IGFBP3 modulation of tumor pathogenesis and cell signaling pathways (Review)

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Abstract. Insulin-like growth factor binding protein 3 (IGFBP3) is the primary carrier of circulating insulin-like growth factors and is the most extensively studied protein among the six high-affinity insulin-like growth factor binding proteins. Alterations in IGFBP3 at both the transcriptional and post-translational levels may contribute to the occurrence and progression of tumors. The present review focused on the changes in expression levels of IGFBP3 in tumors, as well as the relationship between the activation and inhibition of associated cell signaling pathways, and alterations in cellular biological behavior, aiming to provide a reference for the precise treatment of tumors.

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Abbreviations: IGFBP3, insulin-like growth factor binding protein 3; EMT, epithelial-mesenchymal transition; SRC, Rous sarcoma virus oncogene homolog; TRAIL, TNF-related apoptosis-inducing ligand; WSB2, WD repeat and SOCS box containing protein 2; pRB, retinoblastoma protein; E2F, E2 promoter binding factor; TMEM219, transmembrane protein 219; HIF, hypoxia-inducible factor; miR-19a-3p, microRNA-19a-3p; IGF-1, insulin-like growth factor-1; IGF-1R, IGF-1 receptor; VCAM-1, vascular cell adhesion molecule-1; TCF7L2, transcription factor 7-like 2; KANK1, KNF motif and ankyrin repeat domains 1; TRAIP, TRAF-interacting protein

Key words: insulin-like growth factor binding protein 3, expression changes, tumor pathogenesis, signaling pathway

1. Introduction

Cancer is a global health crisis, which imposes a notable societal and economic burden, and accounts for 16.8% of deaths annually worldwide (1). Despite advancements in targeted therapies and immunotherapy, challenges such as metastasis, drug resistance and late-stage diagnosis persist, particularly in prevalent cancer types such as lung, breast and colorectal carcinomas (2-4). Further understanding of tumor pathogenesis and the identification of novel therapeutic targets are essential to improve patient outcomes.

Insulin-like growth factor (IGF) binding protein 3 (IGFBP3), a key member of the IGFBP family, is encoded by the IGFBP3 gene located on human chromosome 7p13-12. IGFBP3 comprises 264 amino acids, has a molecular weight of 28.7 kDa, and is primarily synthesized by hepatic stellate cells and mesenchymal cells (5-7). The IGFBP3 structure features a highly conserved NH2 terminus and COOH terminus, along with a central segment that distinguishes IGFBP3 from other proteins in the IGFBP family. The other members of this family primarily include IGFBP1, IGFBP2, IGFBP4, IGFBP5 and IGFBP6 (8). IGFBP3 binds to IGF-1 through its termini, thereby regulating the half-life and functionality of IGF-1 (8). Furthermore, the central segment of IGFBP3 undergoes various post-translational modifications, including glycosylation, phosphorylation and protease cleavage, which notably influence its functional expression (5,9). For instance, in non-small cell lung cancer (NSCLC), casein kinase 2 (CK2) phosphorylates IGFBP3, enhances cancer cell resistance to cisplatin, a commonly used antitumor drug in NSCLC treatment, and promotes anti-apoptotic capabilities (10). In patients with melanoma and prostate cancer, the levels of glycosylated and phosphorylated IGFBP3 in peripheral blood are positively associated with disease progression (11,12). Additionally, a disintegrin and metalloprotease 12 (ADAM12) (13) and pregnancy-associated plasma protein-A2 (PAPP-A2) (14) degrade IGFBP3 through proteolysis, thereby reducing the expression levels of IGFBP3.

The importance of IGFBP3 in cancer is multifaceted and has been extensively studied. Numerous studies have

demonstrated the close association between IGFBP3 and tumorigenesis and tumor progression (15-21). In lung adenocarcinoma with brain metastasis, IGFBP3 stimulates the expression of SMAD4, which leads to epithelial-mesenchymal transition (EMT) and promotes cancer cell invasion and migration through the TGF-β1/SMAD4 signaling pathway (15-17). IGFBP3 expression is closely associated with different breast cancer subtypes (18-21). In estrogen receptor (ER)-positive breast cancer cells, IGFBP3 inhibits cell proliferation by preventing the phosphorylation of cell cycle-related proteins, such as Cyclin D, Cyclin A, Cyclin E, cyclin-dependent kinases 2 and 4 (CDK2 and CDK4), as well as retinoblastoma protein (pRB) (18,19). Conversely, in triple-negative breast cancer, increased IGFBP3 expression enhances cancer cell invasiveness and proliferation (20,21). Furthermore, IGFBP3 may serve a potential role in tumor diagnosis and treatment in the future. The detection of IGFBP3 expression serves as a valuable biomarker in diagnosis (22-26). Studies have shown a notable association between IGFBP3 expression, tumor stage and patient survival rates in esophageal squamous cell carcinoma and pancreatic cancer (22-26). These findings indicate that IGFBP3 may be a potential indicator for early tumor detection, disease monitoring and prognosis evaluation. Targeting IGFBP3 and the related signaling pathways may potentially offer novel opportunities to develop anticancer therapies with enhanced efficacy in the future (27-30). For example, modulating the function of IGFBP3 in clear cell renal cell carcinoma and prostate cancer may enhance the sensitivity of tumor cells to chemotherapy drugs or reduce drug resistance and improve overall treatment outcomes (27,28,30).

In conclusion, IGFBP3 serves a key role in cancer research. Understanding the role of IGFBP3 in tumor pathogenesis is essential in the development of targeted and effective strategies for cancer diagnosis, treatment and prevention. The present review aimed to comprehensively summarize the current literature on the changes in IGFBP3 expression in tumors, the impact on cell signaling pathways and implications for tumor development. Table I illustrates the relationships between the changes in expression levels of IGFBP3 in several prevalent cancer types, such as lung cancer (including lung adenocarcinoma and NSCLC), breast cancer (ER-positive, HER2-positive, and triple-negative breast cancer), colorectal cancer, liver cancer (hepatocellular carcinoma), and ovarian cancer, the associated functions and the signaling pathways involving IGFBP3.

2. Changes in the expression levels of IGFBP3 in different tumors and related mechanisms

Lung cancer. According to the Global Cancer Statistics 2022 (1,3), lung cancer remains the most prevalent and lethal cancer type globally among both men and women, with ~50% of patients diagnosed at an advanced stage. Due to advancements in treatment methods and technologies, the median survival period for patients with advanced lung cancer can be extended to ~1 year; however, distant metastasis markedly reduces patient survival rates (3,31). Therefore, managing distant metastasis is key in primary disease treatment. Numerous studies have indicated that high IGFBP3 expression may enhance the invasion and metastasis of lung adenocarcinoma and NSCLC cells (2,16,32,33). For instance, in lung adenocarcinoma brain metastasis, IGFBP3 stimulates the expression of SMAD4, which leads to EMT by upregulating N-cadherin and downregulating E-cadherin expression, thereby promoting cancer cell invasion and metastasis. SMAD4 serves a key role in TGF-β1-induced EMT. Consequently, IGFBP3 may contribute to brain metastasis in lung adenocarcinoma by modulating the TGF-β1/SMAD4 signaling pathway (15-17) (Fig. 1, Part 1). In NSCLC, upregulation of IGFBP3 promoted tumor cell metastasis and invasion by regulating the expression of MMP-9, VEGF and monocyte chemoattractant protein-1 (2,16,32-35) (Fig. 1, Part 2). However, several studies have indicated that the plasma concentration of IGFBP3 in patients with lung cancer was low and exhibited notable negative associations with patient survival rates, clinical tumor stage and tumor grade (22,36-38). Transient transfection of IGFBP3 has been performed to augment IGFBP3 expression in H1299 cancer cells (22). IGFBP3 inhibited spheroid growth and invasion of cancer cells by upregulating MMP-9 expression, while simultaneously downregulating MMP-1 and total MMP expression in these cells (22). These findings contradict previous research conducted by Luo *et al* (32). Potential explanations for these discrepancies include differences in the selected target populations, cancer types and ethnic backgrounds. Luo *et al* (32) included Chinese patients with NSCLC, while Kuhn *et al* (22) examined German patients with lung cancer without specifying the cancer type. Additionally, variations in the research cell lines and transfection methods were observed; Luo *et al* (32) performed lentiviral transfection to increase IGFBP3 expression levels in A549 cancer cells, whereas Kuhn *et al* (22) performed transient transfection in H1299 cancer cells. Thus, IGFBP3 may exhibit varying effects in different types of lung cancer.

Oral cancer. In oral squamous cell carcinoma (OSCC), the expression levels of IGFBP3 are markedly elevated compared with those in normal tissues (39,40). The upregulation of IGFBP3 facilitates IGFBP3 binding to the cell membrane integrin β1 receptor (41,42), which promotes the phosphorylation of MEK and ERK, thereby contributing to OSCC metastasis (43). Additionally, IGFBP3 induces the phosphorylation of recombinant focal adhesion kinase, Rous sarcoma virus oncogene homolog (SRC) and STAT3. Phosphorylated STAT3 is translocated to the nucleus, which leads to increased expression levels of anti-apoptotic proteins such as Bcl-2, c-Myc and MMP-9 (Fig. 1, Part 3 and Part 4). Bcl-2 provides resistance to chemotherapy drugs, while c-Myc functions as an oncogene. MMP-9, a key regulator of cell proliferation, differentiation and malignant transformation, cleaves various extracellular matrix (ECM) proteins, such as collagen, laminin, and fibronectin (44), and influences ECM remodeling associated with tumor invasion, angiogenesis and metastasis (45). Consequently, high levels of IGFBP3 expression may enhance proliferation, metastasis and drug resistance in OSCC cells. Furthermore, elevated expression levels of IGFBP3 have been observed in tongue squamous cell carcinoma (TSCC) (46). Following knockdown of IGFBP3 in SAS cells, cell cycle analysis was performed using the Fucci reporter system, which revealed that SAS cells were arrested in the G_1 phase. Subsequently, western blot analyses were

Table I. Expression status and related functions of IGFBP3 in common tumors.

First author/s, year	System	Organ	Cancer type	Expression status	Cellular activities	Affected signaling pathways	(Refs.)
Yang *et al*, 2019	Respiratory	Lung	Lung adenocarcinoma	Up	Invasion, metastasis	TGF-β1/SMAD4 via EMT	(16)
Sun *et al*, 2015; Luo *et al*, 2021; Gharib *et al*, 2004			NSCLC	Up	Invasion, metastasis, promotion of angiogenesis	IGFBP3-MMP-9/VEGF/MCP-1	(2,32,33)
Kuhn *et al*, 2023			Lung cancer (unspecified)	Down	Invasion, spheroid growth	No clear pathway specified	(22)
Bao *et al*, 2016		Pharynx	Nasopharyngeal carcinoma	Up	Invasion, metastasis	No clear pathway specified	(24)
Zhong *et al*, 2008	Digestive	Oral cavity	OSCC	Up	Proliferation, metastasis, drug resistance, promotion of angiogenesis	IGFBP3-Integrin β1-MEK-ERK; IGFBP3-Integrin β1-FAK/ SRC-STAT3-Bcl-2/c-Myc/MMP-9	(39)
Ng *et al*, 2022			TSCC	Up	Invasion, metastasis, cell cycle arrest (G_1/S phase)	IGFBP3-Integrin β1-FAK-MEK-ERK (hypothetically)	(46)
Williams *et al*, 2007		Colon	Colorectal cancer	Down	Apoptosis	IGFBP3-TRAIL-DISC/NF-κB	(49)
Li *et al*, 2024; Hanafusa *et al*, 2005; Alexia *et al*, 2004; Buckbinder *et al*, 1995; Whittaker *et al*, 2010; Subramaniam *et al*, 2010		Liver	HCC	Down (wild-type p53)	Tumorigenesis, metastasis	WSB2-p53-IGFBP3-PI3K-AKT-mTOR	(52,54,57, 126-128)
Song *et al*, 2020; Playford *et al*, 2000				Up	Angiogenesis, EMT	Galectin-3-PI3K-AKT-GSK-3β-β-catenin-IGFBP3	(58,59)
Jang *et al*, 2023		Pancreas	Pancreatic cancer	Down	Proliferation	IGFBP3-IGF-1/IGF-1R-PI3K-mTOR	(23)
Kim *et al*, 2010; Butt *et al*, 2000; Jia *et al*, 2010	Genitourinary	Breast	ER-positive breast cancer	Down	Proliferation, apoptosis, cell cycle arrest (G_1/S phase)	IGFBP3-CDK2/4-pRB-E2F; IGFBP3-TMEM219-DISC-caspase 8	(18,64,65)
Qiu *et al*, 2019			HER2-positive breast cancer	Down	Proliferation, drug resistance	IGFBP3-IGF-1/IGF-1R-PI3K-AKT-Wnt-β-catenin-TCF7L2	(62)
Martin *et al*, 2014; Pitson *et al*, 2005			TNBC	Up	Invasiveness, proliferation	IGFBP3-EGFR-PI3K-AKT; IGFBP3-EGFR-Ras-MEK-ERK	(20,66)
Chen *et al*, 2024; Shih *et al*, 2020; Shih *et al*, 2021		Ovary	Ovarian cancer	Down	Angiogenesis, glycolysis	miR-19a-3p-IGFBP3-IGF-1/IGF-1R-PI3K-AKT-PKM2	(68-70)

Table I. Continued.

First author/s, year	System	Organ	Cancer type	Expression status	Cellular activities	Affected signaling pathways	(Refs.)
Du *et al*, 2022		Cervix	Cervical cancer	Up	Lymph angiogenesis	No clear pathway specified	(101)
Liu *et al*, 2021		Kidney	Clear cell renal cell carcinoma	Up	Proliferation, EMT	IGFBP3-TGF-β1-SMAD2/4 via EMT; IGFBP3-PI3K-AKT; IGFBP3-MAPK	(76)
Shariat *et al*, 2002; Zhong *et al*, 2024		Prostate	Prostate cancer	Down	Cell cycle arrest (G_0/G_1 phase), induction of apoptosis	IGFBP3-IGF-1/IGF-1R-PI3K-AKT-NF-κB; IGFBP3-TMEM219-DISC-caspase 8	(78,79)
Vaezi *et al*, 2022; Chao *et al*, 2021	Skeletal system	Bone	Osteosarcoma	Up	Metastasis	IGFBP3-PI3K-AKT-c-Jun-VCAM-2	(99,100)
Li *et al*, 2021; Ressler *et al*, 2009				Down	Invasion, proliferation	TRAIP-KANK1-IGFBP3-PI3K-AKT	(96,97)
Huang *et al*, 2020	Other	Thyroid	Papillary thyroid carcinoma	Up	Metastasis	No clear pathway specified	(102)
Giuliano *et al*, 1998		Eye	Retinoblastoma	Down	Apoptosis	IGFBP3-IGF-1/IGF-1R-PI3K-AKT-p21	(103)
Naspi *et al*, 2017		Skin	Metastatic melanoma	Down	Invasion	IGFBP3-Wnt/β-catenin	(104)

IGFBP3, insulin-like growth factor binding protein 3; NSCLC, non-small cell lung cancer; OSCC, oral squamous cell carcinoma, TSCC, tongue squamous cell carcinoma; SRC, Rous sarcoma virus oncogene homolog; HCC, hepatocellular carcinoma; TNBC, triple-negative breast cancer; EMT, epithelial-mesenchymal transition; MCP-1, monocyte chemoattractant protein-1; FAK, focal adhesion kinase; TRAIL, TNF-related apoptosis-inducing ligand; DISC, death-inducing signaling complex; WSB2, WD repeat and SOCS box containing 2; IGF-1, insulin-like growth factor-1; IGF-1R, IGF-1 receptor; ER, estrogen receptor; pRB, retinoblastoma protein; E2F, early region 2 binding factor; TMEM219, transmembrane protein 219; TCF7L2, transcription factor 7-like 2; miR-19a-3p, microRNA-19a-3p; PKM2, pyruvate kinase M2; VCAM-2, vascular cell adhesion molecule 2; TRAIP, TRAF interacting protein; KANK1, KNF motif and ankyrin repeat domains 1.

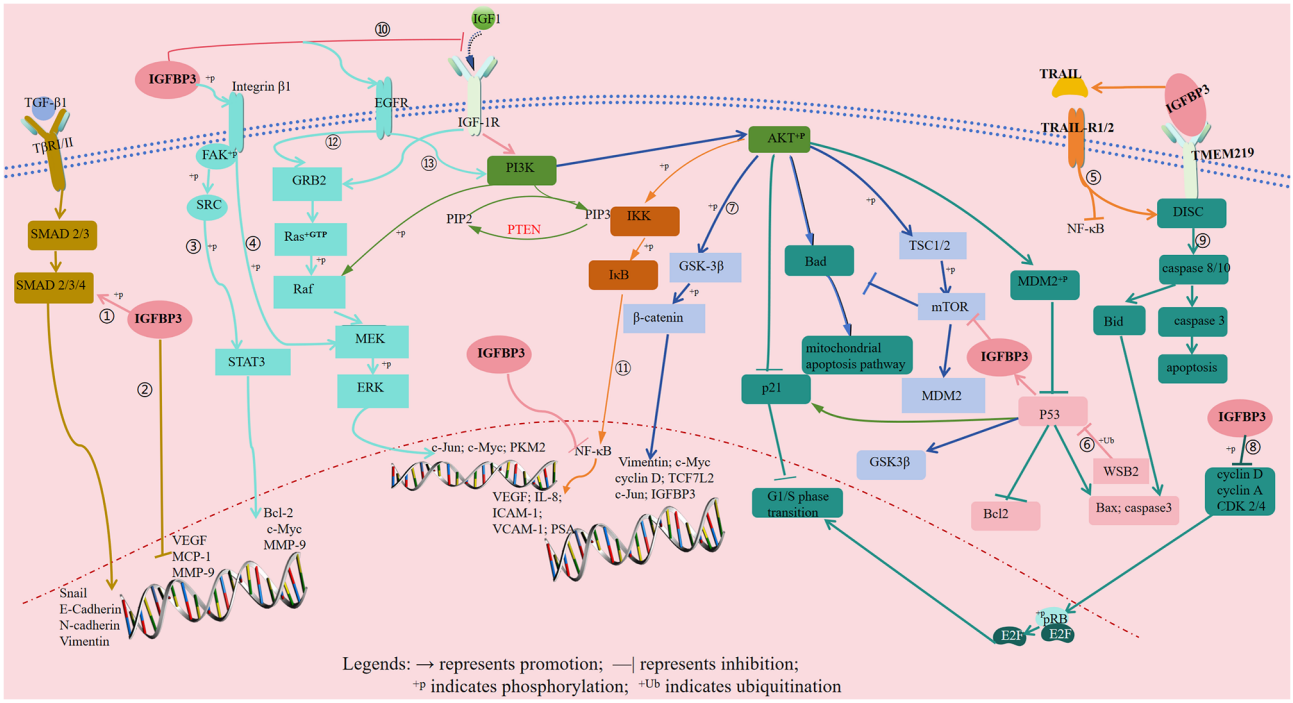

Figure 1. Key signaling pathways involving IGFBP3 expression in different tumors. 1, IGFBP3-TGF-β1/SMAD4 → EMT → invasion and metastasis (lung adenocarcinoma; clear cell renal cell carcinoma); 2, IGFBP3-MMP-9/VEGF/MCP-1 → invasion, metastasis and promotion of angiogenesis (non-small cell lung cancer); 3, IGFBP3-Integrin β1-FAK/SRC-STAT3-Bcl-2/c-Myc/MMP-9 → proliferation, metastasis, drug resistance and promotion of angiogenesis (OSCC); 4, IGFBP3-Integrin β1-MEK-ERK→proliferation, metastasis and drug resistance (OSCC; TSCC); 5, IGFBP3-TRAIL-DISC/NF-κB → apoptosis (colorectal cancer); 6, WSB2-p53-IGFBP3-PI3K-AKT-mTOR → tumorigenesis and metastasis [HCC (wild-type p53)]; 7, PI3K-AKT-GSK-3β → angiogenesis and EMT (HCC; HER2-positive breast cancer); 8, IGFBP3-CDK2/4-pRB-E2F → proliferation and cell cycle arrest (G_1/S phase) (ER-positive breast cancer); 9, IGFBP3-TMEM219-DISC-caspase-8 → apoptosis, proliferation and cell cycle arrest (G_1/S phase) (ER-positive breast cancer; prostate cancer); 10, GFBP3-IGF-1/IGF-1R-PI3K-AKT-PKM2 → angiogenesis and glycolysis (ovarian cancer; osteosarcoma); 11, IGFBP3-IGF-1/IGF-1R-PI3K-AKT-NF-κB → cell cycle arrest (G_0/G_1 phase) and apoptosis induction (prostate cancer); 12, IGFBP3-EGFR-Ras/Raf-MEK-ERK → proliferation and metastasis (triple-negative breast cancer); 13, IGFBP3-EGFR-PI3K-AKT → proliferation and metastasis (triple-negative breast cancer). IGFBP3, insulin-like growth factor binding protein 3; EMT, epithelial-mesenchymal transition; OSCC, oral squamous cell carcinoma; MCP-1, monocyte chemoattractant protein-1; SRC, Rous sarcoma virus oncogene homolog; PKM2, pyruvate kinase M2; TRAIL, TNF-related apoptosis-inducing ligand; DISC, death-inducing signaling complex; WSB2, WD repeat and SOCS box containing protein 2; HCC, hepatocellular carcinoma; pRB, retinoblastoma protein; E2F, E2 promoter binding factor; TMEM219, transmembrane protein 219; ER, estrogen receptor; IGF-1, insulin-like growth factor-1; IGF-1R, IGF-1 receptor; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; PSA, prostate-specific antigen; TCF7L2, transcription factor 7-like 2; TβR I/II, transforming growth factor β receptor type I/II; Bid, BH3-interacting domain death agonist; TSC1/2, tuberous sclerosis complex 1/2.

conducted to validate the results observed in SAS cells after IGFBP3 knockout and MEK inhibitor treatment. The findings indicated that IGFBP3 enhanced the migration of cancer cells by promoting the phosphorylation of MEK and ERK. Furthermore, the direct addition of exogenous IGFBP3 did not affect the migration of the cells (46). Therefore, the elevated expression levels of IGFBP3 in TSCC modulated cancer cell migration through the MEK/ERK signaling pathway (Fig. 1, Part 4). In conclusion, the upregulation of IGFBP3 in both OSCC and TSCC cells can stimulate tumor cell proliferation, invasion and metastasis.

Colorectal cancer. In colorectal cancer, the methylation of the IGFBP3 gene promoter frequently results in reduced IGFBP3 expression (47,48). TNF-related apoptosis-inducing ligand (TRAIL) binds to the membrane receptors TRAIL-R1 and TRAIL-R2, forming a death-inducing signaling complex with Fas-associated protein with death domain and procaspase-8, which ultimately activates caspase-8 and initiates cell death (5). Williams *et al* (49) demonstrated that upregulation of IGFBP3 expression in colon cancer HT29 cells via lentiviral transfection enhanced the effects of TRAIL, inhibited the activation of the NF-κB signaling pathway and suppressed colon cancer development. Furthermore, exogenous IGFBP3 promoted cell apoptosis by inhibiting the NF-κB signaling pathway (Fig. 1, Part 5). Therefore, regulating IGFBP3 expression in colorectal cancer may potentially represent a promising therapeutic approach for colorectal cancer in the future.

Liver cancer. Hepatocellular carcinoma (HCC) is the most prevalent form of liver cancer, and accounts for ~90% of all liver cancer cases (50). Early symptoms of HCC are often subtle and HCC is frequently diagnosed at an advanced stage, when treatment becomes exceedingly challenging. The 5-year survival rate for patients diagnosed with HCC is <20% (51). Li *et al* (52) performed co-immunoprecipitation and ubiquitin amino acid substitution techniques. Findings from the study demonstrated that in HCC with wild-type p53, the elevated expression of WD repeat and SOCS box containing protein 2 (WSB2) induced polyubiquitination and degradation of p53, while simultaneously downregulating the expression of Bax and IGFBP3, and promoted the phosphorylation of

AKT and mTOR, thereby facilitating tumor progression. Furthermore, when Li *et al* (52) targeted and inhibited mTOR expression with everolimus, a blockade of tumorigenesis and metastasis of HCC mediated by WSB2 was observed *in vivo*. These results further suggested that WSB2 upregulation contributed to HCC tumorigenesis and metastasis via the ubiquitin-mediated degradation of wild-type p53 and the activation of the IGFBP3-AKT/mTOR axis (Fig. 1, Part 6). However, in HCC cells harboring mutant p53, high WSB2 expression did not markedly impact the IGFBP3-AKT-mTOR signaling pathway (53). Additionally, Hanafusa *et al* (54) reported that the reduction in IGFBP3 expression in human HCC cells was due to hypermethylation of the IGFBP3 gene promoter. The decrease in IGFBP3 expression resulted in a relative increase in IGF-1 levels. Upon binding to IGF-1 receptor (IGF-1R), the PI3K-AKT signaling pathway was activated, which promoted the occurrence and metastasis of HCC. Conversely, the introduction of exogenous IGFBP3 inhibited the activation of the PI3K-AKT signaling pathway, thereby suppressing the proliferation of HCC cells (55-57). On the contrary, studies have indicated that galectin-3 activated the PI3K-AKT-GSK-3β-β-catenin signaling pathway in HCC cases characterized by elevated galectin-3 expression (58). Activated β-catenin directly enhanced the expression of IGFBP3 and vimentin, which induced angiogenesis and EMT-driven tumor metastasis, and ultimately impacted patient survival (58,59) (Fig. 1, Part 7). The dual role of IGFBP3 in both inhibition of tumorigenesis and promotion of cancer within the same HCC tumor may be attributed to several factors. First, the effects of IGFBP3 vary depending on its localization. Previous studies by Li *et al* (52) and Alexia *et al* (57) have demonstrated that extracellular IGFBP3 primarily inhibited tumorigenesis by preventing the binding of IGF-1 to IGF-1R. Conversely, the studies by Song *et al* (58) have focused on the intracellular effects of IGFBP3. Second, Li *et al* (52) and Song *et al* (58) have identified distinct key pathways influenced by IGFBP3. In the study conducted by Li *et al* (52), IGFBP3 was primarily involved in the PI3K-AKT-mTOR pathway. Conversely, Song *et al* (58) found that IGFBP3 mainly participates in the regulation of the PI3K-Akt-GSK-3β-β-catenin -IGFBP3 pathway in HCC. The human body functions as a complex system and tumor development may entail the activation of multiple signaling pathways. Consequently, IGFBP3 may interact with various pathways at different stages of tumor development and lead to divergent outcomes.

Breast cancer. Breast cancer is a prevalent type of tumor among women and is the second most common cause of cancer-related mortality globally (60). Based on histological characteristics, breast cancer can be classified into three subtypes: ER-positive, HER2-positive and triple-negative. Currently, chemotherapy, hormonal therapies and targeted therapies represent the primary treatment options for breast cancer. While these methods have demonstrated effectiveness in reducing mortality rates-e.g., due to these treatments, in 2016, the breast cancer mortality rate in the European Union decreased by ~8%-notable challenges such as drug toxicity and resistance remain (61). Therefore, further research is warranted to explore novel treatments and enhance patient outcomes. Previous studies have indicated that the expression levels of IGFBP3 were reduced in both ER-positive and HER2-positive breast cancer cells (18,19,62). For instance, in ER-positive breast cancer cells, IGFBP3 expression prevents the phosphorylation of cell cycle-related proteins, including Cyclin D, Cyclin A, Cyclin E, CDK2, CDK4 and pRB (18,19). Unphosphorylated pRB forms a heterodimer with E2 promoter binding factor (E2F) in cells, which suppresses E2F activity and obstructs the G_1/S transition of the cell cycle, and consequently exerts a tumor suppressor effect (18). However, CDKs counteract the effect by phosphorylating pRB, which leads to the dissociation of pRB from the pRB/E2F heterodimer, thereby abolishing the inhibitory effect on E2F, and ultimately promoting the G_1/S transition of the cell cycle and cell proliferation (18,19). Consequently, IGFBP3 inhibits the activity of CDK2 and CDK4, reduces the phosphorylation of pRB and induces cell cycle arrest in the G_1 phase of ER-positive breast cancer cells, and inhibits cell proliferation (Fig. 1, Part 8). Additionally, IGFBP3 interacts with the transmembrane protein 219 (TMEM219) receptor located on the cell surface. The interaction results in the phosphorylation and activation of procaspase-8, which binds to TMEM219 during the resting phase and initiates the death receptor-mediated apoptotic pathway (63). This regulation also impacts the expression of Bax and Bcl-2, which promotes apoptosis in breast cancer cells (30,64,65) (Fig. 1, Part 9). In trastuzumab-resistant HER2-positive breast cancer cells, the upregulation of Cullin7 had dual effects (62). On one hand, Cullin7 promoted the degradation of insulin receptor substrate-1 (IRS-1) phosphorylated at the serine position and induced the accumulation of phosphorylated tyrosine IRS-1 within the cells. The accumulation subsequently phosphorylated and activated downstream proteins with SRC homolog 2 domains such as PI3K. On the other hand, Cullin7 inhibited the expression of IGFBP3, which activated the IGF-1R signaling pathway. IGFBP3 is known as a Wnt signaling inhibitor that suppresses the transcription of β-catenin and downstream factors such as transcription factor 7-like 2 (TCF7L2). TCF7L2 binds to the TCF/lymphoid enhancer-binding factor-1 binding motif within the Cullin7 promoter, and enhances Cullin7 transcription. Consequently, in trastuzumab-resistant HER2-positive breast cancer cells, high expression levels of Cullin7 activated the PI3K-AKT signaling pathway by suppressing IGFBP3 expression, which promoted resistance to trastuzumab treatment (62) (Fig. 1, Part 7). By contrast, in triple-negative breast cancer, the expression levels of both IGFBP3 and sphingosine kinase-1 (SphK1) are elevated. The increased activity of SphK1 catalyzes the conversion of sphingosine in the cell membrane to sphingosine-1-phosphate (S1P). S1P subsequently mediates the enhancement of the EGFR signaling pathway by IGFBP3 in breast cancer cells, which leads to the phosphorylation of ERK1/2 and AKT. The process enhances the invasiveness and proliferative capacity of breast cancer cells, ultimately affecting patient prognosis (20,21,66) (Fig. 1, Part 12 and 13). In summary, the processes of tumorigenesis and progression are determined by the activation of key signaling pathways within cells. In breast cancer, the diverse functions of IGFBP3 may be significantly affected by tumor cell phenotypes and genetic markers. For example, in ER-positive breast cancer cells, IGFBP3 inhibits cell proliferation through regulating cell cycle-related proteins. In triple-negative

breast cancer, however, it promotes cancer cell invasiveness and proliferation.

Ovarian cancer. In ovarian cancer, the expression levels of IGFBP3 are notably reduced (67,68). High expression levels of IGFBP3 inhibit tumor cell proliferation and angiogenesis. In the absence of blood vessels, tumors become hypoxic, which activates hypoxia-inducible factor-1α (HIF-1α) in the early stages of hypoxia. HIF-1α promotes angiogenesis and stimulates the synthesis of IGFBP3. Increased IGFBP3 levels subsequently upregulate thrombospondin-1 (69), which in turn inhibits tumor angiogenesis and exacerbates tumor hypoxia. Prolonged hypoxia leads to methylation and silencing of the IGFBP3 promoter, which results in the activation of hypoxia-inducible factor-2α (HIF-2α). This cascade accelerates the progression of ovarian cancer, increases resistance to chemotherapy, and enhances tumor invasion and metastasis (68-72). Concurrently, previous studies (67,73) have demonstrated that microRNA (miR)-19a-3p was markedly upregulated in ovarian cancer. miR-19a-3p binds to the 3' untranslated region of IGFBP3, thereby inhibiting IGFBP3 expression (67). The inhibitory effect of miR-19a-3p further obstructs the binding of IGFBP3 to IGF-1 and activates the IGF-1/IGF-1R/PI3K-AKT signaling pathway. The activation of the IGF-1/IGF-1R/PI3K-AKT signaling pathway promotes the expression of enzymes associated with aerobic glycolysis, such as pyruvate kinase M2, lactate dehydrogenase A, glucose transporter 1 and glucose transporter 3, which facilitates the proliferation and metastasis of tumor cells, and promotes the progression of ovarian cancer (Fig. 1, Part 10). In summary, current research suggests that IGFBP3 serves a key role in inhibiting the occurrence and progression of ovarian cancer and is closely linked to the tumor hypoxic microenvironment and the activation of the IGF-1/IGF-1R/PI3K-AKT signaling pathway. Further research on IGFBP3 may potentially provide valuable insights for the prevention and treatment of ovarian cancer in the future.

Clear cell renal cell carcinoma. IGFBP3 has been reported to be upregulated in clear cell renal cell carcinoma (74-76). Liu *et al* (76) demonstrated that IGFBP3 enhanced the activation of the PI3K/AKT and MAPK signaling pathways, which led to the downregulation of E-cadherin, while upregulating N-cadherin and vimentin. This modulation influenced processes such as proliferation, angiogenesis and apoptosis, which ultimately promoted the progression of clear cell renal cell carcinoma (Fig. 1, Part 1). Similarly, Rosendahl *et al* (77) showed that IGFBP3 promoted tumor cell proliferation in Caki-2 cells derived from renal cell carcinoma by triggering the TGF-β1 signaling pathway. Therefore, targeting IGFBP3 expression in clear cell renal cell carcinoma and inhibiting the activation of these pathways could potentially provide a promising therapeutic approach for the management of these tumors in the future.

Prostate cancer. The expression levels of IGFBP3 are reduced in the serum of patients with prostate cancer, with a gradual decrease observed as the tumor progresses (78,79). A study conducted by Boyle *et al* (80) reported that 1,25-hydroxyvitamin D (vitamin D) impedes the proliferation of prostate cancer cells. Vitamin D induces biological functions such as inhibiting the proliferation, invasion and metastasis of tumor cells (81,82) through the vitamin D receptor (81). Upon binding with vitamin D, this receptor activates target genes, including IGFBP3, which is known to contain a vitamin D receptor element. The activation of target genes led to the upregulation of cell cycle regulatory proteins such as p21/WAF1, ultimately halting cell proliferation in the G_0/G_1 phase (80). Short-term exposure to vitamin D resulted in sustained secretion of IGFBP3 (28,83,84). Furthermore, the expression of NK3 homeobox 1 (NKX3.1), a prostate-specific homeobox gene, key for prostate development and maturation, is often downregulated in primary prostate cancer tissues (85). Upregulation of NKX3.1 in prostate cancer cells increased IGFBP3 expression, which in turn hindered the phosphorylation of IGF-1R, IRS-1, PI3K and AKT induced by IGF-1, and inhibited prostate cancer cell proliferation. Conversely, inhibition of IGFBP3 expression in prostate cancer cells could reverse the inhibitory effect of NKX3.1 on IGF-1R signaling (86,87). The results suggested that the inhibitory effect of NKX3.1 on tumor growth was mediated through the activation of IGFBP3 expression (87). Additionally, previous studies have demonstrated that the NF-κB signaling pathway is implicated in prostate cancer. The activation of NF-κB and its translocation to the nucleus upregulated the expression of various factors, including VEGF, IL-8, intercellular adhesion molecule-1, vascular cell adhesion molecule-1 (VCAM-1) and prostate-specific antigen, and impacted the survival, adhesion, inflammation, proliferation and angiogenesis of prostate cancer cells (88-90) (Fig. 1, Part 11). Furthermore, IGFBP3 expression triggers the apoptotic pathway by binding to the TMEM219 receptor on the cell surface. Elevated expression levels of caspase-3 facilitate the degradation of IκBα and NF-κB, inhibiting the activation of the NF-κB signaling pathway and impeding the progression of prostate cancer (91,92) (Fig. 1, Part 9). In summary, IGFBP3 acts as a tumor suppressor in prostate cancer by hindering the binding of IGF-1 to IGF-1R, blocking the activation of the PI3K-AKT-NF-κB signaling pathway, or directly engaging with the cell membrane receptor TMEM219 to initiate the apoptotic pathway, which restrains tumor initiation and progression.

Osteosarcoma. Osteosarcoma, a highly aggressive and metastatic malignant bone tumor, predominantly affects adolescents and children, with >70% of cases occurring within this demographic (93). The tumor typically arises in the metaphysis of long bones. At the time of diagnosis, 15-20% of patients exhibit visible metastatic lesions, with lung metastasis being the most prevalent symptom (94). Previous studies (95-97) have indicated that in children and adolescents with osteosarcoma, the expression levels of IGFBP3 and KNF motif and ankyrin repeat domains 1 (KANK1) are markedly lower compared with those in normal tissues, while TRAF interacting protein (TRAIP) expression is upregulated. Elevated expression levels of TRAIP have been associated with decreased metastasis-free survival and overall survival rates in patients with osteosarcoma. TRAIP functions as an E3 ubiquitin ligase in osteosarcoma, which facilitates the degradation of KANK1 through ubiquitination and leads to reduced expression levels of IGFBP3, the downstream target gene of

KANK1. This mechanism results in the phosphorylation of AKT and the subsequent activation of the AKT signaling pathway, which promotes osteosarcoma invasion and metastasis (96,97) (Fig. 1, Part 10). Additionally, Schedlich *et al* (98) reported that elevated expression levels of TGF-β1 in the initial phases of osteosarcoma can enhance IGFBP3 expression. Elevated IGFBP3 expression, in turn, inhibit the activation of the MAPK pathway and the phosphorylation of SMAD2, induced by TGF-β1, and hinder the proliferation and invasion of tumor cells. However, previous studies have also demonstrated that the expression levels of IGFBP3 in osteosarcoma tissues were notably higher compared with those in normal tissues (99,100). For example, Chao *et al* (100) identified that elevated expression levels of IGFBP3 could facilitate the nuclear translocation of the transcription activator c-Jun via the PI3K-AKT signaling pathway, which led to increased VCAM-1 expression and myeloma cell metastasis, and impacted patient prognosis. The contrasting outcomes may be attributed to two main factors: i) In the study conducted by Chao *et al* (100), the osteosarcoma cell lines MG63 and U2OS were treated with exogenous IGFBP3. The effects of IGFBP3 on cell migration were evaluated using Transwell assays, wound healing assays and western blot analysis. Conversely, Li *et al* (96) utilized small interfering RNA (siRNA) to target and inhibit the expression of endogenous IGFBP3 in MG63 and MNNG/HOS cells. They assessed the expression and phosphorylation levels of the AKT protein, which are associated with cell invasion and proliferation, through western blotting techniques; and ii) IGFBP3 plays a critical role in regulating tumor cell functions in osteosarcoma through various signaling pathways. For instance, Chao *et al* (100) demonstrated that IGFBP3 can activate the PI3K-AKT-c-Jun-VCAM-2 signaling pathway, which promotes tumor cell metastasis and consequently impacts patient prognosis. Conversely, research by Li *et al* (96) revealed that IGFBP3, as a key protein in the TRAIP-KANK1-IGFBP3-PI3K-AKT signaling pathway, has its expression inhibited by the TRAIP protein, ultimately leading to tumor cell invasion and metastasis. The detailed signaling pathways involved are illustrated in Fig. 1.

Other tumors. Previous studies have demonstrated that IGFBP3 notably contributes to the occurrence and progression of other tumors. For instance, in cervical cancer and papillary thyroid carcinoma, elevated expression levels of IGFBP3 enhanced tumor cell metastasis by facilitating the formation of lymphatic vessels (101,102). In nasopharyngeal carcinoma, the upregulation of IGFBP3 led to the downregulation of E-cadherin and the upregulation of N-cadherin, thereby promoting metastasis and invasion (24). Conversely, IGFBP3 is downregulated in certain tumors, such as pancreatic cancer, retinoblastoma and diffuse metastatic melanoma. In pancreatic cancer, increased IGFBP3 expression inhibited the PI3K-mTOR signaling pathway, and impeded cancer cell proliferation (23). Similarly, the upregulation of IGFBP3 in retinoblastoma Y79 cells counteracted the anti-apoptotic effects of IGF-1 (103). Additionally, previous studies (104-106) have shown that in diffuse metastatic melanoma, IGFBP3 dephosphorylated GSK-3β, which led to the degradation of cytoplasmic β-catenin and subsequent inhibition of the Wnt signaling pathway, and resulted in reduced tumor cell migration and invasion (104).

3. Post-translational modifications of IGFBP3: Impacts on tumorigenesis and development

Current research has indicated that IGFBP3 serves a key role in the initiation and progression of tumors. However, the functional efficacy of IGFBP3 is influenced by variations in expression levels and post-translational modifications, which notably affect IGFBP3 functionality. The primary post-translational modifications of IGFBP3 include glycosylation, phosphorylation and proteolysis. Glycosylation, an important modification, enhances the stability of IGFBP3; however, its role varies across different tumor types (11,107-113). In melanoma, glycosylated IGFBP3 is cleaved by proteases, which results in decreased affinity for IGF-1 and increased release of free IGF-1, and ultimately promotes tumor cell proliferation (11). In patients that succumbed to breast cancer, glycosylated IGFBP3 retained its binding capacity to IGF-1; however, the ability to bind to the cell surface was inferior compared with that of the non-glycosylated form, which potentially affected the localization and function of IGFBP3 within the tumor microenvironment (107). Phosphorylation also serves a role in regulating the function of IGFBP3. For example, in head and neck squamous cell carcinoma and prostate cancer, the phosphorylation and subsequent degradation of IGFBP3 mediated by protein kinase C and CK2 inhibits tumor cell apoptosis, thereby promoting tumor progression (12,114). In NSCLC, CK2 phosphorylates IGFBP3, which obstructs the interaction between IGFBP3 and hyaluronic acid, and activates the hyaluronic acid-CD44 signaling pathway, leading to increased tumor cell survival and enhanced resistance to cisplatin (107). In terms of proteolytic modification, specific proteases such as ADAM12 and PAPP-A2 degrade IGFBP3 through proteolysis, thereby reducing IGFBP3 expression levels and releasing IGF-1, which promotes fetal or child growth and development (113,115-117). Additionally, previous studies have demonstrated that in colitis-associated colorectal cancer and breast cancer, serine proteases and matrix metalloproteinase-7 facilitated the proteolysis of IGFBP3, which inhibited IGFBP3 function, and consequently promoted tumor initiation and progression (108-113).

In summary, post-translational modifications of IGFBP3 notably influence tumor initiation and development. Various types of post-translational modifications affect the function of IGFBP3 through complex and diverse mechanisms, exerting notable effects on the biological behaviors of tumor cells. For instance, in NSCL, CK2 can induce the phosphorylation of IGFBP3, thereby inhibiting its interaction with hyaluronic acid. This process activates the HA-CD44 pathway, leading to tumor cell proliferation and the development of cisplatin resistance (107). In melanoma, glycosylated IGFBP3 can be cleaved by proteases, resulting in decreased levels of IGFBP3, which activates the Akt-GSK3β axis and ultimately promotes cell proliferation (10). However, current research is focusing on the post-translational modifications of IGFBP3, with numerous specific molecular mechanisms yet to be fully elucidated. Further research is necessary to investigate the detailed mechanisms of IGFBP3 post-translational modifications in different tumors, as well as the relationships between these modifications, the clinical characteristics and prognosis of tumors, to provide a more robust theoretical basis and potential

therapeutic targets for the precise diagnosis and treatment of tumors in the future.

4. IGFBP3 and cancer: Novel perspectives on precision treatment and clinical challenges

IGFBP3 plays a complex and diverse role in the processes of tumorigenesis and tumor development. It can influence various aspects of cancer cells, including proliferation, apoptosis, invasion and metastasis, through different mechanisms. This complexity offers new opportunities for developing targeted cancer therapies. The expression and function of IGFBP3 vary significantly among different tumor types. These differences can be utilized to design patient-stratified treatment strategies. For instance, in clear cell renal carcinoma, elevated IGFBP3 expression is associated with increased invasion and metastasis of tumor cells (74-76). Liu *et al* (27), through spatial conformation analysis, demonstrated that cyclovirobuxines formed hydrogen bonds with two amino acid residues, GLU-64 and GLU-86, in the IGFBP3 molecule. These hydrogen bonds inhibited IGFBP3 function. The interaction disrupted the IGFBP3-AKT/STAT3/MAPK-Snail signaling pathway, which ultimately hindered the progression of clear cell renal carcinoma. In the context of glioblastoma, Chen *et al* (118) utilized convection-enhanced delivery to administer IGFBP3 small interfering RNA into the brains of mice, which successfully inhibited intracranial tumor growth and extended the survival of the mice. For patients exhibiting high IGFBP3 expression, targeted inhibitors can be developed to mitigate IGFBP3 function and effectively prevent tumor progression. Conversely, for patients with low IGFBP3 expression, treatment strategies aimed at enhancing IGFBP3 expression, such as gene therapy or pharmacological activation of relevant signaling pathways, like the vitamin D signaling pathway and the p53 signaling pathway, can be explored to amplify the antitumor effects of IGFBP3 (28,52,83,84). For instance, in the research on gastric cancer, it has been found that infecting gastric cancer cells with lentiviruses carrying IGFBP3 can effectively upregulate the expression level of IGFBP3 in the cells. The upregulated IGFBP3 can inhibit the activity of NF-κB in gastric cancer cells, thereby significantly enhancing the cell growth inhibition effect induced by etoposide (119).

Findings from previous studies (78,120,121) regarding IGFBP3-related signaling pathways hold notable promise for clinical translation. The detection of IGFBP3 and its downstream signaling molecules in tumor tissues or blood is key for the diagnosis and prognostic evaluation of patients with cancer. Previous studies have indicated that in the peripheral blood of patients with tumors, such as prostate cancer and colorectal cancer, the concentration of IGFBP3 was reduced compared with that in healthy individuals. This reduction was associated with a higher metastasis rate and poorer prognosis (78,120,121). Conversely, some studies have suggested that in certain tumors, elevated expression levels of IGFBP3 may promote tumor progression and decrease patient survival rates. For instance, in the peripheral blood of individuals with OSCC and glioblastoma, IGFBP3 expression levels were markedly higher compared with those in the control group (43,122). Thus, in OSCC and glioblastoma, IGFBP3 expression can serve as a biomarker for the assessment of tumor development stages and patient prognosis (43,122). Regarding drug development for cancer treatment, although some drugs have been utilized to target tumors by directly or indirectly modulating IGFBP3 expression, the variable effects and associated signaling pathways of IGFBP3 across different tumors pose challenges for clinical translation and drug selection. For example, drug specificity is key to ensure that drugs precisely target IGFBP3-related signaling pathways while minimizing adverse effects on normal cells. Additionally, prolonged use of targeted therapies may lead to the development of drug resistance in tumor cells, thereby diminishing treatment efficacy (123-125). Therefore, comprehensive research on the aforementioned issues and the pursuit of effective solutions are essential to potentially achieve clinical translation in the future.

IGFBP3 exhibits dual functions across various cancer types, such as ovarian cancer and HCC. These cancers which are influenced by the tumor microenvironment and genetic background. Factors such as hypoxia and inflammation within the tumor microenvironment modulate IGFBP3 activity (68-72,126). In ovarian cancer, during the initial hypoxic phase, elevated levels of HIF-1α promote IGFBP3 synthesis, which inhibits tumor angiogenesis and hinders tumor progression. However, as hypoxia intensifies, increased HIF-2α induces methylation of the IGFBP3 gene promoter and adversely affects IGFBP3 function (68-72). From a genetic standpoint, mutations in genes across different tumor cells can alter the role of IGFBP3. For example, in liver cancer cells with wild-type p53, high WSB2 expression enhances the polyubiquitination and degradation of p53, which leads to the downregulation of IGFBP3 expression, and promotion of AKT and mTOR phosphorylation, and ultimately accelerates HCC progression. Conversely, in HCC with mutant p53, WSB2 expression does not promote the progression of HCC as it does in the case of wild-type p53 (126-128). The aforementioned differences underline the importance of developing personalized treatment plans to potentially improve therapeutic outcomes in the future.

In summary, a comprehensive exploration of the mechanisms underlying IGFBP3 expression in tumors, the clinical translation of the associated signaling pathways and the factors influencing the dual function of IGFBP3 is key to further the current understanding of tumorigenesis and progression, and provide theoretical bases for the development of more effective treatment strategies in the future. Future research on integrating research with clinical practice is warranted to potentially enhance the application of IGFBP3-related research in cancer therapy in the future.

5. Summary and outlook

IGFBP3, an important protein in the human body, has garnered notable attention in recent years due to its role in various diseases, particularly in tumorigenesis and tumor development. Numerous studies have demonstrated that alterations in IGFBP3 expression and its post-translational modifications are closely associated with the progression, treatment efficacy and prognosis of multiple tumors. For instance, in OSCC and TSCC, the upregulated expression of IGFBP3 promotes the proliferation, invasion and metastasis of tumor cells through signaling pathways such as the

MEK/ERK pathway. In colorectal cancer, the methylation of the IGFBP3 gene promoter leads to a decrease in its expression. Upregulating its expression can enhance the effect of TRAIL, inhibit the NF-κB signaling pathway, and suppress tumor development (43,46-48). The present review systematically summarizes the role of IGFBP3 in the occurrence and development of different tumors, as well as the cellular signaling pathways involving IGFBP3. Although the present review has reported changes in IGFBP3 expression in tumors such as clear cell renal cell carcinoma, ovarian cancer and colorectal cancer, and the impact on tumor cell metastasis, studies on the underlying molecular mechanisms and signaling pathways are considerably less comprehensive compared with studies on liver and breast cancer. The disparity in research depth primarily stems from the availability of existing data and the varying clinical significance of different tumors. To achieve a more comprehensive understanding of the role of IGFBP3 in tumorigenesis and development, and to establish a theoretical foundation for targeted therapies, future research is warranted to address the current gaps and investigate the mechanisms underlying the role of IGFBP3 in understudied cancer types.

In conclusion, conducting in-depth research on the expression level changes of IGFBP3 in tumors and other diseases, as well as IGFBP3 regulation via post-translational modifications, holds notable scientific and clinical value. From a scientific perspective, the present review provides further understanding of the specific mechanisms by which IGFBP3 contributes to the onset and progression of cancer. Clinically, the present review highlights the identification of novel diagnostic markers, the discovery of potential therapeutic targets and the development of innovative strategies for disease prevention. Therefore, the present review facilitates the establishment of a more comprehensive disease management system, which offers novel insights and methodologies to address related diseases.

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Competing interests

The authors declare that they have no competing interests.

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