poor outcomes in NSCLC	(Sankar et al., 2008; Kim et al., 2017)
Survivin	Negative	Transcriptional	Possible contribution to cancer progression	(Galloway et al., 2014)
C/EBPalpha	Negative	Transcriptional	Suppression of miR-34a and YY1 upregulation in renal cell carcinoma cells	(Weng et al., 2014)
IL-6	Positive	Transcriptional	Induced neuroinflammation and rheumatoid arthritis inflammation	(Zhang et al., 2018b)
IL-17	Positive	Transcriptional	Th17 cell differentiation and rheumatoid arthritis pathogenesis	(Kwon et al., 2018)
IL-5	Negative	Transcriptional	Regulation of IL-5 expression has implications in several immune functions	(Mordvinov et al., 1999)
Foxp3 expression	Negative	Transcriptional	Inhibition of T regulatory cell differentiation and function	(Hwang et al., 2016)
IL-8	Positive	Transcriptional	Pro-inflammatory activity in rheumatoid arthritis	(Lin et al., 2018a)
miR-146a	Negative	Transcriptional	Delayed progression of prostate cancer	(Huang et al., 2017)
HDAC1	Positive	Transcriptional	Reduced sensitivity of hepatocellular carcinoma cells to HDACi	(Dong et al., 2017)
FEN1	Negative	Transcriptional	Low expression of FEN1 prevents FEN1 from promoting tumor progression in breast cancer cells	(Wang et al., 2015a)
P38	Positive	Transcriptional	Osteogenic differentiation	(Chen et al., 2018)
RKIP	Negative	Indirect Transcriptional	Enhanced tumor growth, metastasis, and anticancer drug resistance	(Wottrich et al., 2017)
CDKN3	Negative	Transcriptional	Progression of pancreatic tumorigenesis and cancer development	(Liu et al., 2018)
G6PD	Positive	Transcriptional	Altered tumor cell metabolism by upregulation of the pentose phosphate pathway	(Wu et al., 2018)
GLUT3	Positive	Transcriptional	Enhanced cancer cell metabolism by increased entry of glucose into the cell	(Wang et al., 2018a)
DNAJB4(HLJ1) and E-cadherin	Positive	Transcriptional	Decreased cancer cell invasion ability	(Wang et al., 2005)
KLF4 (tumor supressor)	Positive	Transcriptional	Regulation of drug resistance in Burkitt's Non-Hodgkin Lymphoma	(Vega et al., 2013)
MDR1	Positive	Transcriptional	Increased resistance to chemotherapy	(Antonio-Andrés et al., 2018)
PLZF	Positive	Transcriptional	Regulation of iNKT cell development	(Ou et al., 2018)
Type I cytokines (IL-2 and IFN-γ)	Negative	Transcriptional	Regulation of T-cell exhaustion	(Balkhi et al., 2018)
PD1, Lag3, and Tim3	Positive	Transcriptional	Upregulation of cell checkpoint receptors in exhausted T-cells	(Balkhi et al., 2018)
TGF-β	Negative	Transcriptional	Repression of TGF-β nuclear signaling	(Yan et al., 2014)
MUC4	Negative	Transcriptional	Regulation of pancreatic cancer development	(Zhang et al., 2013a)
BRCA1	Positive	Transcriptional	Inhibition of mammary cancer cell proliferation and tumor growth	(Lee et al., 2012)

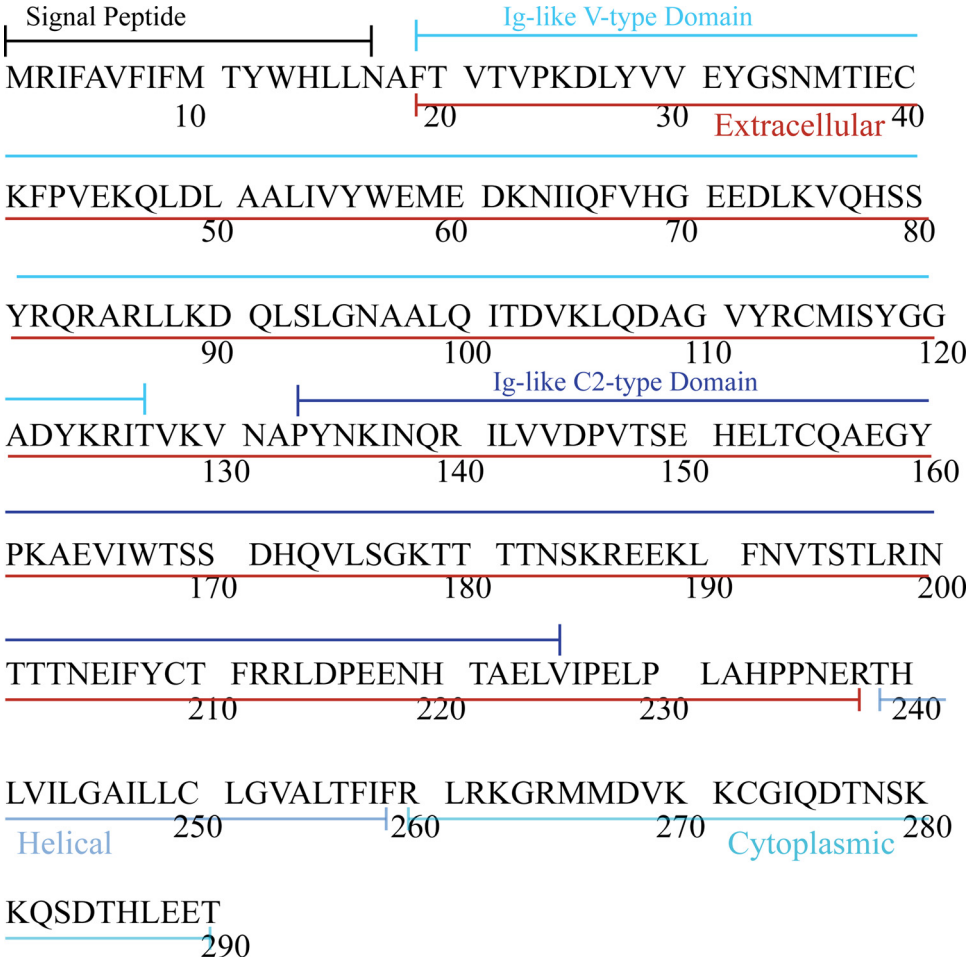

Fig. 2. Annotated amino acid sequence of the PD-L1 gene with labeled domains. Signal peptide (1–22), Ig-like V-type domain (26–131), Ig-like C2-type domain (132–234), extracellular domain (26–238), transmembrane domain (240–260), cytoplasmic domain (260–290) (Dong et al., 1999).

Table 4
Regulators of PD-L1 expression. The name of the factor that influences PD-L1 expression (left column), up-regulation or down-regulation on PD-L1 (second column), type of regulation (third column), reference (fourth column).

Regulatory factor	Effect on PD-L1	Type of Regulation	Reference
LipopolysaccharideIFN-γ, Polyinosinic-polycytidylic acid Toll-like Receptor 4 STAT1 Th1 cells	Up-regulation	Induces transcription factors of PD-L1	(Loke and Allison, 2003)
PI3K/Akt pathway	Up-regulation	Transcriptional, post-transcriptional, and post-translational	(Song et al., 2013)
NF-kB	Up-regulation	Transcriptional	(Gowrishankar et al., 2015)
HIF-1α	Up-regulation	Transcriptional	(Noman et al., 2014)
STAT3	Up-regulation	Transcriptional	(Chen et al., 2015a)
IL-6 and IL-10	Up-regulation	Transcriptional	(Wölfle et al., 2011)
PTEN	Down-regulation	Post-transcriptional	(Song et al., 2013)
MYC	Up-regulation	Transcriptional	(Casey et al., 2016)
Cyclin D-CDK4 and Cullin 3-SPOP E3 ligase	Down-regulation	Post-translational (Proteasome-mediated degradation)	(Zhang et al., 2018a)
miR-197	Down-regulation	Transcriptional by targeting STAT3	(Fujita et al., 2015)
miR-34a	Down-regulation	Post-transcriptional	(Wang et al., 2015b)
miR-200	Down-regulation	Post-transcriptional	(Noman et al., 2017)
miR-142-5p	Down-regulation	Post-transcriptional	(Jia et al., 2017)
miR-140	Down-regulation	Post-transcriptional	(Ji et al., 2018)
miR-181a	Down-regulation	Reduces IFN-γ expression leading to PD-L1 down-regulation	(Sang et al., 2015)
miR-424	Down-regulation	Post-transcriptional	(Xu et al., 2016)
miR-513	Down-regulation	Translational (degrades PD-L1 mRNA directly)	(Gong et al., 2009)
miR-570	Down-regulation	Translational (degrades PD-L1 directly)	(Wang et al., 2013)
miR20b, 21, and 130b	Up-regulation	Reduce PTEN expression leading to PD-L1 overexpression	(Zhu et al., 2014)

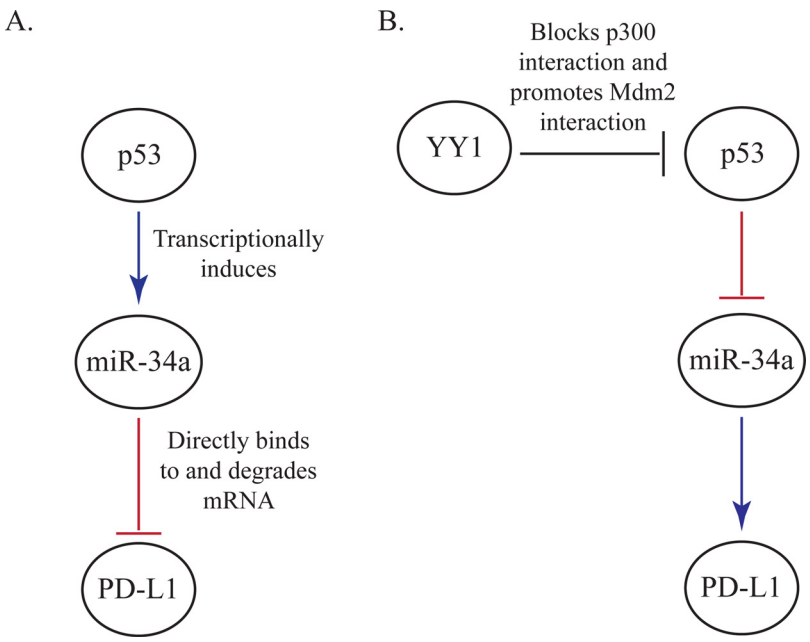

Fig. 3. YY1 Regulation of PD-L1 via p53 and miR-34a. A. Degradation of PD-L1. p53 transcriptionally induces miR-34a, which directly binds to, and degrades PD-L1 mRNA. B. Induction of PD-L1. The regulatory effect of YY1 on PD-L1 is shown via p53 and miR-34a. YY1 down-regulates p53 by inhibiting its interaction with p300 and enhancing the interaction with Mdm2, which ubiquitinates and represses p53. When p53 is repressed, it can no longer transcriptionally induce miR-34a and miR-34a can no longer degrade PD-L1. Through down-regulation of p53 activity, YY1 may have an enhancing effect on PD-L1 expression.

the regulation of PD-L1 expression (Wang et al., 2017d). Several examples are shown in Table 4. Understanding how PD-L1 expression on tumor cells is regulated through crosstalks with other signaling pathways may aid in developing new drug targets and combination therapies to reverse the resistance of cancers to immunotherapies.

3.5. PD-1/PD-L1 interaction and cell signaling

PD-1 is expressed on activated T lymphocytes and plays a role in the inactivation of T cells (Vibhakar et al., 1997; Hutten et al., 2018; Brunner-Weinzierl and Rudd, 2018). The absence of PD-1 on T-cells leads to enhanced generation of CD4/CD8 double-negative peripheral T-cells, suggesting a role for PD-1 in thymic development (Blank et al., 2003; Verstichel et al., 2017). PD-1 knockout mice develop lupus-like proliferative arthritis and glomerulonephritis, while PD-1-mutated mice develop a chronic and systemic graft-versus-host-like disease (Nishimura et al., 1999; Cochain et al., 2014). This suggests that PD-1 is essential in regulating peripheral self-tolerance. PD-1 has two ligands, PD-L1 and PD-L2, which are found on antigen-presenting cells. When PD-L1 binds to PD-1 on T-cells, the signal causes a decrease in T-cell proliferation and cytokine synthesis (Mazanet and Hughes, 2002; Zou et al., 2016; Arasanz et al., 2017). The binding causes T-cell apoptosis, anergy, exhaustion, and interleukin-10 (IL-10) expression (Zou et al., 2016). This type of signal has evolved to prevent autoimmune diseases resulting from self-reactive T-cells. However, some cancerous tumor cells also express PD-L1 upon stimulation by IFN-γ, which allows for immune evasion and tumor progression (Iwai et al., 2002; Garcia-Diaz et al., 2017; Mandai et al., 2016). Following PD-1/PD-L1 binding, Ca^{2+} flux is inhibited, which alters T-cell's sensitivity to TCR signals and inhibits production of cytokines (Wei et al., 2013). The interaction of PD-L1 with the PD-1 receptor inhibits IFN-γ production in the liver after antigen recognition (Maier et al., 2007). It also inhibits interleukin-2 (Keir et al., 2006) and TNF-α (Wei et al., 2013) production during T-cell activation. The cytoplasmic tail of PD-1 contains an immunoreceptor tyrosine-based switch motif (ITSM) at the C-terminus and an immunoreceptor tyrosine-based inhibition motif (ITIM) at the N-terminus, which recruits src homology-2 (SH2) domain containing phosphatases (Boussiotis et al., 2014). The ITSM tyrosine (Y248) associates with SHP-2, which is essential for PD-1 inhibition of the PI3K/Akt pathway and blockade of T-cell activation (Boussiotis et al., 2014). The mechanism by which PD-1 inhibits the activation of the PI3K/Akt pathway is via reduction of casein kinase 2 (CK2) expression, which decreases PTEN's stability and increases phosphatase activity (Patsoukis et al., 2013). The association between the ITSM Y248 and SHP-2 also inhibits phosphorylation of Igβ, Syk, PLC-γ2 and Erk1/2 (Boussiotis et al., 2014). These molecular signals lead to the inhibition of T-cell growth and survival. PD-L1 expression also increases the immunosuppressive T-reg cell population by down-regulating phospho-Akt, mTOR, S6, and ERK2 and up-regulating PTEN (Francisco et al., 2009; Tripathi and Guleria, 2015). The regulation of these signaling molecules promotes the induction and maintenance of T-reg cells and inhibits T-cell responses. PD-1 ligation has also been shown to inhibit glycolysis in T-cells, which is essential during differentiation to effector T-cells and, instead, promotes fatty acid oxidation (Patsoukis et al., 2015). Thus, through many mechanisms, PD-1 ligation promotes the inactivation of T-cells. Therefore, by up-regulating PD-L1, cancer cells increase their ability to inactivate T-cells and host immune responses.

4. Crosstalks between YY1 and PD-L1 signaling pathways

As discussed in previous sections, both YY1 and PD-L1 are implicated in various cancer-related mechanisms and pathways. In the following section, the molecular relationship between the expression of YY1 and PD-L1 and how it may affect cancer progression will be explored.

4.1. YY1 Regulation of PD-L1 expression via p53 and miR34a

It is known that YY1 inhibits the activation of the p53 tumor suppressor (Sui et al., 2004). Specifically, YY1 regulates the transcriptional activity, acetylation, ubiquitination and stability of p53 by blocking its interaction with p300 and enhancing its interaction with Mdm2 (Grönroos et al., 2004; Khachigian, 2018). p53 has been found to negatively regulate PD-L1 expression via miR-34a (Cortez et al., 2016). p53 transcriptionally induces miR-34a, which then directly binds to the PD-L1 mRNA 3′ untranslated region in models of NSCLC (Cortez et al., 2016). Additionally, PD-L1 and miR-34a expressions are inversely correlated in acute myeloid leukemia and miR-34a reduces PD-L1 specific T-cell apoptosis (Wang et al., 2015b). Because p53 promotes down-regulation of PD-L1 and YY1 inhibits p53, YY1 may have an up-regulating effect on PD-L1. A schematic diagram of this regulatory interaction is illustrated in Fig. 3.

4.2. YY1 regulation of PD-L1 via cytokines: IL6, IL17, TGFβ, and IFNγ

YY1 is involved in the regulation of PD-L1 via several cytokines. YY1 has been shown to directly regulate the transcription of interleukin-6 (IL-6) by binding to the promoter region in rheumatoid arthritis (Lin et al., 2017). High levels of IL-6 have been shown to increase STAT-3, which directly binds to and activates the transcription of PD-L1 (Wölfle et al., 2011). Thus, YY1 may lead to the up-regulation of PD-L1 by activating IL-6 transcription and STAT-3. YY1 has also been shown to induce IL-17 production in murine CD4+ T-cells (Kwon et al., 2018). IL-17 has been shown to induce PD-L1 protein expression in prostate and colon cancer cells (Wang et al., 2017b). The mechanism of IL-17-mediated activation involves the activation of the transcription factor NF-κB (Wang et al., 2017b). NF-κB positively regulates the transcription of YY1 by directly binding to the YY1 promoter via a p50/p65 heterodimer complex (Wang et al., 2007; Zhang et al., 2018b). Thus, YY1 may have an inducing effect on PD-L1 via IL-17 and NF-κB and may be further involved in a positive feedback loop, resulting in an increase in PD-L1 expression (Fig. 5).

YY1 has been shown to have both negative and positive regulatory effects on TGF-β. In HaCaT keratinocytes, YY1 inhibits TGF-β by repressing the transcriptional activity of Smad (Kurisaki et al., 2003; AlHossiny et al., 2016). However, in human brain gliomas and meningiomas, YY1 overexpression correlates with TGF-β mRNA levels (Baritaki et al., 2009). TGF-β has been shown to induce PD-L1 expression on dendritic cells via STAT-3 signaling in cancer cells (Song et al., 2013). Thus, upregulation of TGF-β by YY1 may result in up-regulation of PD-L1 expression. Consistent with these findings, the upregulation of PD-L1 in gliomas was reported to correlate with poor survival (Wang et al., 2016b). YY1 also has a dual activator/repressor role on IFNγ (Weill et al., 2003; Sun et al., 2017). IFNγ has been shown to induce PD-L1 expression and promote progression of ovarian cancer (Abiko et al., 2015) and colorectal cancer (Song et al., 2013). Furthermore, IFN-γ-dependent up-regulation of PD-L1 expression has been shown to be mediated by the activation of JAK1, JAK2, and STAT1 (Bellucci et al., 2015). Thus, YY1 may lead to either up-regulation or the down-regulation of PD-L1 via differential regulation by IFNγ. A diagram of the potential crosstalks between YY1 and PD-L1 via cytokines is shown in Fig. 4.

4.3. YY1 regulation of PD-L1 via the PTEN/PI3K/Akt/mTOR pathway

PTEN is a phosphatase that inhibits the phosphoinositide 3-kinase (PI3K)/AKT pathway to regulate cell growth and survival (Georgescu, 2010). Loss-of-function PTEN mutations result in the consistent activation of PI3K/Akt pathways that are commonly observed in many human cancers and that lead to enhanced cell proliferation, survival, and chemoresistance (Mayer and Arteaga, 2016). YY1 has also been shown to activate the PI3K/Akt signaling pathway. The phosphorylation of PI3K and Akt proteins was significantly decreased following the blocking of YY1 in peripheral blood mononuclear cells, indicating a role for YY1 in the activation of this pathway (Lin et al., 2018a). PI3K activation phosphorylates Akt, which in turn activates mTOR. The activation of the Akt/mTOR pathway promotes PD-L1 expression, which was confirmed in mouse models of NSCLC (Lastwika et al., 2016). Therefore, YY1 may be able to drive PD-L1 expression by activating the PI3K/Akt/mTOR pathway, leading to increased T-cell exhaustion and immune escape. Another mechanism by which YY1 activates the PI3K/Akt pathway is by regulating PTEN. YY1 is a suppressor of p53 (Sui et al., 2004); the latter is a tumor suppressor which transcriptionally induces PTEN gene expression and PTEN further stabilizes p53 and protects it from MDM2-dependent degradation (Nakanishi et al., 2014). PTEN is a phosphatase that inhibits the PI3K/Akt pathway (Carnero and Paramio, 2014) and loss of PTEN increases PD-L1 expression in cancer (Song et al., 2013). Thus, by downregulation of PTEN via p53 and activation of the PI3K/Akt/mTOR pathway, YY1 enhances PD-L1 expression and cancer growth (Fig. 5).

4.4. YY1 Regulation of PD-L1 via c-Myc

YY1 may also negatively regulate the expression of PD-L1 in certain cancers. YY1 has been shown to repress the proto-oncoprotein, c-Myc, by forming a complex with p300 and HDAC3. This complex binds to the Myc promoter upstream of the YY1-binding site, resulting in the deacetylation and repression of c-Myc (Sankar et al., 2008; Li et al., 2019) (Fig. 6B). Myc expression levels have been shown to correlate with both high PD-L1 expression and poor clinical outcomes in NSCLC patients (Kim et al., 2017). C-Myc is also deregulated in most forms of cancer (Dang, 1999). C-Myc binds directly to the PD-L1 gene promoter to promote gene expression (Casey et al., 2016) (Fig. 6A). Thus, YY1 may have a suppressing role on PD-L1 through the repression of c-Myc. Consistent with this finding, YY1 overexpression is correlated with c-Myc inhibition and positive survival prognosis in nasopharyngeal carcinoma (Li et al., 2019).

4.5. YY1 regulation of PD-L1 via COX-2

COX-2 (cyclooxygenase-2) is an enzyme involved in the production of prostaglandins, is associated with inflammation of the intestine and colorectal cancer (CRC) and is correlated with dismal outcome in CRC patients, which has made it a target for cancer therapies (Wang and DuBois, 2010). YY1 binds to the COX-2 promoter, induces gene expression, and increases COX-2 transcriptional activity during inflammation (Joo et al., 2007). COX-2 expression has been shown to be positively correlated with tumor progression in several types of cancers, including melanoma (Botti et al., 2017). It has also been identified as a resistance factor against antigen-specific T-cell cytotoxicity and contributes to immune evasion (Göbel et al., 2014). COX-2 is positively correlated and co-localizes with PD-L1 expression in human melanoma cells (Botti et al., 2017). COX-2 catalyzes the formation of prostaglandin E2 (PGE2) which is involved in cancer progression. Overexpression of an enzyme that degrades PGE2 reduces PD-L1 expression, instigating a role for PGE2 and COX-2 in the up-regulation of PD-L1 (Fig. 7A) (Prima et al., 2017).

In addition to being stimulated by YY1, COX-2 and PGE2 are stimulated by TGF-β and go on to activate the PI3K/Akt pathway by inducing the phosphorylation of AKT in prostate cancer cells (Vo et al., 2013). As previously discussed, PI3K activation phosphorylates Akt, which activates mTOR. The activation of the Akt/mTOR pathway promotes PD-L1 expression in mouse models of NSCLC (Lastwika et al., 2016). YY1 has been shown to have inhibitory effects on TGF-β in normal HaCaT keratinocytes by inhibiting Smad transcriptional activity (Kurisaki et al., 2003). However, in brain gliomas, YY1expression is positively correlated with TGF-β levels (Baritaki et al., 2009). Hence, YY1 correlates with TGF-β in gliomas, which stimulates COX-2, PGE-2, and PI3K/Akt activation, leading to increased expression of PD-L1 (Fig. 7B). Consistent with these findings, PD-L1 is upregulated in gliomas and correlates with a significantly shorter survival, especially in glioblastoma (Wang et al., 2016b). In agreement, a recent report found that inhibition of COX-2 and the epidermal growth factor receptor (EGFR) led to a decrease in PD-L1, TGF-β expression as well as decreased PI3K/Akt activity in lung cancer cells (Tang et al., 2019). When YY1 represses TGF-β in non-cancerous cells, this leads to inhibition of COX-2, PGE2, the PI3K/Akt pathway, and PD-L1 expression (Fig. 7C). Thus, by inducing COX-2 transcriptionally and stimulating TGF-β in gliomas, YY1 has both a direct and indirect enhancing effect on PD-L1 expression via COX-2 and PGE-2.

5. Discussion

Immunotherapy with checkpoint inhibitors has resulted in significant clinical responses in subsets of patients with several cancers

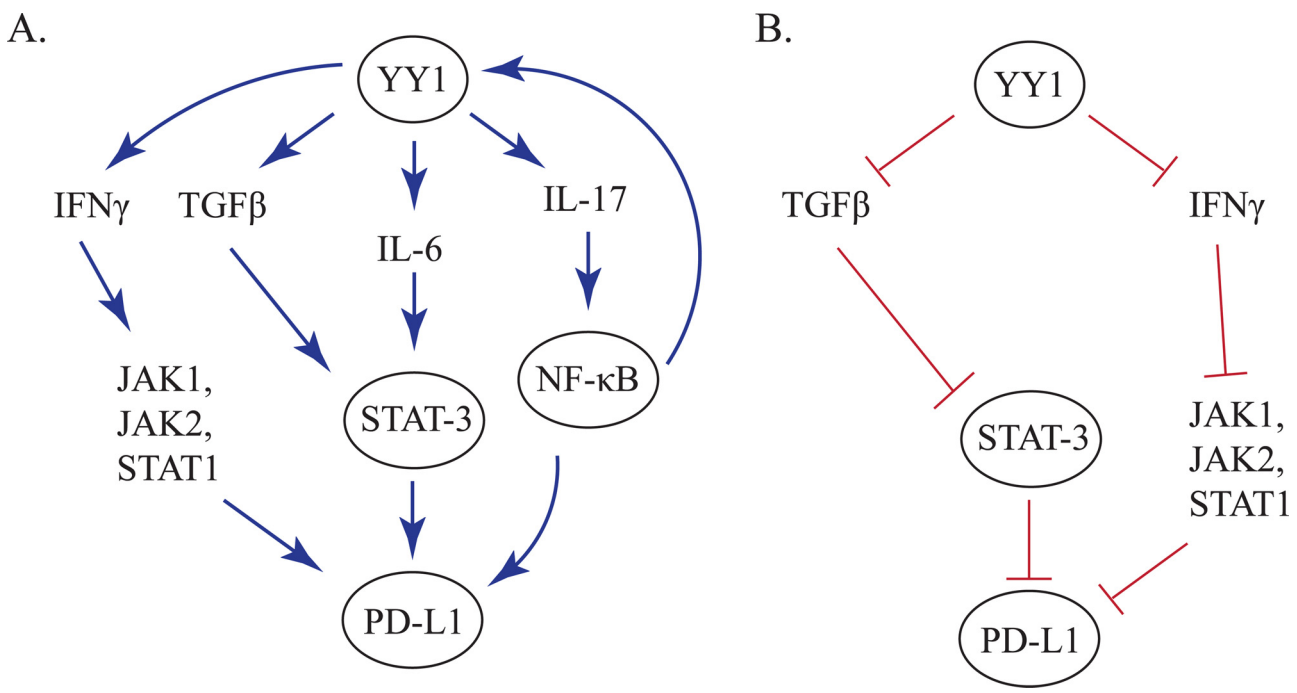

Fig. 4. YY1 Regulation of PD-L1 via cytokines. A. Expression of PD-L1. This diagram shows the enhancing effect of YY1 on PD-L1 expression via promoting IFN-γ, TGF-β, IL-6, and IL-17. IFN-γ activates JAK1, JAK2, and STAT1, which increase PD-L1 expression. TGF-β increases PD-L1 via STAT3 signaling. IL-6 activates STAT-3, which induces the transcription of PD-L1. IL-17 activates NF-κB which increases PD-L1 transcription and promotes YY1 expression, forming a positive feedback loop that leads to more PD-L1 expression. B. This diagram shows the alternate regulation of PD-L1 by YY1 in some cancers when TGF-β and IFN-γ are inhibited by YY1. TGF-β would then decrease STAT3 leading to less PD-L1 expression. A decrease in IFN-γ expression would lead to less activation of JAK1, JAK2, and STAT1 and thus, less PD-L1 expression.

that were resistant to prior therapies. Therefore, several attempts have been made to circumvent the resistance to checkpoint inhibitors, including modulation of the expression of PD-L1 on cancer cells. To address the regulation of PD-L1 expression on cancer cells, we have examined the role of the transcription factor, YY1, that was reported to regulate tumor cell resistance to cytotoxic T-cell-mediated immunotherapies. In our analyses, we have found several crosstalk pathways between YY1 and PD-L1 and, thus, highlighted potential novel strategies to downregulate the expression of PD-L1 by several interventions of these crosstalks. Below, we discuss the various findings and provide several examples of current therapeutics that target several factors in the crosstalk pathways that were designed independently of PD-L1 expression. Therefore, these drugs may now be used in combination with immunotherapies to reverse immune resistance.

Our findings have revealed the presence of correlations between the regulation of PD-L1 and YY1 expressions and, primarily, the role of YY1 in regulating PD-L1 expression. Prior reports have demonstrated that most cancers overexpress YY1, which is intimately involved in the regulation of cell proliferation, cell survival, and resistance to both chemotherapy and immunotherapy (Cho and Bonavida, 2017). Briefly, the various crosstalks that were delineated herein and their targeting by therapeutic drugs are discussed below.

p53 has been shown to negatively regulate the transcription of PD-L1 via activation of miR-34a transcription (Cortez et al., 2016). YY1 inhibits the activation of the p53 tumor suppressor (Sui et al., 2004; Khachigian, 2018), thus, preventing its negative regulation of PD-L1. This suggests that YY1 can contribute to the upregulation of PD-L1 by inhibiting its regulator proteins.

YY1 can also transcriptionally activate the cytokines IL-6 and IL-17, leading to increased expression of PD-L1 transcription factors, STAT-3 and NF-κB (Lin et al., 2017; Kwon et al., 2018). YY1 can also have positive or inhibitory effects on TGF-β and IFN-γ (Kurisaki et al., 2003; Abiko et al., 2015), which can lead to either an increase or decrease in PD-L1 expression via regulation of STAT-3 and JAK1, JAK2, and STAT1, respectively (Wolfe et al., 2011; Bellucci et al., 2015). This suggests that YY1's transcriptional role in the network of immune cytokines plays a role in cancer cell immune resistance via regulation of PD-L1. Inhibition of tumor-promoting factors is another approach to prevent tumor growth. An miR inhibitor of TGFβ, miR-202, has been shown to block EMT characteristics and tumor metastasis in mouse models of pancreatic cancer (Mody et al., 2017). Additionally, a current two-year study is evaluating whether or not TGFβ inhibition during radiation therapy, inhibits tumor metabolism, growth and promotes T-cell activation in a murine model of breast cancer brain metastases (Franc, 2018).

YY1 also regulates PD-L1 via its influence in pathways necessary for cell growth and survival. YY1 can promote the activation of PI3K/Akt signaling pathway by repressing the p53 tumor suppressor, which reduces PTEN and subsequent inhibition of the PI3K/Akt pathway. Activation of the PI3K/Akt pathways has been shown to promote PD-L1 expression in mouse models of NSCLC (Lastwika et al., 2016). Thus, YY1 plays a role in regulating cell growth pathways, which can influence PD-L1 expression and immune resistance in cancer cells. In agreement, targeting the PI3K-Akt-mTOR pathway has been shown to impact not only cancer cells, but also host immunity.

In rare cases, YY1 may not only induce PD-L1 expression, but also repress its expression. YY1 can transcriptionally repress c-Myc, which is a proto-oncoprotein that transcriptionally promotes PD-L1 expression (Sankar et al., 2008). Thus, by inhibiting a transcriptional activator of PD-L1, YY1 may contribute to negatively regulating tumor cell immune resistance.

YY1 transcriptionally induces COX-2 (Joo et al., 2007), leading to increased PGE-2 and PD-L1 expression. YY1 can also regulate COX-2 indirectly through regulation of TGF-β. TGF-β has been shown to stimulate COX-2 and PGE-2, leading to activation of the PI3K/Akt pathway (Vo et al., 2013). Since YY1 correlates with TGF-β expression in gliomas (Baritaki et al., 2009), COX-2 and PGE-2 are stimulated and induce PD-L1 expression via activation of the PI3K/Akt pathway.

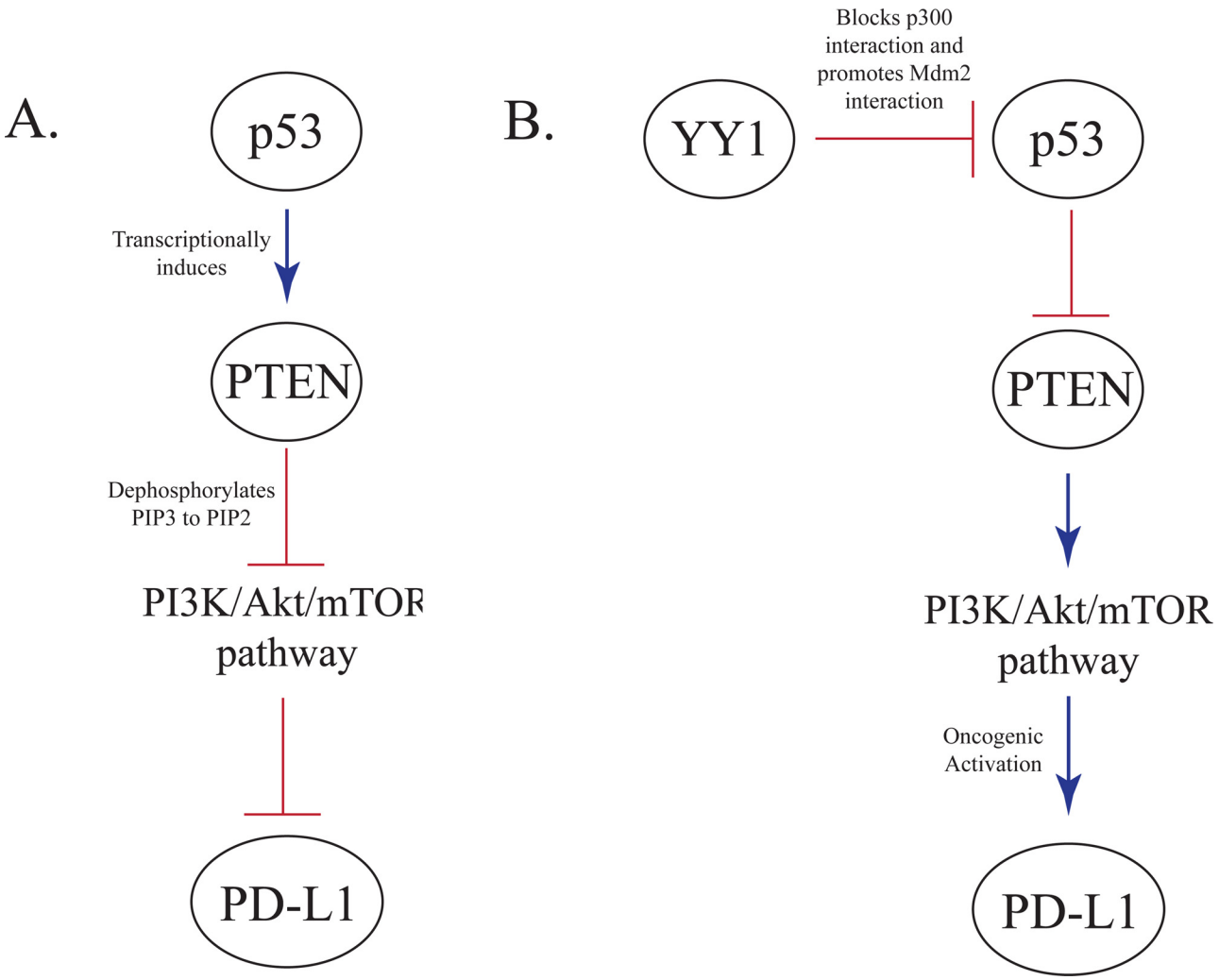

Fig. 5. YY1 regulation of PD-L1 via PI3K/Akt/mTOR and p53/PTEN. A. Absence of YY1. This diagram shows how PD-L1 is regulated by p53, PTEN, and the PI3K/Akt/mTOR pathway in the absence of YY1. p53 inhibits PD-L1 expression by transcriptionally inducing PTEN, which inhibits the PI3K/Akt pathway via dephosphorylation of PIP3 by PTEN. B. Presence of YY1. This diagram shows how YY1 inhibits p53 and the negative regulation of PD-L1, leading to up-regulation of PD-L1. Additionally, YY1 promotes PI3K/Akt phosphorylation which activates the pathway and leads to an increase in PD-L1 expression and cell proliferation.

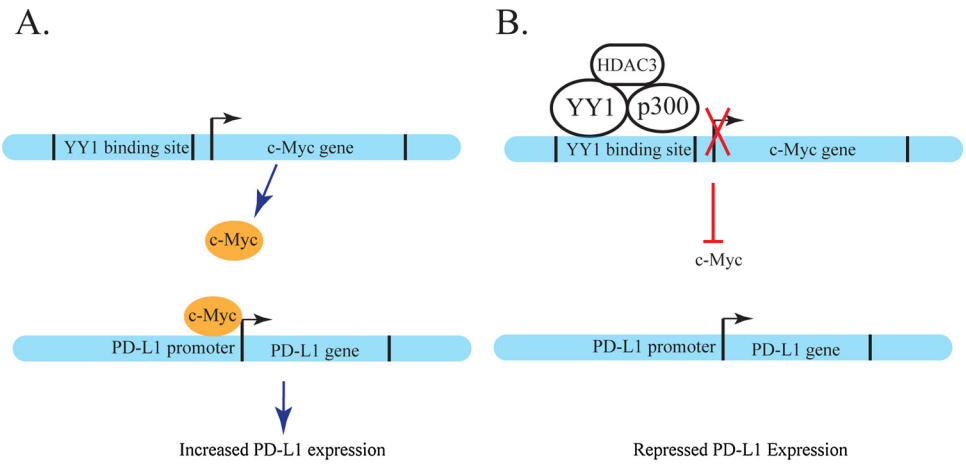

Fig. 6. YY1 Regulation of PD-L1 via C-Myc. A. Absence of YY1. C-Myc is transcribed and directly binds to the PD-L1 promoter to activate transcription. B. Presence of YY1. YY1 forms a complex with HDAC3 and p300, which binds to the upstream region of the c-Myc promoter and inhibits c-Myc transcription and subsequent PD-L1 transcription.

Indeed, PD-L1 is overexpressed and correlates with glioma development and poor survival, supporting these findings. In agreement with our findings, a recent study assessed whether dual inhibition of COX2 and EGFR could lead to the inhibition of PD-L1 expression in lung cancer cells.

In addition to the various therapeutic targets described above that interfere with the crosstalk pathways that regulate PD-L1 expression, there are also potential therapeutic interventions that aim to inhibit PD-L1 expression in cancer cells and PD-1 in cytotoxic T-cells. We and others have previously reported that the inhibition of YY1 reverses

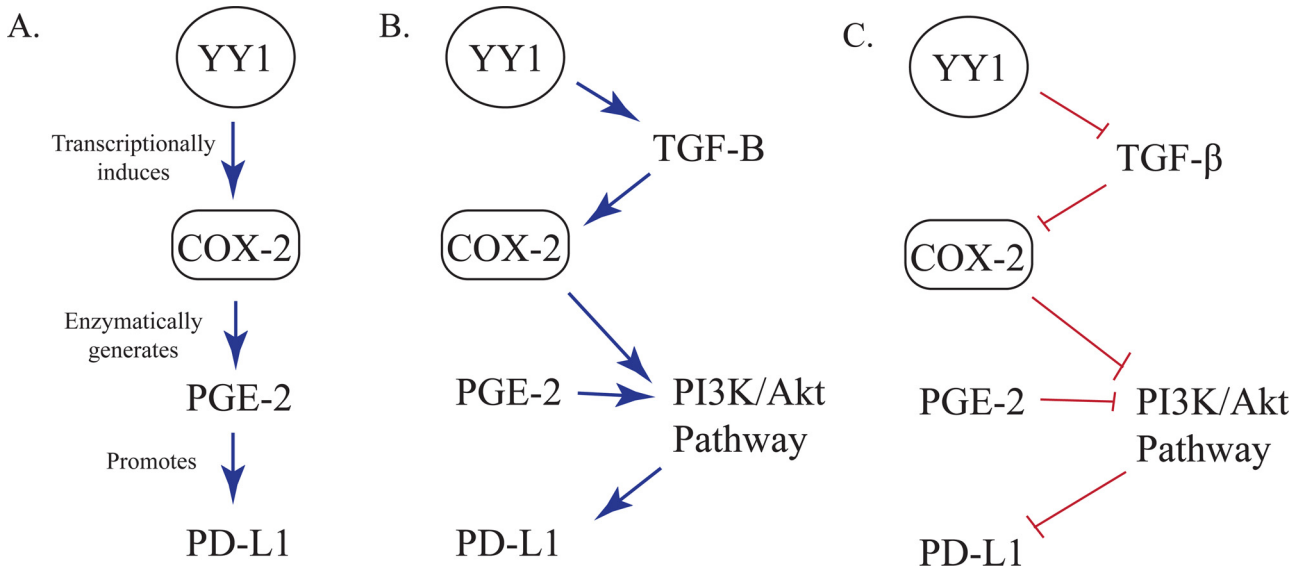

Fig. 7. YY1 Regulation of PD-L1 via COX-2. A. Induction of PD-L1 via PGE-2. YY1 induces COX-2 expression and activity, which then generates PGE-2 and induces PD-L1 expression. B. Induction of PD-L1 via TGF-β. YY1 stimulates TGF-β in gliomas, which induces COX-2 and PGE-2 expression, thus activating the PI3K/Akt pathway and inducing PD-L1 expression. C. Inhibition of PD-L1 via TGF-β. YY1 represses TGF-β which leads to repression of PD-L1 expression by reversing the mechanism illustrated in B.

tumor cell resistance to chemotherapy and immunotherapies as well as metastasis (Cho and Bonavida, 2017). Most of these inhibitory activities were primarily established in laboratory and animal models. Those include inhibition of YY1 by siRNAs (Baritaki et al., 2007), nitric oxide (NO) donors (Bonavida, 2010; Huerta-Yepez et al., 2013; Baritaki and Bonavida, 2019), and more recently, small peptides (Qi et al., 2018). Inhibition of YY1 via siRNAs has been shown to increase the sensitization of human prostate carcinoma cells to chemotherapeutic drugs and to both FasL and TRAIL-mediated apoptosis (Garbán and Bonavida, 2001; Baritaki et al., 2007). Using siRNAs for cancer therapy has been shown to be ineffective due to their rapid degradation by RNases and filtration by the kidneys. However, various delivery methods are still being developed to carry siRNAs to solid tumors, such as cationic lipids, polymers, and inorganic nanoparticles (Kim et al., 2016). NO has also been shown to increase TRAIL-mediated apoptosis in human prostate carcinoma cells via inhibition of YY1 DNA-binding and transcriptional function (Huerta-Yepez et al., 2013). Recently, small peptides targeting YY1 interactions have been developed to inhibit cancer cell proliferation. The oncoprotein binding domain (OPB) of YY1, which mediates its interaction with oncogenes such as MDM2 and AKT, was mutated and expressed in breast cancer cells. Expression of the OPB was able to increase p53 expression, reduce AKT phosphorylation, and inhibit cell proliferation (Qi et al., 2018). The above findings related to the inhibition of YY1 and sensitization to cytotoxic T-cells may be explained, in part, by the inhibition of PD-L1 expression, as reported here. These various potential therapeutic interventions clearly await their validation in dedicated clinical studies.

Whereas our findings in this review have primarily focused on PD-L1, YY1 has also been identified as a transcription factor of the checkpoint receptor PD-1 and was confirmed as an elevated protein in melanoma exhausted PD1 + T-cells (Balkhi et al., 2018). Therefore, any inhibitory activity directed against YY1 in tumor cells will also inhibit PD-1 expression in lymphocytes and altogether, amplify the sensitivity of tumor cells to cytotoxic T-cells.

Based on these findings, the combination of drugs that target YY1 and the crosstalks identified herein and immunotherapies are potential approaches to enhance the cytotoxic T-cell response and reversing cancer cell immune resistance. While our current findings have focused on the relationship between YY1 and PD-L1, future studies should delineate whether YY1 also regulates other checkpoint ligands and receptors.

6. Future perspectives

Since the successful introduction of the treatment of a subset of cancer patients with checkpoint inhibitors to enhance cell-mediated anti-tumor immunotherapy in a variety of cancers, a new therapeutic strategy is warranted to treat the unresponsive patients. One approach is to deregulate the overexpression of the inhibitory ligands on tumor cells that are, in large part, responsible in inhibiting the cytotoxic CD8 + T cells in killing the tumor cells. Various crosstalk pathways have been identified by which the overexpressed oncogenic tumor suppressor YY1 was involved in the regulation of PD-L1 expression in cancer cells, both directly and indirectly. Therefore, targeting YY1 directly or targeting the various crosstalk pathways should result in the downregulation of PD-L1 expression on tumor cells; thus, allowing the resistant tumor cells to respond to the combination of checkpoint inhibitors and CD8 + T cell anti-tumor response. Several examples of clinical and pre-clinical drugs have been reported to target the above crosstalk pathways and are good examples for their use to deregulate PD-L1 expression. For instance, strategies have been developed to block p53 inhibition and restore its tumor suppressor activity such as by the small peptide, ReACp53 (Soragni et al., 2016). Blocking the inhibition of p53 by YY1 in cancer cells may be an additional strategy to decrease PD-L1 expression and reverse the resistance to cytotoxic T cells. Further, multiple inhibitors of STAT3 have also been developed, such as the antisense oligonucleotide, AZD9150, which targets the STAT3 DNA-binding domain and also inhibit PD-L1 expression (Hong et al., 2015; Reilley et al., 2018). Likewise, inhibitors of the PI3K-AKT-mTOR pathway are under development and some have already been shown to be effective in subsets of hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer in phase I to III clinical trials (Lee et al., 2015). Additionally, mTOR inhibitors and Streptozotocin-based chemotherapy were shown to synergistically inhibit liver tumor growth in mouse models (Bollard et al., 2018). These findings demonstrate that inhibitors of the PI3K-AKT-mTOR pathway, which will also inhibit PD-L1 expression, can be used in combination with cytotoxic immune therapy. Small inhibitory molecules of c-Myc have been shown to induce cell arrest, apoptosis, and differentiation of human acute myeloid leukemia cells (Huang

et al., 2006; Delmore et al., 2011; Oronsky et al., 2018). One of these c-Myc inhibitors, RRx-001, has been shown to stimulate macrophages and exhibit antitumor activity in multiple tumor types in phase II clinical trials (Oronsky et al., 2017) and may be implicated in the inhibition of PD-L1. The dual inhibition of COX-2 and EGFR by Melafolone led to the downregulation of PD-L1, TGF-β, VEGF, and the PI3K/AKT pathway (Tang et al., 2019). This inhibition decreased cancer cell proliferation, enhanced the proliferation of CD8+ T-cells (presumably via inhibition of PD-L1 expression) and improved the checkpoint blockade therapy (Tang et al., 2019).

While the above findings have focused on the regulation of PD-L1 expression by YY1, additional studies should be examined for the regulation of other inhibitory ligands by YY1 or by other gene products.

The above examples with clinical drugs are good candidates to be used in combination with checkpoint inhibitors and immunotherapies to augment the anti-tumor response and to enhance the killing of tumor cells that were resistant to checkpoint inhibitors alone. The present findings also suggest the exploration of other clinical drugs for their potential effects in the regulation of the overexpression of inhibitory ligands on tumor cells or cells in the TME and their use in combination with immunotherapy.

Acknowledgements

We wish to acknowledge the assistance of Martina Rama, Yuhao Wang, and Inesa Navasardyan for their valuable assistance in reviewing this chapter. We also acknowledge the department of Microbiology, Immunology, and Molecular Genetics at the University of California Los Angeles and the David Geffen School of Medicine for their general support.

References

Abiko, K., Matsumura, N., Hamanishi, J., Horikawa, N., Murakami, R., Yamaguchi, K., Yoshioka, Y., Baba, T., Konishi, I., Mandai, M., 2015. IFN-γ from lymphocytes induces PD-L1 expression and promotes progression of ovarian cancer. Br. J. Cancer 112 (9), 1501.

Agarwal, N., Theodorescu, D., 2017. The role of transcription factor YY1 in the biology of cancer. Crit. Rev. Oncog.

Alam, A., 2018. Chemotherapy treatment and strategy schemes: a review. Open Access J. Toxicol. 2 (5), 555600.

Alexander, K.E., Rizkallah, R., 2017. Aurora a phosphorylation of YY1 during mitosis inactivates its DNA binding activity. Sci. Rep. 7 (1), 10084.

AlHossiny, M., Luo, L., Frazier, W.R., Steiner, N., Gusev, Y., Kallakury, B., Glasgow, E., Creswell, K., Madhavan, S., Kumar, R., Upadhyay, G., 2016. Ly6E/K signaling to TGFβ promotes breast cancer progression, immune escape, and drug resistance. Cancer Res. 76 (11), 3376–3386.

Antonio-Andrés, G., Rangel-Santiago, J., Tirado-Rodríguez, B., Martinez-Ruiz, G.U., Klunder-Klunder, M., Vega, M.I., Lopez-Martinez, B., Jimenez-Hernández, E., Torres Nava, J., Medina-Sanson, A., Huerta-Yepez, S., 2018. Role of Yin Yang-1 (YY1) in the transcription regulation of the multi-drug resistance (MDR1) gene. Leuk. Lymphoma 1–11.

Arasanz, H., Gato-Cañas, M., Zuazo, M., Ibañez-Vea, M., Breckpot, K., Kochan, G., Escors, D., 2017. PD1 signal transduction pathways in T cells. Oncotarget 8 (31), 51936–51945.

Balkhi, M.Y., Wittmann, G., Xiong, F., Junghans, R.P., 2018. YY1 upregulates checkpoint receptors and downregulates type I cytokines in exhausted, chronically stimulated human T cells. iScience 2, 105–122.

Banerjee, A., Sindhava, V., Vuyyuru, R., Jha, V., Hodewadekar, S., Manser, T., Atchison, M.L., 2016. YY1 is required for germinal center B cell development. PLoS One 11 (5), e0155311.

Baritaki, S., Bonavida, B., 2019. Nitric oxide (NO): a multifaceted target for reversal of cancer cell pleiotropic properties by NO-modulating therapies. Therapeutic Application of Nitric Oxide in Cancer and Inflammatory Disorders. Academic Press, pp. 311–312.

Baritaki, S., Huerta-Yepez, S., Sakai, T., Spandidos, D.A., Bonavida, B., 2007. Chemotherapeutic drugs sensitize cancer cells to TRAIL-mediated apoptosis: up-regulation of DR5 and inhibition of Yin Yang 1. Mol. Cancer Ther. 6 (4), 1387–1399.

Baritaki, S., Chatzinikola, A.M., Vakis, A.F., Soulitzis, N., Karabetsos, D.A., Neonakis, I., Bonavida, B., Spandidos, D.A., 2009. YY1 over-expression in human brain gliomas and meningiomas correlates with TGF-β1, IGF-1 and FGF-2 mRNA levels. Cancer Invest. 27 (2), 184–192.

Bar-Zeev, M., Livney, Y.D., Assaraf, Y.G., 2017. Targeted nanomedicine for cancer therapeutics: towards precision medicine overcoming drug resistance. Drug Resist. Updates 31, 15–30.

Becker, K.G., Jedlicka, P., Templeton, N.S., Liotta, L., Keiko, O., 1994. Characterization of hUCRBP (YY1, NF-E1, δ): a transcription factor that binds the regulatory regions of many viral and cellular genes. Gene 150 (2), 259–266.

Beketaev, I., Zhang, Y., Kim, E.Y., Yu, W., Qian, L., Wang, J., 2015. Critical role of YY1 in cardiac morphogenesis. Dev. Dyn. 244 (5), 669–680.

Bellucci, R., Martin, A., Bommarito, D., Wang, K., Hansen, S.H., Freeman, G.J., Ritz, J., 2015. Interferon-γ-induced activation of JAK1 and JAK2 suppresses tumor cell susceptibility to NK cells through upregulation of PD-L1 expression. Oncoimmunology 4 (6), e1008824.

Berchuck, A., Iversen, E.S., Lancaster, J.M., Pittman, J., Luo, J., Lee, P., Murphy, S., Dressman, H.K., Febbo, P.G., West, M., Nevins, J.R., 2005. Patterns of gene expression that characterize long-term survival in advanced stage serous ovarian cancers. Clin. Cancer Res. 11 (10), 3686–3696.

Berger, K.N., Pu, J.J., 2018. PD-1 pathway and its clinical application: a 20 year journey after discovery of the complete human PD - 1 gene. Gene 638, 20–25.

Bertucci, F., Finetti, P., Colpaert, C., Mamessier, E., Parizel, M., Dirix, L., Viens, P., Birnbaum, D., Van Laere, S., 2015. PDL1 expression in inflammatory breast cancer is frequent and predicts for the pathological response to chemotherapy. Oncotarget 6 (15), 13506.

Bérubé-Simard, F.A., Prudhomme, C., Jeannotte, L., 2014. YY1 acts as a transcriptional activator of Hoxa5 gene expression in mouse organogenesis. PLoS One 9 (4), e93989.

Blank, C., Brown, I., Marks, R., Nishimura, H., Honjo, T., Gajewski, T.F., 2003. Absence of programmed death receptor 1 alters thymic development and enhances generation of CD4/CD8 double-negative TCR-transgenic T cells. J. Immunol. 171 (9), 4574–4581.

Blättler, S.M., Cunningham, J.T., Verdeguer, F., Chim, H., Haas, W., Liu, H., Romanino, K., Rüegg, M.A., Gygi, S.P., Shi, Y., Puigserver, P., 2012. Yin Yang 1 deficiency in skeletal muscle protects against rapamycin-induced diabetic-like symptoms through activation of insulin/IGF signaling. Cell Metab. 15 (4), 505–517.

Bollard, J., Patte, C., Massoma, P., Goddard, I., Gadot, N., Benslama, N., Hervieu, V., Ferraro-Peyret, C., Cordier-Bussat, M., Scoazec, J.Y., Roche, C., 2018. Combinatorial treatment with mTOR inhibitors and streptozotocin leads to synergistic in vitro and in vivo antitumor effects in insulinoma cells. Mol. Cancer Ther. 17 (1), 60–72.

Bommarito, D., Hall, C., Taams, L.S., Corrigall, V.M., 2017. Inflammatory cytokines compromise programmed cell death-1 (PD-1)-mediated T cell suppression in inflammatory arthritis through up-regulation of soluble PD-1. Clin. Exp. Immunol. 188 (3), 455–466.

Bonavida, B. (Ed.), 2010. Nitric Oxide (NO) and Cancer. Springer/Humana Press.

Bonavida, B., 2015. Sensitization of immune-resistant tumor cells to CTL-mediated apoptosis via interference at the dysregulated NF-κB/Snail/YY1/PI3K/RKIP/PTEN resistant loop. Resistance of Cancer Cells to CTL-Mediated Immunotherapy. Springer, Cham, pp. 177–208.

Bonavida, B., Chouaib, S., 2017. Resistance to anticancer immunity in cancer patients: potential strategies to reverse resistance. Ann. Oncol. 28 (3), 457–467.

Bonavida, B., Garban, H., 2015. Nitric oxide-mediated sensitization of resistant tumor cells to apoptosis by chemo-immunotherapeutics. Redox Biol. 6, 486–494.

Bonavida, B., Kaufhold, S., 2015. Prognostic significance of YY1 protein expression and mRNA levels by bioinformatics analysis in human cancers: a therapeutic target. Pharmacol. Ther. 150, 149–168.

Boorjian, S.A., Sheinin, Y., Crispen, P.L., Farmer, S.A., Lohse, C.M., Kuntz, S.M., Leibovich, B.C., Kwon, E.D., Frank, I., 2008. T-cell coregulatory molecule expression in urothelial cell carcinoma: clinicopathologic correlations and association with survival. Clin. Cancer Res. 14 (15), 4800–4808.

Botti, G., Fratangelo, F., Cerrone, M., Liguori, G., Cantile, M., Anniciello, A.M., Scala, S., D'Alterio, C., Trimarco, C., Ianaro, A., Cirino, G., 2017. COX-2 expression positively correlates with PD-L1 expression in human melanoma cells. J. Transl. Med. 15 (1), 46.

Boucherat, O., Landry-Truchon, K., Bérubé-Simard, F.A., Houde, N., Beuret, L., Lezmi, G., Foulkes, W.D., Delacourt, C., Charron, J., Jeannotte, L., 2015. Epithelial inactivation of Yy1 abrogates lung branching morphogenesis. Development 142 (17), 2981–2995.

Boussiotis, V.A., Chatterjee, P., Li, L., 2014. Biochemical signaling of PD-1 on T cells and its functional implications. Cancer J. 20 (4), 265.

Brunner-Weinzierl, M.C., Rudd, C.E., 2018. CTLA-4 and PD-1 control of T-Cell motility and migration: implications for tumor immunotherapy. Front. Immunol. 9, 2737–2744.

Bushmeyer, S., Park, K., Atchison, M.L., 1995. Characterization of functional domains within the multifunctional transcription factor, YY1. J. Biol. Chem. 270 (50), 30213–30220.

Carnero, A., Paramio, J.M., 2014. The PTEN/PI3K/AKT pathway in vivo, cancer mouse models. Front. Oncol. 4, 252.

Carrington, E.M., Tarlinton, D.M., Gray, D.H., Huntington, N.D., Zhan, Y., Lew, A.M., 2017. The life and death of immune cell types: the role of BCL-2 anti-apoptotic molecules. Immunol. Cell Biol. 95, 870–877.

Casey, S.C., Tong, L., Li, Y., Do, R., Walz, S., Fitzgerald, K.N., Gouw, A.M., Baylot, V., Gütgemann, I., Eilers, M., Felsher, D.W., 2016. MYC regulates the antitumor immune response through CD47 and PD-L1. Science 352 (6282), 227–231.

Chen, L., Han, X., 2015. Anti–PD-1/PD-L1 therapy of human cancer: past, present, and future. J. Clin. Invest. 125 (9), 3384–3391.

Chen, C.Y., Schwartz, R.J., 1997. Competition between negative acting YY1 versus positive acting serum response factor and tinman homologue Nkx-2.5 regulates cardiac α-actin promoter activity. Mol. Endocrinol. 11 (6), 812–822.

Chen, Q.R., Yu, L.R., Tsang, P., Wei, J.S., Song, Y.K., Cheuk, A., Chung, J.Y., Hewitt, S.M., Veenstra, T.D., Khan, J., 2010. Systematic proteome analysis identifies transcription factor YY1 as a direct target of miR-34a. J. Proteome Res. 10 (2), 479–487.

Chen, J., Jiang, C.C., Jin, L., Zhang, X.D., 2015a. Regulation of PD-L1: a novel role of pro-survival signalling in cancer. Ann. Oncol. 27 (3), 409–416.

Chen, F., Zhuang, X., Lin, L., Yu, P., Wang, Y., Shi, Y., Hu, G., Sun, Y., 2015b. New

horizons in tumor microenvironment biology: challenges and opportunities. BMC Med. 13 (1), 45.
Chen, Z., Han, S., Huang, W., Wu, J., Liu, Y., Cai, S., He, Y., Wu, S., Song, W., 2016. MicroRNA-215 suppresses cell proliferation, migration and invasion of colon cancer by repressing Yin-Yang 1. Biochem. Biophys. Res. Commun. 479 (3), 482–488.
Chen, Y.H., Chung, C.C., Liu, Y.C., Lai, W.C., Lin, Z.S., Chen, T.M., Li, L.Y., Hung, M.C., 2018. YY1 and HDAC9c transcriptionally regulate p38-mediated mesenchymal stem cell differentiation into osteoblasts. Am. J. Cancer Res. 8 (3), 514–525.
Chinnappan, D., Xiao, D., Ratnasari, A., Andry, C., King, T.C., Weber, H.C., 2009. Transcription factor YY1 expression in human gastrointestinal cancer cells. Int. J. Oncol. 34 (5), 1417–1423.
Cho, A.A., Bonavida, B., 2017. Targeting the overexpressed YY1 in Cancer Inhibits EMT and metastasis. Crit. Rev. Oncog. 22 (1–2), 49.
Cochain, C., Chaudhari, S.M., Koch, M., Wiendl, H., Eckstein, H.H., Zernecke, A., 2014. Programmed cell death-1 deficiency exacerbates T cell activation and atherogenesis despite expansion of regulatory T cells in atherosclerosis-prone mice. PLoS One 9 (4), e93280.
Cortez, M.A., Ivan, C., Valdecanas, D., Wang, X., Peltier, H.J., Ye, Y., Araujo, L., Carbone, D.P., Shilo, K., Giri, D.K., Kelnar, K., 2016. PDL1 Regulation by p53 via miR-34. JNCI 108 (1).
Cunningham, J.T., Rodgers, J.T., Arlow, D.H., Vazquez, F., Mootha, V.K., Puigserver, P., 2007. mTOR controls mitochondrial oxidative function through a YY1–PGC-1α transcriptional complex. Nature 450 (7170), 736–740.
Curtis, C., Shah, S.P., Chin, S.F., Turashvili, G., Rueda, O.M., Dunning, M.J., Speed, D., Lynch, A.G., Samarajiwa, S., Yuan, Y., Gräf, S., 2012. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature 486 (7403), 346.
D'incecco, A., Andreozzi, M., Ludovini, V., Rossi, E., Capodanno, A., Landi, L., Tibaldi, C., Minuti, G., Salvini, J., Coppi, E., Chella, A., 2015. PD-1 and PD-L1 expression in molecularly selected non-small-cell lung cancer patients. Br. J. Cancer 112 (1), 95.
D'Souza, M.P., Adams, E., Altman, J.D., et al., 2019. Casting a wider net: immunosurveillance by nonclassical MHC molecules. PLoS Pathog. 15 (2), e1007567.
Dang, C.V., 1999. c-Myc target genes involved in cell growth, apoptosis, and metabolism. Mol. Cell. Biol. 19 (1), 1–11.
Daraiseh, S.I., Kassardjian, A., Alexander, K.E., Rizkallah, R., Hurt, M.M., 2018. c-Abl phosphorylation of Yin Yang 1's conserved tyrosine 254 in the spacer region modulates its transcriptional activity. Biochim. Biophys. Acta (BBA)—Mol. Cell Res. 1865 (9), 1173–1186.
de Nigris, F., Botti, C., de Chiara, A., Rossiello, R., Apice, G., Fazioli, F., Fiorito, C., Sica, V., Napoli, C., 2006. Expression of transcription factor Yin Yang 1 in human osteosarcomas. Eur. J. Cancer 42 (15), 2420–2424.
de Nigris, F., Zanella, L., Cacciatore, F., De Chiara, A., Fazioli, F., Chiappetta, G., Apice, G., Infante, T., Monaco, M., Rossiello, R., De Rosa, G., 2011. YY1 overexpression is associated with poor prognosis and metastasis-free survival in patients suffering osteosarcoma. BMC Cancer 11 (1), 472.
de Nigris, F., Mancini, F.P., Schiano, C., Infante, T., Zullo, A., Minucci, P.B., Al-Omran, M., Giordano, A., Napoli, C., 2012. Osteosarcoma cells induce endothelial cell proliferation during neo-angiogenesis. J. Cell. Physiol. 228 (4), 846–852.
Delmore, J.E., Issa, G.C., Lemieux, M.E., Rahl, P.B., Shi, J., Jacobs, H.M., Kastritis, E., Gilpatrick, T., Paranal, R.M., Qi, J., Chesi, M., 2011. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell 146 (6), 904–917.
Deng, Z., Wan, M., Sui, G., 2007. PIASy-mediated sumoylation of Yin Yang 1 depends on their interaction but not the RING finger. Mol. Cell. Biol. 27 (10), 3780–3792.
Di Croce, L., Helin, K., 2013. Transcriptional regulation by Polycomb group proteins. Nat. Struct. Mol. Biol. 20 (10), 1147.
Dirix, L.Y., Takacs, I., Nikolinakos, P., Jerusalem, G., Arkenau, H.T., Hamilton, E.P., Von Heydebreck, A., Grote, H.J., Chin, K., Lippman, M.E., 2016. Abstract S1-04: avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase Ib JAVELIN solid tumor trial. Am. Assoc. Cancer Res. 76 (4 Suppl), S1–04.
Do Kim, J., Yu, S., Kim, J., 2009. YY1 is autoregulated through its own DNA-binding sites. BMC Mol. Biol. 10 (1), 85.
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 (12), 1365.
Dong, S., Ma, X., Wang, Z., Han, B., Zou, H., Wu, Z., Zang, Y., Zhuang, L., 2017. YY1 promotes HDAC1 expression and decreases sensitivity of hepatocellular carcinoma cells to HDAC inhibitor. Oncotarget 8 (25), 40583.
Donohoe, M.E., Zhang, X., McGinnis, L., Biggers, J., Li, E., Shi, Y., 1999. Targeted disruption of mouse Yin Yang 1 transcription factor results in peri-implantation lethality. Mol. Cell. Biol. 19 (10), 7237–7244.
Draghi, A., Chamberlain, C.A., Furness, A., Donia, M., 2019. Acquired resistance to cancer immunotherapy. Seminars in Immunopathology, vol. 41. Springer, Berlin Heidelberg, pp. 31–40 January 1.
Fabrizio, F.P., Trombetta, D., Rossi, A., Sparaneo, A., Castellana, S., Muscarella, L.A., 2018. Gene code CD274/PD-L1: from molecular basis toward cancer immunotherapy. Ther. Adv. Med. Oncol. 10 1758835918815598.
Fang, M., Huang, W., Wu, X., Gao, Y., Ou, J., Zhang, X., Li, Y., 2018. MiR-141–3p suppresses tumor growth and metastasis in papillary thyroid cancer via targeting Yin Yang 1. Anat. Rec. 302 (2), 171–363.
Farhood, B., Najafi, M., Mortezaee, K., 2019. CD8+ cytotoxic T lymphocytes in cancer immunotherapy: a review. J. Cell. Physiol. 234, 8509–8521.
Favot, L., Hall, S.M., Haworth, S.G., Kemp, P.R., 2005. Cytoplasmic YY1 is associated with increased smooth muscle-specific gene expression: implications for neonatal pulmonary hypertension. Am. J. Pathol. 167 (6), 1497–1509.
Ficzycz, A., Eskiw, C., Meyer, D., Eliassen-Marley, K., Hurt, M., Ovsenek, N., 2001. Expression, activity and subcellular localization of the Yin Yang 1 transcription factor in Xenopus oocytes and embryos. J. Biol. Chem. 276, 22819–22825.
Flanagan, J.R., 1995. Autologous stimulation of YY1 transcription factor expression: role of an insulin-like growth factor. Cell Growth Differ. 6 (2), 185–190.
Franc, B., 2018. Dual Benefit of TGFB Inhibition on Tumor Control in the Context of Radiotherapy for Breast Cancer Brain Metastases. University of California San Francisco, San Francisco United States.
Francisco, L.M., Salinas, V.H., Brown, K.E., Vanguri, V.K., Freeman, G.J., Kuchroo, V.K., Sharpe, A.H., 2009. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. J. Exp. Med. 206 (13), 3015–3029.
Fujita, Y., Yagishita, S., Hagiwara, K., Yoshioka, Y., Kosaka, N., Takeshita, F., Fujiwara, T., Tsuta, K., Nokihara, H., Tamura, T., Asamura, H., 2015. The clinical relevance of the miR-197/CKS1B/STAT3-mediated PD-L1 network in chemoresistant non-small-cell lung cancer. Mol. Ther. 23 (4), 717–727.
Gabriele, M., Vulto-van Silfhout, A.T., Germain, P.L., et al., 2017. YY1 haploinsufficiency causes an intellectual disability syndrome featuring transcriptional and chromatin dysfunction. Am. J. Hum. Genet. 100 (6), 907–925.
Galloway, N.R., Osterman, C.J.D., Reiber, K., Jutzy, J.M., Li, F., Sui, G., Soto, U., Wall, N.R., 2014. Yin Yang 1 regulates the transcriptional repression of surviving. Biochem. Biophys. Res. Commun. 445 (1), 208–213.
Galvin, K.M., Shi, Y., 1997. Multiple mechanisms of transcriptional repression by YY1. Mol. Cell. Biol. 17 (7), 3723–3732.
Gandini, S., Massi, D., Mandalà, M., 2016. PD-L1 expression in cancer patients receiving anti PD-1/PD-L1 antibodies: a systematic review and meta-analysis. Crit. Rev. Oncol. Hematol. 100, 88–98.
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., Xu, Y., 2009. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin. Cancer Res. 15 (3), 971–979.
Garbán, H.J., Bonavida, B., 2001. Nitric oxide inhibits the transcription repressor Yin-Yang 1 binding activity at the silencer region of the Fas promoter: a pivotal role for nitric oxide in the up-regulation of Fas gene expression in human tumor cells. J. Immunol. 167 (1), 75–81.
Garcia-Diaz, A., Shin, D.S., Moreno, B.H., Saco, J., Escuin-Ordinas, H., Rodriguez, G.A., Zaretsky, J.M., Sun, L., Hugo, W., Wang, X., Parisi, G., Saus, C.P., Torrejon, D.Y., Graeber, T.G., Comin-Anduix, B., Hu-Lieskovan, S., Damoiseaux, R., Lo, R.S., Ribas, A., 2017. Interferon receptor signaling pathways regulating PD-L1 and PD-L2 expression. Cell Rep. 19 (6), 1189–1201.
Georgescu, M.M., 2010. PTEN tumor suppressor network in PI3K-Akt pathway control. Genes Cancer 1 (12), 1170–1177.
Göbel, C., Breitenbuecher, F., Kalkavan, H., Hähnel, P.S., Kasper, S., Hoffarth, S., Merches, K., Schild, H., Lang, K.S., Schuler, M., 2014. Functional expression cloning identifies COX-2 as a suppressor of antigen-specific cancer immunity. Cell Death Dis. 5 (12), e1568.
Goldberg, M.V., Maris, C.H., Hipkiss, E.L., Flies, A.S., Zhen, L., Tuder, R.M., Grosso, J.F., Harris, T.J., Getnet, D., Whartenby, K.A., Brockstedt, D.G., 2007. Role of PD-1 and its ligand, B7-H1, in early fate decisions of CD8 T cells. Blood 110 (1), 186–192.
Gonen, N., Assaraf, Y.G., 2012. Antifolates in cancer therapy: structure, activity and mechanisms of drug resistance. Drug Resist. Updates 15 (4), 183–210.
Gong, A.Y., Zhou, R., Hu, G., Li, X., Splinter, P.L., O'Hara, S.P., LaRusso, N.F., Soukup, G.A., Dong, H., Chen, X.M., 2009. MicroRNA-513 regulates B7-H1 translation and is involved in IFN-γ-induced B7-H1 expression in cholangiocytes. J. Immunol. 182 (3), 1325–1333.
Gotwals, P., Cameron, S., Cipolletta, D., Cremasco, V., Crystal, A., Hewes, B., Mueller, B., Quaratino, S., Sabatos-Peyton, C., Petruzzelli, L., Engelman, J.A., 2017. Prospects for combining targeted and conventional cancer therapy with immunotherapy. Nat. Rev. Cancer 17 (5), 286.
Gowrishankar, K., Gunatilake, D., Gallagher, S.J., Tiffen, J., Rizos, H., Hersey, P., 2015. Inducible but not constitutive expression of PD-L1 in human melanoma cells is dependent on activation of NF-κB. PLoS One 10 (4), e0123410.
Gregoire, S., Li, G., Sturzu, A.C., Schwartz, R.J., Wu, S.M., 2017. YY1 expression is sufficient for the maintenance of cardiac progenitor cell state. Stem Cells 35 (8), 1913–1923.
Grönroos, E., Terentiev, A.A., Punga, T., Ericsson, J., 2004. YY1 inhibits the activation of the p53 tumor suppressor in response to genotoxic stress. Proc. Natl. Acad. Sci. U. S. A. 101 (33), 12165–12170.
Hamanishi, J., Mandai, M., Iwasaki, M., Okazaki, T., Tanaka, Y., Yamaguchi, K., Higuchi, T., Yagi, H., Takakura, K., Minato, N., Honjo, T., 2007. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc. Natl. Acad. Sci. U. S. A. 104 (9), 3360–3365.
Hara, Y., Kusumi, Y., Mitsumata, M., Li, X.K., Fujino, M., 2008. Lysophosphatidylcholine upregulates LOX-1, chemokine receptors, and activation-related transcription factors in human T-cell line Jurkat. J. Thromb. Thrombol. 26 (2), 113–118.
Heriansyah, T., Nafisatuzzamrudah, N., Aini, F.N., Ridwan, M., Primardhika, R.F., Wijayanti, M., Bekti, R.S., Wihastuti, T.A., 2019. Reduction in vasa vasorum angiogenesis by Lp-PLA2 selective inhibitor through the HIF-1α and VEGF expression under dyslipidemic conditions in atherosclerosis pathogenesis. Cardiovasc. Hematol. Agents Med. Chem. 16 (2), 114–119.
Hiromura, M., Choi, C.H., Sabourin, N.A., Jones, H., Bachvarov, D., Usheva, A., 2003. YY1 is regulated by *O*-linked *N*-acetylglucosaminylation (*O*-GlcNAcylation). J. Biol. Chem. 278 (16), 14046–14052.
Hong, D., Kurzrock, R., Kim, Y., Woessner, R., Younes, A., Nemunaitis, J., Fowler, N., Zhou, T., Schmidt, J., Jo, M., Lee, S.J., 2015. AZD9150, a next-generation antisense oligonucleotide inhibitor of STAT3 with early evidence of clinical activity in lymphoma and lung cancer. Sci. Transl. Med. 7 (314) 314ra185.
Hongo, F., Garban, H., Huerta-Yepez, S., Vega, M., Jazirehi, A.R., Mizutani, Y., Miki, T.,

Bonavida, B., 2005. Inhibition of the transcription factor Yin Yang 1 activity by S-nitrosation. Biochem. Biophys. Res. Commun. 336 (2), 692–701.
Hou, J., Aerts, J., Den Hamer, B., Van Ijcken, W., Den Bakker, M., Riegman, P., van der Leest, C., van der Spek, P., Foekens, J.A., Hoogsteden, H.C., Grosveld, F., 2010. Gene expression-based classification of non-small cell lung carcinomas and survival prediction. PLoS One 5 (4), e10312.
Huang, M.J., Cheng, Y.C., Liu, C.R., Lin, S., Liu, H.E., 2006. A small-molecule c-Myc inhibitor, 10058-F4, induces cell-cycle arrest, apoptosis, and myeloid differentiation of human acute myeloid leukemia. Exp. Hematol. 34 (11), 1480–1489.
Huang, Y., Tao, T., Liu, C., Guan, H., Zhang, G., Ling, Z., Zhang, L., Lu, K., Chen, S., Xu, B., Chen, M., 2017. Upregulation of miR-146a by YY1 depletion correlates with delayed progression of prostate cancer. Int. J. Oncol. 50 (2), 421–431.
Huerta-Yepez, S., Vega, M., Garban, H., Bonavida, B., 2006. Involvement of the TNF-α autocrine–paracrine loop, via NF-κB and YY1, in the regulation of tumor cell resistance to Fas-induced apoptosis. Clin. Immunol. 120 (3), 297–309.
Huerta-Yepez, S., Rivera-Pazos, C., Libra, M., Baritaki, S., Chen, H., Berenson, J.R., Bonavida, B., 2008. Prognostic significance of both the cytoplasmic and nuclear overexpression of Yin-Yang 1 (YY1) among patients with multiple myeloma (MM). Blood 112 (11), 2730.
Huerta-Yepez, S., Baritaki, S., Baay-Guzman, G., Hernandez-Luna, M.A., Hernandez-Cueto, A., Vega, M.I., Bonavida, B., 2013. Contribution of either YY1 or BclXL-induced inhibition by the NO-donor DETANONOate in the reversal of drug resistance, both in vitro and in vivo. YY1 and BclXL are overexpressed in prostate cancer. Nitric Oxide 29, 17–24.
Huerta-Yepez, S., Liu, H., Baritaki, S., Del Lourdes Cebrera-Muñoz, M., Rivera-Pazos, C., Maldonado-Valenzuela, A., Valencia-Hipolito, A., Vega, M.I., Chen, H., Berenson, J.R., Bonavida, B., 2014. Overexpression of Yin Yang 1 in bone marrow-derived human multiple myeloma and its clinical significance. Int. J. Oncol. 45 (3), 1184–1192.
Hutten, T.J., Norde, W.J., Woestenenk, R., Wang, R.C., Maas, F., Kester, M., Falkenburg, J.H.F., Berglund, S., Luznik, L., Jansen, J.H., Schaap, N., Dolstra, H., Hobo, W., 2018. Increased coexpression of PD-1, TIGIT, and KLRG-1 on tumor-reactive CD8 t cells during relapse after allogeneic stem cell transplantation. Biol. Blood Marrow Transplant. 24 (4), 666–677.
Hwang, S.S., Jang, S.W., Kim, M.K., Kim, L.K., Kim, B.S., Kim, H.S., Kim, K., Lee, W., Flavell, R.A., Lee, G.R., 2016. YY1 inhibits differentiation and function of regulatory T cells by blocking Foxp3 expression and activity. Nat. Commun. 7, 10789.
Iacovelli, R., Nolè, F., Verri, E., Renne, G., Paglino, C., Santoni, M., Rocca, M.C., Giglione, P., Aurilio, G., Cullurà, D., Cascinu, S., 2016. Prognostic role of PD-L1 expression in renal cell carcinoma. A systematic review and meta-analysis. Target. Oncol. 11 (2), 143–148.
Iwai, Y., Ishida, M., Tanaka, Y., Okazaki, T., Honjo, T., Minato, N., 2002. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc. Natl. Acad. Sci. U. S. A. 99 (19), 12293–12297.
Iwai, Y., Noda, K., Yamazaki, M., Kato, A., Mezawa, M., Takai, H., Nakayama, Y., Ogata, Y., 2018. Tumor necrosis factor-α regulates human follicular dendritic cell-secreted protein gene transcription in gingival epithelial cells. Genes Cells 23 (3), 161–171.
Jeon, Y., Lee, J.T., 2011. YY1 tethers Xist RNA to the inactive X nucleation center. Cell 146 (1), 119–133.
Ji, K., Zheng, J., Lv, J., Xu, J., Ji, X., Luo, Y.B., Li, W., Zhao, Y., Yan, C., 2015. Skeletal muscle increases FGF21 expression in mitochondrial disorders to compensate for energy metabolic insufficiency by activating the mTOR–YY1–PGC1α pathway. Free Radic. Biol. Med. 84, 161–170.
Ji, X., Wang, E., Tian, F., 2018. MicroRNA-140 suppresses osteosarcoma tumor growth by enhancing anti-tumor immune response and blocking mTOR signaling. Biochem. Biophys. Res. Commun. 495 (1), 1342–1348.
Jia, L., Xi, Q., Wang, H., Zhang, Z., Liu, H., Cheng, Y., Guo, X., Zhang, J., Zhang, Q., Zhang, L., Xue, Z., 2017. miR-142-5p regulates tumor cell PD-L1 expression and enhances anti-tumor immunity. Biochem. Biophys. Res. Commun. 488 (2), 425–431.
Jin, M., Wu, Y., Wang, Y., Yu, D., Yang, M., Yang, F., Feng, C., Chen, T., 2016. MicroRNA-29a promotes smooth muscle cell differentiation from stem cells by targeting YY1. Stem Cell Res. 17 (2), 277–284.
Joo, M., Wright, J.G., Hu, N.N., Sadikot, R.T., Park, G.Y., Blackwell, T.S., Christman, J.W., 2007. Yin Yang 1 enhances cyclooxygenase-2 gene expression in macrophages. Am. J. Physiol.-Lung Cell. Mol. Physiol. 292 (5), L1219–L1226.
Joshi, B., Rastogi, S., Morris, M., Carastro, L.M., DeCook, C., Seto, E., Chellappan, S.P., 2007. Differential regulation of human YY1 and caspase 7 promoters by prohibitin through E2F1 and p53 binding sites. Biochem. J. 401 (1), 155–166.
Kang, W., Tong, J.H., Chan, A.W., Zhao, J., Dong, Y., Wang, S., Yang, W., Sin, F.M., Ng, S.S., Yu, J., Cheng, A.S., 2014. Yin Yang 1 contributes to gastric carcinogenesis and its nuclear expression correlates with shorter survival in patients with early stage gastric adenocarcinoma. J. Transl. Med. 12 (1), 80.
Kassardjian, A., Rizkallah, R., Riman, S., Renfro, S.H., Alexander, K.E., Hurt, M.M., 2012. The transcription factor YY1 is a novel substrate for Aurora B kinase at G2/M transition of the cell cycle. PLoS One 7 (11), e50645.
Kaufhold, S., Aziz, N., Bonavida, B., 2017. The forgotten YY2 in reported YY1 expression levels in human cancers. Crit. Rev. Oncog. 22 (1-2), 63–73.
Keir, M.E., Liang, S.C., Guleria, I., Latchman, Y.E., Qipo, A., Albacker, L.A., Koulmanda, M., Freeman, G.J., Sayegh, M.H., Sharpe, A.H., 2006. Tissue expression of PD-L1 mediates peripheral T cell tolerance. J. Exp. Med. 203 (4), 883–895.
Khachigian, L.M., 2018. The Yin and Yang of YY 1 in tumor growth and suppression. Int. J. Cancer 143 (3), 460–465.
Kim, H.J., Kim, A., Miyata, K., Kataoka, K., 2016. Recent progress in development of siRNA delivery vehicles for cancer therapy. Adv. Drug Deliv. Rev. 104, 61–77.
Kim, E.Y., Kim, A., Kim, S.K., Chang, Y.S., 2017. MYC expression correlates with PD-L1 expression in non-small cell lung cancer. Lung Cancer 110, 63–67.
Kleiman, E., Jia, H., Loguercio, S., Su, A.I., Feeney, A.J., 2016. YY1 plays an essential role at all stages of B-cell differentiation. Proc. Natl. Acad. Sci. U. S. A. 113 (27), E3911–20.
Knauss, J.L., Miao, N., Kim, S.N., Nie, Y., Shi, Y., Wu, T., Pinto, H.B., Donohoe, M.E., Sun, T., 2018. Long noncoding RNA Sox2ot and transcription factor YY1 co-regulate the differentiation of cortical neural progenitors by repressing Sox2. Cell Death Dis. 9 (8), 799.
Krause, M., Dubrovska, A., Linge, A., Baumann, M., 2017. Cancer stem cells: radioresistance, prediction of radiotherapy outcome and specific targets for combined treatments. Adv. Drug Deliv. Rev. 109, 63–73.
Krippner-Heidenreich, A., Walsemann, G., Beyrouthy, M.J., Speckgens, S., Kraft, R., Thole, H., Talanian, R.V., Hurt, M.M., Lüscher, B., 2005. Caspase-dependent regulation and subcellular redistribution of the transcriptional modulator YY1 during apoptosis. Mol. Cell. Biol. 25 (9), 3704–3714.
Kumar, N., Srivillibhuthur, M., Joshi, S., Walton, K.D., Zhou, A., Faller, W.J., Perekatt, A.O., Sansom, O.J., Gumucio, D.L., Xing, K., Bonder, E.M., 2016. A YY1-dependent increase in aerobic metabolism is indispensable for intestinal organogenesis. Development 143 (20), 3711–3722.
Kume, N., Gimbrone, M.A., 1994. Lysophosphatidylcholine transcriptionally induces growth factor gene expression in cultured human endothelial cells. J. Clin. Invest. 93 (2), 907–911.
Kurisaki, K., Kurisaki, A., Valcourt, U., Terentiev, A.A., Pardali, K., ten Dijke, P., Heldin, C.H., Ericsson, J., Moustakas, A., 2003. Nuclear factor YY1 inhibits transforming growth factor β-and bone morphogenetic protein-induced cell differentiation. Mol. Cell. Biol. 23 (13), 4494–4510.
Kwon, J.E., Lee, S.Y., Seo, H.B., Moon, Y.M., Ryu, J.G., Jung, K.A., Jhun, J.Y., Park, J.S., Hwang, S.S., Kim, J.M., Lee, G.R., 2018. YinYang1 deficiency ameliorates joint inflammation in a murine model of rheumatoid arthritis by modulating Th17 cell activation. Immunol. Lett. 197, 63–69.
Kythreotou, A., Siddique, A., Mauri, F.A., Bower, M., Pinato, D.J., 2018. PD-L1. J. Clin. Pathol. 71 (3), 189–194.
Lanzolla, G., Coppelli, A., Cosottini, M., Del Prato, S., Marcocci, C., Lupi, I., 2019. Immune checkpoint blockade Anti-PD-L1 as a trigger for autoimmune polyendocrine syndrome. J. Endocr. Soc. 3 (2), 496–503.
Lastwika, K.J., Wilson, W., Li, Q.K., Norris, J., Xu, H., Ghazarian, S.R., Kitagawa, H., Kawabata, S., Taube, J.M., Yao, S., Liu, L.N., 2016. Control of PD-L1 expression by oncogenic activation of the AKT-mTOR pathway in non-small cell lung cancer. Cancer Res. 76 (2), 227–238.
Lee, M.H., Lahusen, T., Wang, R.H., Xiao, C., Xu, X., Hwang, Y.S., He, W.W., Shi, Y., Deng, C.X., 2012. Yin Yang 1 positively regulates BRCA1 and inhibits mammary cancer formation. Oncogene 31 (1), 116.
Lee, J.J., Loh, K., Yap, Y.S., 2015. PI3K/Akt/mTOR inhibitors in breast cancer. Cancer Biol. Med. 12 (4), 342.
Li, H., Liu, H., Wang, Z., Liu, X., Guo, L., Huang, L., Gao, L., McNutt, M.A., Li, G., 2008. The role of transcription factors Sp1 and YY1 in proximal promoter region in initiation of transcription of the mu opioid receptor gene in human lymphocytes. J. Cell. Biochem. 104 (1), 237–250.
Li, W., Zhang, H., Assaraf, Y.G., Zhao, K., Xu, X., Xie, J., Yang, D.H., Chen, Z.S., 2016. Overcoming ABC transporter-mediated multidrug resistance: molecular mechanisms and novel therapeutic drug strategies. Drug Resist. Updates 27, 14–29.
Li, M., Liu, Y., Wei, Y., Wu, C., Meng, H., Niu, W., Zhou, Y., Wang, H., Wen, Q., Fan, S., Li, Z., 2019. Zinc-finger protein YY1 suppresses tumor growth of human nasopharyngeal carcinoma by inactivating c-Myc–mediated microRNA-141 transcription. J. Biol. Chem. jbc-RA118.
Liang, S.C., Latchman, Y.E., Buhlmann, J.E., Tomczak, M.F., Horwitz, B.H., Freeman, G.J., Sharpe, A.H., 2003. Regulation of PD-1, PD-L1, and PD-L2 expression during normal and autoimmune responses. Eur. J. Immunol. 33 (10), 2706–2716.
Lin, D.Y.W., Tanaka, Y., Iwasaki, M., Gittis, A.G., Su, H.P., Mikami, B., Okazaki, T., Honjo, T., Minato, N., Garboczi, D.N., 2008. The PD-1/PD-L1 complex resembles the antigen-binding Fv domains of antibodies and T cell receptors. Proc. Natl. Acad. Sci. U. S. A. 105 (8), 3011–3016.
Lin, J., He, Y., Chen, J., Zeng, Z., Yang, B., Ou, Q., 2017. A critical role of transcription factor YY1 in rheumatoid arthritis by regulation of interleukin-6. J. Autoimmun. 77, 67–75.
Lin, J., He, Y., Wang, B., Xun, Z., Chen, S., Zeng, Z., Ou, Q., 2018a. Blocking of YY1 reduce neutrophil infiltration by inhibiting IL-8 production via PI3K-Akt-mTOR signaling pathway in rheumatoid arthritis. Clin. Exp. Immunol. 195 (2), 226–236.
Lin, H., Wei, S., Hurt, E.M., Green, M.D., Zhao, L., Vatan, L., Szeliga, W., Herbst, R., Harms, P.W., Fecher, L.A., Vats, P., 2018b. Host expression of PD-L1 determines efficacy of PD-L1 pathway blockade–mediated tumor regression. J. Clin. Invest. 128 (2).
Liu, M., Guo, F., 2018. Recent updates on cancer immunotherapy. Precis. Clin. Med. 1 (2), 65–74.
Liu, H., Schmidt-Supprian, M., Shi, Y., Hobeika, E., Barteneva, N., Jumaa, H., Pelanda, R., Reth, N., Skok, J., Rajewsky, K., Shi, Y., 2007. Yin Yang 1 is a critical regulator of B-cell development. Genes Dev. 21 (10), 1179–1189.
Liu, D., Zhang, J., Wu, Y., Shi, G., Yuan, H., Lu, Z., Zhu, Q., Wu, P., Lu, C., Guo, F., Chen, J., 2018. YY1 suppresses proliferation and migration of pancreatic ductal adenocarcinoma by regulating the CDKN3/MdM2/P53/P21 signaling pathway. Int. J. Cancer 142 (7), 1392–1404.
Livney, Y.D., Assaraf, Y.G., 2013. Rationally designed nanovehicles to overcome cancer chemoresistance. Adv. Drug Deliv. Rev. 65 (13–14), 1716–1730.
Loke, P.N., Allison, J.P., 2003. PD-L1 and PD-L2 are differentially regulated by Th1 and Th2 cells. Proc. Natl. Acad. Sci. U. S. A. 100 (9), 5336–5341.
Lu, L., Zhou, L., Chen, E.Z., Sun, K., Jiang, P., Wang, L., Su, X., Sun, H., Wang, H., 2012. A

novel YY1-miR-1 regulatory circuit in skeletal myogenesis revealed by genome-wide prediction of YY1-miRNA network. PLoS One 7 (2), e27596.
Lu, S., Wang, M.S., Chen, P.J., Ren, Q., Bai, P., 2017. miRNA-186 inhibits prostate cancer cell proliferation and tumor growth by targeting YY1 and CDK6. Exp. Ther. Med. 13 (6), 3309–3314.
Maier, H., Isogawa, M., Freeman, G.J., Chisari, F.V., 2007. PD-1: PD-L1 interactions contribute to the functional suppression of virus-specific CD8+ T lymphocytes in the liver. J. Immunol. 178 (5), 2714–2720.
Mandai, M., Hamanishi, J., Abiko, K., Matsumura, N., Baba, T., Konishi, I., 2016. Dual faces of IFN-γ in cancer progression: a role of PD-L1 induction in the determination of Pro- and antitumor immunity. Clin. Cancer Res. 22 (10), 2329–2334.
Mandal, K., Bader, S.L., Kumar, P., Malakar, D., Campbell, D.S., Pradhan, B.S., Majumdar, S.S., 2017. An integrated transcriptomics-guided genome-wide promoter analysis and next-generation proteomics approach to mine factor(s) regulating cellular differentiation. DNA Res. 24 (2), 143–157.
Matsumura, N., Huang, Z., Baba, T., Lee, P.S., Barnett, J.C., Mori, S., Chang, J.T., Kuo, W.L., Gusberg, A.H., Whitaker, R.S., Gray, J.W., 2009. Yin yang 1 modulates taxane response in epithelial ovarian cancer. Mol. Cancer Res. 7 (2), 210–220.
Mayer, I.A., Arteaga, C.L., 2016. The PI3K/AKT pathway as a target for cancer treatment. Annu. Rev. Med. 67, 11–28.
Mazanet, M.M., Hughes, C.C., 2002. B7-H1 is expressed by human endothelial cells and suppresses T cell cytokine synthesis. J. Immunol. 169 (7), 3581–3588.
Mody, H.R., Hung, S.W., Pathak, R.K., Griffin, J., Cruz-Monserrate, Z., Govindarajan, R., 2017. miR-202 diminishes TGFβ receptors and attenuates TGFβ1-Induced EMT in pancreatic cancer. Mol. Cancer Res. 15 (8), 1029–1039.
Mordvinov, V.A., Schwenger, G.T., Fournier, R., De Boer, M.L., Peroni, S.E., Singh, A.D., Karlen, S., Holland, J.W., Sanderson, C.J., 1999. Binding of YY1 and Oct1 to a novel element that downregulates expression of IL-5 in human T cells. J. Allergy Clin. Immunol. 103 (6), 1125–1135.
Morgan, M.J., Woltering, J.M., der Rieden, P.M.I., Durston, A.J., Thiery, J.P., 2004. YY1 regulates the neural crest-associated slug gene in Xenopus laevis. J. Biol. Chem. 279 (45), 46826–46834.
Morozzi, G., Beccafico, S., Bianchi, R., Riuzzi, F., Bellezza, I., Giambanco, I., Arcuri, C., Minelli, A., Donato, R., 2017. Oxidative stress-induced S100B accumulation converts myoblasts into brown adipocytes via an NF-κB/YY1/miR-133 axis and NF-κB/YY1/BMP-7 axis. Cell Death Differ. 24 (12), 2077–2088.
Motohashi, S., Okamoto, Y., Yoshino, I., Nakayama, T., 2011. Anti-tumor immune responses induced by iNKT cell-based immunotherapy for lung cancer and head and neck cancer. Clin. Immunol. 140 (2), 167–176.
Motzer, R.J., Rini, B.I., McDermott, D.F., Redman, B.G., Kuzel, T.M., Harrison, M.R., Vaishampayan, U.N., Drabkin, H.A., George, S., Logan, T.F., Margolin, K.A., 2015. Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. J. Clin. Oncol. 33 (13), 1430.
Mudduluru, G., Walther, W., Kobelt, D., Dahlmann, M., Treese, C., Assaraf, Y.G., Stein, U., 2016. Repositioning of drugs for intervention in tumor progression and metastasis: old drugs for new targets. Drug Resist. Updates 26, 10–27.
Muro, K., Chung, H.C., Shankaran, V., Geva, R., Catenacci, D., Gupta, S., Eder, J.P., Golan, T., Le, D.T., Burtness, B., McRee, A.J., 2016. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. Lancet Oncol. 17 (6), 717–726.
Naidoo, K., Clay, V., Hoyland, J.A., Swindell, R., Linton, K., Illidge, T., Radford, J.A., Byers, R.J., 2011. YY1 expression predicts favourable outcome in follicular lymphoma. J. Clin. Pathol. 64 (2), 125–129.
Nakanishi, A., Kitagishi, Y., Ogura, Y., Matsuda, S., 2014. The tumor suppressor PTEN interacts with p53 in hereditary cancer. Int. J. Oncol. 44 (6), 1813–1819.
Nguyen, N., Zhang, X., Olashaw, N., Seto, E., 2004. Molecular cloning and functional characterization of the transcription factor YY2. J. Biol. Chem. 279 (24), 25927–25934.
Nishimura, H., Nose, M., Hiai, H., Minato, N., Honjo, T., 1999. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. Immunity 11 (2), 141–151.
Noman, M.Z., Desantis, G., Janji, B., Hasmim, M., Karray, S., Dessen, P., Bronte, V., Chouaib, S., 2014. PD-L1 is a novel direct target of HIF-1α, and its blockade under hypoxia enhanced MDSC-mediated T cell activation. J. Exp. Med. 211 (5), 781–790.
Noman, M.Z., Janji, B., Abdou, A., Hasmim, M., Terry, S., Tan, T.Z., Mami-Chouaib, F., Thiery, J.P., Chouaib, S., 2017. The immune checkpoint ligand PD-L1 is upregulated in EMT-activated human breast cancer cells by a mechanism involving ZEB-1 and miR-200. Oncoimmunology 6 (1), e1263412.
O'Donnell, J.S., Long, G.V., Scolyer, R.A., Teng, M.W., Smyth, M.J., 2017. Resistance to PD1/PDL1 checkpoint inhibition. Cancer Treat. Rev. 52, 71–81.
Oei, S.L., Shi, Y., 2001. Poly (ADP-ribosyl) ation of transcription factor Yin Yang 1 under conditions of DNA damage. Biochem. Biophys. Res. Commun. 285 (1), 27–31.
Oronsky, B., Paulmurugan, R., Foygel, K., Scicinski, J., Knox, S.J., Peehl, D., Zhao, H., Ning, S., Cabrales, P., Summers Jr., T.A., Reid, T.R., 2017. RRx-001: a systemically non-toxic M2-to-M1 macrophage stimulating and prosensitizing agent in Phase II clinical trials. Expert Opin. Investig. Drugs 26 (1), 109–119.
Oronsky, B., Reid, T.R., Oronsky, A., Caroen, S., Carter, C.A., Cabrales, P., 2018. Brief report: RRx-001 is a c-Myc inhibitor that targets cancer stem cells. Oncotarget 9 (34), 23439.
Ou, X., Huo, J., Huang, Y., Li, Y.F., Xu, S., Lam, K.P., 2018. Transcription factor YY1 is essential for iNKT cell development. Cell. Mol. Immunol. 1.
Palko, L., Bass, H.W., Beyrouthy, M.J., Hurt, M.M., 2004. The Yin Yang-1 (YY1) protein undergoes a DNA-replication-associated switch in localization from the cytoplasm to the nucleus at the onset of S phase. J. Cell. Sci. 117 (3), 465–476.
Palmer, M.B., Majumder, P., Cooper, J.C., Yoon, H., Wade, P.A., Boss, J.M., 2009. Yin Yang 1 regulates the expression of snail through a distal enhancer. Mol. Cancer Res. 7 (2), 221–229.
Park, A., Lee, J., Mun, S., Kim, D.J., Cha, B.H., Moon, K.T., Yoo, T.K., Kang, H.G., 2017. Identification of transcription factor YY1 as a regulator of a prostate cancer-specific pathway using proteomic analysis. J. Cancer 8 (12), 2303–2311.
Patsoukis, N., Li, L., Sari, D., Petkova, V., Boussiotis, V.A., 2013. PD-1 increases PTEN phosphatase activity while decreasing PTEN protein stability by inhibiting CK2. Mol. Cell. Biol. 33 (16), 3091–3098.
Patsoukis, N., Bardhan, K., Chatterjee, P., Sari, D., Liu, B., Bell, L.N., Karoly, E.D., Freeman, G.J., Petkova, V., Seth, P., Li, L., 2015. PD-1 alters T-cell metabolic reprogramming by inhibiting glycolysis and promoting lipolysis and fatty acid oxidation. Nat. Commun. 6, 6692.
Paucek, R.D., Baltimore, D., Li, G., 2019. The cellular immunotherapy revolution: arming the immune system for precision therapy. Trends Immunol. 40 (2) Pages Unavailable.
Pentland, I., Campos-León, K., Cotic, M., Davies, K.J., Wood, C.D., Groves, I.J., Burley, M., Coleman, N., Stockton, J.D., Noyvert, B., Beggs, A.D., West, M.J., Roberts, S., Parish, J.L., 2018. Disruption of CTCF-YY1-dependent looping of the human papillomavirus genome activates differentiation-induced viral oncogene transcription. PLoS Biol. 16 (10), e2005752.
Perekatt, A.O., Valdez, M.J., Davila, M., Hoffman, A., Bonder, E.M., Gao, N., Verzi, M.P., 2014. YY1 is indispensable for Lgr5+ intestinal stem cell renewal. Proc. Natl. Acad. Sci. U. S. A 111 (21), 7695–7700.
Pothoulakis, C., Torre-Rojas, M., Duran-Padilla, M.A., Gevorkian, J., Zoras, O., Chrysos, E., Chalkiadakis, G., Baritaki, S., 2017. CRHR2/Ucn2 signaling is a novel regulator of miR-7/YY1/Fas circuitry contributing to reversal of colorectal cancer cell resistance to Fas-mediated apoptosis. Int. J. Cancer 142 (2), 334–346.
Prima, V., Kaliberova, L.N., Kaliberov, S., Curiel, D.T., Kusmartsev, S., 2017. COX2/mPGES1/PGE2 pathway regulates PD-L1 expression in tumor-associated macrophages and myeloid-derived suppressor cells. Proc. Natl. Acad. Sci. U. S. A. 114 (5), 1117–1122.
Qi, Y., Yan, T., Chen, L., Zhang, Q., Wang, W., Han, X., Li, D., Shi, J., Sui, G., 2018. Characterization of YY1 OPB peptide for its anticancer activity. Curr. Cancer Drug Targets.
Qu, S.Y., Sun, Y.Y., Li, Y.H., Xu, Z.M., Fu, W.N., 2017. YY 1 directly suppresses MYCT 1 leading to laryngeal tumorigenesis and progress. Cancer Med. 6 (6), 1389–1398.
Quail, D.F., Joyce, J.A., 2013. Microenvironmental regulation of tumor progression and metastasis. Nat. Med. 19 (11), 1423.
Ralph Jr., W.M., Liu, K., Auborn, K.J., 2006. CCAAT/enhancer-binding protein β represses human papillomavirus 11 upstream regulatory region expression through a promoter-proximal YY1-binding site. J. Gen. Virol. 87 (1), 51–59.
Rangel-Santiago, J.F., Baay-Guzman, G.J., Duran-Padilla, M.A., Lopez-Bochm, K.A., Garcia-Romero, B.L., Hernandez-Cueto, D.D., Pantoja-Escobar, G., Vega, M.I., Hernandez-Pando, R., Huerta-Yepez, S., 2016. A novel role of Yin-Yang-1 in pulmonary tuberculosis through the regulation of the chemokine CCL4. Tuberculosis 96, 87–95.
Reck, M., Rodríguez-Abreu, D., Robinson, A.G., Hui, R., Csőszi, T., Fülöp, A., Gottfried, M., Peled, N., Tafreshi, A., Cuffe, S., O'Brien, M., 2016. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N. Engl. J. Med. 375 (19), 1823–1833.
Reddy, S.D.N., Pakala, S.B., Molli, P.R., Sahni, N., Karanam, N.K., Mudvari, P., Kumar, R., 2012. Metastasis associated protein1/histone deacetylase 4-nucleosome remodeling and deacetylase complex regulates PTEN expression and function. J. Biol. Chem. 287 (33), 27843.
Reilley, M.J., McCoon, P., Cook, C., Lyne, P., Kurzrock, R., Kim, Y., Woessner, R., Younes, A., Nemunaitis, J., Fowler, N., Curran, M., 2018. STAT3 antisense oligonucleotide AZD9150 in a subset of patients with heavily pretreated lymphoma: results of a phase 1b trial. J. Immunother. Cancer 6 (1), 119.
Rieth, J., Subramanian, S., 2018. Mechanisms of intrinsic tumor resistance to immunotherapy. Int. J. Mol. Sci. 19 (5), 1340.
Riman, S., Rizkallah, R., Kassardjian, A., Alexander, K.E., Lüscher, B., Hurt, M.M., 2012. Phosphorylation of the transcription factor YY1 by CK2α prevents cleavage by caspase 7 during apoptosis. Mol. Cell. Biol. 32 (4), 797–807.
Rizkallah, R., Hurt, M.M., 2009. Regulation of the transcription factor YY1 in mitosis through phosphorylation of its DNA-binding domain. Mol. Biol. Cell 20 (22), 4766–4776.
Rizkallah, R., Batsomboon, P., Dudley, G.B., Hurt, M.M., 2015. Identification of the oncogenic kinase TOPK/PBK as a master mitotic regulator of C2H2 zinc finger proteins. Oncotarget 6 (3), 1446.
Roy, S., Barke, R.A., Loh, H.H., 1998. Mu-opioid receptor-knockout mice: role of μ-opioid receptor in morphine mediated immune functions. Mol. Brain Res. 61 (1–2), 190–194.
Sanchez-Carbayo, M., Socci, N.D., Lozano, J., Saint, F., Cordon-Cardo, C., 2006. Defining molecular profiles of poor outcome in patients with invasive bladder cancer using oligonucleotide microarrays. J. Clin. Oncol. 24 (5), 778–789.
Sandison, H.E., Usher, S., Karimiani, E.G., Ashton, G., Menasce, L.P., Radford, J.A., Linton, K., Byers, R.J., 2013. PLK1 and YY1 interaction in follicular lymphoma is associated with unfavourable outcome. J. Clin. Pathol. 66 (9), 764–767.
Sang, W., Zhang, C., Zhang, D., Wang, Y., Sun, C., Niu, M., Sun, X., Zhou, C., Zeng, L., Pan, B., Chen, W., 2015. MicroRNA-181a, a potential diagnosis marker, alleviates acute graft versus host disease by regulating IFN-γ production. Am. J. Hematol. 90 (11), 998–1007.
Sankar, N., Baluchamy, S., Kadeppagari, R.K., Singhal, G., Weitzman, S., Thimmapaya, B., 2008. p300 provides a corepressor function by cooperating with YY1 and HDAC3 to repress c-Myc. Oncogene 27 (43), 5717.
Santiago, F.S., Lowe, H.C., Bobryshev, Y.V., Khachigian, L.M., 2001. Induction of the transcriptional repressor Yin Yang-1 by vascular cell injury autocrine/paracrine role of endogenous fibroblast growth factor-2. J. Biol. Chem. 276 (44), 41143–41149.

Seligson, D., Horvath, S., Huerta-Yepez, S., Hanna, S., Garban, H., Roberts, A., Shi, T., Liu, X., Chia, D., Goodglick, L., Bonavida, B., 2005. Expression of transcription factor Yin Yang 1 in prostate cancer. Int. J. Oncol. 27 (1), 131–141.
Sen, D.R., Kaminski, J., Barnitz, R.A., Kurachi, M., Gerdemann, U., Yates, K.B., Tsao, H.W., Godec, J., LaFleur, M.W., Brown, F.D., Tonnerre, P., Chung, R.T., Tully, D.C., Allen, T.M., Frahm, N., Lauer, G.M., Wherry, E.J., Yosef, N., Haining, W.N., 2016. The epigenetic landscape of T cell exhaustion. Science 354 (6316), 1165–1169.
Sepulveda, M.A., Emelyanov, A.V., Birshtein, B.K., 2004. NF-κB and Oct-2 synergize to activate the human 3′ Igh hs4 enhancer in B cells. J. Immunol. 172 (2), 1054–1064.
Shi, L., Chen, S., Yang, L., Li, Y., 2013. The role of PD-1 and PD-L1 in T-cell immune suppression in patients with hematological malignancies. J. Hematol. Oncol. 6 (1), 74.
Shi, J., Hao, A., Zhang, Q., Sui, G., 2015. The role of YY1 in oncogenesis and its potential as a drug target in cancer therapies. Curr. Cancer Drug Targets 15 (2), 145–157.
Siednienko, J., Maratha, A., Yang, S., Mitkiewicz, M., Miggin, S.M., Moynagh, P.N., 2011. Nuclear factor κB subunits RelB and cRel negatively regulate Toll-like receptor 3-mediated β-interferon production via induction of transcriptional repressor protein YY1. J. Biol. Chem. 286 (52), 44750–44763.
Song, M., Chen, D., Lu, B., Wang, C., Zhang, J., Huang, L., Wang, X., Timmons, C.L., Hu, J., Liu, B., Wu, X., 2013. PTEN loss increases PD-L1 protein expression and affects the correlation between PD-L1 expression and clinical parameters in colorectal cancer. PLoS One 8 (6), e65821.
Soragni, A., Janzen, D.M., Johnson, L.M., Lindgren, A.G., Nguyen, A.T.Q., Tiourin, E., Soriaga, A.B., Lu, J., Jiang, L., Faull, K.F., Pellegrini, M., 2016. A designed inhibitor of p53 aggregation rescues p53 tumor suppression in ovarian carcinomas. Cancer Cell 29 (1), 90–103.
Spranger, S., Spaapen, R.M., Zha, Y., Williams, J., Meng, Y., Ha, T.T., Gajewski, T.F., 2013. Up-regulation of PD-L1, IDO, and Tregs in the melanoma tumor microenvironment is driven by CD8+ T cells. Sci. Transl. Med. 5 (200), 200ra116.
Sui, G., Affar, E.B., Shi, Y., Brignone, C., Wall, N.R., Yin, P., Donohoe, M., Luke, M.P., Calvo, D., Grossman, S.R., Shi, Y., 2004. Yin Yang 1 is a negative regulator of p53. Cell 117 (7), 859–872.
Sun, W., Wu, H.Y., Chen, S., 2017. Influence of TBX21 T-1993C variant on autoimmune hepatitis development by Yin-Yang 1 binding. World J. Gastroenterol. 23 (48), 8500–8511.
Tang, J., Yu, J.X., Hubbard-Lucey, V.M., Neftelinov, S.T., Hodge, J.P., Lin, Y., 2018. Trial watch: the clinical trial landscape for PD1/PDL1 immune checkpoint inhibitors. Nat. Rev. Drug Discov. 17 (12), 854–855.
Tang, H., Liu, Y., Wang, C., Zheng, H., Chen, Y., Liu, W., Chen, X., Zhang, J., Chen, H., Yang, Y., Yang, J., 2019. Inhibition of COX-2 and EGFR by melafolone improves anti-PD-1 therapy through vascular normalization and PD-L1 downregulation in lung cancer. J. Pharmacol. Exp. Ther. 368 (3), 401–413.
Topalian, S.L., Drake, C.G., Pardoll, D.M., 2012. Targeting the PD-1/B7-H1 (PD-L1) pathway to activate anti-tumor immunity. Curr. Opin. Immunol. 24 (2), 207–212.
Torabi, A., Amaya, C.N., Wians, F.H., Bryan, B.A., 2017. PD-1 and PD-L1 expression in bone and soft tissue sarcomas. Pathology 49 (5), 506–513.
Tripathi, S., Guleria, I., 2015. Role of PD1/PDL1 pathway, and TH17 and treg cells in maternal tolerance to the fetus. Biomed. J. 38 (1), 25–31.
Vega, M.I., Valencia-Hipolito, A., Hernandez-Atenogenes, M., Vega, G.G., Mayani, H., Mendez-Tenorio, A., Martinez-Maza, O., Huerta-Yepez, S., Bonavida, B., 2013. High expression of Krüppel-Like Factor 4 (KLF4) and its regulation by Yin Yang 1 (YY1) in non-Hodgkin9s B-cell lymphomas: clinical implication. Am. Assoc. Cancer Res. 73 (8 Suppl), 5450.
Verstichel, G., Vermijlen, D., Martens, L., Goetgeluk, G., Brouwer, M., Thiault, N., Van Caeneghem, Y., De Munter, S., Weening, K., Bonte, S., Leclercq, G., Taghon, T., Kerre, T., Saeys, Y., Van Dorpe, J., Cheroutre, H., Vandekerckhove, B., 2017. The checkpoint for agonist selection precedes conventional selection in human thymus. Sci. Immunol. 2 (8), eaah4232.
Vesely, M.D., Kershaw, M.H., Schreiber, R.D., Smyth, M.J., 2011. Natural innate and adaptive immunity to cancer. Annu. Rev. Immunol. 29, 235–271.
Vibhakar, R., Juan, G., Traganos, F., Darzynkiewicz, Z., Finger, L.R., 1997. Activation-induced expression of human programmed death-1 gene in T-lymphocytes. Exp. Cell Res. 232 (1), 25–28.
Vo, B.T., Morton Jr, D., Komaragiri, S., Millena, A.C., Leath, C., Khan, S.A., 2013. TGF-β effects on prostate cancer cell migration and invasion are mediated by PGE2 through activation of PI3K/AKT/mTOR pathway. Endocrinology 154 (5), 1768–1779.
Wang, D., DuBois, R.N., 2010. The role of COX-2 in intestinal inflammation and colorectal cancer. Oncogene 29 (6), 781.
Wang, G.Z., Goff, S.P., 2015. Regulation of Yin Yang 1 by tyrosine phosphorylation. J. Biol. Chem. 290 (36), 21890–21900.
Wang, C.C., Tsai, M.F., Hong, T.M., Chang, G.C., Chen, C.Y., Yang, W.M., Chen, J.J., Yang, P.C., 2005. The transcriptional factor YY1 upregulates the novel invasion suppressor HLJ1 expression and inhibits cancer cell invasion. Oncogene 24 (25), 4081–4093.
Wang, Chi-Chung, Chen, J.J.W., Yang, Pan-Chyr, 2006. Multifunctional transcription factor YY1: a therapeutic target in human cancer? Expert Opin. Ther. Targets 10 (2), 253–266.
Wang, H., Hertlein, E., Bakkar, N., Sun, H., Acharyya, S., Wang, J., Carathers, M., Davuluri, R., Guttridge, D.C., 2007. NF-κB regulation of YY1 inhibits skeletal myogenesis through transcriptional silencing of myofibrillar genes. Mol. Cell. Biol. 27 (12), 4374–4387.
Wang, H., Garzon, R., Sun, H., Ladner, K.J., Singh, R., Dahlman, J., Cheng, A., Hall, B.M., Qualman, S.J., Chandler, D.S., Croce, C.M., 2008. NF-κB–YY1–miR-29 regulatory circuitry in skeletal myogenesis and rhabdomyosarcoma. Cancer Cell 14 (5), 369–381.
Wang, W., Li, F., Mao, Y., Zhou, H., Sun, J., Li, R., Liu, C., Chen, W., Hua, D., Zhang, X., 2013. A miR-570 binding site polymorphism in the B7-H1 gene is associated with the risk of gastric adenocarcinoma. Hum. Genet. 132 (6), 641–648.
Wang, A.M., Huang, T.T., Hsu, K.W., Huang, K.H., Fang, W.L., Yang, M.H., Lo, S.S., Chi, C.W., Lin, J.J., Yeh, T.S., 2014. Yin Yang 1 is a target of microRNA-34 family and contributes to gastric carcinogenesis. Oncotarget 5 (13), 5002.
Wang, J., Zhou, L., Li, Z., Zhang, T., Liu, W., Liu, Z., Yuan, Y.C., Su, F., Xu, L., Wang, Y., Zhou, X., 2015a. YY1 suppresses FEN1 over-expression and drug resistance in breast cancer. BMC Cancer 15 (1), 50.
Wang, X., Li, J., Dong, K., Lin, F., Long, M., Ouyang, Y., Wei, J., Chen, X., Weng, Y., He, T., Zhang, H., 2015b. Tumor suppressor miR-34a targets PD-L1 and functions as a potential immunotherapeutic target in acute myeloid leukemia. Cell. Signal. 27 (3), 443–452.
Wang, Z.T., Chen, Z.J., Jiang, G.M., Wu, Y.M., Liu, T., Yi, Y.M., Zeng, J., Du, J., Wang, H.S., 2016a. Histone deacetylase inhibitors suppress mutant p53 transcription via HDAC8/YY1 signals in triple negative breast cancer cells. Cell. Signal. 28 (5), 506–515.
Wang, Z., Zhang, C., Liu, X., Wang, Z., Sun, L., Li, G., Liang, J., Hu, H., Liu, Y., Zhang, W., Jiang, T., 2016b. Molecular and clinical characterization of PD-L1 expression at transcriptional level via 976 samples of brain glioma. Oncoimmunology 5 (11), e1196310.
Wang, W., Li, D., Sui, G., 2017a. YY1 Is an inducer of cancer metastasis. Crit. Rev. Oncog. 22 (1–2), 1–11.
Wang, X., Yang, L., Huang, F., Zhang, Q., Liu, S., Ma, L., You, Z., 2017b. Inflammatory cytokines IL-17 and TNF-α up-regulate PD-L1 expression in human prostate and colon cancer cells. Immunol. Lett. 184, 7–14.
Wang, M., Liu, C., Su, Y., Zhang, K., Zhang, Y., Chen, M., Ge, M., Gu, L., Lu, T., Li, N., Yu, Z., 2017c. miRNA-34c inhibits myoblasts proliferation by targeting YY1. Cell Cycle 16 (18), 1661–1672.
Wang, Q., Lin, W., Tang, X., Li, S., Guo, L., Lin, Y., Kwok, H., 2017d. The roles of microRNAs in regulating the expression of PD-1/PD-L1 immune checkpoint. Int. J. Mol. Sci. 18 (12), 2540.
Wang, Y., Wu, S., Huang, C., Li, Y., Zhao, H., Kasim, V., 2018a. Yin Yang 1 promotes the Warburg effect and tumorigenesis via glucose transporter GLUT3. Cancer Sci. 109 (8), 2423–2434.
Wang, W., Yue, Z., Tian, Z., Xie, Y., Zhang, J., She, Y., Yang, B., Ye, Y., Yang, Y., 2018b. Expression of Yin Yang 1 in cervical cancer and its correlation with E-cadherin expression and HPV16 E6. PLoS One 13 (2), e0193340.
Wang, J., Wu, X., Wei, C., Huang, X., Ma, Q., Huang, X., Faiola, F., Guallar, D., Fidalgo, M., Huang, T., Peng, D., Chen, L., Yu, H., Li, X., Sun, J., Liu, X., Cai, X., Chen, X., Wang, L., Ren, J., Wang, J., Ding, J., 2018c. YY1 positively regulates transcription by targeting promoters and super-enhancers through the BAF complex in embryonic stem cells. Stem Cell Rep. 10 (4), 1324–1339.
Weaver, B.A., Cleveland, D.W., 2005. Decoding the links between mitosis, cancer, and chemotherapy: the mitotic checkpoint, adaptation, and cell death. Cancer Cell 8 (1), 7–12.
Wei, F., Zhong, S., Ma, Z., Medvec, A., Ahmed, R., Freeman, G.J., Krogsgaard, M., Riley, J.L., 2013. Strength of PD-1 signaling differentially affects T-cell effector functions. Proc. Natl. Acad. Sci. U. S. A. 110 (27), E2480–E2489.
Weill, L., Shestakova, E., Bonnefoy, E., 2003. Transcription factor YY1 binds to the murine beta interferon promoter and regulates its transcriptional capacity with a dual activator/repressor role. J. Virol. 77 (5), 2903–2914.
Weintraub, A.S., Li, C.H., Zamudio, A.V., Sigova, A.A., Hannett, N.M., Day, D.S., Abraham, B.J., Cohen, M.A., Nabet, B., Buckley, D.L., Guo, Y.E., Hnisz, D., Jaenisch, R., Bradner, J.E., Gray, N.S., Young, R.A., 2017. YY1 is a structural regulator of enhancer-promoter loops. Cell 171 (7), 1573–1588.
Weng, W., Wang, M., Xie, S., Long, Y., Li, F., Sun, F., Yu, Y., Li, Z., 2014. YY1-C/EBPα-miR34a regulatory circuitry is involved in renal cell carcinoma progression. Oncol. Rep. 31 (4), 1921–1927.
Wijdeven, R.H., Pang, B., Assaraf, Y.G., Neefjes, J., 2016. Old drugs, novel ways out: drug resistance toward cytotoxic chemotherapeutics. Drug Resist. Updates 28, 65–81.
Wilke, C.M., Wei, S., Wang, L., Kryczek, I., Kao, J., Zou, W., 2011. Dual biological effects of the cytokines interleukin-10 and interferon-γ. Cancer Immunol. Immunother. 60 (11), 1529.
Wilkinson, F., Pratt, H., Atchison, M.L., 2010. PcG recruitment by the YY1 REPO domain can be mediated by Yaf2. J. Cell. Biochem. 109 (3), 478–486.
Wölfle, S.J., Strebovsky, J., Bartz, H., Sähr, A., Arnold, C., Kaiser, C., Dalpke, A.H., Heeg, K., 2011. PD-L1 expression on tolerogenic APCs is controlled by STAT-3. Eur. J. Immunol. 41 (2), 413–424.
Woo, S.R., Corrales, L., Gajewski, T.F., 2015. Innate immune recognition of cancer. Annu. Rev. Immunol. 33, 445–474.
Wottrich, S., Kaufhold, S., Chrysos, E., Zoras, O., Baritaki, S., Bonavida, B., 2017. Inverse correlation between the metastasis suppressor RKIP and the metastasis inducer YY1: contrasting roles in the regulation of chemo/immuno-resistance in cancer. Drug Resist. Updates 30, 28–38.
Wu, S., Wang, H., Li, Y., Xie, Y., Huang, C., Zhao, H., Miyagishi, M., Kasim, V., 2018. Transcription factor YY1 promotes cell proliferation by directly activating the pentose phosphate pathway. Cancer Res. 78 (16), 4549–4562.
Xia, B., Li, H., Yang, S., Liu, T., Lou, G., 2016. MiR-381 inhibits epithelial ovarian cancer malignancy via YY1 suppression. Tumor Biol. 37 (7), 9157–9167.
Xu, W., Banerji, S., Davie, J.R., Kassie, F., Yee, D., Kratzke, R., 2013. Yin Yang gene expression ratio signature for lung cancer prognosis. PLoS One 8 (7), e68742.
Xu, S., Tao, Z., Hai, B., Liang, H., Shi, Y., Wang, T., Song, W., Chen, Y., OuYang, J., Chen, J., Kong, F., 2016. miR-424 (322) reverses chemoresistance via T-cell immune response activation by blocking the PD-L1 immune checkpoint. Nat. Commun. 7, 11406.
Yan, X., Pan, J., Xiong, W., Cheng, M., Sun, Y., Zhang, S., Chen, Y., 2014. Yin Yang 1 (YY1) synergizes with Smad7 to inhibit TGF-β signaling in the nucleus. Sci. China Life

Sci. 57 (1), 128–136.
Yang, W.M., Inouye, C., Zeng, Y., Bearss, D., Seto, E., 1996. Transcriptional repression by YY1 is mediated by interaction with a mammalian homolog of the yeast global regulator RPD3. Proc. Natl. Acad. Sci. U. S. A. 93 (23), 12845–12850.
Yang, C., Zhang, J.J., Peng, Y.P., Zhu, Y., Yin, L.D., Wei, J.S., Gao, W.T., Jiang, K.R., Miao, Y., 2017. A Yin-Yang 1/miR-30a regulatory circuit modulates autophagy in pancreatic cancer cells. J. Transl. Med. 15 (1), 211.
Yao, Y.L., Ghosh, S., Fang, Y., Seto, E., Dupont, B.R., Leach, R.J., 1998. Cloning, chromosomal localization and promoter analysis of the human transcription factor YY1. Nucleic Acids Res. 26 (16), 3776–3783.
Yao, Y.L., Yang, W.M., Seto, E., 2001. Regulation of transcription factor YY1 by acetylation and deacetylation. Mol. Cell. Biol. 21 (17), 5979–5991.
Yin, W.Z., Li, F., Zhang, L., Ren, X.P., Zhang, N., Wen, J.F., 2014. Down-regulation of microRNA-205 promotes gastric cancer cell proliferation. Eur. Rev. Med. Pharmacol. Sci. 18 (7), 1027–1032.
Yuan, P., He, X., Rong, Y., Cao, J., Li, Y., Hu, Y., Liu, Y., Li, D., Lou, W., Liu, M., 2017. KRAS/NF-κB/YY1/miR-489 signaling axis controls pancreatic cancer metastasis. Cancer Res. 77 (1), 100–111.
Yue, Y., Lv, W., Zhang, L., Kang, W., 2018. MiR-147b influences vascular smooth muscle cell proliferation and migration via targeting YY1 and modulating Wnt/β-catenin activities. Acta Biochim. Biophys. Sin. 50 (9), 905–913.
Zak, K.M., Grudnik, P., Magiera, K., Domling, A., Dubin, G., Holak, T.A., 2017. Structural biology of the immune checkpoint receptor PD-1 and its ligands PD-L1/PD-L2. Structure (London, England: 1993) 25 (8), 1163–1174.
Zaprazna, K., Atchison, M.L., 2012. YY1 controls immunoglobulin class switch recombination and nuclear AID levels. Mol. Cell. Biol. 32 (8), 1542–1554.
Zaprazna, K., Basu, A., Tom, N., Jha, V., Hodawadekar, S., Radova, L., Malcikova, J., Tichy, B., Pospisilova, S., Atchison, M.L., 2017. Transcription factor YY1 can control AID-mediated mutagenesis in mice. Eur. J. Immunol. 48 (2), 273–282.
Zhang, H., Chen, J., 2018. Current status and future directions of cancer immunotherapy. J. Cancer 9 (10), 1773.
Zhang, J.J., Zhu, Y., Zhang, X.F., Liang, W.B., Xie, K.L., Tao, J.Q., Peng, Y.P., Xu, Z.K., Miao, Y., 2013a. Transcriptional regulation of human MUC4 gene: identification of a novel inhibitory element and its nuclear binding protein. Mol. Biol. Rep. 40 (8), 4913–4920.
Zhang, J.J., Zhu, Y., Xie, K.L., Peng, Y.P., Tao, J.Q., Tang, J., Li, Z., Xu, Z.K., Dai, C.C., Qian, Z.Y., Jiang, K.R., 2014. Yin Yang-1 suppresses invasion and metastasis of pancreatic ductal adenocarcinoma by downregulating MMP10 in a MUC4/ErbB2/p38/MEF2C-dependent mechanism. Mol. Cancer 13 (1), 130.
Zhang, Q., Wan, M., Shi, J., Horita, D.A., Miller, L.D., Kute, T.E., Kridel, S.J., Kulik, G., Sui, G., 2016a. Yin Yang 1 promotes mTORC2-mediated AKT phosphorylation. J. Mol. Cell Biol. 8 (3), 232–243.
Zhang, W.J., Wu, X.N., Shi, T.T., Xu, H.T., Yi, J., Shen, H.F., Huang, M.F., Shu, X.Y., Wang, F.F., Peng, B.L., Xiao, R.Q., 2016b. Regulation of transcription factor Yin Yang 1 by SET7/9-mediated lysine methylation. Sci. Rep. 6, 21718.
Zhang, J.J., Zhu, Y., Zhang, X.F., Liu, D.F., Wang, Y., Yang, C., Shi, G.D., Peng, Y.P., Zhang, K., Tian, L., Miao, Y., 2017. Yin Yang-1 suppresses pancreatic ductal adenocarcinoma cell proliferation and tumor growth by regulating SOX2OT-SOX2 axis. Cancer Lett. 408, 144–154.
Zhang, J., Bu, X., Wang, H., Zhu, Y., Geng, Y., Nihira, N.T., Tan, Y., Ci, Y., Wu, F., Dai, X., Guo, J., 2018a. Cyclin D-CDK4 kinase destabilizes PD-L1 via cullin 3-SPOP to control cancer immune surveillance. Nature 553 (7686), 91.
Zhang, X.C., Liang, H.F., Luo, X.D., Wang, H.J., Gu, A.P., Zheng, C.Y., Su, Q.Z., Cai, J., 2018b. YY1 promotes IL-6 expression in LPS-stimulated BV2 microglial cells by interacting with p65 to promote transcriptional activation of IL-6. Biochem. Biophys. Res. Commun. 502 (2), 269–275.
Zhang, Y., He, S., Mei, R., Kang, Y., Duan, J., Wei, R., Xiang, C., Wu, Y., Lu, X., Cai, Z., Xiong, L., 2018c. miR-29a suppresses IL-13-induced cell invasion by inhibiting YY1 in the AKT pathway in lung adenocarcinoma A549 cells. Oncol. Rep. 39 (6), 2613–2623.
Zheng, L., Chen, Y., Ye, L., Jiao, W., Song, H., Mei, H., Li, D., Yang, F., Li, H., Huang, K., Tong, Q., 2017. miRNA-584-3p inhibits gastric cancer progression by repressing Yin Yang 1-facilitated MMP-14 expression. Sci. Rep. 7 (1), 8967.
Zhitomirsky, B., Assaraf, Y.G., 2016. Lysosomes as mediators of drug resistance in cancer. Drug Resist. Updates 24, 23–33.
Zhou, L., Wang, L., Lu, L., Jiang, P., Sun, H., Wang, H., 2012. A novel target of microRNA-29, Ring1 and YY1 binding protein (Rybp), negatively regulates skeletal myogenesis. J. Biol. Chem. 287 (30), 25255–25265.
Zhou, W.Y., Chen, J.C., Jiao, T.T., Hui, N., Qi, X., 2015. MicroRNA-181 targets Yin Yang 1 expression and inhibits cervical cancer progression. Mol. Med. Rep. 11 (6), 4541–4546.
Zhu, J., Chen, L., Zou, L., Yang, P., Wu, R., Mao, Y., Zhou, H., Li, R., Wang, K., Wang, W., Hua, D., 2014. MiR-20b,-21, and-130b inhibit PTEN expression resulting in B7-H1 over-expression in advanced colorectal cancer. Hum. Immunol. 75 (4), 348–353.
Zou, W., Wolchok, J.D., Chen, L., 2016. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: mechanisms, response biomarkers, and combinations. Sci. Transl. Med. 8 (328), 328rv4.