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# The role of hypoxia-inducible factor 1 in tumor immune evasion

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## Abstract

Hypoxia-inducible factor 1 (HIF-1) plays an indispensable role in the hypoxic tumor microenvironment. Hypoxia and HIF-1 are involved in multiple aspects of tumor progression, such as metastasis, angiogenesis, and immune evasion. In innate and adaptive immune systems, malignant tumor cells avoid their recognition and destruction by HIF-1. Tumor immune evasion allows cancer cells to proliferate and metastasize and is associated with immunotherapy failure and chemoresistance. In the hypoxic tumor microenvironment, HIF-1 signaling suppresses the innate and adaptive immune systems to evade immune attack by inducing the expression of immunosuppressive factors and immune checkpoint molecules, including vascular endothelial growth factor, prostaglandin $E_2$, and programmed death-ligand 1/programmed death-1. Moreover, HIF-1 blocks tumor-associated antigen presentation via major histocompatibility complex class I chain-related/natural killer group 2, member D signaling. Tumor-associated autophagy and the release of tumor-derived exosomes contribute to HIF-1-mediated immune evasion. This review focuses on recent findings on the potential mechanism(s) underlying the effect of hypoxia and HIF-1 signaling on tumor immune evasion in the hypoxic tumor microenvironment. The effects of HIF-1 on immune checkpoint molecules, immunosuppressive molecules,

  

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autophagy, and exosomes have been described. Additionally, the potential role of HIF-1 in the regulation of tumor-derived exosomes, as well as the roles of HIF-1 and exosomes in tumor evasion, are discussed. This study will contribute to our understanding of HIF-1-mediated tumor immune evasion, leading to the development of effective HIF-1-targeting drugs and immunotherapies.

**KEYWORDS**

exosomes, HIF-1, hypoxia, PD-L1, tumor immune evasion

## 1 | INTRODUCTION

Innate and adaptive immune responses play crucial roles in tumor immune surveillance and in preventing tumor progression.[1] Tumor cells suppress the immune system of an organism to evade immune destruction and facilitate tumor growth, metastasis, and invasion.[2,3] The role of immune surveillance is to recognize and eliminate abnormal or malignant cells. To evade destruction by host immune cells, tumor cells have developed numerous strategies to escape immune control and recognition.[2] Tumor immune evasion allows cancer cells to proliferate and metastasize after overcoming immune surveillance, leading to chemotherapy and radiotherapy resistance, immunotherapy failure, and poor prognosis.[3] Tumor immune evasion is a multifaceted process. Malignant tumors recruit immunosuppressive cells, such as $CD4^+$ $FoxP3^+$ regulatory T cells,[4,5] anti-inflammatory M2 macrophages,[6] and myeloid-derived suppressor cells (MDSCs).[7,8] These cells accumulate around the tumors and secrete immunosuppressive factors, such as prostaglandin $E_2$ ($PGE_2$), to suppress T cell functions.[2,9,10] Tumor cells suppress tumor-associated antigen presentation pathways to block innate and adaptive immune recognition by reducing the expression of major histocompatibility complex (MHC) class I chain-related (MIC) molecules.[11] Cancer cells inhibit immune cell responses by inducing the expression of immune checkpoint molecules and their receptors, such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4).[3,6,12–14]

Hypoxia facilitates malignant tumor escape from immune surveillance.[15–17] Hypoxia decreases natural killer (NK) and T cell survival and weakens the immune function of dendritic cells (DCs) through a mechanism involving hypoxia-inducible factor-1 (HIF-1).[18] HIF-1, a principal regulator of hypoxia, is a heterodimeric transcription factor that directly or indirectly controls hypoxia-mediated tumor immune evasion.[19,20] HIF-1 signaling is an essential component of immune evasion in the hypoxic tumor microenvironment, including immunosuppression and immune tolerance, which promote innate and adaptive immune system evasion.[6,12,21] In innate tumor immunity, HIF-1 inhibits the motility, differentiation, immune function, and maturation of NK cells and DCs by inducing the expression of immunosuppressive molecules.[9,22] HIF-1 activates downstream target genes, such as cyclooxygenase-2 (COX-2), hypoxia-inducible gene 2 (HIG2), and galactosylceramide sulfotransferase (GAL3ST1), to facilitate cancer cell escape from NK cell-mediated killing.[23–26] NK cell cytotoxicity is decreased because the expression of NK group 2, member D (NKG2D) is downregulated by HIF-1α, which affects tumor-associated antigen presentation.[27] In response to hypoxia, tumor cells activate autophagy through HIF-1-regulated B cell lymphoma 2 (Bcl-2) and adenovirus E1B 19 kDa-interacting protein 3 (BNIP3), thereby suppressing NK cell-mediated immune responses.[7,27–29] In adaptive tumor immunity, HIF-1 mediates T cell exhaustion by inducing the release of immunosuppressive molecules and the transcription of downstream targets, such as the cytokine CCL20.[30] HIF-1-induced CD39 and CD73 expression results in the production of extracellular adenosine, which impairs T cell-mediated antitumor immunity.[31–34] HIF-1 induces the expression of immune checkpoint molecules, resulting

in tumor cells not being recognized or destroyed by T cells.[35–37] HIF-1-mediated tumor immune evasion is complex and requires further investigation.

Tumor immunotherapy is challenging because of the diversity of the mechanisms by which tumors escape immune surveillance. HIF-1 plays a critical role in tumor immune evasion.[38] Therefore, understanding the link between HIF-1 and tumor immune evasion may help develop immunotherapy strategies. The link between HIF-1 and tumor immune evasion has become a hot topic in recent years.[39–41] The 2019 Nobel Prize in Physiology or Medicine was jointly awarded for discoveries regarding how cells perceive and adapt to oxygen obtainability, and HIF-1 is known to be involved in this process;[40] however, the related findings are scattered throughout the literature, thereby preventing us from gaining a global understanding of the advances in this field. There are few systematic reviews that specifically discuss the mechanisms underlying the function of HIF-1 in tumor immune evasion. Recently, Vito et al.[39] studied hypoxia-driven immune evasion in the tumor microenvironment and mainly focused on poor prognostic outcomes, hypoxia-driven therapeutic resistance, and hypoxia-targeted immunotherapies. In addition, the programmed death-ligand 1 (PD-L1)-mediated regulation of liver cancer cells in immune evasion under hypoxic conditions was discussed by Wen et al.[42] In this review, we provide a comprehensive outline of recent research advances contributing to elucidating the molecular mechanisms underlying the role of hypoxia and HIF-1 in tumor immune evasion, as well as the regulation of HIF-1 in the hypoxic tumor microenvironment. The molecular mechanisms underlying HIF-1-regulated tumor immune evasion suggest that HIF-1 is a crucial molecular target for cancer therapy.

## 2 | HYPOXIA, HIF-1, AND TUMORS

Hypoxia plays a key role in tumor progression, metastasis, invasion, angiogenesis, epigenetic reprogramming, metabolic reprogramming, and immune evasion.[4,43] Immunohistochemical analyses show that HIF-1 levels are significantly higher in hypoxic tumor tissues than in normal tissues.[44–46] HIF-1 controls hypoxia-mediated tumor physiology and pathogenesis by activating downstream target genes, mediating tumor-associated autophagy and the release of exosomes, inducing immunosuppressive molecule expression, and impairing tumor-associated antigen presentation.[16,19,43]

HIF-1 is composed of an oxygen-regulated α subunit (HIF-1α) and an aryl hydrocarbon nuclear translocator β subunit (HIF-1β).[29,47] HIF-1α and HIF-1β are basic helix–loop–helix/PER-ARNT-SIM (bHLH–PAS) homology domain proteins.[31] Hypoxia activates HIF-1 signaling by promoting the protein stability of the oxygen-sensitive HIF-1α subunit. Under normoxic conditions, HIF-1α is easily unstable and degraded. It is rapidly hydroxylated by the $O_2$-dependent enzyme prolyl hydroxylase domain 2 (PHD2), leading to the interaction of HIF-1α with the von Hippel–Lindau tumor suppressor (pVHL) protein.[43] The interaction of pVHL with HIF-1α leads to the E3 ubiquitin ligase-mediated polyubiquitination and proteasomal degradation of HIF-1α.[16,48] Under hypoxic conditions, the inhibition of PHD activity leads to the accumulation of HIF-1α.[19] HIF-1α proteins that escape proteasomal degradation dimerize with HIF-1β to activate different pathways.[9,43,49]

HIF-1 activation occurs in hypoxia during tumor progression and metastasis. Mammalian cells maintain adequate oxygen homeostasis through the oxidative phosphorylation pathway, which generates adenosine triphosphate (ATP) and mediates aerobic metabolism.[50,51] In solid tumors, cellular oxygen availability is significantly reduced, leading to intratumoral hypoxic conditions.[52] Tumor cells in the hypoxic environment undergo HIF-1-mediated metabolic reprogramming of glucose transporter 1 (GLUT1), GLUT3, and lactate dehydrogenase A (LDHA), which play roles in glucose and energy metabolism.[12,45,53] Tumor hypoxia induces HIF-1 overexpression, which is associated with leaky and disorganized tumor vasculature and increased genetic instability.[54,55] In response to intratumoral hypoxia, HIF-1 overexpression activates the vascular endothelial growth factor (VEGF) transcription, thereby stimulating the development of new blood vessels and contributing to tumor progression and metastasis.[50] Furthermore, HIF-1 promotes tumor metastasis into other tissues by activating the transcription of target genes, such as

interleukin-10 (IL-10) and $PGE_2$, thereby inhibiting tumor responses to immune cells and targeted therapies.[9,55] In breast tumors, human recombinant follicle-stimulating hormone induces the recruitment of HIF-1 and binding of HIF-1α to the hypoxia response element (HRE) of the multidrug resistance-1 (*MDR-1*) gene, thereby increasing the expression of P-glycoprotein (P-gp).[56–58] The HIF-1/MDR-1/P-gp axis suppresses the accumulation of intracellular doxorubicin (DOX), inducing chemoresistance.[56,59] Similarly, increasing the expression of the collagen subunit protein prolyl 4-hydroxylase alpha 1 (P4HA1) by modulating HIF-1-dependent triple-negative breast cancer cell stemness inhibits the chemotherapeutic agents DOX and docetaxel (DOC) and promotes chemoresistance.[60] Hypoxia-induced HIF-1 activates the expression of the hedgehog transcription factor GLI2 through the binding of HIF-1α to the GLI2 promoter, resulting in the GLI2-dependent resistance of colorectal tumors to chemotherapy.[61] HIF-1 can induce epithelial-to-mesenchymal transition (EMT) and repress the expression of epithelial markers (E-cadherin) by directly targeting the transcription of lysyl oxidase (LOX), LOX-like 2 (LOXL2), and urokinase plasminogen activator receptor.[62,63] EMT contributes to tumor drug resistance via nuclear factor-κB (NF-κB)/HIF-1α signaling, the Snail1/HIF-1α axis, and the phosphatidylinositol 3 kinase (PI3K)/Akt/HIF-1α pathway.[35,64–67] HIF-1 promotes tumor progression under hypoxic conditions, and HIF-1α is a major regulator of metabolism, angiogenesis, autophagy, and immune evasion.[55,68] In the tumor microenvironment, one of the main strategies for tumor survival is immune evasion.[6] HIF-1 signaling facilitates immune system repression in the hypoxic tumor microenvironment to allow cancer cells to evade immune attack by triggering immunosuppressive molecule expression, disabling tumor-associated antigen presentation, and preventing immune cell surveillance.[31,45,69]

The tumor hypoxic microenvironment is an essential factor responsible for poor tumor immunotherapy and resistance to radiotherapy and chemotherapy.[16,70] Increased HIF-1 levels may cause tumors to develop malignant phenotypes. Inhibiting the expression and transcriptional activity of HIF-1 is expected to become a new immunotherapy approach for malignant tumors. As an important transcription factor under hypoxic conditions, HIF-1α regulates angiogenesis, glucose metabolism, apoptosis, and autophagy and participates in the regulation of multiple signaling pathways.[12,29,71] By studying the structure and function of HIF-1α, signaling pathways, and crosstalk between signaling pathways, we have moderately elucidated the role of the HIF-1α-mediated immune evasion mechanism in the tumor microenvironment; however, many specific issues are obscure, for example, how HIF-1α and VEGF act together on tumor cells, whether there is a connection between the simultaneous expression of inflammatory factors and HIF-1α, and the interaction mechanism between exosomes and HIF-1α in the development of tumors. Research on the HIF-1α signaling pathway has shifted from a single signal transduction study to a signal pathway network. In the future, a more complete network system will be established to open up novel directions for disease prevention and treatment. Hence, hypoxia-activated HIF-1 plays a central role in tumor progression, metastasis, and immune evasion.[21]

## 3 | EFFECT OF HIF-1 ON IMMUNE CHECKPOINT MOLECULES

Immune checkpoint molecules are inhibitory regulatory molecules in the immune system.[6,13] Once activated, these molecules inhibit immune cell function, resulting in the inability of cells to produce an effective antitumor immune response. Tumor cells weaken the immune response by generating abnormal immune checkpoint signals to escape the immune system.[6] In this section, we discuss several immune checkpoint molecules regulated by HIF-1 and how they cause immune evasion.

PD-L1 interacts with its receptor programmed death-1 (PD-1), which is expressed on immune cells and escapes immune elimination.[5,6] In tumor-infiltrating MDSCs, hypoxic stress treatment significantly increased the PD-L1 level, while no change in the CTLA-4 expression was observed.[72] These results indicated that hypoxia regulated the expression of the immune checkpoint molecule PD-L1 instead of CTLA-4. However, the authors did not study whether HIF-1 causes changes in CTLA-4 expression. They further found that HIF-1 upregulated PD-L1 expression by directly binding to the HIF-1α binding site HRE4 in the PD-L1 proximal promoter.[72] After treatment with anti-

PD-L1 monoclonal antibody in response to hypoxia, MDSCs lost the ability to inhibit T cell function by increasing the ratio of interferon $\gamma^+$ (IFN-$\gamma^+$) $CD8^+$ and IFN-$\gamma^+$ $CD4^+$ T cells and decreasing the expression of IL-6 and IL-10.[72] Therefore, we suspect that there may be an irreversible process: blocking PD-L1 under hypoxic conditions cannot fully restore T cell proliferation and function, and PD-L1 only partially participates in the immune suppressive function of MDSCs, indicating that other signaling or immune checkpoint molecules participate in the immunosuppressive effect of MDSCs in response to hypoxia. The interaction between PD-1 on the surface of T cells and PD-L1 on tumor cells leads to T cell inactivation, thereby promoting tumor cell escape from the immune system.[73] PD-L2, another PD-1 ligand, is also regulated by HIF-1 and is expressed at higher levels than PD-L1 in malignant phaeochromocytomas and paragangliomas. The expression of PD-L2 and VEGF-A have shown a non-uniform relationship, while CD4 showed the strongest correlation with PD-L2 expression.[74] These results imply that PD-L2 regulation in hypoxic signals might involve other molecules, and PD-L2 is associated with the enrichment of an exhausted immune response related to innate adaptive immune evasion and inflammation. The binding of PD-L2 to PD-1 contributes to tumor cell evasion from adaptive immunity. However, the mechanism by which HIF-1 regulates PD-L2 in hypoxic tumor environments is not fully understood. The PD-1/PD ligand (PD-L1, PD-L2) is a key molecule that mediates immune evasion in the tumor microenvironment and has been found to be regulated by HIFs.[72,74] Targeted blocking of their signaling pathways can relieve tumor cells from inhibiting T lymphocytes and strengthen immune responses to recognize and kill tumors.

The immune checkpoint molecule HLA-G is related to tumor immune evasion.[36,75] HLA-G expression is regulated via HIF-1 and is cell type dependent. HIF-1 controls HLA-G transcription through HLA-G HRE, which contains specific binding sites for HIF-1. IFN-$\gamma$ and tumor necrosis factor-$\alpha$ (TNF-$\alpha$) are suppressed by HLA-G, leading to nondestructive and detectable tumors associated with NK and T cells.[36,76] HLA-G mediated immunosuppressive effect by binding to immunoglobulin-like transcript-2, which is expressed on immune cells, such as B and T cells, in tuberculosis pleural effusion patients.[76] The HLA-G antigen was expressed in some tumor tissues[36] and was found to impede the body's immune response by inhibiting the effects of NK cells and cytotoxic T lymphocytes, changing the mode of cytokine secretion and thereby enabling tumor cells to escape from the immune response, survive, and develop.[36,76] However, it should be noted that the relationship between HLA-G and tumorigenesis remains to be further clarified. Drugs that can downregulate the expression of HLA-G in tumor tissues may restore the tumor-killing effect of immune cells, break through the body's immune tolerance to tumors, and curb tumor growth.

The immune checkpoint molecule CD137 (4-1BB) is a costimulatory member of the TNF receptor family and is expressed on T cells.[35] The interaction of CD137 with its ligand CD137L activates DCs, B cells, and macrophages to recognize and lyse cancer cells. Hypoxia increased CD137 expression on T cells stimulated by CD3/CD28 and had no influence on CD137 expression in cultured T lymphocytes without T cell receptor/CD3 triggering.[77] HIF-1$\alpha$ induced the transcription of soluble CD137 (sCD137) in tumor cells (colon carcinoma, renal carcinoma, and melanoma cell lines). sCD137 binds to CD137L and prevents the interaction between CD137 and CD137L, thereby promoting tumor cell escape from the adaptive immune system.[77–79] The costimulatory signal generated by the interaction between CD137 and its ligand participates in the activation, proliferation, and apoptosis of various immune cells in the immune response.[78] Further studies on their relationship with various immune cells and their mechanisms of action will prove beneficial in the diagnosis and treatment of antitumor immunity, transplant rejection, autoimmune diseases, and acute/chronic inflammatory diseases.

The use of immune checkpoint inhibitors is important for tumor immunotherapy. HIF-1 regulates PD-L1/PD-1 and HLA-G; however, the relationship between HIF-1 and other immune checkpoint molecules, including CTLA-4, remains unknown. Future studies should explore the relationship between other immune checkpoint molecules and HIF-1 and how this relationship affects tumor immune evasion. In addition, the development of targeted immunotherapy drugs that block HIF-1-regulated immune checkpoint molecules, especially PD-L1/PD-1, would be beneficial. The potential mechanism underlying the function of HIF-1 in the regulation of immune checkpoint molecules and tumor immune evasion is illustrated in Figure 1.

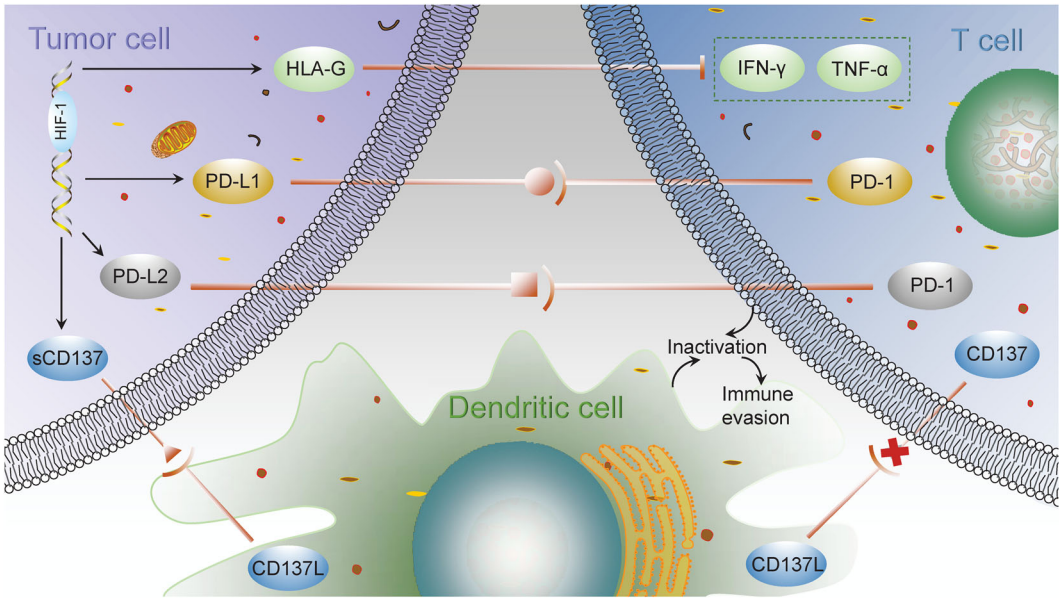


**FIGURE 1** The proposed mechanism by which HIF-1 mediates the regulation of immune checkpoint molecules to promote tumor immune evasion. HLA-G expression is regulated by HIF-1, suppressing IFN-γ and TNF-α production and decreasing tumor cell recognition by T cells. HIF-1 regulates the immune checkpoint molecules PD-L1 and PD-L2 in tumors; the interaction of PD-1 with PD-L1 and PD-L2 on the T cell surface leads to T cell inactivation, thereby promoting tumor cell escape from the immune system. HIF-1 induces the transcription of soluble CD137 (sCD137) in tumor cells. sCD137 binds to CD137L, preventing the interaction between CD137 and CD137L to activate dendritic cells, thereby promoting tumor cell escape from adaptive immunity.
HIF-1, hypoxia-inducible factor 1; IFN-γ, interferon-γ; PD-L1, programmed death-ligand 1; TNF-α, tumor necrosis factor-α [Color figure can be viewed at wileyonlinelibrary.com]

## 4 | HIF-1 INDUCES IMMUNOSUPPRESSIVE MOLECULE AND TARGET GENE EXPRESSION

In response to hypoxic stress, HIF-1α mediates the release of a variety of immunosuppressive molecules from tumor cells, including VEGF, transforming growth factor-β (TGF-β), IL-10, and $PGE_2$.[9] These immunosuppressive molecules further lead to tumor cell escape from immune system attack. VEGF (also referred to as VEGF-A) promotes angiogenesis and endothelial cell proliferation, survival, and migration.[80] HIF-1 is a critical regulator of VEGF activation and immune evasion. HIF-1α induces VEGF transcription by binding to the *VEGF* gene promoter and recruiting additional transcription factors to the promoter, leading to the upregulation of *VEGF* messenger RNA (mRNA) expression.[81,82] HIF-1-induced VEGF interacts with VEGF receptor 2 (VEGFR2) on the DC membrane, resulting in the upregulation of cofilin 1 (COF1) expression. Increased phosphorylation of COF1 leads to filamentary actin (F-actin) dysfunction, which impairs the motility and differentiation of DCs.[18] The VEGF/VEGFR2 axis upregulates PD-1 expression in cytotoxic $CD8^+$ T cells.[83] Thus, HIF-1 induction of the VEGF/VEGFR2 axis contributes to the upregulation of COF1 and PD-1, resulting in T cell exhaustion and impairing the immune function of DCs.[18,83] Many studies have focused more on the role of VEGF in angiogenesis rather than hypoxia-mediated tumor immune evasion. Although we mentioned that HIF-1-regulated VEGF is involved in immune evasion, VEGF is caused by stimulating its downstream targets. Therefore, in the future, investigating whether VEGF itself could also inhibit or exhaust immune cells is encouraged.

IL-10 and TGF-β, which are secreted into the tumor microenvironment, are key elements in the suppression of activated T cell cytolytic activity and DC function.[84] In $CD1d^{hi}CD5^+$ B cells, HIF-1α but not HIF-2α regulated

glycolysis and IL-10 transcription.[15] However, another study showed that HIF-1α deficiency contributed to the cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB)-driven upregulation of IL-10 production in myeloid cells during *Histoplasma capsulatum* infection.[85] As HIF-1 and IL-10 have a positive or negative correlation in different cell models, we speculate that HIF-1 and IL-10 are related to other upstream and downstream signaling-dependent regulations, suggesting that when the HIF-1 inhibitors are used for tumor immunotherapy, the dose and the related protein signaling pathways should be carefully considered. TGF-β and HIF-1 may interact during hypoxia; TGF-β induces plasminogen activator inhibitor-1 expression via HIF-1α accumulation in primary alveolar macrophages, and HIF-1 can act synergistically on the Smad signaling pathway mediated by TGF-β to promote the development of keloids.[86,87] HIF-1α induces IL-10 and TGF-β transcription by binding to the corresponding HRE regions, and these cytokines are related to decreased immune responses.[15,84,85,87] On the DC surface, HIF-1-induced IL-10 and TGF-β bind to the IL-10 and TGF-β receptors, thereby activating Janus kinase-signal transducer and activator of transcription and TGF-β/Smad signaling pathways, respectively. These receptor–ligand interactions prevent DCs from stimulating the generation of $CD8^+$ T cells and differentiation of $CD4^+$ T cells. Upregulation of IL-10 and TGF-β production allows cancer cells to resist immune evasion.[29,88] Therefore, future studies on immunosuppressive cytokines promoting tumor immune evasion by reducing the antitumor immune response in the tumor microenvironment in various cancer cell models are encouraged.

HIF-1 binds to the COX-2 promoter at the HRE3 site, upregulating the expression of COX-2 and promoting the generation of $PGE_2$.[89,90] Secreted $PGE_2$ is involved in tumor proliferation and invasiveness.[26] Under hypoxic conditions, $PGE_2$ is upregulated via the HIF-1/COX-2 pathway, suppressing the immune system and promoting escape from immune surveillance by activating PD-L1 expression and suppressing the maturation of DCs.[25,26] The metabolism of $PGE_2$ correlates with PD-L1 expression. The $PGE_2$-forming enzymes COX-2 and microsomal $PGE_2$ synthase 1 upregulate the expression of PD-L1, whereas the $PGE_2$-degrading enzyme 15-hydroxyprostaglandin dehydrogenase downregulates the expression of PD-L1.[25] Zinc has an anti-inflammatory role and can contribute to the downregulation of the HIF-1/COX-2/$PGE_2$ signaling pathways in homeodomain-interacting protein kinase 2-depleted cells, as well as restore DC maturation.[26] In this study, zinc constrained the tumor immune evasion induced by hypoxia to protect DCs effectively; however, further studies with different tumor cells are required to further confirm the authors' working model.

*HIG2* is another target gene of HIF-1 that is induced by hypoxia.[24] HIG2 upregulates IL-10 expression via the AMP-activated protein kinase (AMPK)/CREB signaling pathway, inhibiting the cytotoxicity of NK cells and promoting the escape of hepatocellular carcinoma cells from NK cell-mediated killing.[24] GAL3ST1, which catalyzes the sulfonation of sulfolipid sulfatide, participates in development of clear cell renal cell carcinoma (ccRCC). *GAL3ST1* is a target gene of HIF-1. The loss of pVHL results in the upregulation of GAL3ST1 by HIF-1, leading to the accumulation of the GAL3ST1 enzymatic product sulfatide. The reduction in galactosylceramide levels protects ccRCC cells from NK cell-mediated destruction.[16,23]

HIF-1 directly upregulates CCL20 expression by binding to the HRE in the *CCL20* gene promoter and activating its transcription. In monocyte-derived macrophages, the tumor-derived cytokine CCL20 upregulates the expression of indoleamine 2,3-dioxygenase (IDO) via the IFN-γ signaling pathway.[30] IDO inhibits $CD8^+$ T cell responses and induces tumor immune evasion.[91,92] In melanoma metastases comprising $CD8^+$ T cells, the immunosuppressive factors IDO and PD-L1 were observed to have higher expression levels, preventing T cell function.[92] The authors, in this context, focused their attention on two immunosuppressive molecules related to the $CD8^+$ T cell infiltration (PD-L1 and IDO). Whether other immunosuppressive molecules, such as COX-2, IL-10, and TGF-β, are related to T cell infiltration in melanoma metastasis remains to be explored; however, these factors may lead to immune evasion of melanoma metastasis.

In summary, HIF-1 directly and indirectly contributes to tumor development by mediating immune surveillance evasion through the induction of immunosuppressive factors and downstream target genes. Although the role of HIF-1 in the regulation of specific targets has been investigated extensively, the detailed underlying mechanism remains to be explored. Blocking the HIF-1-mediated regulation of immunosuppressive molecules and downstream

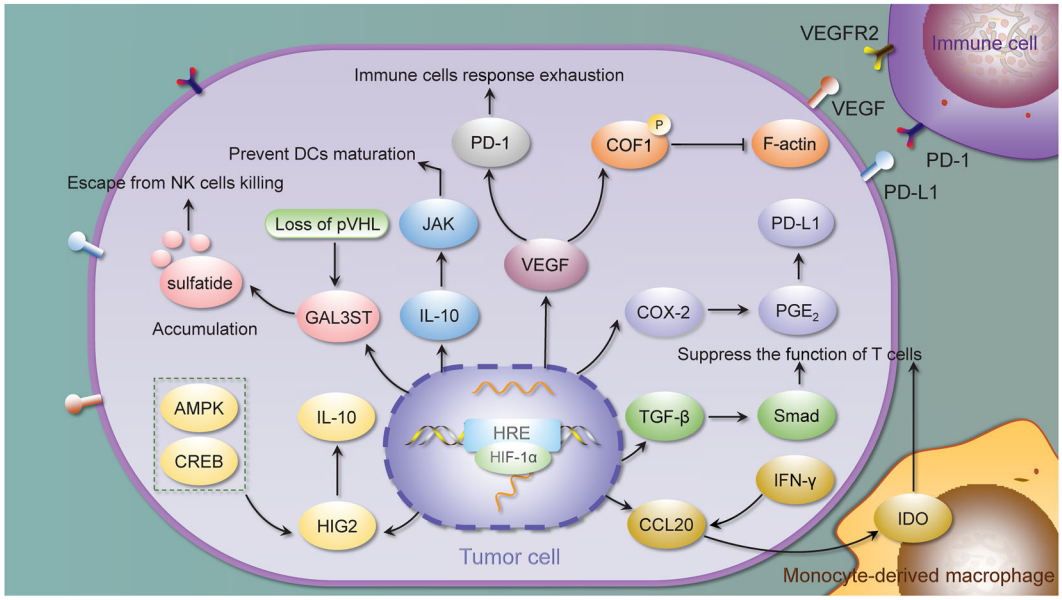


**FIGURE 2** The regulatory mechanism of HIF-1-induced immunosuppressive molecules and target genes. HIF-1α-induced VEGF interacts with VEGFR2, resulting in the upregulation of COF1 and PD-1. COF1 phosphorylation leads to dysfunction of F-actin, which impairs the immune function of DCs. HIF-1α induces TGF-β and IL-10 transcription, which activates JAK and Smad signaling, respectively. Upregulation of IL-10 and TGF-β expression by HIF-1 allows cancer cells to resist immune evasion. HIF-1 upregulates COX-2 expression and promotes $PGE_2$ generation. Secreted $PGE_2$ activates PD-L1 expression and suppresses the maturation of DCs. HIF-1α-induced HIG2 upregulates IL-10 expression via the AMPK/CREB signaling pathway, inhibiting the cytotoxicity of NK cells. Loss of pVHL results in GAL3ST1 upregulation by HIF-1, leading to sulfatide accumulation to escape NK cell-mediated death. HIF-1 directly upregulates CCL20 expression, thereby increasing the expression of IDO in monocyte-derived macrophages via the IFN-γ signaling pathway. COF1, cofilin 1; COX-2, cyclooxygenase-2; DC, dendritic cell; F-actin, filamentary actin; HIF-1, hypoxia-inducible factor 1; HIG2, hypoxia-inducible gene 2; IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon γ; JAK, Janus kinase; IL-10, interleukin-10; NK, natural killer; PD-1, programmed death-1; $PGE_2$, prostaglandin $E_2$; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2 [Color figure can be viewed at wileyonlinelibrary.com]

target genes or inhibiting the transcription of these molecules and genes prevents tumor immune evasion. Additionally, the mutual activation of pathways involving HIF-1-mediated immunosuppressive molecules may help tumors to escape immune surveillance. HIF-1 induces immunosuppressive molecules and target genes to promote tumor immune evasion, as illustrated in Figure 2.

## 5 | ROLE OF HIF-1α IN TUMOR-ASSOCIATED ANTIGEN PRESENTATION

MIC molecules play important roles in antigen presentation.[11] NK cells and T cells are activated when MICA/B interacts with NKG2D, a receptor for MICA/B expressed on the surface of NK cells.[27] Hypoxia mediated the downregulated expression of MIC molecules in the tumor microenvironment,[93,94] thereby promoting escape from innate and adaptive immunity. In pancreatic carcinoma cells, HIF-1α downregulates NKG2D levels and NK cell cytotoxicity; the nitric oxide signaling stimulators glyceryl trinitrate and 8-bromoguanosine cyclic monophosphate promoted the NKG2D levels and NK cell cytotoxicity, whereas the nitric oxide signaling inhibitor

NG-monomethyl-L-arginine achieved the opposite effect, suggesting that NO signaling is necessary in hypoxia-mediated immune evasion.[27] Additionally, HIF-1α caused MICA shedding from cancer cell membranes.[27] All of the experiments in this study were carried out in vitro; performing in vivo experiments would provide more complete conclusions. Nude mouse models have been used to explore the effect of simulated NO-mimetic drugs on tumorigenicity and immune evasion under hypoxia, to compare the in vivo and in vitro experiments. The detachment of MICA from the tumors or other cell types surface is required for the activity of a disintegrin and metalloproteinase 10 (ADAM10), a transmembrane metalloproteinase.[95] This enzyme is upregulated via an HIF-1α-dependent pathway, leading to the shedding of MICA and escape from immune surveillance.[96,97]

Recent research has shed new light on the mechanism of HIF-1α-mediated immune evasion in the context of the circular RNA (circRNA)/microRNA (miRNA)/mRNA axis.[98] The circRNA circ_0000977 modulates HIF-1α-mediated immune evasion in pancreatic carcinoma cells by acting as a sponge for miR-153, counteracting the repression of ADAM10 and HIF-1α through an miR-153-dependent pathway. HIF-1α downregulates the expression of membrane MICA (mMICA) on the surface of pancreatic carcinoma cells, whereas soluble MICA (sMICA) expression is upregulated.[98] ADAM10 is responsible for transforming mMICA shed by tumor cells into sMICA. The binding of sMICA to NKG2D promotes the degradation of NKG2D and leads to NK cell hyporesponsiveness. Therefore, downregulation of mMICA and NKG2D expression prevents cancer cell lysis.[98] The limitation of this report was that it was based only on in vitro studies and online databases. Future research should take into consideration both in vivo experiments and clinical studies focusing on the circ_0000977/miR-153/HIF-1α/ADAM10 axis.

miRNAs, a class of noncoding RNAs (ncRNAs) comprising 18–24 nucleotides, participate in tumor immune evasion by the transcriptional regulation of the PD-L1/PD-1 axis.[99–101] In human ovarian cancer Skov3 cells, miR-424 decreased the PD-L1 and CD80 levels by binding to the 3′-untranslated region.[100] miR-424 played a negative role in tumor immune evasion, as it contributed to the inhibition of PD-L1 expression, IL-10 production, and $CD8^+$ T cell apoptosis induced by TNF-α or IFN-γ.[100] In breast tumor-bearing mice, miR-149-3p downregulated exhausted $CD8^+$ T cells and mRNA level of the inhibitory receptor *PD-1*; restored the activity-associated cytokine IL-2, TNF-α, and IFN-γ levels; decreased $CD8^+$ T cell apoptosis;[102] and reversed $CD8^+$ T cell depletion, which is beneficial to antitumor immunity and effectively prevents immune evasion. These results support the possibility of miRNA-based breast tumor immunotherapy. Long noncoding RNAs (lncRNAs) longer than 200 nucleotides are also related to hypoxia and immune evasion. For example, lncRNA DARS-AS1 was upregulated by HIF-1 in myeloma cells; overexpression of lncRNA DARS-AS1 significantly enhanced tumor growth, while knockdown of lncRNA DARS-AS1 inhibited tumorigenesis.[103] NKILA lncRNA interacted with NF-κB by binding to p65; inhibiting NF-κB expression could cause tumor-specific T cell death to escape immunological destruction in breast and lung tumor microenvironments.[104] Moreover, lncRNAs are able to prevent immune evasion.[105] In hepatocellular carcinoma, cox-2 lncRNA promoted M1 macrophage polarization and inhibited M2 macrophage polarization, thereby inhibiting metastasis and immune evasion.[105] These discoveries revealed the potential relationship of ncRNAs (especially miRNAs and lncRNAs) with hypoxia and immune evasion and indicated that they play both positive and negative roles in immune evasion; this is consistent with their ability to act as both oncogene suppressors and oncogenes.[101,106] Further studies are needed to identify the related proteins that are regulated by HIF-1 during tumor-associated antigen presentation.

## 6 | HIF-1 REGULATES CELL SURFACE RECOGNITION PROTEINS

Tumor-associated cell surface recognition proteins, such as CD47, are associated with chemotherapy resistance,[70] and HIF-1 is involved in the mechanism of immune evasion in tumors. CD47, a cell surface protein and a direct target of HIF-1, enables the escape of tumor cells from innate immunity.[70] HIF-1 activates the translation of CD47, and overexpressed CD47 interacts with its receptor signal regulatory protein α (SIRPα) on the surface of

macrophages, thereby blocking phagocytosis by bone marrow-derived macrophages and contributing to breast cancer cell evasion of the innate immune response.[70,107,108] CD47 and PD-L1 expressed by tumor cells synergistically inhibit the immune system, to escape the control of immune cells (such as T cells and DCs).[109] Using MC38-CD47 knockout (CD47-lacking colorectal tumor line) cancer cells to subcutaneously inoculate immune-competent mice caused tumor cells to grow more slowly; however, their growth was not completely inhibited. Therefore, the CD47 protein may only play a part in the immune evasion of tumor cells in this context, and there were other signals that affected tumor immune evasion with or without CD47. CD47 and PD-L1 coordinated to escape the immune system, and bispecific anti-PD-L1-SIRPα simultaneously targeted and blocked the CD47 and PD-L1 pathways, significantly enhancing cancer cell targeting and therapeutic effects.[109] Hence, in addition to CD47 and PD-L1 synergy, the relationship between CD47 and other immune checkpoint molecules, such as CTLA-4 and HLA-G, should be studied in the future.

Mechanistically, HIF-1α induces the expression of CD39 and CD73 on MDSCs.[32] CD39 converts extracellular ATP to AMP, which is converted to adenosine by CD73.[49] The extracellular adenosine formed by CD39 and CD73 impairs NK and T cell-mediated antitumor immunity.[31–34] In the tumor hypoxic microenvironment, cancer cells are able to highly express CD38, CD39, CD73, and other molecules to produce a large amount of adenosine to recruit immunosuppressive cells, including regulatory T cells and MDSCs, to prevent the activity of the immune system.[110] Moreover, adenosine directly binds to the adenosine A2a receptor on the surface of immune cells to activate the inhibitory signaling pathways in the immune cells to inhibit the activity of immune cells.[49,110]

CD38 is related to cytotoxic T cell suppression by adenosine receptor signaling.[110] Tumor rejection may require the simultaneous inhibition of both CD38 and PD-L1.[110] PD-L1 (knockout)-CD38 (negative) cells transplanted into immunocompetent mice did not form tumor cells, while PD-L1 (knockout)-CD38 (highly expressed) cells could trigger a large number of primary tumor cells (metastasis).[110] Subsequently, in vitro experiments were implemented to detect the expression of IFN-γ and TNF-α under the coculture of PD-L1 (knockout)-CD38 (negative) cells/PD-L1 (knockout)-CD38 (highly expressed) cells and $CD8^+$ T cells and to determine the tumor cell killing ability. In vivo and in vitro experiments have effectively shown that CD38 has an inhibitory influence on $CD8^+$ T cell function.[110] Blocking the binding of cell surface proteins that are upregulated by HIF-1 to their receptors could be a potential immunotherapeutic strategy. Although the animal model data in these articles suggested a variety of potential strategies to overcome cell surface protein (such as CD47, CD73, and CD38) mediated resistance to immune checkpoint inhibitors, there were questions about how to best integrate these proteins into immunotherapy strategies. In the future, the immune tolerance mechanism of anti-PD-L1/PD-1 or other immune checkpoint molecules, including CTLA-4, mediated by cell surface proteins, such as CD47, CD73, and CD38, should be elucidated to provide a clear theoretical basis for recruiting cancer patients for clinical trials to prevent and treat drug resistance.

## 7 | HIF-1 INDUCES AUTOPHAGY TO PROMOTE TUMOR IMMUNE EVASION

HIF-1 promotes tumor cell immune evasion by inducing autophagy.[111,112] Autophagy is a conserved catabolic process by which intracellular contents, including proteins and cytoplasmic organelles, are degraded in lysosomes.[113] Hypoxia activates HIF-1-dependent autophagy, thereby promoting tumor cell survival by counteracting cytotoxic T lymphocyte- and NK cell-mediated antitumor immune responses.[114–117]

During tumor progression, autophagy acts as a survival mechanism that is induced by different stresses, including hypoxia, extracellular matrix detachment, and nutrient deprivation.[118,119] BNIP3, a member of the Bcl-2 family, is directly regulated by HIF-1.[28] BNIP3 and BNIP3-like (BNIP3L) are thus upregulated, resulting in the dissociation of the beclin 1–Bcl-2 complex.[119] In response to hypoxia, HIF-1 activates the BH3 domains of BNIP3 and BNIP3L, thereby inducing autophagy.[28] Hypoxia weakened NK cell-mediated MCF-7 breast adenocarcinoma

cell lysis; the proportion of hypoxic MCF-7 cells lysed by NK cells isolated from peripheral blood monocellular cells was reduced compared to that of normoxic MCF-7 cells.[120] This impairment is related to the induction of autophagic flux in hypoxic cells by p62 degradation and autophagosome formation. Cytotoxicity tests showed that NK cells killed more autophagy-lacking MCF-7 cells than autophagy-capable MCF-7 cells in response to hypoxia.[120] The level of granzyme B in normal cells was significantly higher than that in hypoxic cells, and the level of granzyme B was restored in cells by BECN1 knockout for targeted autophagy.[120] The activation of autophagy in the hypoxic tumor environment contributes to innate immune evasion by downregulating the levels of NK cell-derived granzyme B, which was loaded into autophagosomes and subsequently degraded in lysosomes.[120,121] Moreover, Baginska et al. showed that in addition to hypoxia, NK cell-mediated tumor lysis was impaired under starvation conditions.[120] Therefore, future research should consider whether the degradation of granzyme B is independent of stimuli that activate autophagy in target tumor cells. HIF-1α-mediated microtubule-associated protein light chain 3-I (LC3-I) is converted to LC3-II,[115] which is degraded by lysosomal enzymes in autolysosomes during autophagy, decreasing the total amount of LC3.[115] LC3 contributes to nonselective autophagy. The role of the HIF-1-dependent reduction of the total LC3 levels in tumor survival and immune evasion requires further study. The autophagy receptor protein NBR1 showed significant biotinylation in a proximity biotinylation assay, and NBR1 knockdown increased MHC-I plasma membrane levels in pancreatic ductal adenocarcinoma (PDAC) cells.[71] These results indicate that the NBR1 protein interacts with MHC-I and is related to MHC-I degradation in PDAC cells. Doxycycline treatment upregulated MHC-I surface levels and inhibited autophagy, implying that autophagy is a vital regulator to reduce MHC-I levels and may assist PDAC cells in escaping from $CD8^+$ T cells, which distinguish tumor antigens presented by MHC-I.[71] In this study, the authors focused on $CD8^+$ T cells that directly interacted with MHC-I on tumors. Additionally, they noticed changes in other immune cells, including $CD4^+$ T cells and $CD103^+$ DCs, after autophagy inhibition. Proteins secreted by PDAC cells after autophagy inhibition may be involved in the changes in these and other immune cell types, and studying how these changes are mediated would be important in future research. In addition, further research is required to identify the more subtle immune cell response after inhibiting autophagy and how to effectively combine autophagy or lysosomal blockade with immunotherapy.

## 8 | HIF-1 REGULATES EXOSOMES DURING TUMOR IMMUNE EVASION

Exosomes are endocytic intraluminal membrane nanovesicles. Exosomes fused with the plasma membrane are released from the extracellular environment via the inward budding of late endosomes.[122] Exosomes cover a broad array of biological molecules, including lipids, mRNAs, and miRNAs. In the hypoxic tumor microenvironment, tumor-derived exosomes promote tumor progression, angiogenesis, immune evasion, immunosuppression, and metastasis by directly stimulating antigen-presenting molecules and transferring surface receptors and target genes to cells.[122,123]

Tumor-derived exosomes are involved in immunosuppressive effects and tumor immune evasion. In ccRCC, exosomal TGF-β1 activates the TGF-β1/Smad pathway to inhibit NK cell cytotoxicity, thereby promoting innate immune escape.[124] In prostate cancer cells, tumor-derived exosomes (22Rv1 exosomes) express NKG2D ligands, such as MICA/B and UL-16 binding protein-2. These exosomes downregulate the expression of cell surface NKG2D on NK and $CD8^+$ T cells.[125] Tumor-derived exosomes expressing Fas ligand (FasL), a T cell-killing molecule, mediate $CD8^+$ T cell apoptosis.[126,127] In breast cancer cells, hypoxia increases the HIF-1-mediated release of exosomes.[128] HIF-1α upregulates the mRNA expression of the GTPase RAB27A, which is required for exosome biogenesis in tumors, inducing microvesicle formation and thereby stimulating tumor cell invasion and metastasis.[129] In addition, HIF-1 induces the upregulation and secretion of miR-10a and miR-21 in glioma-derived exosomes, leading to the activation of MDSCs via the Rora/IκBα/NF-κB and Pten/PI3K/Akt pathways.[123,130] Additionally, HIF-1 upregulates miR-301a expression in pancreatic cancer cell-derived exosomes, mediating M2 macrophage polarization via the

PTEN/PI3Kγ pathway.[131] Hence, HIF-1 can counteract NK and T cell-mediated antitumor immune responses by escaping the immune system through the release of tumor-derived exosomes. However, the role of exosomes containing HIF-1-regulated proteins, mRNAs, and miRNAs in immune escape remains to be elucidated. We speculate that tumor-derived exosomes play a role similar to that of HIF-1 in immune evasion, and evidence indicates that HIF-1 can induce exosomes. In the future, the relationship between HIF-1 and tumor-derived exosomes should be further explored.

PD-L1 is involved in an alternative mechanism that mediates its secretion in tumor-derived exosomes.[132] Exosomal PD-L1 is upregulated by IFN-γ and interacts with PD-1. The interaction between exosomal PD-L1 and PD-1 suppresses the function of T cells and facilitates tumor adaptive immune evasion.[133] Although HIF-1 induces the release of exosomes, whether the regulation of exosomal PD-L1 involves the transcription factor HIF-1 is not clear. The discovery of exosomal PD-L1 secretion by tumors sheds light on the immune checkpoint molecule mechanism and provides valuable insight into hypoxia-mediated immune evasion.[133] The prospect of using exosomes for treatment mainly includes the control of intercellular information exchange and targeted drug delivery. The mechanism by which the uptake of exosomal ncRNA leads to changes in tumor cell proliferation, invasion, metastasis, drug resistance, and immune evasion behavior and whether exosomes can be used as markers for early tumor liquid biopsy require further exploration. The proposed mechanism underlying the roles of HIF-1 and exosomes in regulating tumor immune evasion is illustrated in Figure 3. The role of HIF-1 signaling in tumor immune evasion is summarized in Table 1.

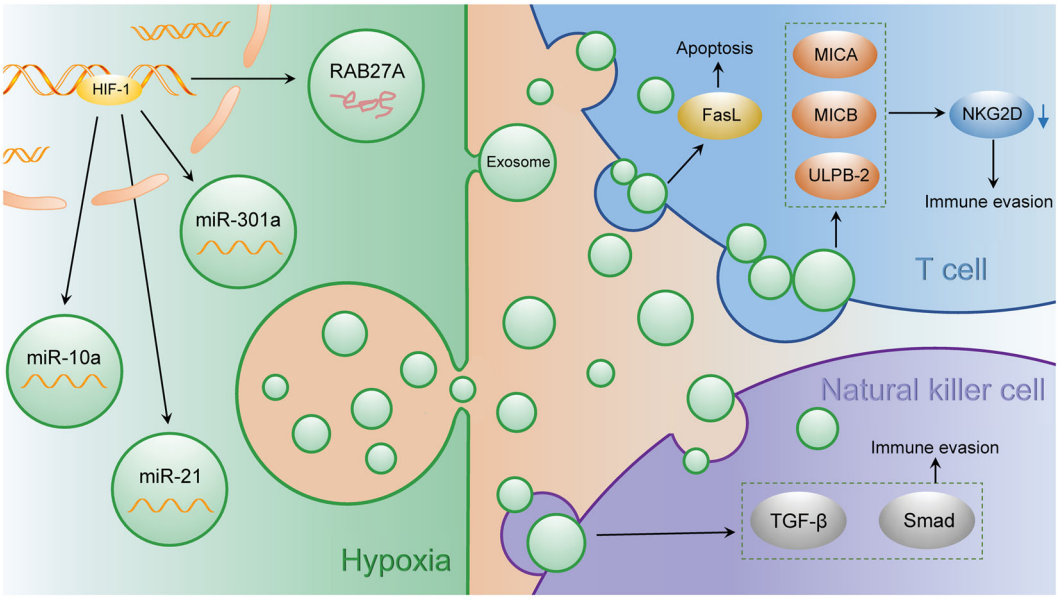


**FIGURE 3** Role of exosomes in HIF-1-mediated tumor immune evasion. In the hypoxic environment, HIF-1 induces the mRNA expression of the GTPase RAB27A, as well as the expression of miR-301a, miR-10a, and miR-21 in cancer cell-derived exosomes, which are released into the extracellular environment. These tumor-derived exosomes express FasL and activate the TGF-β/Smad pathway to mediate T cell apoptosis and inhibit the cytotoxicity of NK cells. Tumor-derived exosomes downregulate the expression of cell surface NKG2D on T cells by expressing the ligands MICA/B and ULBP-2. FasL, Fas ligand; mRNA, messenger RNA; TGF-β, transforming growth factor-β; ULBP-2, UL-16 binding protein-2 [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 1** The role of HIF-1 signaling in tumor immune evasion

| Targets/ effectors | Model | Regulatory mechanisms | Reference |
|---|---|---|---|
| MDR-1 | Human breast carcinoma cell lines | Human recombinant follicle-stimulating hormone enhances the HIF-1 level and recruits HIF-1 to participate in the transcriptional activity of target genes such as PDK1, PGK1, and VEGF | 56 |
| | MCF7 human breast cancer epithelial cells | The binding of HIF-1 to the MDR-1 gene promoter activates MDR-1 gene transcriptional activity, which increases concomitant functional expression of its product P-gp | 57 |
| GLI2 | Human CRC TMA tissue samples; resected CRC tissue samples | HIF-1 cooperates with TGF-β2 to induce GLI2 expression, resulting in GLI2-dependent chemotherapy resistance | 61 |
| LOX | Hep3B, HEK293, and HeLa cells | LOX and LOX-like 2 are directly regulated by HIF-1, which mediates a reduction in E-cadherin expression | 62 |
| PD-L1 | Peripheral blood samples; rats | Monocytes undergo immunosuppression via HIF-1 signaling, which induces the upregulation of PD-L1 protein expression | 17 |
| | Human lung cancer tissues | EZH2 downregulates PD-L1 expression via HIF-1 and promotes chemotherapeutic resistance and poor prognosis | 46 |
| | B16-F10 melanoma cells | HIF-1 upregulates the PD-L1 expression, and PD-L1 blockade under hypoxic conditions contributes to MDSC-mediated T cell activation | 72 |
| | Lewis lung carcinoma cells | | |
| | CT26 colon carcinoma cells | | |
| PD-L2 | Pheochromocytoma cells | HIF-1-regulated PD-L2 has a more predominant role in cancer progression than PD-L1 | 74 |
| | Paraganglioma cells | | |
| sCD137 | RCC10 renal cell carcinoma | HIF-1-induced sCD137 binds to CD137L and blocks the interaction of CD137L with costimulatory CD137 | 78 |
| | HEPG2 hepatocellular carcinoma cells | | |
| | AXBI human melanoma cells | | |
| VEGF | HPV-16 $E7^+$ cells | HIF-1 drives an antiapoptotic network in tumor cells through triggering VEGF activation and initiating AKT/ERK signaling | 81 |
| IL-10 | C57BL/6 WT mice | HIF-1 and STAT3 cooperatively regulate IL-10 transcription in B cells, thereby influencing T cell-mediated autoimmune diseases such as EAE and arthritis | 15 |

(Continues)

**TABLE 1** (Continued)

| Targets/ effectors | Model | Regulatory mechanisms | Reference |
|---|---|---|---|
| | *Histoplasma capsulatum* strain G217B and yeast cells | HIF-1 deficiency in myeloid cells contributes to enhance IL-10 production | 85 |
| COX-2 | Human cervical tissues | COX-2 gene expression is induced by HIF-1, increases prostaglandin production, and results in the loss of the MiTF-CX gene | 89 |
| | HT29 and HCT116 carcinoma cell lines | COX-2 is transcriptionally upregulated by direct binding of HIF-1 to the COX-2 promoter | 90 |
| HIG2 | Hepatic HepG2 cells | The HIF-1 target gene HIG2 upregulates IL-10 expression via AMPK/CREB signaling and activates STAT3 signaling by IL-10 secretion, thereby constraining the NK cells cytotoxicity | 24 |
| | SMMC-7721 cells | | |
| GAL3ST1 | 786-O cells | The GAL3ST1 gene is regulated by HIF-1, leading to enhanced sulfatides levels and promoting platelet binding to cancer cells | 23 |
| | RCC4 cells | | |
| CCL20 | HL-7702 and human hepatoma cell lines | HIF-1 induces the expression of the cytokine CCL20, and CCL20 upregulates IDO expression, resulting in phosphorylation and nuclear translocation of STAT1 | 30 |
| NKG2D | PANC-1 cells | HIF-1 has a negative effect on NKG2D expression and NK cell cytotoxicity | 27 |
| ADAM10 | Human DU145 prostate cancer cells | ADAM10 expression is increased in a HIF-1-dependent manner, thereby inducing a reduction in MICA levels | 95 |
| | MDA-MB-231 breast cancer cells | | |
| | The human PC cell line Panc-1 | The expression of HIF-1 and ADAM10 is significantly upregulated in PC tissues, consequently upregulating sMICA and downregulating mMICA levels | 98 |
| | HEK-293 cells | | |
| CD47 | MDA-MB-231 cells | Chemotherapy induces HIF-1-dependent expression, directly activating CD47, CD73, and PD-L1 gene transcription and promoting immune evasion in human TNBC cells | 70 |
| | SUM159 and SUM149 cells | | |
| | Human breast cell lines | Hypoxia increases CD47 expression in a HIF-1-dependent manner, and HIF-1 binds to the CD47 promoter directly | 108 |
| CD73 | Nonsmall cell lung cancer samples | TGF-β stimulates the expression of CD73 and CD39 on MDSCs by activation of mTOR/HIF-1 singling pathway | 32 |
| BNIP3 | CCL39 cells | Hypoxia induces autophagy as a survival mechanism in a HIF-1-dependent manner | 28 |

**TABLE 1** (Continued)

| Targets/ effectors | Model | Regulatory mechanisms | Reference |
|---|---|---|---|
| LC3-I | U87MG and T98G glioma cell lines | HIF-1 and AMPK contribute to hypoxia-induced conversion of LC3-I to LC3-II, inhibiting hypoxia-induced autophagy to increase human glioblastoma cell death | 115 |
| RAB27A mRNA | Human breast cancer cells | Hypoxia induces HIF-1-dependent RAB22A expression, and microvesicle formation requires RAB22A expression | 129 |
| miR-21 | The human OSCC cell lines SCC-9 and CAL-27 | Hypoxia regulates exosomal miR-21 expression, which depends on HIF-1 and HIF-2, to induce tumor cell migration and invasion | 123 |
| | Human glioma cell line U87 | MDSC activation is mediated by hypoxia-induced miR-10a and miR-21, thereby promoting immunosuppressive environments | 130 |
| | The mouse glioma cell lines GL261 and G422 | | |
| | C57BL/6 male mice | | |
| miR-301a | Pancreatic cancer cell lines; the monocytic cell line THP-1 | miR-301a, which is regulated by HIF-1, is upregulated in exosomes derived from hypoxic pancreatic tumors and induces macrophages M2 polarization | 131 |

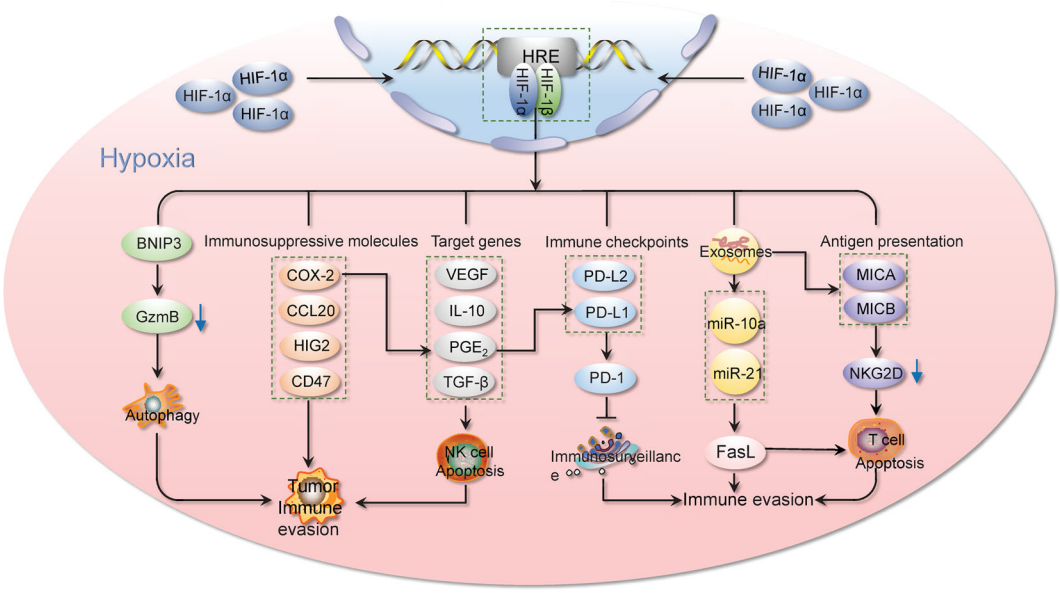


**FIGURE 4** The proposed mechanism of HIF-1-mediated tumor immune evasion in the hypoxic environment. BNIP3, Bcl-2 and adenovirus E1B 19 kDa-interacting protein 3; CCL20, C-C motif chemokine ligand 20; COX-2, cyclooxygenase-2; FasL, Fas ligand; HIF-1, hypoxia-inducible factor 1; HIG2, hypoxia-inducible gene 2; HRE, hypoxia response element; MIC, MHC class I chain; NK, natural killer; PD-1, programmed death-1; PG-L2, programmed death-ligand 2; $PGE_2$, prostaglandin $E_2$; TGF-β, transforming growth factor β; VEGF, vascular endothelial growth factor [Color figure can be viewed at wileyonlinelibrary.com]

## 9 | CONCLUDING REMARKS

The hypoxic microenvironment drives tumor immune evasion in large part by activating HIF-1. HIF-1 mediates innate and adaptive tumor immune evasion by inducing the expression of immunosuppressive molecules such as VEGF, TGF-β, IL-10, and $PGE_2$. HIF-1 activates downstream target genes (*COX-2*, *HIG2*, *CD47*, *CCL20*, *GAL3ST1*, *CD39*, and *CD73*) and immune checkpoint molecules (PD-L1/PD-1 and HLA-G) to promote the evasion of immune surveillance by cancer cells. During tumor-associated antigen presentation, the HIF-1α-mediated MIC/NKG2D pathway represses NK cell cytotoxicity. Under hypoxic conditions, tumor cells activate autophagy through the HIF-1-regulated Bcl-2/BNIP3 axis, thereby suppressing immune responses. In addition, HIF-1 counteracts anti-tumor immune responses by mediating escape from the immune system through the release of tumor-derived exosomes. The HIF-1-mediated tumor immune evasion process under hypoxic conditions is summarized in Figure 4.

The role of HIF-1 signaling in tumor immune evasion has become a research hot spot in the fields of antitumor immunity and immunotherapy. However, inhibitors and targeted drugs for HIF-1 immunotherapy have not achieved satisfactory effects in the treatment of various types of cancer.[27] HIF-1-mediated immune evasion is a dynamic system that involves multiple molecular and metabolic regulatory processes. A link between HIF-1-regulated molecules could be identified in the future. We propose that an HIF-1-induced molecule (PD-L1) may directly impair immune cells, whereas other HIF-1-mediated immunosuppressive molecules, such as $PGE_2$, may achieve immune evasion by regulating PD-L1 expression.[25] The regulatory mechanism with the strongest effect on immune evasion remains to be identified. Moreover, because HIF-1 regulates immune evasion, upstream targets of HIF-1 may also play a role in this process. The association between HIF-1-regulated molecules and upstream and downstream targets of HIF-1 may play an important regulatory role.[25,46] Therefore, blocking upstream or downstream HIF-1 signals could be an important immunotherapeutic strategy. Exosomes have recently become a focus of research, and HIF-1 induces their release; however, the HIF-1-mediated transcriptional regulation of exosomal PD-L1 remains unclear. Tumor-derived exosomes function in a manner similar to that of HIF-1 in immune evasion, and the relationship between HIF-1 and tumor-derived exosomes should be further explored. In addition, the role of HIF-1 in autophagy in the intratumoral hypoxic environment raises many questions. The effect of HIF-1 on the regulation of BNIP3/BNIP3L expression indicates that there may be other HIF-1-regulated proteins involved in autophagy that contribute to immune evasion. In addition, whether HIF-1 mediates tumor immune evasion by regulating exosomes and subsequently affecting autophagy remains unclear. We look forward to the discovery of additional ncRNA molecules as new biomarkers for therapies used in the detection of hypoxia and tumor immune evasion in the future. The tumor immune evasion mechanism induced by hypoxia is always in a complex immune network, and immunotherapy research should not be limited to certain types of antigenic peptides, factors, and cells. Further investigation of the molecular mechanisms underlying HIF-1-mediated immune evasion is required for the development of novel immunotherapies.

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### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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