Tumor-intrinsic signaling pathways: key roles in the regulation of the immunosuppressive tumor microenvironment

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Abstract
Immunotherapy is a currently popular treatment strategy for cancer patients. Although recent developments in cancer immunotherapy have had significant clinical impact, only a subset of patients exhibits clinical response. Therefore, understanding the molecular mechanisms of immunotherapy resistance is necessary. The mechanisms of immune escape appear to consist of two distinct tumor characteristics: a decrease in effective immunocyte infiltration and function and the accumulation of immunosuppressive cells in the tumor microenvironment. Several host-derived factors may also contribute to immune escape. Moreover, inter-patient heterogeneity predominantly results from differences in somatic mutations between cancers, which has led to the hypothesis that differential activation of specific tumor-intrinsic pathways may explain the phenomenon of immune exclusion in a subset of cancers. Increasing evidence has also shown that tumor-intrinsic signaling plays a key role in regulating the immunosuppressive tumor microenvironment and tumor immune escape. Therefore, understanding the mechanisms underlying immune avoidance mediated by tumor-intrinsic signaling may help identify new therapeutic targets for expanding the efficacy of cancer immunotherapies.

Keywords: Immunosuppressive tumor microenvironment, Immune escape, T cell infiltration, Immunosuppressive cells, Tumor-intrinsic signaling

Background
The recent developments in cancer immunotherapy show significant clinical impact. Particularly, monoclonal antibodies targeting the immune checkpoints cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) have shown dramatic efficacy and have been approved by the FDA for cancer treatment [1–4]. Nevertheless, only a subset of patients experiences clinical benefit. Furthermore, chimeric antigen receptor-T (CAR-T) cell therapy has been approved for the treatment of certain hematological malignancies, yet solid cancers are often less susceptible to CAR-T cell therapy mostly due to the immunosuppressive tumor microenvironment [5, 6]. Therefore, understanding the molecular mechanisms of immunotherapy resistance, specifically those induced by the tumor microenvironment, is necessary.

The tumor microenvironment consists of the non-cancerous cells present in the tumor, which includes immune cells, fibroblasts, and cells that comprise the blood vessels [7, 8]. It has been shown that a subset of melanoma patients with metastases exhibits a T cell-inflamed tumor microenvironment as evidenced by gene expression profiling [9]. The T cell-inflamed phenotype also shows activated immune-inhibitory pathways as well as expression of PD-L1 and indoleamine-2,3-dioxygenase (IDO) [10]. In contrast, the lack of T cell infiltration in the tumor microenvironment appears to avoid antitumor immunity through the exclusion of T cells from the tumor site. In addition, immunosuppressive cells,
including tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), T regulatory cells (Tregs), and tumor-associated neutrophils (TANs), are also responsible for an immunosuppressive tumor microenvironment and tumor immune escape [7, 11–13]. Thus, the mechanisms of immune escape appear to be distinct in two major subsets of tumors, that is, a decrease in effective immunocyte infiltration and function and an increase in immunosuppressive cells in the tumor microenvironment.

Several host-derived factors may also contribute to immune escape. Inter-patient heterogeneity predominantly results from differences in somatic mutations between cancers [14], which has led to the hypothesis that differential activation of specific tumor-intrinsic pathways may explain the phenomenon of immune exclusion in a subset of cancers. In addition to the activation of tumor-intrinsic pathways within the tumor cells themselves, exposure to chronic viral infections, the composition of the intestinal microbiota of patients, and the accumulation of germline polymorphisms in immune regulatory genes may also influence the antitumor immunotherapy response [15, 16].

Tumor-intrinsic signaling pathways are considered to be oncogenic pathways. Increasing evidence has shown that tumor-intrinsic signaling plays a key role in regulating the immunosuppressive tumor microenvironment and tumor immune escape [17, 18]. Successful identification of these pathways would lead to new therapeutic strategies that can enable immunocyte entry into non-inflamed tumors and attenuate the immunosuppressive microenvironment to increase the number of patients capable of responding to immunotherapies. In this review, we will describe the mechanisms by which tumor-intrinsic signaling pathways regulate the immunosuppressive tumor microenvironment, including the decrease in effective immunocyte infiltration and function and the accumulation of immunosuppressive cells in the tumor microenvironment, which may help identify new therapeutic targets for enhancing the efficacy of cancer immunotherapy.

**Effective immunocyte exclusion and dysfunction**

The innate and adaptive immune cells in the tumor microenvironment harbor both tumor-promoting and tumor-suppressing activities, which may predict clinical outcome [19, 20]. It has been shown that oncogenic drivers of tumors may function to limit host immunity in the remaining non-immunocyte inflamed tumors or dysfunction of immunocytes in the tumor microenvironment, thereby leading to immunoresistance (Fig. 1, Table 1).
| Subtype                                      | Signaling                | Tumor type                        | Effect                                                                                     | Ref                        |
|---------------------------------------------|--------------------------|-----------------------------------|-------------------------------------------------------------------------------------------|---------------------------|
| Effective immunocyte exclusion and dysfunction | β-Catenin                | Melanoma                          | Decreased T cell infiltration                                                            | 18, 21, 22                |
|                                             |                          |                                   | Inhibition of IFN-γ production by CTLs                                                    | 23                        |
|                                             |                          |                                   | Upregulating the expression and activity of IDO by DCs                                   | 24                        |
|                                             | STAT3                    | Lung cancer                       | Inhibition of CCL5 and CXCL10 production to decrease T cell infiltration                   | 25, 26, 28                |
|                                             | PI3K/PTEN/AKT/mTOR       | Breast, prostate, and lung cancer, gliomas | Regulation of PD-L1 expression to induce T cell dysfunction                              | 29, 31–33                |
|                                             |                          | Triple-negative breast cancer      | Decreased T cell infiltration, regulation of PD-L1 expression                            | 30                        |
|                                             |                          | Multiple cancers                  | Decreased the therapeutic efficacy of an E7-specific vaccine or CD8⁺ T cell adoptive transfer | 34                        |
|                                             | p53                      | Liver carcinoma                   | Increased recruitment and activation of innate immune cells                              | 37, 38                    |
|                                             |                          | Triple-negative breast cancer      | Regulation of T cell infiltration                                                        | 39                        |
|                                             | NF-κB                    | Epithelial ovarian cancer          | Immunosuppression of DCs and macrophages                                                 | 42                        |
|                                             |                          | Colitis-associated cancer, cervical cancer, etc. | Increased T cell infiltration and activation                                             | 43–46                    |
|                                             | RAS/RAF/MAPK             | Lung adenocarcinoma, RAS mutant cancer | Inducing PD-L1 expression                                                               | 47, 48                    |
|                                             |                          | Melanoma                          | Suppression of DC function                                                              | 50, 51                    |
|                                             |                          | Melanoma                          | Inhibiting the recognition of tumor cell antigens by tumor-infiltrated T lymphocytes     | 52                        |
|                                             |                          | Melanoma                          | Suppression of proliferation and function of specific cytotoxic T cells                  | 53                        |
|                                             | GBE1                     | Lung adenocarcinoma                | Decreased T cell infiltration                                                            | 54                        |
|                                             | KRAS/MYC                 | KRAS-mutant tumor                 | Exclusion of B, T, and NK cells                                                          | 55                        |
|                                             | EGFR                     | Non-small cell lung cancer, head and neck cancer | Upregulation of PD-L1 expression                                                        | 56–60                    |
|                                             | VEGFR                    | Chronic myeloid leukemia           | Inhibited NK cell-mediated immunosurveillance                                            | 61                        |
|                                             | PI3K/PTEN/AKT            | Breast, pancreatic, and lung carcinomas | Recruitment of macrophages and polarization of TAMs                                      | 70–72                    |
|                                             |                          | Sarcomas                          | Enhanced infiltrating myeloid-derived hematopoietic cells                               | 73                        |
|                                             |                          | Prostate cancer                   | Increased expansion and infiltration of MDSCs                                             | 74, 75                    |
|                                             | RAS/RAF/MAPK             | KRAS-driven lung tumorigenesis, melanoma | Increased Treg infiltration                                                             | 76, 78                    |
|                                             |                          | BRAFi-resistant melanoma          | Increased MDSC infiltration                                                             | 77                        |
|                                             | KRAS                     | KRAS-driven non-small cell lung cancer | Accumulation of TANs                                                                    | 79                        |
|                                             |                          | KRAS-mutant tumor                 | Recruitment of proangiogenic macrophages                                                | 55                        |
|                                             | CCRK/mTOR                | Obesity-associated hepatocellular carcinoma | Recruitment of MDSCs                                                                    | 80                        |
|                                             | RAGE                     | Pancreatic carcinogenesis          | Accumulation of MDSCs                                                                    | 81                        |
|                                             | TLR9                     | Prostate cancer                   | Expansion and activation of G-MDSCs                                                      | 82                        |
|                                             | p53 loss-of-function     | Late stage metastatic castration resistant prostate cancer | Accumulation of MDSCs                                                                  | 83                        |
β-Catenin signaling
Differential activation of the β-catenin oncogene pathway within tumor cells themselves contributes to the robustness of a spontaneous antitumor immune response (Fig. 1, Table 1). Recently, Spranger et al. [21] found that 48% of the non-T cell-inflamed tumors show evidence of WNT/β-catenin signaling pathway activation based on gene expression profiling of six defined β-catenin target genes. In vivo experiments demonstrated that activation of the β-catenin pathway within melanoma tumor cells can dominantly exclude immune cell activation and result in a non-T cell-inflamed tumor microenvironment. β-Catenin-mediated immune escape occurs via inhibition of the production of CCL4 derived from tumor cells; this results from induction of the transcriptional repressor ATF3, which blocks CCL4 gene transcription. The lack of CCL4 secretion results in decreased recruitment of CD103+ dendritic cells (DCs), thereby preventing cross-priming of antitumor T cells [18, 22]. In addition, β-catenin-overexpressed melanomas inhibit the production of IFN-γ by melanoma-specific cytotoxic lymphocytes (CTLs) in an interleukin (IL)-10-independent manner and were more resistant to CTL lysis in vitro and in vivo [23]. Moreover, melanoma-derived Wnt5a ligand upregulates the durable expression and activity of IDO enzyme by local DCs in a β-catenin signaling pathway-dependent manner [24].

STAT3 signaling
One potential candidate for oncogenic drivers leading to immunoresistance is activation of the STAT3 signaling pathway (Fig. 1, Table 1). Constitutively active STAT3 signaling in transplantable tumor cell lines has been reported to decrease expression of proinflammatory mediators, while expression of a dominant negative STAT3 variant resulted in augmented expression of proinflammatory factors, including the chemokines CCL5 and CXCL10, which are functionally responsible for T cell recruitment [25, 26]. Recent studies have provided additional evidence for this phenomenon via a carcinogen-induced lung cancer model and a genetically-induced prostate cancer model [27, 28]. Using a conditional knockout model for STAT3, Ihara et al. [28] found an increased antitumor immune response in the absence of STAT3 signaling, which was closely associated with increased expression of CCL5 and CXCL10; this phenotype was associated with increased T cell infiltration and function within the tumor microenvironment. Thus, the STAT3 signaling pathway may represent a viable mechanistic pathway for diminishing immune cell recruitment into tumor sites, and based on the currently available data, it may interfere with T cell recruitment.

PI3K/PTEN/AKT/mTOR signaling
The PI3K/PTEN/AKT/mTOR pathway is another interesting candidate that may impact the host immune response (Fig. 1, Table 1). The expression of PD-L1, a pivotal negative regulator of T cell function, is associated with the activation of PI3K in breast and prostate cancer patients [29]. Recent findings have demonstrated that the expression of tumor suppressor PTEN was closely associated with the lack of T cell infiltration as well as low PD-L1 expression in the tumor microenvironment of triple-negative breast cancer [30], indicating that loss of PTEN expression (and constitutive PI3K activation) is associated with the presence of T cells in the tumor microenvironment. In the LKB1, PTEN-null model, tumor-propagating cells of human lung squamous cell carcinoma highly expressed PD-L1, suggesting a mechanism of immune escape for tumor-propagating cells [31]. Moreover, loss of PTEN function increases PD-L1 expression and immunoresistance in gliomas [32]. Furthermore, oncogenic activation of the AKT-mTOR signaling pathway promotes immune escape by driving the expression of PD-L1, which was confirmed in syngeneic and genetically engineered mouse models of lung cancer where combination therapy of an mTOR inhibitor with a PD-1 antibody decreased tumor growth and increased T cell infiltration [33]. Intratumoral injection of an AKT inhibitor also enhanced the therapeutic efficacy of an E7-specific vaccine or E7-specific CD8+ T cell adoptive transfer against immune-resistant tumors [34]. These findings indicate that activation of the PI3K/AKT signaling pathway represents a new mechanism of

| Subtype | Signaling | Tumor type | Effect | Ref |
|---------|-----------|------------|--------|----|
| IDO     | Advanced cancer | Generation and activation of MDSCs and Tregs | 64 |
| CD200/CD200R | Chemical skin carcinogenesis | Influencing the ratio of Treg/Th17 cells | 84, 85 |
| STAT3   | Hematopoietic system | Recruiting and promoting the proliferation of Tregs | 86, 87 |
| COX2    | Wilms' tumor | Increased Treg infiltration | 90 |
| c-MET   | Melanoma | Increased TAN infiltration | 91 |
immune escape that has important implications for the
development of a novel cancer immunotherapy strategy
against immune-resistant tumors.

p53 signaling
Mutant p53 is another molecular aberration in cancer
cells that is associated with immune response (Fig. 1,
Table 1). Activating/reactivating p53 signaling in the
tumor microenvironment represents a compelling im-
munological strategy for enhancing antitumor immunity
and reversing immunosuppression [35, 36]. It has been
shown that an intact p53 signaling pathway is correlated
with increased recruitment and activation of innate im-
mune cells [37]. In a related study, where cellular senes-
cence is triggered in vivo by inducible p53 expression
using a mouse model of liver carcinoma, tumor regres-
sion associated with re-expression of wildtype p53 was
strongly dependent on the activation and recruitment
of natural killer (NK) cells into the tumor site [38].
Consistent with these findings, a recent study tested for
interaction between TP53 mutation status and integrative
cluster analysis in 1420 breast tumors, indicating a
close correlation between wildtype p53 and the presence
of T cells in the tumor microenvironment of triple-
negative breast cancer [39]. Moreover, in a murine liver
carcinoma model, reactivation of p53 signaling induced
tumor regression, which was associated with increased
expression of proinflammatory chemokines. Collectively,
these findings suggest that steady-state p53 signaling can
contribute to enhanced recruitment of innate and adap-
tive immune cells as well as their activation.

NF-κB signaling
Another candidate oncogenic signaling pathway that has
potential effects on the host immune response is the
NF-κB signaling pathway (Fig. 1, Table 1). Activation of
this pathway in cancer cells has been associated with
tumor progression [40, 41]. In epithelial ovarian cancer
patients, increased plasma IL-6, IL-8, and arginase were
observed, and the NF-κB inhibitor DHMEQ inhibited
the production of IL-6 and IL-8 by epithelial ovarian
cancer cell lines. Treatment with DHMEQ reversed the
immunosuppression of human DCs and macrophages
cultured in the supernatant of epithelial ovarian cancer
cells [42]. The NF-κB signaling pathway induces the pro-
duction of cytokines that regulate the immune response
(e.g., TNFα, IL-1, IL-6, and IL-8) as well as adhesion
molecules that lead to the recruitment of leukocytes into
tumor sites [43]. Constitutive activation of NF-κB has
been shown to increase the expression of tumor cell-
derived chemokines, which can have positive immune
effects [44]. Activation of NF-κB signaling also increases
the production of chemokines that can recruit activated
T cells within the tumor microenvironment [45].

Moreover, full activation of NF-κB is accompanied by in-
creased activity of cytotoxic immune cells against cancer
cells in early cancer stages [46]. Therefore, the impact of
tumor-intrinsic NF-κB signaling activation on host
immunity may depend on the cellular context.

RAS/RAF/MAPK signaling
The RAS/RAF/MAPK pathway is probably the best
characterized signal transduction pathway in cell biology.
The function of this pathway is to transduce signals
from the extracellular milieu to the cell nucleus where
specific genes are activated for cell growth, differenti-
ation, and migration. Thus, the RAS/RAF/MAPK signal-
ing regulates a variety of cellular functions that are
important for tumorigenesis.

The RAS/RAF/MAPK signaling pathway is also involved
in the host immune response (Fig. 1, Table 1). KRAS
mutations induce PD-L1 expression through p-ERK signaling
in lung adenocarcinomas. Blockade of PD-1/PD-L1 signal-
ing would thus be a promising therapeutic strategy for
KRAS-mutant lung adenocarcinoma [47]. Similarly,
Coelho et al. [48] found that oncogenic KRAS signaling
increases PD-L1 expression in tumor cells.

Because DCs are important in the induction of tumor-
specific T cell responses, the effect of MAPK pathway
activation on DC function is critical for the melanoma-
directed immune response [49]. BRAF
V600E-mutant melanoma cells regulate DCs through the MAPK signal-
ing pathway, whose blockade can reverse the suppression
of DC function. The inhibition of MEK, a MAPK/ERK
kinase, negatively impacts DC function and viability [50].
The suppressive activity of melanoma cell culture superna-
tants on the production of IL-12 and TNFαs by DCs
upon lipopolysaccharide stimulation was significantly re-
duced after transduction with BRAF
V600E RNAi [51]. In addition, blocking the BRAF-MAPK signaling pathway in
BRAF signaling-addicted melanoma cells in vitro triggered
the recognition of tumor cell antigens by tumor-infiltrated
T lymphocytes; BRAF blockade and adoptive T cell ther-
apy may confer synergistic effects [52]. Moreover, the
expression of BRAF
V600E induced transcription of IL-1α and IL-1β in melanocytes and melanoma cell lines, which
increased the suppression of proliferation and function of
specific cytotoxic T cells in melanomas [53].

Other signaling
Other oncogenic signaling pathways also contribute to
tumor immune escape (Fig. 1, Table 1). In our previous
study, lung adenocarcinoma-intrinsic glycogen branch-
ing enzyme (GBE1) signaling was found to inhibit anti-
tumor immunity. GBE1 blockade promotes the secretion
of CCL5 and CXCL10 to recruit CD8+ T lymphocytes to
the tumor microenvironment via the IFN-I/STING sig-
naling pathway, accompanied by upregulation of PD-L1
in lung adenocarcinoma cells; this indicates that GBE1 is a promising cancer immunotherapy target for achieving tumor regression in lung adenocarcinomas [54].

Immune suppression in KRAS-mutant mouse tumors with co-activation of MYC may lead to increased expression of IL-23 and CCL9, which mediate the exclusion of B, T, and NK cells [55].

EGFR is also involved in the regulation of PD-L1 expression in non-small cell lung cancer [56–58], which suppresses T cell function. Overexpression of EGFR is correlated with PD-L1 expression in head and neck cancers in a JAK2/STAT1-dependent manner, indicating a novel role for JAK2/STAT1 in EGFR-induced immune evasion [59]. This study found that PD-L1 expression increased significantly in an EGFR-dependent manner by the activation of EGFR signaling and decreased sharply when EGFR signaling was blocked. The upregulated expression of PD-L1 was not associated with EGFR/STAT3 signaling pathway, but may be affected by EGFR/PI3K/AKT, EGFR/RAS/RAF/ERK, and EGFR/PLC-γ signaling pathways [60]. VEGFR2-targeted fusion antibody improved NK cell-mediated immunosurveillance against K562 cells through increasing degranulation and cytokine production of NK cells [61].

Human-specific activation of PD-L1 by a novel Hippo signaling pathway in cancer immune evasion may have a significant impact on immunotherapy research [62]. Moreover, inactivation of Hippo signaling in tumor cells induces a type I interferon response, increases tumor immunogenicity, and enhances tumor vaccine efficacy [63].

Meanwhile, IDO activation in cancers mediates the suppression of T and NK cells [64, 65]. Hennequart et al. [66] highlighted the role of COX-2 in constitutive IDO1 expression by human tumors and demonstrated that COX-2 inhibitors can reduce constitutive IDO1 expression, which contributes to the lack of T cell infiltration in “cold” tumors that fail to respond to immunotherapy. Moretti et al. [67] provided the first evidence of a direct link between IDO1 expression and oncogenic activation of RET in thyroid carcinoma and described the involved signal transduction pathways.

Finally, activation of TLR4 signaling in bladder cancer cells upregulates PD-L1 expression [68]. Isocitrate dehydrogenase mutations in glioma cells lead to acquired resistance to NK cells through epigenetic silencing of NKG2D ligands [69].

**Recruitment and differentiation of immunosuppressive cells**

In addition to alterations in T cell immune checkpoints, an increase in immunosuppressive cells, including TAMs, MDSCs, Tregs, and TANs, and differentiation of these immunosuppressive cells within the tumor microenvironment may also contribute to immunoresistance in cancers (Fig. 2, Table 1).

**PI3K/PTEN/AKT signaling**

The PI3K/PTEN/AKT oncogenic signaling pathway has a positive effect on immunosuppressive cell recruitment and differentiation (Fig. 2, Table 1). Several studies have demonstrated that activated PI3K signaling, either through activating mutations in PIK3CA or loss-of-function mutations in PTEN, can result in the accumulation of TAMs, which induce an immunosuppressive microenvironment [70, 71]. This phenomenon was associated with increased production of TNF, IL-6, CSF-1, VEGF-A, and IL-8 by tumor cells, which contribute to the recruitment of macrophages and the polarization of M2-like macrophages [72]. PTEN-deficient sarcomas exhibit enhanced infiltrating myeloid-derived hematopoietic cells, particularly macrophages and neutrophils, recruited via tumor cell-derived CSF-1 [73]. Furthermore, PTEN-null prostate epithelium triggers the production of inflammatory cytokines and mediates localized Gr-1⁺CD11b⁺ MDSC expansion and immune suppression, thereby promoting tumor progression [74]. In genetically engineered mouse models of prostate cancer, the deletion of PTEN and Smad4 promotes tumor progression and infiltration of MDSCs [75].

**RAS/RAF/MAPK signaling**

The RAS/RAF/MAPK signaling pathway is also involved in the recruitment and differentiation of immunosuppressive cells (Fig. 2, Table 1). Overexpression of the mutant KRAS G12V gene in wildtype KRAS tumor cells led to Treg induction through the activation of the MEK-ERK-AP1 pathway, while KRAS inhibition reduced Treg infiltration in KRAS-driven lung tumorigenesis even before tumor formation [76].

Preclinical studies showed that treatment with BRAFV600E inhibitors (BRAFi) initially reduced MDSC infiltration in the tumor microenvironment of an autochthonous mouse model of melanoma, but resistance to BRAFi was associated with restoration of MDSCs. In contrast to the restoration of MDSCs, Treg levels remained low in BRAFi-resistant tumors. Notably, MDSC restoration relied upon the reactivation of MAPK signaling and downstream production of CCL2, the myeloid attractant, in BRAFi-resistant melanoma cells [77]. Shabaneh et al. [78] found that BRAFV600E signaling was sufficient to recruit Tregs into the tumor microenvironment, establishing a novel role for BRAFV600E as a tumor-intrinsic mediator of immune escape and underscoring the critical early role of Treg-mediated suppression during tumorigenesis.

**KRAS signaling**

The KRAS signaling pathway cooperated with other molecules is also involved in the recruitment and differentiation
of immunosuppressive cells (Fig. 2, Table 1). In a mouse model of KRAS-driven non-small cell lung cancer, STK11/LKB1 loss was found to affect the immune microenvironment. Genetic ablation of STK11/LKB1 resulted in the accumulation of TANs, which results in T cell-suppressive effects along with a corresponding increase in the expression of T cell exhaustion markers and tumor-promoting cytokines [79]. In KRAS-mutant mouse tumors, immune suppression may be a result of MYC co-activation leading to the recruitment of proangiogenic macrophages in the tumor microenvironment [55].

Other signaling
Other oncogenic events common in cancer, such as infiltration and differentiation of MDSCs, TANs, and Tregs, may also have the potential to enhance the immunosuppressive tumor microenvironment (Fig. 2, Table 1).

Hepatic cell cycle-related kinase (CCRK) induction in transgenic mice stimulates mTORC1-dependent G-CSF secretion, which further enhances the recruitment of polymorphonuclear MDSCs [80]. These findings indicate a role for an inflammatory-CCRK signaling pathway in driving immunosuppressive reprogramming through the activation of mTORC1, thereby reeducating the pro-tumorigenic microenvironment of hepatocellular carcinoma. The receptor for advanced glycation end-products (RAGE) promotes accumulation of MDSCs to further induce pancreatic carcinogenesis [81]. Moreover, TLR9+ prostate cancer promotes immune evasion via LIF-mediated expansion and activation of G-MDSCs [82]. In preclinical melanoma mouse models, p53 loss-of-function promotes the accumulation of MDSCs within the tumor microenvironment of late stage metastatic castration resistant prostate cancer [83]. The activation of IDO in cancers can also induce the generation and activation of MDSCs and Tregs [64].

In another study, the CD200/CD200R axis was shown to induce tolerance to external and tumor antigens and to influence the ratio of Treg/Th17 cells and control the balance of Treg/T effector cells, which provides a therapeutic strategy for CD200 blocking antibodies [84, 85]. The STAT3 signaling pathway also plays an important role in recruiting and promoting the proliferation of Tregs [86, 87], which in turn has suppressive activity toward CD8+ effector T cells and other immune cell types within the tumor microenvironment [88, 89]. Moreover, COX2 signaling can increase the infiltration of immune suppressive inflammatory cells, such as Tregs, in tumors [90].

Finally, a study by Glodde et al. [91] showed that c-MET inhibition impairs reactive TAN recruitment to
tumors and lymph nodes, potentiating T cell antitumor immunity.

**Therapeutic targets for tumor-intrinsic signaling in cancer**

As discussed above, there is strong evidence that tumor-intrinsic signaling regulates the immunosuppressive tumor microenvironment via exclusion and dysfunction of effective immunocytes and recruitment and differentiation of immunosuppressive cells. Therefore, targeting tumor-intrinsic signaling is a promising strategy for cancer treatment. In the following sections, we will discuss therapeutic strategies for targeting oncogenic signaling (Table 2, Fig. 3).

**BRAF/MEK inhibitors**

The BRIM8 study (NCT01667419) evaluated the effects of BRAF inhibitor vemurafenib monotherapy in patients with resected, BRAF\textsuperscript{V600}-mutant melanomas and found that 1 year of vemurafenib was well tolerated but may not be an optimal treatment regimen [92]. The safety and efficacy of combined vemurafenib and MEK inhibitor cobimetinib in patients with advanced BRAF-mutated melanoma were also assessed; when administered at their respective maximum tolerated doses, vemurafenib and cobimetinib co-therapy was safe and well tolerated (NCT01271803). This combination therapy shows promising antitumor activity, and confirmatory clinical testing is ongoing [93]. Moreover, Ascierto et al. [94] reported on the clinical benefit of vemurafenib and cobimetinib combination therapy and supported its use as a standard first-line strategy for improving survival in patients with advanced BRAF\textsuperscript{V600}-mutant melanoma. In addition, the combination therapy of vemurafenib and cobimetinib was closely associated with a significant improvement in progression-free survival among patients with BRAF\textsuperscript{V600}-mutated metastatic melanoma, at the cost of some increase in toxicity (NCT01689519) [95].

Dabrafenib is another selective inhibitor of mutated forms of BRAF kinase, and trametinib is another inhibitor of MEK 1/2. It has been shown that prolonged survival of more than 3 years is achievable with dabrafenib plus trametinib in patients with BRAF\textsuperscript{V600}-mutant metastatic melanoma, supporting the long-term first-line use of this combination therapy [96]. BRAF\textsuperscript{V600}-mutant unresectable or metastatic melanoma patients treated with a combination of dabrafenib plus trametinib show a clear benefit over patients receiving vemurafenib monotherapy, such as survival advantage as well as avoidance of disease-associated and adverse-event-associated symptoms, which supports this combination therapy as a standard of care for this population [97]. Another study (NCT01597908) showed that dabrafenib plus trametinib significantly improved overall survival without increased overall toxicity in previously untreated patients with metastatic BRAF\textsuperscript{V600}-mutation melanoma compared with that of vemurafenib monotherapy [98]. Adjuvant use of a dabrafenib plus trametinib combination therapy resulted in a significantly lower risk of recurrence in patients with stage III BRAF\textsuperscript{V600}-mutation melanoma and was not associated with new toxic effects (NCT01682083) [99]. Moreover, dabrafenib combined with trametinib represents a novel therapeutic strategy with meaningful antitumor activity, as evidenced by studies on patients with previously untreated BRAF\textsuperscript{V600}-mutant non-small cell lung cancer [100, 101]. In a phase II trial (NCT02130466), combination therapy with dabrafenib, trametinib, and pembrolizumab conferred longer progression-free survival and duration of response with a higher rate of grade 3/4 adverse events compared with that of dabrafenib and trametinib doublet therapy [102].

Moreover, Uppaluri et al. [103] performed a clinical trial to determine the tumor response of oral cavity squamous cell carcinoma to treatment with the MEK inhibitor trametinib and found that trametinib caused a significant reduction of RAS/MEK/ERK signaling pathway activation and clinical tumor response.

**IDO inhibitors**

Over the past decade, tryptophan catabolism has been considered a mechanism of innate and adaptive immune tolerance. Tryptophan catabolism is a central signaling pathway that maintains homeostasis by inhibiting the immunity that would result from uncontrolled immune responses. It is driven by the key enzymes IDO1 and tryptophan-2,3-dioxygenase 2 (TDO), which result in local depletion of tryptophan and accumulation of tryptophan-2,3-dioxygenase 2 (TDO), which result in local depletion of tryptophan and accumulation of tryptophan metabolites, including kynurenine and its derivatives. This regulation of metabolism leads to a local immunosuppressive microenvironment resulting from several mechanisms whose respective roles remain incompletely understood.

Drugs targeting this signaling pathway and specifically IDO1 have already undergone clinical trials with the aim to revert immunosuppression induced by cancers [104]. Recently, several studies have demonstrated a favorable pharmacokinetic profile for first-generation and second-generation IDO1 inhibitors (INCB024360, NLG919). A set of mechanistically distinct compounds, including epacadostat, indoximod, and navoximod, were the first to be evaluated as IDO inhibitors in clinical trials. In a phase I study, epacadostat was well tolerated and effectively normalized kynurenine levels [105]. However, there was no significant difference in efficacy between epacadostat and tamoxifen for the treatment of advanced epithelial ovarian cancer in a phase II clinical trial [106]. Data from a phase I trial demonstrated that indoximod was safe at doses up to 2000 mg orally twice/day in
| Target | Therapeutic agent | Phase | Tumor type | Effect | Trial number | Ref |
|--------|------------------|-------|------------|--------|--------------|-----|
| BRAF   | Vemurafenib      | III   | BRAF(V600) mutation-positive melanoma | Well tolerated | NCT01667419 | 92  |
| BRAF/MEK | Vemurafenib + cobimetinib | Ia   | Advanced BRAF-mutated melanoma | Safe and tolerable | NCT01271803 | 93  |
|        | Vemurafenib + cobimetinib | III  | Advanced BRAF<sup>V600</sup>-mutant melanoma | Improved progression-free survival, increased toxicity | NCT01689519 | 94, 95 |
|        | Dabrafenib + trametinib | III  | BRAF<sup>V600</sup>-mutant metastatic melanoma | Durable (≥3 years) survival is achievable | NCT01584648 | 96  |
|        | Dabrafenib + trametinib | III  | BRAF<sup>V600</sup>-mutant unresectable or metastatic melanoma | Survival advantage | NCT01597908 | 97  |
|        | Dabrafenib + trametinib | III  | Metastatic melanoma with BRAF<sup>V600</sup> mutation | Improved overall survival | NCT01597908 | 98  |
|        | Dabrafenib + trametinib | III  | Melanoma with BRAF<sup>V600</sup> mutation | Significantly lower risk of recurrence | NCT01682083 | 99  |
|        | Dabrafenib + trametinib | II   | Untreated BRAF<sup>V600</sup>-mutant non-small cell lung cancer | Meaningful antitumor activity, manageable safety profile | NCT01336634 | 100, 101 |
|        | Dabrafenib + trametinib | II   | BRAF-mutant melanoma | Longer progression-free survival and duration of response with a higher rate of grade 3/4 adverse events | NCT02130466 | 102 |
| MEK    | Trametinib       | II    | Oral cavity squamous cell carcinoma | Clinical tumor responses | NCT01553851 | 103 |
| IDO    | Epacadostat      | I     | Advanced Solid Malignancies | Well tolerated, effectively normalized kynurenine levels | NCT01195311 | 105 |
|        | Epacadostat      | II    | Advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer | Well tolerated, no significant efficacy in ovarian cancer | NCT01685255 | 106 |
|        | Indoximod        | I     | Advanced solid tumors | Safe, best response was stable disease for > 6 months in 5 patients | NCT00567931 | 107 |
|        | Navoximod        | Ia    | Recurrent advanced solid tumors | Well tolerated, decreased kynurenine levels in plasma | NCT02048709 | 108 |
|        | Indoximod + docetaxel | I     | Metastatic solid tumors | Well tolerated, no increase in toxicities or pharmacokinetic interactions | NCI #HHSN261201100100C | 110 |
|        | Indoximod + checkpoint inhibitors | II | Advanced melanoma | 52% overall response rate | NA | 109 |
|        | Navoximod + atezolozumab | I  | Advanced cancers | Acceptable safety and tolerability | NCT02471846 | 111 |
| CTNNB1 (β-catenin) | NTRC 0066-0 | Xenograft model | CTNNB1 mutant cancers | Complete inhibition of tumor growth | NA | 112 |
| STAT3  | Stattic + metformin | In vitro experiment | Brain cancer | Inhibited tumor initiating cells | NA | 115 |
|        | Stattic + recombinant vaccinia virus VG9 | Xenograft model | Solid tumors | Superior antitumor ability | NA | 116 |
| PI3K   | Duvelisib        | I     | Relapsed/refractory T cell lymphoma | Promising clinical activity and an acceptable safety profile | NCT01476657 | 117, 118 |
| PI3K/mTOR | Dactolisib      | In vitro and in vivo experiments | Glioblastomas | Antitumor activity | NA | 119 |
|        | Omipalisib       | In vitro | Oncogenically transformed | Inhibited clonogenic growth | NA | 120 |
patients with advanced solid tumors, and the best response was stable disease for > 6 months in five patients; however, induction of hypophysitis, increased tumor antigen autoantibodies, and C-reactive protein levels were observed [107]. A phase Ia study of navoximod (GDC-0919) treatment of patients with recurrent advanced solid tumors found that navoximod was well tolerated at doses up to 800 mg BID and was accompanied with decreased kynurenine levels in blood plasma [108].

Targeting tryptophan catabolism combined with other therapeutic strategies may improve the efficacy of cancer immunotherapy. This combination strategy has potential

### Table 2 Therapeutic strategies of targeting tumor-intrinsic signaling in preclinical studies and clinical trials (Continued)

| Target | Therapeutic agent | Phase | Tumor type | Effect | Trial number | Ref |
|--------|------------------|-------|------------|--------|--------------|-----|
| Akt    | Akti-1/2         | In vitro experiment | Breast cancer | An anticancer therapeutic strategy | NA | 121 |
| NF-κB  | QNZ              | In vitro and in vivo experiment | Colorectal cancer | Decreased cell invasion and migration abilities as well as expression of metastasis-related markers | NA | 122 |
| PDTC   | In vitro and in vivo experiments | Multidrug-resistant breast cancer | Tumor growth inhibition | NA | 123 |
| SN50   | In vitro and in vivo experiments | Malignant brain tumor | Loss of oncogenesis, differentiation of stem-like cells | NA | 124 |
| TLR4   | Rapamycin        | In vitro experiment | Colon cancer | Inhibited IL-6, PGE(2) production, and cell invasion | NA | 125 |

![Fig. 3](image) Tumor-intrinsic signaling as a therapeutic target for cancers. The activation of tumor-intrinsic signaling regulates and promotes the immunosuppressive tumor microenvironment, which includes exclusion and dysfunction of effective immunocytes and recruitment and differentiation of immunosuppressive cells. Therefore, targeting the tumor-intrinsic signaling is a potential strategy for cancer treatment.
as an alternative for patients whose tumors do not respond to standard therapy [109]. Other therapeutic methods include, but are not limited to, checkpoint inhibitors, vaccination, and adoptive cell transfer therapy. Indoximod, an oral inhibitor of IDO1, plus docetaxel were well tolerated without an increase in toxicity and were active in a pretreated population of patients with metastatic solid tumors [110]. In a phase II trial, the combination therapy of indoximod with checkpoint inhibitors resulted in a 52% overall response rate in advanced melanoma patients [109]. Furthermore, navoximod combined with atezolizumab showed acceptable safety and tolerability for patients with advanced cancers; however, combination therapy did not result in a significant benefit [111].

Other therapeutic targets
The spindle assembly checkpoint kinase TTK (Mps1), a key regulator of chromosome segregation, is a novel therapeutic target of small-molecule inhibitors. Treatment of a xenograft model of a CTNNB1-mutant cell line with the TTK inhibitor NTRC 0066-0 resulted in complete inhibition of tumor growth [112].

Small-molecule inhibitors or siRNA for targeting STAT3 signaling have also met with success in mice tumor models [113, 114]. Stattic, an inhibitor of STAT3, combined with metformin can inhibit tumor initiating cells in the brain by reducing STAT3-phosphorylation [115]. Moreover, combination therapy of recombinant vaccinia virus VG9 with Stattic was used to kill tumor cells by both oncolytic activity and inhibition of STAT3 phosphorylation; this combined strategy was superior to VG9 or Stattic alone [116].

Deregulation of the PI3K/Akt signaling pathway that leads to enhanced Akt activity is one of the most frequent changes in tumors. In a phase I trial (NCT01476657), duvelisib (an oral inhibitor of PI3K-δ/γ isoforms) demonstrated promising clinical activity and an acceptable safety profile in relapsed/refractory T cell lymphoma [117, 118]. The dual PI3K/mTOR inhibitor dactolisib also exhibited antitumor activity in vitro and in vivo [119]. When compared to parental cells, the cell invasion and migration abilities of OXA-R cells as well as the expression of metastasis-related markers decreased after treatment with the NF-κB inhibitor QNZ [122]. Moreover, the pH-sensitive co-delivery nanoparticle system of doxorubicin and pyrrolidinedithiocarbamate (PDTC, an inhibitor of NF-κB) showed promising potential for overcome multidrug resistance in breast cancer therapy [123]. SN50, a cell-permeable peptide inhibitor of NF-κB, results in decreased oncogenesis and induced differentiation of human glioma stem-like cells, suggesting that blocking the NF-κB signaling pathway is a potential therapeutic strategy for treating malignant brain tumors [124].

Finally, rapamycin was used for targeting TLR4, which triggered immune escape of tumor cells and inhibited the TLR4-activated NF-κB signaling pathway, uncovering a novel mechanism behind the antitumor effects of rapamycin [125].

Conclusions
In this review, we discussed the mechanisms of how oncogenic signaling mediates tumor immune escape, which includes decreased effective immunocyte infiltration and function and increased levels of immunosuppressive cells in the tumor microenvironment (Fig. 3). Therefore, analyzing such tumor-intrinsic signaling pathways in patients with tumor progression/recurrence is critical as targeting these pathways is a promising strategy for cancer treatment (Fig. 3). The recent preclinical studies and clinical trials of targeting oncogenic signaling have shown encouraging results. We believe that oncogenic signaling-targeted therapies will be utilized for cancer patients in the future.

Abbreviations
CAR-T: Chimeric antigen receptor-T; CCRK: Cell cycle-related kinase; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; DC: Dendritic cell; GBE1: Glycogen branching enzyme; IDO: Indoleamine-2,3-dioxygenase; MDSC: Myeloid-derived suppressor cell; NK: Natural killer; PD-1: Programmed cell death protein 1; RAGE: Advanced glycation end-products; TAM: Tumor-associated macrophage; TAN: Tumor-associated neutrophils; TDO: Tryptophan-2,3-dioxygenase 2; Treg: T regulatory cell

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