

The Emerging Role of YAP/TAZ in Tumor Immunity

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Abstract

Yes-associated protein (YAP)/WW domain-containing transcription regulator 1 (TAZ) is an important transcriptional regulator and effector of the Hippo signaling pathway that has emerged as a critical determinant of malignancy in many human tumors. YAP/TAZ expression regulates the cross-talk between immune cells and tumor cells in the tumor microenvironment through its influence on T cells, myeloid-derived suppressor cells, and macrophages.

However, the mechanisms underlying these effects are poorly understood. An improved understanding of the role of YAP/TAZ in tumor immunity is essential for exploring innovative tumor treatments and making further breakthroughs in antitumor immunotherapy. This review primarily focuses on the role of YAP/TAZ in immune cells, their interactions with tumor cells, and how this impacts on tumorigenesis, progression, and therapy resistance.

Introduction

The tumor microenvironment (TME) is a complex cellular microenvironment established by tumors (1, 2). The TME enables tumor cells to self-repair and evade immune surveillance by actively subverting antitumor immunity, which is favorable to tumor progression, namely tumor growth, invasion, migration, and metastasis (3, 4). The TME is composed of a variety of nonneoplastic cells, including endothelial cells, nonlymphocytic stromal cells, and immune cells including tumor-infiltrating lymphocytes (TIL) and macrophages. Within the component cells, endothelial cells and cancer-associated fibroblasts promote tumor growth and tumor immune escape (5–7), while tumor-infiltrating immune cells in the TME differentially modulate cancer development (8, 9). This adjustment can be divided into antitumor immunity and the inhibition of antitumor immunity. In addition to cancer-associated fibroblasts (10–13), regulatory T cells (Treg), tumor-associated macrophages (TAM), and tumor-associated neutrophils constitute the major tumor-infiltrating immune cells that interact with tumor cells and inhibit antitumor immunity (14–17). Moreover, immune cells participating in the antitumor immunity consist of CTLs, B cells, natural killer (NK) cells, and dendritic cells (DC; refs. 18–20). The activity and functions of immune cells are critical for tumor immunity.

Hippo signaling is a fundamental player in tumor biology (21–26). MST1/2 kinases phosphorylate and activate LATS1/2, which in turn phosphorylate two transcriptional coactivators, Yes-associated protein (YAP) and WW domain-

containing transcription regulator 1 (TAZ), contributing to their cytoplasmic sequestration and functional suppression (27–30). YAP and TAZ, the closely related paralogues of these factors, act as the principal downstream effectors of the Hippo tumor suppressor pathway (31). Nonphosphorylated YAP and TAZ enter the nucleus to enhance the activation of various target oncogenes that regulate tumorigenesis, proliferation, and the suppression of apoptosis (29, 31). However, both YAP and TAZ lack DNA-binding domains and serve as transcriptional coactivators through their association with TEA domain family members (TEAD; refs. 32–34). 14-3-3 proteins have been reported to induce the phosphorylation and cytoplasmic retention of YAP or TAZ (YAP/TAZ; refs. 35–39). Phosphorylated YAP/TAZ recruits the E3 ubiquitin ligase SCF (β -TRCP) to induce its ubiquitination and proteasomal degradation (40–43).

Accumulating evidence has demonstrated the immunomodulatory effects of Hippo signaling components in malignant neoplasms. They regulate the activity and functions of immune cells independently of the canonical Hippo pathway (43–46). Given that YAP/TAZ is a critical effector of Hippo pathway and an important oncoprotein, it plays a pivotal role in tumor progression across numerous tumor types (47–50). Understanding the immunomodulatory effects of YAP/TAZ in malignant neoplasms is essential and meaningful for the development of novel therapeutic strategies. In this review, we detail how YAP/TAZ influences tumor development by regulating protumor and/or antitumor immunity, and how this serves as an indicator of patients' prognosis. We further discuss potential therapeutic interventions in terms of antitumor drugs that prevent YAP/TAZ-mediated TME immunosuppression, which promote the generation of effective antitumor immunotherapies.

The expression of YAP/TAZ in immune cells regulating tumor immunity

Immune cells play critical and indispensable roles in tumorigenesis and progression. Changes in the biological activity of immune cells including development, proliferation, differentiation, and functionality influence tumor progression. The expression of YAP/TAZ in immune cells is an important component of tumor immunity. DC-mediated CD8⁺ T-cell homeostasis and

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priming have been reported to require Mst1/2 to selectively orchestrate immune cell activity, which occurs independently of the classic Hippo-YAP/TAZ signaling (51). Studies pertaining to the role of YAP/TAZ expression in NK cells and myeloid-derived suppressor cells (MDSC) are sparse. Here, we elucidate the biological roles of YAP/TAZ in T cells, B cells, and macrophages, which correlate with tumor development and progression.

YAP/TAZ in regulating T cells

T cells are integral to the adaptive immune system, and can be commonly divided into two subsets according to the expression of CD4 or CD8 (CD4⁺ or CD8⁺ T cells; refs. 52–58). Through antigen recognition, T cell plays a range of immunologic functions including organ injury, infection, and chronic inflammatory disease (59–61). Besides, it is noteworthy that T cells are both essential and indispensable for tumor immunology, including immune evasion by cancers and antitumor immune responses (62, 63). T-cell activity is critical for tumor immunity and T-cell fate is influenced by Hippo signaling (64–68). Geng and colleagues found that the downstream effector of the Hippo signaling, TAZ but not YAP, drives Th17 cell differentiation and attenuates the differentiation of immunosuppressive Tregs (65). Notably, mice with elevated TAZ expression are prone to Th17 cell-mediated autoimmune diseases. TAZ is dispensable for T-cell activation and proliferation. Mechanistically, TAZ coactivates Th17 cell-defining transcriptional factor ROR γ t and facilitates the degradation of the Treg cell master regulator Foxp3, which is independent of the canonical Hippo pathway transcription factors, TEADs (65). Importantly, contacts between activated CD8⁺ T cells mediate the activation of Hippo signaling and triggers the expression of Blimp-1 (66), which is required for the terminal differentiation of CD8⁺ T cells (67, 68). CTLA-4–CD80 is a receptor–ligand pair, that activates Hippo signaling in activated CD8⁺ T cells, leading to YAP phosphorylation and degradation, which promotes Blimp-1 expression. CTLA-4 is suppressed by the addition of nonactivated CD8⁺ T cells. When Hippo signaling is blocked, YAP 5SA inhibits Blimp-1 transcription, consequently suppressing CD8⁺ T-cell differentiation (66).

Tregs play an important role in antitumor immunity through their ability to dampen T-cells function (69). Ni and colleagues found that immunosuppressive activity of Treg was dependent on YAP expression in the melanoma model (70). Antimelanoma immunity is enhanced in the absence of YAP. This finding emphasizes the pivotal role of YAP signaling to the TGF β /SMAD axis (70), which is critical to the functionality of Tregs (71). Moreover, in patients with hepatocellular carcinoma (HCC), YAP-1 expression is upregulated in Tregs within peripheral blood mononuclear cells (72). The 5-year survival rate of high YAP-1 expression group was lower than the YAP-1–low expression group in patients with HCC. YAP-1 promotes Tregs differentiation particularly through its ability to upregulate TGFBR2 expression, consequently facilitating the immunosuppressive TME (72).

To summarize, YAP/TAZ has nonnegligible effects on the development and functionality of T cells, which is crucial for tumor immunity.

YAP/TAZ in regulating B cells

B cells are important components of the immune system, and can be divided into T-cell-independent (B1 cell) and T-cell-dependent cells (B2 cell). B2 cells can be further subdivided into follicular B cells and marginal zone B cells, which play important

roles in the immune response (73, 74). In addition to presenting foreign antigens to T cells and altering T-cell responses, B cells can directly kill tumor cells and impair tumor development (75–77). Despite this knowledge, studies on the role of YAP/TAZ in B-cell function are sparse. Bai and colleagues found that YAP participates in the suppression of B-cell differentiation and functions by activating TEAD2. Activated TEAD2 represses the transcriptional levels of *cd19* by binding to the 3'UTR consensus motif of *cd19*, which mediates BCR signaling, endocytosis, and the differentiation of peripheral B cells (78). When infected with *Salmonella*, YAP coactivator activity is inhibited by phosphorylation and its interaction with Hck, a protein known to bind YAP and sequester it in the cytosol, preventing its nuclear translocation, resulting in the downregulation of a proapoptotic molecule, namely NLR family CARD domain containing protein 4 (NLRC4), which impairs IL1 β secretion and prevents B-cell death (79). *Salmonella* is a good candidate for the specific delivery of therapeutic agents during tumor therapy (80, 81). These results indicate that YAP/TAZ is undeniably important for the functionality and development of B cells and further studies are required to fully elucidate these functions.

YAP/TAZ in regulating macrophages

Macrophages are potent immune cells with established roles in innate and adaptive immunity (82–84). Under different conditions, macrophages can be polarized into classically (M1)-activated macrophages, which are proinflammatory with antitumoral functions, or alternatively (M2)-activated macrophages, which are anti-inflammatory with protumoral and angiogenic tissue-remodeling functions (85).

In addition to the response to injury, infection, and inflammation (86–88), the role of macrophages in tumor progression should not be underestimated (89, 90). YAP/TAZ was recently shown to regulate the development and functionality of macrophages. Zhao and colleagues provided novel insights into the roles of YAP in osteoclasts, which were derived from bone marrow-derived macrophages (91, 92). YAP1 deficiency significantly inhibited the receptor for activation of NF- κ B ligand (RANKL)-induced osteoclast differentiation and osteoclasts resorption activity by impairing activator protein 1 (AP-1) transcriptional activity and RANKL-induced NF- κ B signaling, both of which are key to osteogenesis (91). During *Legionella pneumophila* (*L. pneumophila*) infection, YAP/TAZ contributes to macrophage-mediated innate immunity (87). LegK7, an effector protein from *Legionella pneumophila*, mimics Hippo/MST1, triggering the phosphorylation and degradation of YAP/TAZ in macrophages, altering their transcriptional landscape during infection. TAZ altered the expression of peroxisome proliferator-activated receptor gamma (PPAR γ), rendering *L. pneumophila* maximal intracellular replication and infection (87). Lee and colleagues found that YAP/TAZ participates in the regulation of 135 genes in macrophages, of which 66 were closely related to cell development, differentiation, metabolism, and immunity, including PPAR γ , myoblast determination protein (MyoD), the zinc finger of the cerebellum 1 (Zic1), and lymphocyte function-associated antigen 1 (LF-A1) (87). The transcription factor PPAR γ has also been reported to modulate the polarization and inflammatory responses of macrophages (42, 43, 93). YAP/TAZ plays a crucial role in the biological activity of macrophages. In HCC, YAP mediates the migration of macrophages *in vitro* and *in vivo* (94). SPON2, a secreted extracellular matrix protein, is

significantly overexpressed in HCC cells and induces the migration of macrophages by SPON2- α 4 β 1 integrin signaling mediating the activation of Rho GTPase signaling, leading to the F-Actin accumulation. F-Actin promotes YAP nuclear translocation by inhibiting LATS1 phosphorylation, initiating the expression of downstream YAP genes, and ultimately facilitating M1-like macrophage infiltration (94). Thus, YAP/TAZ is capable of regulating the biological activity and function of macrophages, which is crucial for tumor immunity.

The role of tumoral YAP/TAZ expression in regulating tumor immunity

The development and progression of tumors cannot be separated from the influence of TME. YAP/TAZ expression in tumor cells exerts immunomodulatory effects on tumors by regulating immune checkpoint pathway and immune cells functions. Due to few or no researches about roles of tumoral YAP/TAZ expression in B cells, DCs, and NK cells, in this review, we summarize the most recent advances in the effects of tumoral YAP/TAZ expression on T cells, the programmed cell death ligand 1 (PD-L1), macrophages, and MDSCs, which are the underlying components of TME.

YAP/TAZ in tumor cells regulating T cells

T cells influence tumor immunity in the TME, of which CD8⁺ cytotoxic T-cell responses are the main mechanisms of the immune surveillance of tumors, while CD4⁺CD25⁺ infiltrated Tregs can suppress effector T-cell activity and promote tumor progression (63, 95, 96). Suh and colleagues reported novel observations regarding the positive relationship between tumoral YAP expression and Tregs infiltration according to IHC analysis of 118 gastric adenocarcinoma tissues (97). In pancreatic ductal adenocarcinoma (PDAC), YAP in *Kras:Trp53*-mutant neoplastic pancreatic ductal cells prevents the activation of infiltrating CD8⁺ CTLs, including inhibition of the activation markers *Prf1* and *Gzmb* expression in addition to the proliferation marker *Pcna*, allowing the survival of tumor cells (98). Noticeably, Moroishi and colleagues discovered an unexpected role of YAP/TAZ in tumor immunity (99). In three murine tumor models, including melanoma, squamous cell carcinoma (SCC), and breast cancer, the inhibition of Hippo signaling or YAP/TAZ nuclear localization and hyperactivation promoted the tumor cell growth *in vitro*. Unexpectedly, tumor growth was dramatically inhibited *in vivo* when in the three tumor cell lines in the absence of LATS1/2, indicating that YAP/TAZ overexpression suppresses tumor growth *in vivo* (99). Mechanistically, LATS1/2-deficient tumor cells released nucleic acid-rich extracellular vesicles, which elicited type I IFN signaling through the stimulation of toll-like receptors (TLR)-MYD88/TRIF signaling. Type I IFN played an essential role in antitumor immunity by facilitating CD8⁺ T-cell expansion (99).

These studies highlight the role of YAP/TAZ expression in tumor cells and tumor immunity by directly affecting T-cells infiltration, activation, and functionality. Tumoral YAP/TAZ expression indirectly influences T-cell functionality through other immune cells/molecules, including MDSCs, macrophages, and PD-L1, which will be discussed in subsequent sections.

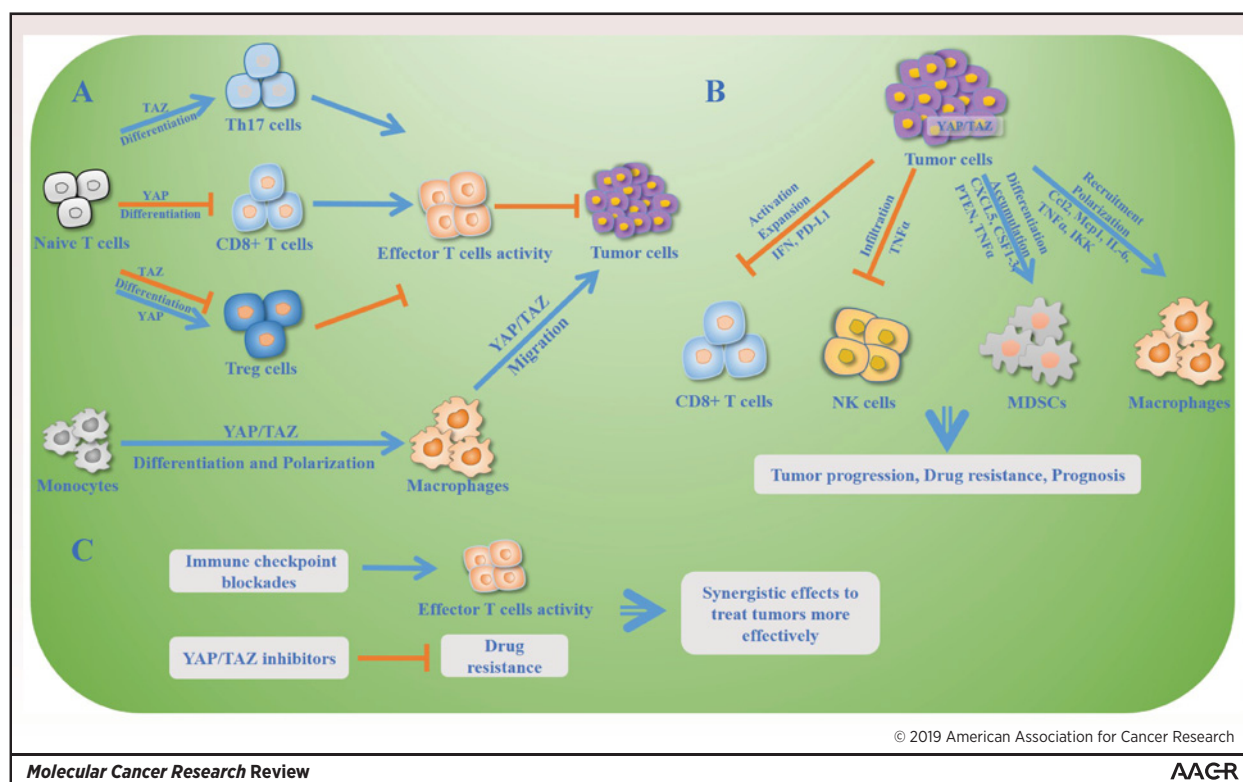
YAP/TAZ in tumor cells regulating MDSCs

MDSCs represent phenotypically heterogeneous immature myeloid cells that can differentiate into DCs, macrophages, and

neutrophils, promoting immunologic anergy and tolerance. MDSCs also promote tumorigenesis by inhibiting T-cell activity, particularly CD8⁺ cytotoxic T cells (100, 101). In prostate adenocarcinoma models, MDSCs were recruited to the TME and facilitated tumor progression, which was YAP dependent (102). YAP activation and nuclear localization in prostate tumor cells promotes secretion of the chemokine Cxcl5, a ligand for Cxcr2-expressing CD11b⁺ Gr-1⁺ MDSCs that attract other MDSCs through Cxcl5-Cxcr2 signaling. MDSCs in turn, strongly impede T-cells proliferation and promote tumor progression (102). In *Kras:p53*-mutant PDAC, YAP induces the expression and secretion of numerous cytokines/chemokines including IL6 and CSF1-3, which promote the differentiation and accumulation of MDSCs, resulting in impaired T-cells activation, macrophages reprogramming, and poor survival of patients with PDAC (98). In colorectal cancer, YAP and phosphatase and tensin homolog (PTEN) are strongly related with the density of CD33⁺ MDSCs and clinical features (103). Mechanistically, YAP drives colorectal cancer-derived MDSC expansion by inhibiting PTEN expression. PTEN suppression promotes the production of cytokine granulocyte-macrophage colony-stimulating factor by activating P-AKT, P-p65, and COX-2 signaling, all of which are closely associated with MDSC differentiation (103). MDSC expansion inhibits the proliferation and activation of T cells, leading to colorectal cancer cells' growth *in vitro* (104, 105). In high-grade ovarian serous carcinoma (HGOSC), YAP was shown to regulate protein kinase C iota type (PRKCI)-mediated immunosuppression in the TME (106, 107). PRKCI activation enhanced the nuclear localization and activation of YAP, leading to upregulated proinflammatory cytokine TNF α expression (107), which contributed to MDSCs recruitment and impaired NK and cytotoxic T-cell infiltration (108, 109). In summary, YAP/TAZ regulates protumor immunity through its effects on MDSC differentiation and expansion in the TME, inhibiting cytotoxic T-cell infiltration, activation, and functionality.

YAP/TAZ in tumor cells regulating PD-L1

Programmed death 1 (PD-1; also known as CD279), is a type I transmembrane protein expressed on activated T cells, B cells, monocytes, NK cells, and DCs and can induce and maintain T-cell tolerance (110, 111). PD-L1 (also known as CD274) is expressed on an array of tumor and immune cells (112). PD-1 and PD-L1 represent a dominant immune checkpoint pathway in the TME, and play an immunosuppressive role through inhibiting the function of T cells and TILs, and blockade of PD-1/PD-L1 has been shown to treat cancer more effectively via enhancing immunity (112). More recent studies have revealed that YAP is capable of regulating PD-L1 in tumor cells, thus influencing tumor immunity. In BRAF inhibitor (BRAFi)-resistant melanoma, YAP-expressing tumor cells evade the CD8⁺ T-cell immune response in a PD-L1-dependent manner (113). YAP regulates PD-L1 by directly binding to the enhancer region of PD-L1, but not by activating the autocrine cytokine signaling in melanoma cells. The relationship between YAP and PD-L1 expression was further validated *in vivo* in 472 human clinical melanoma tumor tissues (113). In breast cancer, TAZ activity determines PD-L1 expression in human tumor cells but not in mice possibly due to species-specific differences (114). TAZ activates PD-L1 through binding to its promoter through the TEADs enhancing promoter activity, suppressing T-cell viability, and triggering tumor immune evasion (114). In human malignant pleural

**Figure 1.**

The role of YAP/TAZ in tumor immunity. **A**, YAP/TAZ expression in immune cells regulates the differentiation and functions of Th17 cells, Tregs, CD8⁺ T cells, and macrophages, which influence the effector T-cell activity and tumor progression. **B**, YAP/TAZ expression in tumor cells in turn regulates various signaling pathways associated with functions and recruitment of TAMs and MDSCs and inhibition of NK cells and CD8⁺ T cells, contributing to the suppression of tumor progression and drug resistance, and YAP/TAZ expression also functions as the indicator of tumor prognosis. **C**, The combinational therapeutic strategy of immune checkpoint blockades and YAP/TAZ inhibitory agent seems to be encouraging and promising to promote the efficacy of tumor immunotherapy.

mesothelioma (MPM), YAP regulates PD-L1 by a similar mechanism, transcriptionally modulating PD-L1 through binding to enhancers of PD-L1, and inhibiting T-cell function, which was helpful to the development of PD-1/PD-L1 inhibitors, a new treatment option for patients with MPM (115–118). In human non-small cell lung cancer (NSCLC), YAP was also found to regulate PD-L1 at the transcriptional level, and the PD-1/PD-L1 pathway enhanced endogenous antitumor immune responses (17, 119). Moreover, lactate, a tumor-promoting factor generated by enhanced glycolysis in human lung cancer cells, played a critical role in the regulation of the PD1/PD-L1 immune checkpoint pathway through the TEAD1–TAZ complex (120). Lactate-mediated PD-L1 induction led to the activation of G protein-coupled receptor 81 (GPR81), which markedly reduced intracellular cAMP levels and repressed protein kinase A (PKA) activity, thereby promoting TAZ activation. The interaction of TAZ and TEAD was required for transcriptional PD-L1 activation, which suppressed T-cell function, thereby facilitating tumor immune evasion (120).

Remarkably, in addition to acting as a ligand of PD1, PD-L1 has an intrinsic role in tumor cell proliferation and migration in human EGFR-tyrosine kinase inhibitor (EGFR-TKI)-resistant lung adenocarcinoma (121). Interestingly, Lee and colleagues first found that YAP regulates PD-L1 by directly binding to the PD-L1 promoter and that YAP/PD-L1 signaling modulated tumor cell

proliferation and migration independently of T cells and PD1 in EGFR-TKI-resistant lung adenocarcinoma (121).

In summary, YAP/TAZ regulates PD-L1 expression in tumor cells, inhibiting T-cell-mediated antitumor immunity, in addition to the direct effects of tumoral YAP/TAZ expression on T-cell activation and function. This indicates that YAP-mediated PD-L1 expression is a positive sign for anti-PD-1 blocking therapy, although PD-L1 expression promotes the immune evasion of tumor cells.

YAP/TAZ in tumor cells regulating macrophages

TAMs are among the most abundant tumor-infiltrating cell types, and can be divided into two subgroups including protumoral TAMs (M2) and antitumoral TAMs (M1), exhibiting pro- or antitumor functions that influence tumor progression and antitumor therapies (122). In most circumstances, TAMs behave like M2 macrophages, with a subset of cells promoting tumor proliferation, migration, neovascularization, and drug resistance (123, 124). However, macrophages with tumor suppressive function cannot be ignored (122).

Macrophages play important roles during tumorigenesis and progression. Guo and colleagues provided deeper insight into the correlation between M2 macrophages and tumor-initiating cells (TIC) at the tumor initiation stage in HCC (125). YAP activation, induced by pathologically relevant oncogenes including AKT/

Table 1. The role of YAP/TAZ in immune cells

Immune	Cell effect	References
Th17 cell	TAZ- but not YAP-derived Th17 cells differentiation by activating ROR γ t.	65
Treg	TAZ inhibited the differentiation of Treg by suppressing Foxp3 expression.	65
	TAZ was dispensable for T-cell activation and proliferation.	65
	YAP determined Treg differentiation by promoting the signaling down the TGF β /SMAD axis, leading to the promotion of melanoma.	70
	YAP-1 was found to promote Treg differentiation by upregulating the TGFBR2 expression, inducing the immunosuppression in HCC.	72
CD8 ⁺ T cell	YAP 5SA suppressed CD8 ⁺ T-cell differentiation by inhibiting the transcription of Blimp-1	66
B cell	YAP participated in the regulation of B-cell differentiation and function by activating TEAD2-mediated BCR signaling reduction.	78, 105
	YAP phosphorylation and interaction with Hck prevented B-cell death by downregulating the expression of proapoptotic molecule NLRC4.	79, 107
Macrophage	YAP1 deficiency significantly inhibited osteoclast differentiation and function by impairing AP-1 transcriptional activity and RANKL-induced NF- κ B signaling.	91
	TAZ regulated <i>L. pneumophila</i> maximal intracellular replication and infection by manipulating PPAR γ expression.	87
	TAZ also could modulate the polarization and inflammatory responses of macrophages by regulating the transcription of PPAR γ .	87
	YAP could promote the migration of M1-like macrophages <i>in vitro</i> and <i>in vivo</i> in HCC by SPON2-integrin α 4 β 1-RhoA signaling-mediated F-actin accumulation.	94

EGFR in tumor cells, not only converts hepatocytes to TICs, but induces TIC-associated macrophages (TICAM) to be recruited to liver TICs through the enhancement of Ccl2/Csf1 secretion at the single-cell stage (125). Interestingly, YAP-induced TICAMs function as a tumor suppressor by eliminating YAP⁺ TICs, and can inhibit immunosurveillance-dependent and p53-dependent clearance of TICs at the single-cell stage, thereby influencing the survival of liver TICs and tumorigenesis (125). In contrast to the findings reported by Guo and colleagues, Kim and colleagues demonstrated that the polarization of M1 and M2 macrophages can be induced by YAP activation in hepatocytes during HCC formation (126). YAP positively regulated the expression of monocyte chemoattractant protein-1 (Mcp1) at the transcriptional level, contributing to macrophage infiltration, which is primarily responsible for liver growth and HCC formation (126). Huang and colleagues also found that, in addition to its oncogenic properties, YAP promotes M2 TAM polarization in colorectal cancer, which enhances their tumor-initiating ability (127). Ovatodiolide, the anti-inflammatory and antitumor agent, inhibits YAP expression in tumor cells, and suppresses M2 TAM polarization via reducing the expression of the pro-M2 polarization-associated cytokines, IL4, and IL13. Reduced M2 TAM generation evoked a loss of oncogenic IL6 secretion, preventing the formation of colon tumor spheres and subsequent tumor progression (127).

While tumoral YAP/TAZ expression above influences macrophage functions, macrophages impact on tumoral YAP/TAZ expression and influence tumor progression. Gao and colleagues discovered that macrophages-derived conditioned medium (CM) influence YAP transcriptional activity in breast cancer cells, and induce the migration of tumor cells (128). TNF α was the major component of the macrophage CM. Mechanistically, macrophage CM or TNF α induce the YAP-mediated upregulation of hexokinase 2 (HK2), a major enzyme controlling the first stage of glycolysis and enhancing tumor cell invasion (129, 130), through I κ B kinase (IKK) β / ϵ signaling, which triggers YAP phosphorylation and activation in breast cancer cells (128).

Although YAP/TAZ-mediated macrophages regulate tumor immunity, this is not applicable to all tumors. It does however exert an important and indispensable role in TME and provides a potential therapeutic target for tumor immunotherapy.

The role of YAP/TAZ signaling of tumor immunity in tumor prognosis and therapy

An increasing number of studies have highlighted the association of YAP/TAZ expression in tumor cells with tumor prognosis and therapeutic responses, but the role of YAP/TAZ in tumor immunity is less well characterized (131–135). The TME encompasses tumor cells, immune cells, and other cell types. So it is meaningful to evaluate the role of YAP/TAZ signaling of tumor immunity in tumor prognosis and therapy. Tregs in particular, are associated with the poor prognosis in many types of malignant tumor (136–139). YAP/TAZ expression in Tregs influences their differentiation and functionality (65, 66, 70), and is closely related to the low 5-year survival rates in patients with tumor (72). Tumoral YAP expression is a predictor of poor prognosis in patients with colorectal cancer, owing to its correlation with the abundance of MDSCs and reduced survival of patients with colorectal cancer (124). Furthermore, recent clinical studies have revealed that increased YAP expression is closely related to poor prognosis in patients with colon cancer due to its ability to promote M2 TAM polarization (127, 135), which correlates with poor prognosis in several types of human cancers (140–142).

The PD-1/PD-L1 immune checkpoint blockade is recognized as an effective immunotherapy for several types of tumor (143). YAP/TAZ can regulate tumoral PD-L1 expression and promotes drug resistance in many tumors (144–147). So, it is worthy of further exploring the role of YAP/TAZ in tumor immunotherapy. In NSCLC, Miao and colleagues found that YAP dictates PD-L1 expression at the transcription level in tumor cells, providing a basis for the exploration of potential therapeutic YAP targets (119). Moreover, Lee and colleagues revealed that the down-regulation of YAP directly inhibits PD-L1, and represents an effective mechanism to overcome gefitinib-resistant lung adenocarcinoma (121). In melanoma, BRAFi resistance is closely related to the suppression of T-cell immune responses. Kim and colleagues demonstrated that targeting YAP leads to immunologic changes, including increased PD-L1 expression and direct inhibitory effects on cytotoxic T cells that drive improved BRAFi therapeutic efficacy and patients' survival (113). In colorectal cancer, Huang and colleagues discovered that YAP suppression in synergy with 5-Fluorouracil (5-FU) significantly inhibited tumorigenesis and enhanced the therapeutic response of patients with colorectal cancer by preventing TAM polarization, infiltration, and TAM-mediated resistance toward 5-FU treatment (127). Whether YAP/TAZ inhibitors in combination with other

Table 2. The role of tumoral YAP/TAZ in regulating tumor immunity

Tumor type	Effector immune cell/checkpoint	Mechanism	References
Gastric cancer	Tregs	Tumoral YAP expression promoted the infiltration of Tregs, which affected tumor progression.	97
PDAC	CTLs	YAP expression in tumor cells prevents the activation of CTLs by inhibiting the activation markers Prfl and Gzmb expression, as well as the proliferation marker Pcn.	98
SCC melanoma breast cancer	CD8 ⁺ T cell	YAP/TAZ overexpression unexpectedly suppressed tumor growth <i>in vivo</i> by facilitating CD8 ⁺ T-cell expansion through TLRs-MYD88/TRIF signaling pathway-mediated activating type I IFN signaling, which provided a novel proof of concept for targeting LATS1/2 in tumor immunotherapy.	99
Prostate cancer	MDSCs	YAP activation induced MDSCs infiltration by promoting Cxcl5 secretion, leading to the impairment of T cell proliferation and tumor-promoting action, which revealed an effective therapeutic way for advanced tumor.	102
PDAC	MDSCs	YAP promoted the differentiation and accumulation of MDSCs by inducing IL6 and CSF1-3 expression and secretion, which correlated with the poor survival of patients.	98
CRC	MDSCs	YAP derived MDSCs differentiation and expansion by inhibiting PTEN signaling, contributing to the promotion of tumor growth. High level MDSCs and YAP expression were identified as the predictor for the prognosis of patients with CRC.	103, 104
HGOSC	MDSCs	PRKCI-induced YAP activation and upregulated TNF α expression, recruiting MDSCs and then impairing the infiltration and functions of NK cells and cytotoxic T cells, which afforded an immune therapeutic strategy for highly deadly ovarian cancer.	106
Melanoma	PD-L1	YAP mediated tumor cells evasion of CD8 ⁺ T-cell immune responses in a PD-L1-dependent way and targeting of YAP-mediated immune evasion could improve prognosis of patients.	113
Breast cancer	PD-L1	TAZ determining PD-L1 expression in tumor cells occurred in human cells but not in mice, which suppressed T-cells viability and triggered tumor immune evasion.	114
MPM	PD-L1	YAP regulated the PD-L1 in a way similar with above, which promoted tumor progression and was helpful for treatment.	115, 116
NSCLC	PD-L1	YAP regulated PD-L1 at transcriptional levels and PD-1/PD-L1 pathway enhanced endogenous antitumor immune responses.	119
Lung cancer	PD-L1	TAZ participated in lactate-mediated PD-L1 induction through GPR81-cAMP/PKA signaling, suppressing T-cell functions and facilitating tumor immune evasion.	120
HCC	Macrophages	YAP induced TICAMs recruitment, which functioned as a tumor suppressor by eliminating YAP ⁺ TICs, and it could also inhibit the immunosurveillance-dependent and p53-dependent clearance of TICs starting from the single-cell stage.	125
HCC	Macrophages	YAP activation in tumor cells induced M1 and M2 macrophages polarization by promoting the production of Mcp1, contributing to liver growth and HCC formation, which provided new targets and strategies to treat HCCs.	126
CRC	Macrophages	YAP functioned on determining tumor-promoting M2 TAM polarization by elevating the expression of pro-M2 polarization-associated cytokines IL4 and IL13, which promoted IL6 secretion, leading to the tumorigenesis and progression promotion. Increased YAP expression correlated with the poor prognosis in patients with colon cancer. YAP inhibitor Ovatodiolide in combination with the antitumor drug 5-FU obviously suppressed tumorigenesis and TAM infiltration, which implied the potentially promising antitumor therapy.	127
Breast cancer	Macrophages	TNF α from the CM of macrophages induced YAP expression in tumor cells and promoted the migration of tumor cells via IKK β / ϵ signaling mediated the upregulation of HK2.	128

Abbreviation: CRC, colorectal cancer.

antitumor drugs act as a more effective treatment for tumors is therefore worthy of future exploration.

Conclusions

YAP/TAZ functions as the important promoter or inhibitor for tumorigenesis and TME. In this study we highlight essential roles of YAP/TAZ in tumor immunity, which ultimately influences tumor progression and has far-reaching significance for tumor prognosis and treatment. YAP/TAZ expression in immune cells, including T cells, B cells, and macrophages, mechanistically regulates the differentiation and functionality of immune cells, which are important for tumor immunity. Conversely, YAP/TAZ expression in tumor cells indirectly affects the recruitment and activity of tumor-infiltrating immune cells or immune checkpoints through specific signaling pathways to influence tumor growth and the TME. YAP/TAZ-associated tumor immunity now require further mechanistic and preclinical studies, and the ability

to regulate YAP/TAZ in combination with antineoplastic drugs represents a novel and effective strategy for tumor immunotherapy. We have also summarized previous studies that describe the roles of YAP/TAZ in tumor immunity (Fig. 1A–C; Tables 1 and 2).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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