ZG16B: A key regulator of tumor progression and immune microenvironment modulation in cancer (Review)

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Abstract. Zymogen granule protein 16B (ZG16B), also known as pancreatic adenocarcinoma upregulated factor, is a secretory lectin-like glycoprotein that serves a crucial role in tumorigenesis and immune regulation. The present review summarizes the latest research progress on the molecular characteristics, biological functions, signaling pathway regulation and clinical importance of ZG16B. Structurally, ZG16B contains an N-terminal hydrophobic signal peptide, a jacalin-related lectin domain and a C-terminal extension. Functionally, ZG16B promotes tumor cell proliferation, migration, invasion and angiogenesis, and increases vascular permeability by activating the Toll-like receptor, C-X-C chemokine receptor type 4, β-catenin and focal adhesion kinase signaling pathways. In the tumor microenvironment, ZG16B can modulate immune responses, enhance the immunosuppressive functions of myeloid-derived suppressor cells and M2 macrophages, and also promote the maturation of dendritic cells. Clinically, ZG16B expression is upregulated in pancreatic cancer, ovarian cancer, colorectal cancer, gastric cancer and oral cancer, and its upregulation is associated with a worse prognosis in these malignancies. Several ZG16B-specific therapeutic strategies, including monoclonal antibodies, RNA aptamers and trans-splicing ribozymes, have shown preclinical efficacy against malignant tumors. Furthermore, a clinical trial is currently testing the efficacy and safety of PBP1510, a humanized ZG16B antibody, for the treatment of advanced pancreatic cancer. In conclusion, ZG16B may be considered a novel target for cancer diagnosis, prognosis and therapy.

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Contents

1. Introduction
2. Structural characteristics of ZG16B
3. Paralogous homolog of *ZG16B*
4. Biological functions of ZG16B
5. Regulation of signaling pathways by ZG16B
6. Relevance of ZG16B to tumors and its translational potential
7. Future research directions for ZG16B
8. Conclusion

1. Introduction

The development and progression of cancer is a complex, multi-step process driven by factors such as the aberrant expression of multiple genes, disruption of key signaling pathways and remodeling of the tumor microenvironment (TME) (1-7). A deeper understanding of the mechanisms underlying the key drivers of cancer is crucial for revealing the malignant nature of tumors, and developing novel diagnostic and therapeutic strategies (8-10).

Zymogen granule protein 16B (ZG16B), also known as pancreatic adenocarcinoma upregulated factor, was discovered and identified in 2009, and was revealed to be highly expressed in pancreatic ductal adenocarcinoma (11). ZG16B is

a secretory lectin-like protein (12), capable of regulating intracellular signaling cascades in various cell types, including tumor cells, endothelial cells and immune cells. ZG16B is involved in key biological processes, such as tumor cell proliferation, migration, invasion, angiogenesis and immune suppression within the TME (13-16). As an oncogenic factor, ZG16B expression is upregulated in malignant tumors, such as pancreatic cancer, ovarian cancer, colorectal cancer and gastric cancer, and is closely associated with the tumorigenesis and progression of these types of cancer (17-19). Currently, drugs targeting ZG16B are under investigation in preclinical studies and clinical trials, with promising prospects for future clinical application (20-25).

The present review aims to integrate the existing research findings, and systematically elucidate the molecular characteristics, biological functions, signaling pathway regulatory networks, expression profiles and clinical relevance of ZG16B. In addition, new advancements in the roles of ZG16B in cancer diagnosis and prognosis, and its potential in targeted therapy, are described. The current review not only provides a new perspective for understanding the complex mechanisms underlying tumor malignant progression, but also lays the theoretical foundation for the development of ZG16B-based diagnostic and therapeutic strategies, which holds notable scientific and clinical value in improving patient prognosis.

2. Structural characteristics of ZG16B

The *ZG16B* gene is located on the short arm of chromosome 16 at region 13.3 in humans, an area that has several genes related to secretory functions, such as *WFIKKN1*, *PRSS22*, *TPSB2*, *NTN3* and *TSC2* (26,27). *ZG16B* consists of four exons (11), and is the human homolog of the mouse demilune cell and parotid protein 1 gene and the rat common salivary protein 1 gene (28,29).

The ZG16B protein is a secretory lectin-like protein that predominantly exists as a monomer in solution (11). The initially translated ZG16B precursor consists of 172 amino acids (aa) and contains three major regions: An N-terminal hydrophobic signal peptide (1-16 aa), a central jacalin-related lectin domain (17-149 aa), and a C-terminal extension (150-172 aa) (Fig. 1A) (12). After cleavage of the signal peptide, the mature protein comprises 156 aa. The theoretical molecular mass of ZG16B is ~17 kDa, whereas the secreted form exhibits an apparent molecular weight of ~25 kDa due to N-linked glycosylation (11). The N-terminal signal peptide directs ZG16B into the endoplasmic reticulum-Golgi secretory pathway, ensuring its proper secretion and transport (30).

The conserved GXXXD motif at the carbohydrate-binding site is crucial for the carbohydrate-binding specificity of proteins, and replacing this motif with the QLLGIK sequence in ZG16B alters its carbohydrate-binding preference, abolishing its ability to bind monosaccharides (12,31). Surrounding this site, positively charged residues Lys87, Arg131, and Lys147 form a potential glycosaminoglycan-binding region (11). The lectin domain also harbors several potential post-translational modification (PTM) sites, which may be essential for protein function and stability (Fig. 1A); these PTM sites include two phosphorylation sites at aa 29-32 and 101-104, and three N-myristoylation sites at aa 40-45, 66-71 and 113-119 (11). The C-terminal extension contains a classical N-linked glycosylation motif (NXS/T; Fig. 1A).

For the present review, Swiss-Model (www.swissmodel.expasy.org) and PyMOL software (version 3.1; www.pymol.org) were used to build the protein structure model (Fig. 1B) (32,33). Within the central jacalin-related lectin domain, ZG16B adopts a characteristic β-prism fold composed of three β-sheets that form a triangular prism-like spatial conformation, with each β-sheet containing 3-4 β-strands (Fig. 1B) (11,12). This domain is responsible for recognizing glycoproteins and mediating cell-cell communication, host-pathogen interaction, cancer metastasis, embryonic development and tissue morphogenesis (11,12).

Evolutionarily, the ZG16B protein is highly conserved among primates. The aa sequence identity between humans and chimpanzees reaches 98% (with 100% similarity), and that between humans and rhesus monkeys is 92% (with 95% similarity) (11). By contrast, the conservation of the ZG16B protein is reduced in rodents with 31% identity and 45% similarity between humans and mice, suggesting that *ZG16B* is a rapidly evolving, primate-specific gene likely associated with specialized physiological functions in primates (11).

3. Paralogous homolog of *ZG16B*

ZG16 and *ZG16B* are paralogous homologs. *ZG16* is located on the short arm of chromosome 16 at region 11.2 in humans, and encodes a secretory ZG16 protein that contains a jacalin-related lectin domain (12). However, structurally, ZG16 differs from ZG16B by having an additional short α-helix and a β-strand (12). Functionally, ZG16 exhibits various carbohydrate-binding abilities, primarily including chondroitin sulfate, heparan sulfate, and heparin (34-36). ZG16 has an important role in immune defense by recognizing specific glycan structures (37,38) and has anticancer effects (39,40). Additionally, ZG16 can regulate the channel switch on the membrane of zymogen granules in pancreatic acinar cells (41,42), participating in the concentration sorting and exocytosis of zymogen granules (43-46).

4. Biological functions of ZG16B

ZG16B can be secreted by tumor cells and can act on tumor cells through autocrine or paracrine mechanisms to promote their proliferation, migration and invasion. ZG16B can also affect vascular endothelial cells in the TME, enhancing angiogenesis and vascular permeability. Additionally, ZG16B can modulate immune cells within the TME, regulating T cell-mediated anti-tumor immunity (Fig. 2).

ZG16B promotes tumor cell proliferation, migration and invasion. ZG16B induces rapid proliferation of pancreatic cancer cells by specifically activating the AKT/GSK-3β signaling pathway to stabilize β-catenin (47). Furthermore, ZG16B can activate the ERK, JNK and AKT signaling pathways to upregulate the expression of C-X-C chemokine receptor type 4 (CXCR4), promoting the *in vitro* proliferation, migration and invasion of pancreatic cancer cells, as well as *in vivo* metastasis of pancreatic cancer (15). Moreover, ZG16B interacts with Toll-like receptor 4 (TLR4) to activate the

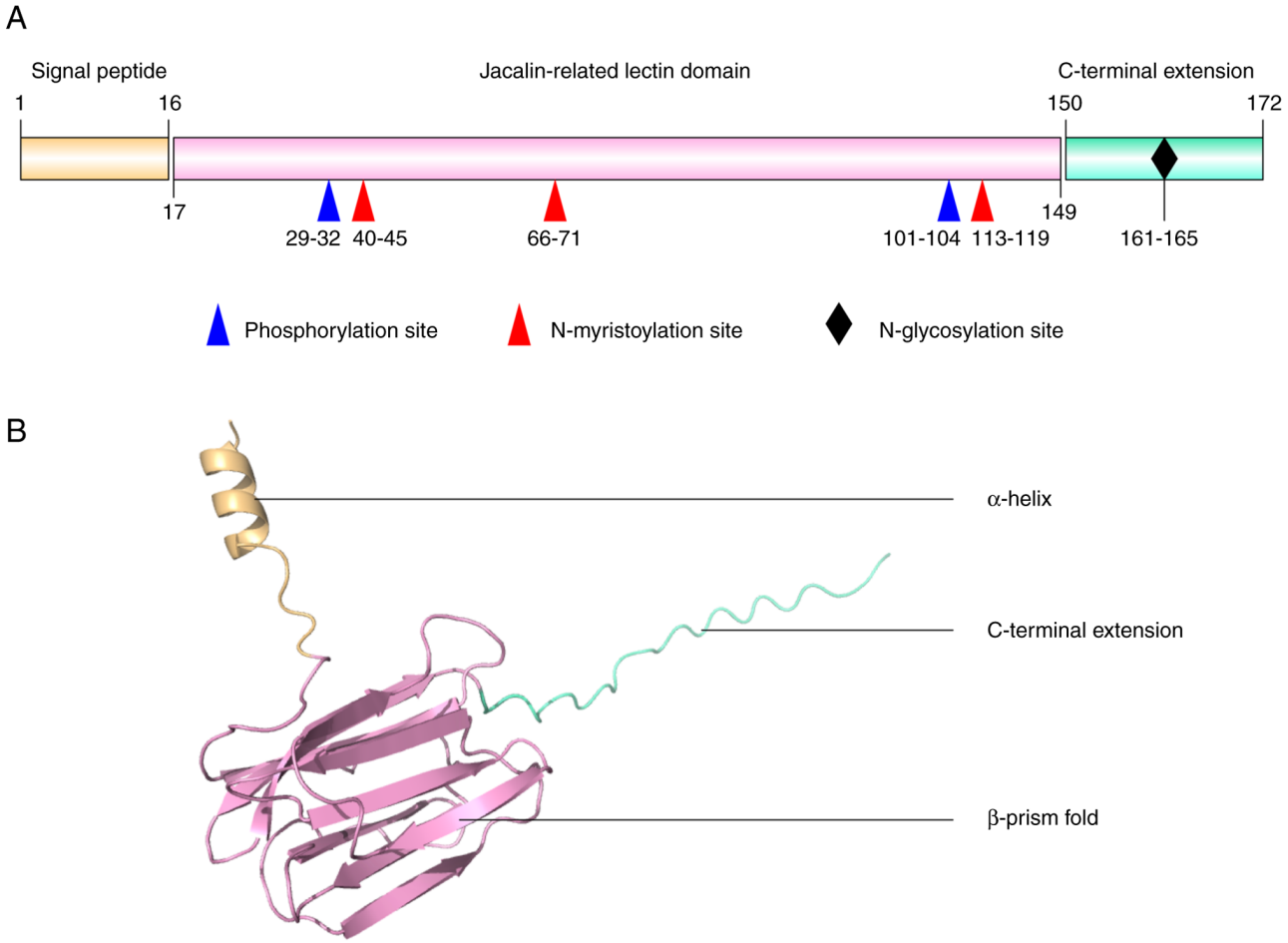

Figure 1. Structure and functional domains of ZG16B. (A) A schematic diagram of ZG16B, including the N-terminal signal peptide (yellow, 1-16 aa), jacalin-related lectin domain (pink, 17-149 aa) and C-terminal extension (turquoise, 150-172 aa). The key post-translational modification sites include one N-glycosylation site (black diamond, 161-165 aa), two phosphorylation sites (blue triangles, 29-32 and 101-104 aa) and three N-myristoylation sites (red triangles, 40-45, 66-71 and 113-119 aa). (B) Predicted crystal structure of ZG16B. The β-prism fold (pink) includes three β-sheets, with an α-helix at the N-terminus (yellow) and a C-terminal extension (turquoise). The structure was modeled using Swiss-Model and PyMOL software. aa, amino acid; ZG16B, zymogen granule protein 16B.

TLR4/MyD88/NF-κB and TLR4/MEK/ERK signaling pathways, and enhances the migration and invasion of pancreatic cancer cells (14,16). Notably, the high expression of ZG16B is significantly associated with positive lymph node metastasis and worse prognosis in patients with pancreatic ductal adenocarcinoma (17).

ZG16B activates the PI3K/AKT1 pathway to enhance the proliferation and migration of breast cancer cells. Notably, ZG16B-induced proliferation, but not migration, of breast cancer cells depends on ERK1/2 phosphorylation and the presence of the estrogen receptor (48). In ovarian cancer, ZG16B promotes cell proliferation by activating the TLR4-mediated ERK, JNK and p38 signaling pathways, while it enhances migration, invasion and adhesion through the Src, ERK and AKT signaling pathways (18,49). Similarly, ZG16B enhances the proliferation, migration, invasion and adhesion of colorectal cancer cells by regulating the Wnt/β-catenin signaling pathway. Notably, silencing ZG16B suppresses these processes by inducing cell-cycle arrest at the G_0/G_1 phase and apoptosis (19,50). Furthermore, ZG16B promotes the proliferation and invasion of oral squamous cell carcinoma cells while inhibiting apoptosis. High expression of ZG16B is significantly associated with positive lymph node metastasis and worse prognosis in patients with oral squamous cell carcinoma (51).

Collectively, ZG16B expression is upregulated in various types of cancer, and promotes the proliferation, migration and invasion of different types of cancer cells by regulating multiple signaling pathways.

ZG16B promotes angiogenesis and vascular permeability. Tumor angiogenesis and vascular density are closely associated with tumor growth, maintenance and metastasis (52-58). ZG16B has been identified as a new endothelial cell activator, distinct from vascular endothelial growth factors, and its expression is markedly associated with tumor microvascular density (59). ZG16B can activate ERK and PI3K/AKT signaling to induce the expression of endothelial nitric oxide synthase (eNOS) in a time- and dose-dependent manner, promoting the proliferation, migration and tubular network formation of human umbilical vein endothelial cells (HUVECs) (59). ZG16B also enhances angiogenesis by upregulating CXCR4 expression in HUVECs to enhance the angiogenic activity of its ligand, stromal cell-derived factor-1 (SDF-1) (59,60).

ZG16B can also induce the Src-dependent phosphorylation of VE-cadherin, resulting in the disruption of cell-cell

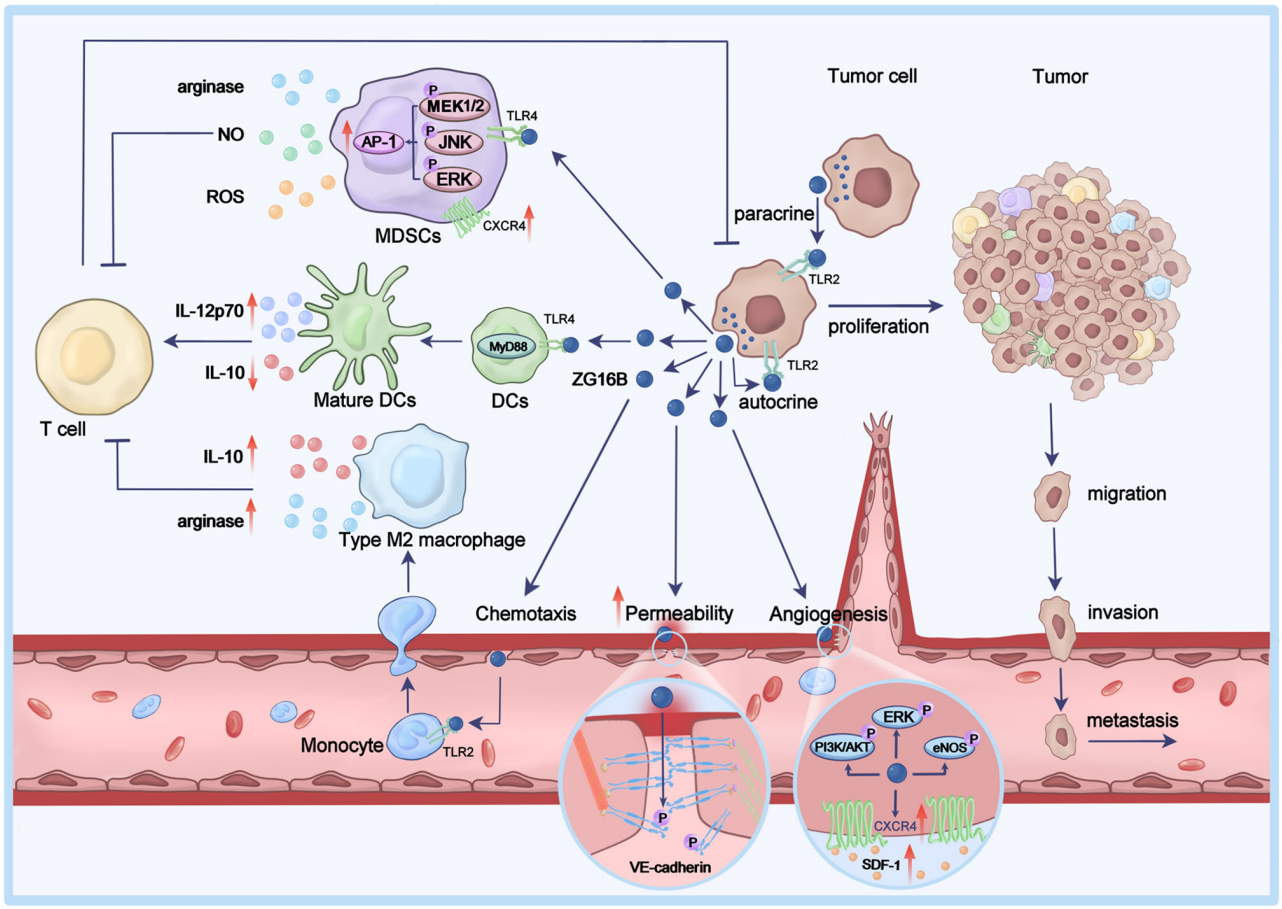

Figure 2. Biological functions of ZG16B. ZG16B promotes tumor cell proliferation, migration and invasion through autocrine and paracrine signaling. In vascular endothelial cells, ZG16B activates the ERK, PI3K/AKT and eNOS pathways to enhance angiogenesis and upregulates CXCR4 expression, increasing SDF-1-induced angiogenesis. ZG16B also promotes the phosphorylation of VE-cadherin, disrupting endothelial junctions and increasing vascular permeability. On MDSCs, ZG16B binds TLR4 to activate the MEK1/2, ERK and JNK pathways, promoting arginase, NO and ROS production to suppress T-cell function. On monocytes, ZG16B binds TLR2, inducing migration to the tumor and differentiation into M2 macrophages, which secrete IL-10 and arginase to inhibit T-cell responses. In DCs, ZG16B activates the TLR4/MyD88 pathway, increasing IL-12p70 and decreasing IL-10 expression, enhancing T cell-mediated immunity. AP-1, activator protein-1; CXCR4, C-X-C chemokine receptor type 4; DCs, dendritic cells; eNOS, endothelial nitric oxide synthase; MDSCs, myeloid-derived suppressor cells; MEK1, mitogen-activated protein kinase kinase 1; NO, nitric oxide; ROS, reactive oxygen species; SDF-1, stromal cell-derived factor-1; TLR, Toll-like receptor; ZG16B, zymogen granule protein 16B.

junctions between endothelial cells to increase vascular permeability (59,61). This suggests that ZG16B may serve as a potential biomarker for angiogenesis-related diseases, and a novel molecular target for the development of antitumor angiogenesis therapy (62).

Regulation of immune cells in the TME by ZG16B. The TME is important for tumorigenesis, progression and immune response (63-69), and contains stromal myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs) and dendritic cells (DCs) (70-72).

Regulation of MDSCs by ZG16B. MDSCs are a group of immature myeloid cells, including immature granulocytes, monocytes and DC precursors (73,74). In the TME, MDSCs can suppress T-cell activity, block antitumor immune responses and promote tumor progression (75-79). ZG16B secreted by tumor cells can enhance the migration of MDSCs by upregulating CXCR4 expression, inducing their recruitment to tumor tissues (13). Additionally, ZG16B interacts with TLR4 on the surface of MDSCs to activate the MEK1/2, ERK, and JNK signaling and the transcription factor activator protein-1 (AP-1). This promotes the production of immune suppressive factors such as arginase, nitric oxide and reactive oxygen species in tumor-infiltrating MDSCs, inducing oxidative damage to T cells and inhibiting $CD8^+$ T-cell responses, exerting an immunosuppressive effect (13).

Regulation of TAMs by ZG16B. TAMs are a type of specialized macrophages present in the TME. Depending on the stimulating signals, mature macrophages can differentiate into M1 and M2 types (80-85). M1 macrophages have antitumor functions, whereas M2 macrophages exhibit protumor functions and become the predominant macrophages during tumor progression, which are associated with a poor prognosis (86-88). ZG16B in the TME, through binding to TLR2 on monocytes, recruits circulating monocytes into the TME, where ZG16B can induce the differentiation of monocytes into M2 macrophages (89). The ZG16B-induced M2 macrophages can secrete immune suppressive factors such as IL-10 and arginase, inhibiting the proliferation of $CD4^+$ T cells and the activity of $CD8^+$ T cells. This weakens T cell-mediated

antitumor immune responses, allowing tumor cells to evade immune surveillance, and promoting tumor growth and progression (89).

Regulation of DCs by ZG16B. DCs are the professional antigen-presenting cells in the TME, and their maturation and activation status directly influence the strength of T-cell immune responses (78,90-93). ZG16B activates TLR4/MyD88 signaling in DCs, promoting their maturation, activation and migration. ZG16B can also upregulate IL-12p70 expression and downregulate IL-10 expression in DCs, favoring the activation and differentiation of naïve $CD4^+$ T cells into T helper 1 cells, enhancing the levels of cytotoxic T lymphocyte immune activity, and mediating antitumor immunity (94). Furthermore, when DCs treated with recombinant ZG16B are pulsed with tumor-associated antigen peptides HPV16 E7 and OVA257-264, they can activate antigen peptide-specific $CD8^+$ T cells and induce memory T-cell responses, leading to effective antitumor responses and long-term tumor suppression, prolonging the survival of tumor-bearing mice. This result suggests that ZG16B may enhance the antitumor efficacy of DC vaccines and serve as a potential novel adjuvant in humans (94).

5. Regulation of signaling pathways by ZG16B

ZG16B in the TME can act on signaling pathways such as the TLR, CXCR4, β-catenin and focal adhesion kinase (FAK) pathways, regulating the functions of tumor cells, endothelial cells and immune cells (Fig. 3). Additionally, the expression of ZG16B in tumor cells can be induced by TGF-β.

ZG16B and the TLR signaling pathway. TLRs are key components of the innate immune system. As a type of pattern recognition receptor, they can recognize pathogen-associated molecular patterns and damage-associated molecular patterns, initiating both innate and adaptive immune responses (95-97). Additionally, TLR signaling regulates tumor cell proliferation, migration and invasion, and contributes to the process of immune evasion (98-100).

ZG16B can act as an endogenous ligand for TLR2 and TLR4 on the cell surface to activate the TLR2-mediated ERK, JNK and p38 signaling in human acute monocytic leukemia THP-1 cells (31). Similarly, ZG16B activates IKK-β and tumor progression locus 2/MEK/ERK signaling in 293T cells through exogenously expressed TLR2 (31). As a result, ZG16B increases AP-1 expression to promote the secretion of cytokines, such as RANTES, macrophage migration inhibitory factor and IL-1RA, which favor tumor progression, metastasis and angiogenesis (31). However, ZG16B does not activate TLR2 or TLR4-mediated NF-κB signaling in THP-1 and 293T cells (31). By contrast, ZG16B can induce the migration and invasion of pancreatic cancer cells by activating the TLR4/MyD88/NF-κB signaling, independent of the TLR4/TRIF pathway (16). Additionally, through TLR4, ZG16B activates MEK/ERK signaling to promote the migration and invasion of pancreatic cancer cells (14).

ZG16B and the CXCR4 signaling pathway. The CXCR4 signaling pathway is crucial for organ-specific metastasis in various types of malignancies. The increased expression of CXCR4 by ZG16B markedly enhances the migration and invasion of tumor cells (101-103).

In pancreatic cancer cells, ZG16B can induce rapid and transient activation of the ERK, JNK and PI3K/AKT signaling pathways in an autocrine manner. Activated ERK can activate p90 ribosomal s6 kinase, and downstream transcription factors cAMP-responsive element binding protein and ELK-1; activated JNK can activate the transcription factors c-Jun (*JUN*), activating transcription factor 2 and *ELK-1*. These transcription factors synergistically regulate the expression of CXCR4 to promote the motility and metastasis of pancreatic cancer cells (15). In addition, ZG16B enhances the responses of endothelial cells to SDF-1, the CXCR4 ligand, by activating the ERK and PI3K/AKT/eNOS signaling pathways, and upregulating CXCR4 expression, thus enhancing angiogenesis. This creates a TME that favors tumor progression and metastasis (59,60). In THP-1 cells, ZG16B binds to the CXCR4/TLR2 receptor complex to activate cAMP and cAMP-dependent protein kinase A (PKA). Subsequently, PKA inhibits the TLR2-mediated NF-κB activation, reducing TNF-α production and contributing to the immune evasion of tumor cells (31).

ZG16B and the β-catenin signaling pathway. The Wnt/β-catenin signaling is aberrantly activated in various types of cancer and is crucial for biological processes, such as tumor cell proliferation, differentiation and apoptosis resistance (104-108). In resting non-tumor cells, β-catenin binds to a destruction complex consisting of APC, Axin, casein kinase-1α (CK-1α) and GSK-3β. CK-1α and GSK-3β phosphorylate β-catenin at the Ser45 and Ser33/37/Thr41 sites, respectively, leading to β-catenin ubiquitination and proteasomal degradation to maintain β-catenin levels at a low baseline (109).

In pancreatic cancer cells, ZG16B can activate the AKT/GSK-3β pathway, leading to slight phosphorylation of β-catenin at Ser33/37/Thr41 and Ser675, while greatly reducing phosphorylation at Ser45, thus stabilizing and activating β-catenin (47). In the nucleus, β-catenin forms a complex with the T-cell factor/lymphoid enhancer factor family, activating the expression of β-catenin-targeted genes, such as *CCND1* and *JUN*, to promote the rapid proliferation of pancreatic cancer cells (47). The deacetylase sirtuin 1 (SIRT1) can mediate the proteasomal degradation of β-catenin and inhibit the expression of the target gene *CCND1*, thereby suppressing the ZG16B-mediated pancreatic cancer cell proliferation, independent of SIRT1 nuclear translocation (110).

ZG16B and the FAK signaling pathway. FAK is a non-receptor tyrosine kinase usually present at cell focal adhesion sites. FAK is important for tumor cell adhesion, proliferation, migration, and regulating the interactions between tumor cells and the extracellular matrix. FAK is a marker of tumor progression and an indicator of poor prognosis (111-113).

In pancreatic cancer cells, ZG16B activates FAK signaling, which recruits Src to the focal adhesion sites, forming a stable FAK/Src complex; this can phosphorylate the scaffold protein paxillin to promote the formation of F-actin. This process increases the focal adhesion density and enhances tumor cell

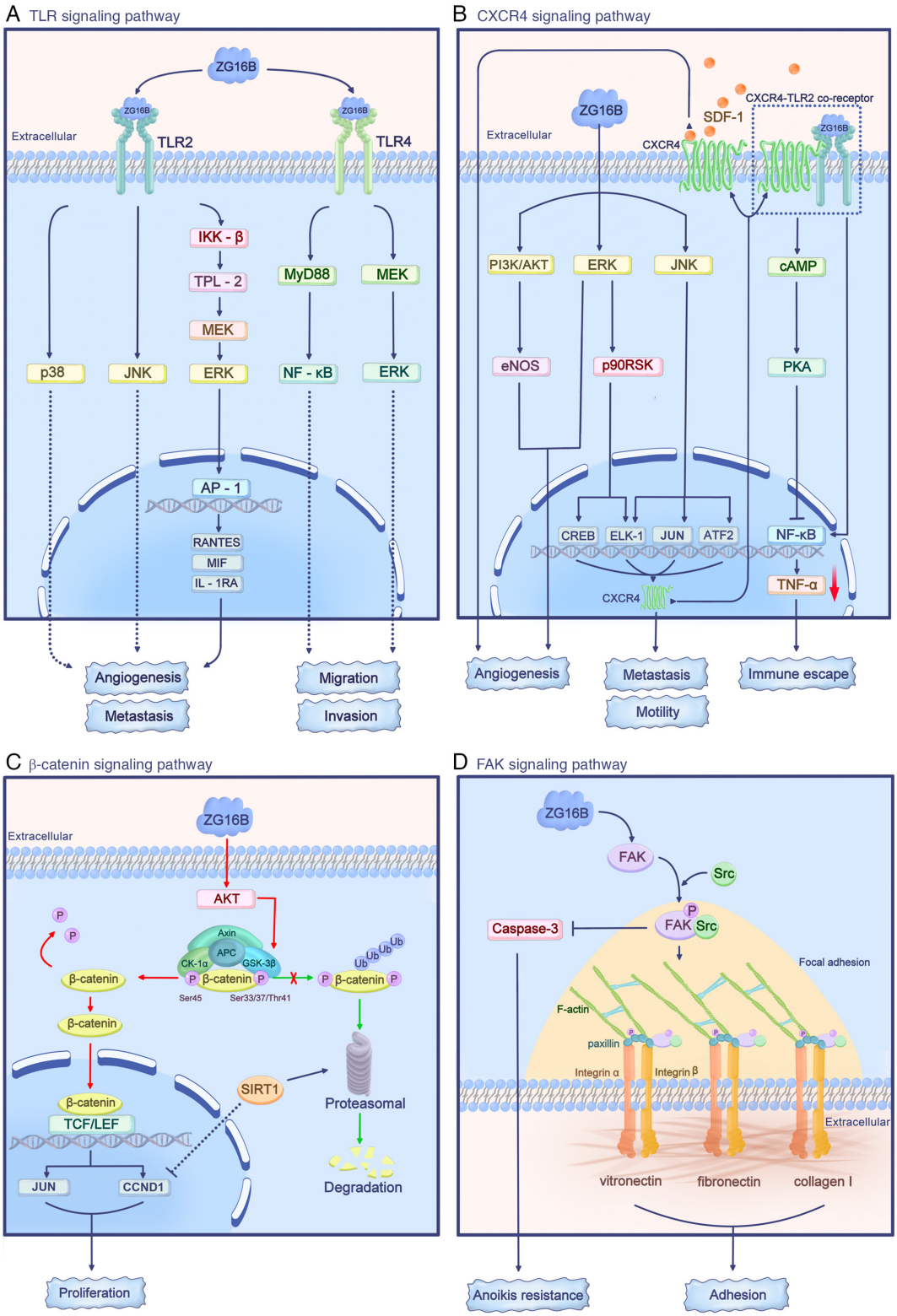

Figure 3. Signaling pathways regulated by ZG16B. (A) TLR signaling pathway. ZG16B activates TLR2-JNK, p38 and IKK-β/TPL-2/MEK/ERK signaling, enhancing AP-1-mediated cytokine expression, and promoting angiogenesis and metastasis. Through TLR4, ZG16B triggers the MyD88/NF-κB and MEK/ERK pathways to enhance tumor cell migration and invasion. (B) CXCR4 signaling pathway. ZG16B activates the ERK/p90RSK and JNK pathways, upregulating *CXCR4* gene transcription to increase tumor motility and metastasis. ZG16B also stimulates ERK and PI3K/AKT/eNOS-dependent angiogenesis and enhances SDF-1/CXCR4-mediated angiogenic signaling. Through the CXCR4-TLR2 co-receptor, ZG16B activates cAMP/PKA to suppress NF-κB activity and reduce TNF-α production, contributing to immune escape. (C) β-catenin signaling pathway. ZG16B activates AKT, inhibiting β-catenin degradation and promoting its nuclear accumulation, which induces TCF/LEF-dependent CCND1 and JUN transcription to drive proliferation. SIRT1 counteracts this effect by promoting β-catenin degradation. (D) FAK signaling pathway. ZG16B promotes formation of the FAK/Src complex at focal adhesions to enhance integrin-mediated adhesion and F-actin assembly. This signaling also inhibits caspase-3 activity, supporting anoikis resistance. AP-1, activator protein-1; ATF2, activating transcription factor 2; CCND1, cyclin D1; CK-1α, casein kinase-1α; CREB, cAMP-responsive element binding protein; CXCR4, C-X-C chemokine receptor type 4; eNOS, endothelial nitric oxide synthase; FAK, focal adhesion kinase; JUN, c-Jun; LEF, lymphoid enhancer factor; MIF, macrophage migration inhibitory factor; PKA, protein kinase A; p90RSK, p90 ribosomal s6 kinase; SDF-1, stromal cell-derived factor-1; SIRT1, sirtuin 1; TCF, T-cell factor; TLR, Toll-like receptor; TPL-2, tumor progression locus 2; ZG16B, zymogen granule protein 16B.

adhesion to extracellular matrix molecules, such as fibronectin, collagen I and vitronectin (114). Additionally, ZG16B activates the FAK/Src signaling to inhibit the activity of the apoptosis-related protein caspase-3, thereby enhancing the resistance of pancreatic cancer cells to anoikis, and promoting the progression and metastasis of pancreatic cancer (114,115).

TGF-β signaling pathway promotes ZG16B expression. TGF-β is a pleiotropic cytokine, which activates Smad signaling through its receptors; this is important in regulating processes such as immune regulation and wound healing (116,117). The TGF-β/Smad signaling pathway can promote TME remodeling by inducing the epithelial-mesenchymal transition (EMT), regulating angiogenesis, immune suppression, activating fibroblasts, extracellular matrix remodeling and inflammation modulation, ultimately promoting malignant tumor progression (118-120).

In pancreatic cancer cells, TGF-β binds to the TGF-β receptor 2 to activate the phosphorylation of Smad2/3, and facilitate the formation of a complex of Smad2/3 and Smad4 in the cytoplasm. Subsequently, this complex translocates into the nucleus and binds to the Smad-binding element in the ZG16B promoter, enhancing ZG16B expression (14). TGF-β/Smad-mediated ZG16B expression promotes the expression of transcription factors *SNAI1* and *ZEB1* via the MEK/ERK signaling pathway, upregulating mesenchymal vimentin and α-SMA expression, while downregulating epithelial E-cadherin and ZO-1 expression, inducing the EMT process in pancreatic cancer (14).

6. Relevance of ZG16B to tumors and its translational potential

Clinical relevance and prognostic importance of ZG16B in tumors. Physiologically, ZG16B is expressed at a low level in most non-tumor tissues, but it is highly expressed in the placenta (11). Additionally, ZG16B expression is markedly upregulated in various types of tumor tissues, including pancreatic cancer, colorectal cancer, ovarian cancer and gastric cancer (11). ZG16B is crucial for the pathogenesis of multiple types of cancer and disease, and ZG16B has broad activities and clinical potential.

ZG16B expression is low or undetectable in non-tumor pancreatic tissues, whereas its expression is notably upregulated in pancreatic cancer cells at the tumor margins. High ZG16B expression is associated with cancer progression and cachexia (15,17,121). Similarly, ZG16B is highly expressed in colorectal cancer (19,50), ovarian cancer (18,122) and cervical cancer (123,124), and its high expression is an independent prognostic risk factor, markedly associated with tumor stage progression, shorter overall survival, disease-free survival and progression-free survival. Furthermore, ZG16B is highly expressed in prostate cancer (125,126) and oral squamous cell carcinoma (51,127), supporting malignant behaviors. By contrast, high ZG16B expression in breast cancer is associated with a favorable prognosis (128). This may be explained by the fact that ZG16B is co-expressed with several tumor-suppressive genes, such as *SPINT1*, *TFAP2A*, *FOXA1* and *FAM96B* in breast cancer; its high expression predominantly occurs in hormone receptor-positive breast cancers, which are intrinsically associated with better outcomes; and its upregulation is mainly driven by promoter demethylation rather than oncogenic mutations (128). Functionally, ZG16B can act as a marker of hormone receptor-related differentiation or luminal epithelial differentiation, but not a driver factor, or an indicator of tumor aggressiveness in breast cancer (128). This clinical association suggests that the function of ZG16B may vary among different types of cancer.

Additionally, ZG16B appears to participate in the physiological processes and pathogenesis of several non-tumor diseases. Notably, ZG16B is highly expressed in reflex tears (129) and amniotic fluid (130), constituting a part of their specific protein components. In the oral cavity, through its lectin structure, ZG16B binds to the cell wall lipopolysaccharides of the commensal bacterium *Streptococcus vestibularis* and interacts with salivary mucin 7. This inhibits the growth of these microorganisms through mucin-assisted clearance mechanisms, contributing to the maintenance of oral microecological balance (131). ZG16B also binds to the lipoteichoic acid of the oral bacterium *Enterococcus faecalis*, inhibiting activation of the TLR2/NF-κB pathway in macrophages, alleviating inflammation and regulating immune responses to oral infections (132). ZG16B expression is downregulated in the oral salivary glands and saliva of patients with chronic graft-vs.-host disease, which may be related to salivary gland dysfunction (133). Furthermore, ZG16B has potential value as a biomarker or therapeutic target in diseases such as atherosclerosis (decreased expression in urine), acute coronary syndrome (decreased expression in urine) (134), dry eye syndrome (decreased expression in tear fluid) (135), multiple sclerosis (decreased expression in tear fluid) (136), Parkinson's disease (elevated expression in brain tissue) (137) and idiopathic pulmonary fibrosis (elevated expression in lung tissue) (138).

Overall, ZG16B shows promise as a biomarker for both diagnosis and prognosis. Its high expression in pancreatic, colorectal and ovarian cancers supports its potential for use in early diagnosis. Elevated ZG16B levels are also associated with worse survival in patients with colorectal or ovarian cancer, whereas they are linked to a more favorable prognosis in patients with hormone receptor-positive breast cancer. These findings highlight the value of ZG16B in cancer diagnosis and prognosis, with potential for tailored therapies.

Notably, while most current research focuses on the tissue-level expression of ZG16B and its relevance to cancer, clinical evidence supporting the detection of circulating ZG16B for early diagnosis or prognostic prediction in patient cohorts remains lacking (19). As a secreted protein with carbohydrate-binding sites and glycosaminoglycan-binding capabilities, ZG16B possesses the biological potential to be released into blood and other body fluids, making it a promising candidate for liquid biopsy (139-144). Future prospective cohort studies are required to validate critical parameters such as sensitivity, specificity and area under the curve for testing circulating ZG16B in patients with cancer, and to compare its performance with existing biomarkers.

Targeting ZG16B in tumor prevention and therapy. Targeting ZG16B has potential for tumor prevention and therapy in

different types of cancer. In a mouse model susceptible to breast cancer, treatment with both the chemopreventive agents bexarotene and carvedilol has been reported to suppress ZG16B expression, reducing the proliferation and migration of non-malignant breast cells (48). Similarly, treatment with anti-ZG16B antibody, together with docetaxel displays strong antitumor effects in an ovarian cancer mouse model (49). Furthermore, inhibiting ZG16B expression in pancreatic cancer stem cells can reduce the expression levels of multidrug resistant protein 5 and ribonucleotide reductase M2, thus increasing the sensitivity of these cells to gemcitabine and 5-fluorouracil in a pancreatic cancer mouse model (145,146). Additionally, ZG16B can upregulate the expression of type I interferon-α receptor in pancreatic cancer cells to activate downstream TYK2 and STAT1, which increases their resistance to oncolytic virus H-1 infection, suggesting the important role of targeting ZG16B in oncolytic virotherapy (147).

Currently, there are various therapeutic strategies for targeting ZG16B. Kim *et al* (22) designed an RNA aptamer (P12FR2) that specifically binds to the ZG16B protein, and effectively inhibited pancreatic cancer growth. Kim *et al* (20) also developed a trans-splicing ribozyme (TSR) targeting ZG16B mRNA to selectively kill ZG16B$^+$ tumor cells. Additionally, Kim *et al* (21) designed a humanized monoclonal antibody against ZG16B (PMAb83), which effectively inhibited the proliferation and invasiveness of pancreatic cancer cells, tumor angiogenesis, and suppressed tumor growth and metastasis.

A multicenter, open-label Phase I/IIa clinical trial is currently testing the efficacy and safety of humanized anti-ZG16B for patients with advanced pancreatic cancer (NCT05141149, ClinicalTrials.gov) (23-25). The study population consists of adults with locally advanced or metastatic pancreatic cancer who have relapsed in response to multiple lines of chemotherapy. These patients receive PBP1510, a novel humanized IgG1 monoclonal antibody against ZG16B, either as monotherapy or in combination with gemcitabine. If successful, this therapeutic strategy may offer new treatment options for patients with pancreatic cancer in the future.

In summary, targeting ZG16B offers promising therapeutic strategies across multiple types of cancer. Preclinical studies have demonstrated that inhibiting ZG16B expression in cancer models may reduce tumor cell proliferation, migration and resistance to chemotherapy. Therapeutic approaches include RNA aptamers, TSRs and monoclonal antibodies, such as PMAb83, which have potential to inhibit tumor growth, metastasis and angiogenesis. Additionally, the ongoing clinical trial of PBP1510, a monoclonal antibody against ZG16B for patients with pancreatic cancer, holds potential for providing new treatment options for patients with advanced cancer.

7. Future research directions for ZG16B

ZG16B is a promising regulator in tumor progression and immune responses, but several challenges remain. The lack of high-resolution structural data, unclear role of PTMs and unidentified receptors hinder a full understanding of its molecular mechanisms. Its multifunctional roles and varied expression across diseases further complicate its therapeutic targeting. Overcoming these challenges will require advanced structural studies, molecular profiling and disease-specific models to fully explore its therapeutic potential.

Structural and functional studies. Future research should clarify the carbohydrate-binding specificity of the ZG16B lectin domain and determine how PTMs, such as phosphorylation, N-myristoylation and glycosylation, affect its structural stability and downstream signaling. Integrating high-resolution structural approaches with site-directed mutagenesis or PTM-deficient ZG16B mutants will enable to precisely map its modification-dependent functional motifs. These studies will reveal how ZG16B orchestrates tumor progression and immune modulation at the molecular level.

Molecular regulatory network studies. Defining the upstream and downstream regulatory networks of ZG16B remains essential for understanding its pleiotropic roles across different types of cancer. Particular attention should be paid to transcriptional and post-transcriptional regulation by noncoding RNAs (such as microRNAs and long noncoding RNAs) as well as modulation by major oncogenic pathways, such as NF-κB, MAPK and PI3K/AKT. Parallel efforts to identify and validate ZG16B receptors, including integrins, TLR family members or as-yet-uncharacterized surface proteins, will clarify how extracellular ZG16B is converted into cellular responses. CRISPR-based regulatory screening and multi-omics profiling may accelerate the discovery of ZG16B-centered signaling hubs and refine the understanding of its functional connectivity in the TME.

Drug design. A deeper understanding of ZG16B-receptor interactions will lay the foundation for developing ZG16B-targeted precision therapies. High-resolution structural studies should map critical binding interfaces to support rational design of small-molecule inhibitors using computational docking and molecular dynamics modeling. Concurrently, developing monoclonal antibodies or biologics that disrupt ZG16B or its receptor engagement may provide new options for modulating immune suppression or tumor progression. Rigorous evaluation of these therapeutic strategies in *in vitro* and *in vivo* models, particularly in tumors with high ZG16B expression, will be crucial for determining feasibility and guiding translational development.

Exploration in non-tumor diseases. ZG16B expression dysregulation in cardiovascular, neurological and autoimmune diseases suggests that its biological relevance extends far beyond malignancy. Investigating its roles in chronic inflammation, endothelial activation or immune dysregulation using disease-specific models, such as atherosclerosis, neuroinflammation or autoimmune liver disease, may reveal conserved mechanisms shared with cancer biology. These studies have the potential not only to define ZG16B as a cross-disease biomarker but also to provide therapeutic opportunities in non-oncological conditions where ZG16B-driven pathways remain largely unexplored.

8. Conclusion

The present review comprehensively summarizes the research progress on the oncogenic roles of ZG16B. As a secretory protein, ZG16B can activate multiple signaling pathways, including TLR, CXCR4, β-catenin and FAK, to promote tumor cell proliferation, migration, invasion and angiogenesis. ZG16B is crucial for tumor development and metastasis by reshaping the TME and regulating immune cell functions, including MDSCs, TAMs and DCs. ZG16B is highly expressed in various types of cancer, and also has potential value for non-invasive tumor diagnosis and prognosis. Furthermore, treatment strategies targeting ZG16B have potential to serve as new therapeutic options for multiple types of cancer.

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Availability of data and materials

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Authors' contributions

PW and YK conceived and designed the study. XMC, YBL, JXZ, ZSY, LYZ and XYZ contributed equally to literature review, interpretation, synthesis, and writing the first draft of the manuscript and preparing the figures. PW and YK edited the manuscript and were responsible for critical revisions. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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