IGFBP2 in cancer: Pathological role and clinical significance (Review)

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Abstract. The versatility of IGFBP2, as a secreted protein in cancer cells or a cytoplasmic signaling effector, has been extensively investigated in many malignant cancers. Over the last few decades, IGFBP2, a key member of the IGFBP family, has been identified as an important oncogene in multiple human cancers. In addition, a growing number of studies have shown that IGFBP2 is greatly elevated in serum or tissue in patients with malignant tumors and plays an essential role in several key oncogenic processes, such as tumor cellular proliferation, migration, invasion, angiogenesis, epithelial-to-mesenchymal transition, and immunoregulation, which are involved in a variety of signal pathways, usually via an IGF-independent means. Moreover, growing evidence indicates that aberrant overexpression of IGFBP2 may serve as a useful biomarker for the diagnosis and prognosis of patients, as well as act as a potential therapeutic target for the management of clinical treatment in patients with malignant disease. In the present review, we summarize the current points of view that IGFBP2 performs a role in the initiation and progression of various types of cancer by interacting with several key molecules involved in cancer signaling pathways. We also discuss its potential clinical application value as a diagnostic/prognostic biomarker for patients with malignant tumors.

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1. Introduction

IGFBP2 is one of six homologous proteins in the IGFBP family. Based on its ability to bind IGFs with high affinity, IGFBP2 can exert its functions by interacting with IGFs in the circulation to control the function and activity of IGFs, and prevent the interaction between IGFs and IGF receptors. Moreover, it can also bind to IGFs and confer an IGF-dependent growth inhibitory or stimulatory effect in many cell types (1,2). On the other hand, IGFBP2 has intrinsic bioactivities as a result of its protein structure, which includes an arginine-glycine-aspartic acid (RGD) motif, heparin-binding domain (HBD) and nuclear localization sequence (NLS) (1,3).

The role of IGFBP2 in the development of cancer is complicated. IGFBP2 performs IGF-independent roles in cancer development and progression through a variety of molecular networks. For example, IGFBP2 can bind to integrins through its C-terminal RGD motif, as well as bind to the extracellular matrix components, such as glycosaminoglycans, through its heparin-binding domain, and the cytoplasm-nuclear transporter importin-α through its nuclear localization signal (4-6). It also interacts with important cell signaling regulatory molecules, which are involved in phosphatase and tensin homolog (PTEN) regulation (7), EGFR/STAT3 modulation (8) and activation of NF-kB (9). Aberrant overexpression of IGFBP2 is associated with an aggressive phenotype of a broad range of human cancers, including glioma (10-15), ovarian (16-21), prostate (22-25), pancreatic (9,26,27), breast (28-31), lung (32,33), colorectal (34-36), melanoma (37), liver cancer (38-40), gastric (41,42), rhabdomyosarcoma (43) and leukemia (44,45). Moreover, high circulating IGFBP2 levels may serve as a usable diagnostic or prognostic tumor

biomarker in many types of cancer (20,26,35), and is closely associated with relapse and a poorer outlook for patients with cancer (20,33).

2. Oncogenic processes modulated by IGFBP2

As a multifunctional oncogenic protein, IGFBP2 participates in oncogenic processes involving various signaling pathways that are required for tumor initiation and progression (Fig. 1). It is known that IGFBP2 promotes cancer metastasis by regulating invasion-associated signaling networks (46); however, the role of IGFBP2 on other oncogenic processes remains to be elucidated. Therefore, we systematically examined the involvement of IGFBP2 in several key oncogenic processes in the present review, and summarized the potential regulatory network of IGFBP2 in different cancer types. (Table I).

Epithelial-to-mesenchymal transition. Epithelial-to-mesenchymal transition (EMT) plays a vital role in tumorigenesis (65). Aberrant reactivation of EMT can increase the plasticity of malignant cancer cells, and subsequently promote tumor initiation and metastasis (66). IGFBP2 is considered a key inducer of EMT in pancreatic ductal adenocarcinoma (PDAC), of which the reactivation contributes to promoting invasive characteristics and lymph node metastasis (9). NF-κB, a vital inflammation-related transcription factor, has also been identified as an important regulator of EMT (67). In addition, NF-κB may be a critical mediator for the stimulatory effect of IGFBP2 on EMT, because IGFBP2 induces EMT via activation of NF-κB-associated pathways in PDAC (9). Similar findings for hepatocellular carcinoma (HCC) have also been reported by Guo *et al*, who showed that IGFBP2 activates NF-κB signaling by promoting p65 nuclear translocation, which then triggers EMT (40). In addition, IGFBP2 also promotes EMT through enhancing the expression of ZEB1 in an NF-κB (p65)-dependent manner in salivary adenoid cystic carcinoma (SACC). Conversely, mutation in the nuclear localization signal of IGFBP2 may block nuclear translocation of p65 and attenuate ZEB1 expression, ultimately inhibiting EMT (64).

Angiogenesis. Aberrant angiogenesis provides abundant blood perfusion for the tumor, eventually promoting uncontrolled cell proliferation and malignant progression. A large number of studies demonstrated a crucial role for IGFBP2 in pathologic angiogenesis in many cancers (63,68,69). IGFBP2 is considered an inducer of angiogenesis in melanoma. IGFBP2 upregulates the expression of proangiogenic factor VEGF-A, and then triggers angiogenesis by interacting with αVβ3 integrin and activating the PI3K/AKT pathway (63). Similarly, IGFBP2 overexpression upregulates the expression of VEGF in human neuroblastoma (68), and coexpression of IGFBP2 and VEGF can be observed in the vicinity of tumor necrosis in glioblastoma (70), suggesting that IGFBP2 is involved in angiogenesis via the induction of VEGF expression. Interestingly, nuclear IGFBP2, mediated by the NLS sequence within the linker region, is responsible for the transcriptional activation of VEGF (71). It is known that endothelial cell (EC) mobility is crucial to angiogenesis. In a breast cancer metastasis model, IGFBP2 secreted by metastatic cells induces angiogenesis via recruiting endothelia and endothelial cells in an IGF-I-dependent manner (69).

Vasculogenic mimicry (VM) is a novel manner of tumor perfusion, and consists of vascular channel formation by aggressive tumor cells rather than endothelial cells. In the case of aggressive melanoma cells, a high expression of MMP-2, MT1-MMP and laminin 5 γ2 chain is required for vasculogenic mimicry to facilitate tumor perfusion independent of angiogenesis by endothelial cells (72,73). Previous findings have shown that IGFBP2 expression is positively associated with VM in patients with glioma, and a higher expression of IGFBP2 promotes VM *in vitro* and *in vivo* by enhancing CD144 and MMP2 expression in an integrin/FAK/ERK pathway-dependent manner (48). As noted above, IGFBP2 has a pivotal role in the pro-angiogenic process. Thus, further understanding of the proangiogenic mechanism of IGFBP2 may offer novel insight for vascular therapy.

Immune regulation. It is being increasingly recognized that IGFBP2 plays a vital role in immune modulation, and numerous findings indicate IGFBP2 induces antitumor immunity by not only serving as a human tumor antigen, but also inducing an IGFBP2-specific T-cell response in several cancers, including glioma, colorectal carcinoma, and breast cancer (74-76). Activated microglia/macrophages, which are important components of brain tumor immune cells, may contribute to glioma development (77). In addition, the accumulation of IGFBP2 can be found in activated microglia/macrophages (78). Similarly, IGFBP2 immunoreactivity is observed in both glioma cells and macrophages/microglia, with the IGFBP2-positive macrophages/microglia and glioma cells observed to frequently accumulate near the focal necrosis areas of glioma, suggesting an important immune action for IGFBP2 in glioma (79). Recently, gene expression profiles from 2447 glioma samples and bioinformatic analysis by Cai *et al* demonstrated that IGFBP2 has immunosuppressive activities in glioblastoma (GBM), and IGFBP2 is closely correlated with the expression of immunosuppressive molecules, including CHI3L1, TNFRSF1A, LGALS1, TIMP1, VEGFA, ANXA1 and LGALS3 (75). Furthermore, a recent study by Li and coworkers also revealed a novel immune-associated tumor function of IGFBP2 in malignant melanoma, where IGFBP2 upregulates the expression of PD-L1 and contributes to the immune evasion of cancer cells from host immunosurveillance (62). As mentioned above, there is evidence that IGFBP2 plays a crucial role in tumor immune modulation. Thus, it is important to thoroughly investigate immunoregulation by IGFBP2 in human cancers, and search for potent anti-IGFBP2 therapy.

3. Regulatory network of IGFBP2 in cancers

IGF-associated signaling pathways. As an IGF-binding protein, IGFBP2 has been reported as an inhibitory factor for IGF functions (80). In the human MCF-7β3 breast cancer cell line, IGFBP2 inhibits IGF-I- and IGF-II-mediated migration, but the mechanism underlying of this phenomenon is not clearly understood (81). It has been proposed that complex formation of IGFBP2 with αvβ3 integrin blocks the amplification of IGF-I signaling, because αvβ3 integrin can promote

Table I. Molecular network of IGFBP2 in multiple cancers.

Tumor type	Authors	Regulatory network	Description
Glioma	Holmes *et al* (47)	Integrin/ILK/NF-κB	Interacts with integrin α5β1 and activates downstream ILK/NF-κB pathways
	Liu *et al* (48)	FAK/ERK/SP1/CD144	Increases CD144 expression via FAK/ERK/SP1 signaling
	Chua *et al* (8)	EGFR/STAT3	Stimulates nuclear accumulation of EGFR and increases STAT3 transactivation activity
	Lin *et al* (49)	HIF1α	Promotes glioblastoma cell growth via IGFBP2-HIF1α feedback
	Mehrian-Shai *et al* (50)	PTEN/Akt/PI3K	Shows a negative correlation with PTEN level and promotes the activation of PI3K/Akt
	Patil *et al* (51)	β-catenin/FAK/GSK3β	Regulates the β-catenin pathway in activation of FAK, and inactivation of GSK3β
	Han *et al* (52)	Integrin β1/ERK	Induces cell proliferation, invasion and chemoresistance via the integrin β1/ERK signaling pathway
Prostate cancer	Mehrian-Shai *et al* (50)	PTEN/Akt/PI3K	Associates with PTEN loss and activation of the PI3K/Akt pathway
	Moore *et al* (53)	hTERT, telomerase	Upregulates expression of hTERT and potentiates activation of telomerase
	Moore *et al* (53)	MAPK/PI3K	Stimulates cell growth through the MAPK and PI3K pathways
	Uzoh *et al* (54)	Integrin β1/PTEN	Interacts with integrin β1 and consequently increases PTEN phosphorylation
Breast cancer	Sehgal *et al* (55)	β-catenin/Wnt	Promotes tumor progression via activating the β-catenin/Wnt pathway
	Perks *et al* (56)	Integrin/PTEN/p21/	Blocks the feedback loop of PTEN and then increases p21, which contributes to tumor progression
Ovarian cancer	Chakrabarty *et al* (57)	MAPK	Promotes cell proliferation via activating the MAPK pathway
Lung cancer	Lu *et al* (58)	FAK	Induces dasatinib resistance through activating the FAK pathway in NSCLC
Colorectal cancer	Ben-Shmuel *et al* (59)	L1/ezrin/NF-κB	Promotes CRC progression mediated by the L1/ezrin/NF-κB pathway
Pancreatic cancer	Gao *et al* (9)	NF-κB/PI3K/Akt/IKKβ/PTEN	Activates NF-κB through the PI3K/Akt/IKKβ pathway, and inhibits PTEN expression, which contributes to EMT
Esophageal cancer	Zhou *et al* (60)	EGFR-DNA-PKcs	Promotes cell survival via activating the EGFR-DNA-PKcs signaling axis
Hepatocellular carcinoma	Guo *et al* (40)	NF-κB/ZEB1	Promotes HCC tumorigenesis via activating the NF-κB/ZEB1 signaling pathway
Leukemia	Chen *et al* (61)	PTEN/Akt	Promotes survival and migration of acute leukemia cells through regulating the PTEN/Akt pathway
Melanoma	Li *et al* (62)	EGFR/STAT3	Upregulates PD-L1 expression by activating the EGFR-STAT3 signaling pathway
	Das *et al* (63)	Integrin αVβ3, PI3K/AKT	Promotes angiogenesis through interacting with integrin αVβ3 and activating the PI3K/AKT pathway
Salivary adenoid cystic carcinoma	Yao *et al* (64)	NF-κB/ZEB1	Promotes metastasis of SACC through the NF-κB/ZEB1 signaling pathway

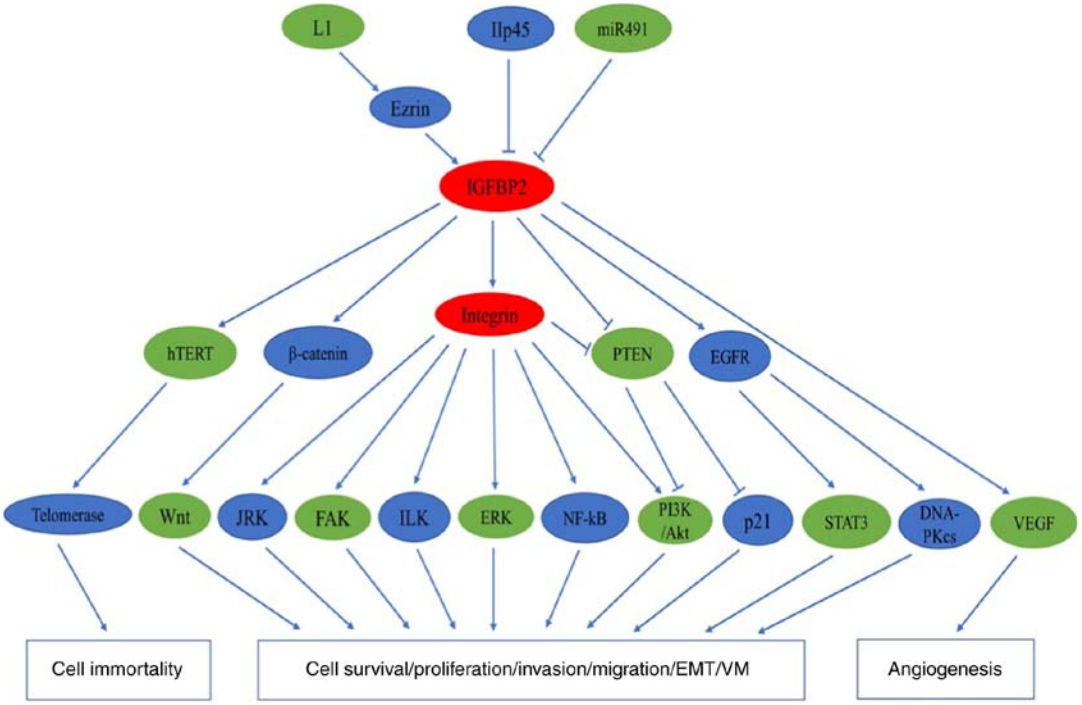

Figure 1. Schematic representation of the oncogenic pathways mediated by IGFBP2. IGFBP2 regulates cancer cell immortality, survival, proliferation, invasion, migration, and angiogenesis, as well as endothelial-mesenchymal transition (EMT), which involve various signaling pathways.

IGF-I-mediated proliferation and migration when binding to vitronectin. IGFBP2 shows an inhibitory action for normal somatic growth *in vivo* by directly interfering with the growth-promoting effects of the GH/IGF-I axis (82). However, a paradoxical stimulatory role of IGFBP2 in modulating IGF signaling has also been reported in the majority of the literature. For example, IGFBP2 can bind to IGF to form a binary complex in circulation, and this IGFBP2/IGF2 complex can stimulate osteoblast proliferation, although the detailed mechanism is unclear (83). In addition, the IGFBP2/IGF2 complex binds with increased affinity to 2- or 3-carbon O-sulfated glycosaminoglycans (GAGs) via the IGFBP2 HBD, compared with free intact IGFBP2, and could prevent IGF2 clearance by interfering with IGF2R-mediated endocytosis (84). It is known that the release of IGF-II from the IGF-II/IGFBP2 complex can occur by proteolysis by matrix metalloprotease-7 (MMP-7) and has a stimulatory effect on neoplastic transformation of cells in colorectal cancer (85,86), and contributes to the motility and growth in the case of LN229 astrocytoma cells (87). In this context, IGFBP2 serves as a reservoir of IGFs in the pericellular microenvironment. IGFBP2 binds to receptor protein tyrosine phosphatase β (RPTPβ) via its HBD, leading to RPTPβ dimerization and inactivation and then regulation of IGF-I signaling functions. RPTPβ inhibits IGF-I-stimulated AKT activation via PTEN dephosphorylation, whereas IGFBP2 functions via inhibition of this signaling pathway, which consequently leads to the acceleration of vascular smooth muscle cell (VSMC) proliferation (88). Similarly, IGFBP2 enhances IGF-induced proliferation, migration and invasion of neuroblastoma cells in a manner that requires an intact HBD domain, suggesting that the growth-promoting effects of IGF are associated with pericellular matrix proteins and/or proteoglycans or glycosaminoglycans on the cell surface (89). Moreover, IGFBP2 can activate IGFRs by increasing local IGF accumulation in the circulation or directly interact with IGFs via its IGF-binding site. The secretion of IGFBP2 from metastatic breast cancer cells can recruit endothelial cells to the cancer site by regulating IGF1-mediated activation of the IGFIR, which is a typical feature of metastatic breast cancer (69).

Integrin-mediated signaling pathways. The interaction between IGFBP2 and integrins is mediated by the C-terminal RGD domain, which is a known integrin-binding domain. The expression of integrin β and α can be seen in various tumor cell types, and the crosstalk between IGFBP2 with integrin α5 and β1 has been significantly implicated in tumorigenesis (47,48,52,54,90,91).

IGFBP2 enhances tumor cell proliferation and mobility by directly binding with integrin and/or via integrin-associated downstream signaling, which contributes to tumor cell dissemination and tumor progression (91). For example, IGFBP2 enhances DU145 prostate cancer cell proliferation by binding to integrin β1 receptors, and the action may be blocked by a short RGD-containing disintegrin peptide or by an integrin β1 receptor-blocking antibody (54). Microarray studies indicate that IGFBP2 activates the expression of integrin α5, but the underlying regulatory mechanism is unclear. Furthermore, IGFBP2 promotes glioblastoma cell mobility *in vitro* via direct binding to integrin α5, whereas decreasing expression of integrin α5 by siRNA or RGD mutation may attenuate cell mobility (90). Moreover, exogenous IGFBP2 induces glioma cell proliferation and invasion via integrin β1/ERK signaling. However, blocking integrin β1 function by anti-integrin β1-neutralizing antibody or integrin β1 knockdown inhibits IGFBP2-induced ERK activation, and subsequent cell proliferation and invasion (52). A recent study

in vitro also found that IGFBP2 promotes VM formation by glioma cells via the binding to integrin α5 and β1 subunits through its RGD domain (48). These findings indicate that the IGFBP2/integrin pathway may provide a strong driving force for tumor progression. Of note, the interaction between IGFBP2 and integrins can regulate an array of signaling pathways. An *in vivo* model of glioma progression demonstrated that high IGFBP2 expression regulates downstream invasion pathways, such as the NF-κB and integrin-linked kinase (ILK) pathways, via activation of integrin β1. Most significantly, the IGFBP2/integrin/ILK/NF-κB network is essential to glioma progression and can be prevented by interfering at any point in the pathway (47). A study by Mendes *et al* showed that the activation of the JNK pathway is closely related to the IGFBP2-integrin α5 signaling cascade, which accelerates glioma cell migration (92).

PTEN-associated signaling pathways. PTEN is a tumor suppressor gene, and the loss of PTEN function is often observed in many human cancers (50). The loss of PTEN function contributes to the accumulation of the lipid phosphatidylinositol-3,4,5-triphosphate (PIP3), which is the product of PI3K, and then activates the Akt pathway to promote cell survival and proliferation (93). The interaction between IGFBP2 and PTEN has been linked to multiple tumorigenic processes in breast, glioma, and prostate cancer (29,50,54). A study by Dean *et al*, using immunohistochemistry, revealed that the loss of PTEN is tightly associated with IGFBP2 overexpression in triple-negative breast cancer, indicating that IGFBP2 expression may be inversely associated with PTEN in breast cancer (29). The evidence from *in vitro* studies using glioma U251 cell lines also shows that overexpression of PTEN can reduce IGFBP2 expression and inhibit cell proliferation. Mechanically, it is proposed that the lipid phosphatase activity of PTEN is responsible for restraining IGFBP2 expression (94). Similarly, in prostate cancer and GBM, the expression of serum IGFBP2 increases in PTEN-null tumors, but not PTEN-expressing tumors (50). In addition, microarray-based expression profiling identified IGFBP2 to be an important marker for PTEN loss and activation of the PI3K/Akt pathway in prostate cancer and GBM (50). In an acute myelocytic leukemia (AML) transplantation mouse model, inhibition of IGFBP2 expression impeded leukemia development and led to the upregulation of PTEN expression and downregulation of AKT activation. However, this condition was reversed by treatment with a PTEN inhibitor, suggesting that the PTEN/Akt pathway is essential to IGFBP2-induced leukemia development (61). Notably, IGFBP2 has also been shown to suppress the activity of PTEN. PTEN reduces tumor cell proliferation and increases apoptosis, and these actions may be substantially attenuated in the context of high IGFBP2 expression (94). In human breast cancer cells, PTEN expression is stimulated by IGF-II forming a feedback loop where IGFBP2 can block the feedback response for PTEN, which then leads to an increase in p21-mediated pro-tumorigenic activity (56). In DU145 prostate cancer cells, IGFBP2 increases PTEN phosphorylation in an integrin β1-dependent manner, leading to the inactivation of PTEN, which eventually potentiates cell proliferation (54). The same result is also observed in MCF-7 breast cancer cells (56). Therefore, PTEN may be a downstream mediator of IGFBP2/integrin-mediated signaling. Moreover, IGFBP2 has been shown to reduce the expression of PTEN protein levels, but not transcript levels, suggesting that the mechanism by which IGFBP2 modulates PTEN may be post-transcriptional (9).

Nuclear EGFR-STAT3 signaling pathways. Increasing evidence has shown that IGFBP2 possesses a nuclear regulatory effect that is closely associated with EGFR and STAT3. For example, co-overexpression of the EGFR and IGFBP2 genes has been reported to be strongly associated with poor prognosis in astrocytoma (95). A study by Chua *et al* also found a close relationship between IGFBP2, STAT3 phosphorylation and nuclear co-localization of IGFBP2 and EGFR in glioma (8). Moreover, IGFBP2 is considered to be involved in the regulation of an EGFR-STAT3 pathway in glioma progression, since treatment with IGFBP2-neutralizing antibody decreases the activation of EGFR and STAT3, and reduces the expression of STAT3 downstream genes, such as Bcl-xL and LSD1; however, the underlying mechanism by which expression is regulated has not been well characterized (15). Moreover, high IGFBP2 expression has been reported to increase the nuclear accumulation of EGFR and eventually activate the nuclear EGFR signaling pathway, which contributes to potentiating STAT3 transactivation (8). These findings provide a novel oncogenic effect of IGFBP2 in glioma through activation of EGFR/STAT3 signaling (8,15). Similarly, IGFBP2 upregulates PD-L1 expression by activating the nuclear EGFR-STAT3 signaling pathway in malignant melanoma, which may contribute to tumor progression (62).

Other regulatory networks. Highly expressed in basal cell carcinoma (BCC), IGFBP2 is considered as a mediator of the effects of Hedgehog (Hh) signaling on epidermal progenitors, and is essential for promoting BCC development (96). IGFBP2 induces colorectal cancer (CRC) cell motility and metastasis mediated by an L1-ezrin-NF-κB pathway. It can be found that L1 induces IGFBP2 expression through activating ezrin phosphorylation and NF-κB-mediated transactivation of the IGFBP2 promoter, which is essential for increasing tumorigenesis and inducing liver metastasis (59). Moreover, IGFBP2 promotes esophageal adenocarcinoma (EAC) cell survival via stabilization and activation of an EGFR-DNA-PKcs signaling axis (60). IGFBP2 promotion of tumor development may also be linked to the β-catenin/Wnt signaling pathway. In breast cancer cells, IGFBP2 regulates the expression of β-catenin, an effector of the Wnt pathway, in an IGF1R- and FAK-dependent manner, and combined overexpression of IGFBP2 and β-catenin is associated with lymph node metastasis in breast tumors (55). Similarly, IGFBP2 regulates the β-catenin pathway involving the activation of Akt and inactivation of GSK3b in glioma cells, and co-expression of high levels of IGFBP-2 and β-catenin is correlated to worse prognosis (51). In addition, IGFBP2 seems to directly stimulate hypoxia-inducible factor 1α (HIF1α) expression. HIF1α also promotes the expression of IGFBP2 in the absence of oxygen, and the feedback between IGFBP2 and HIF1α may play an important role in glioblastoma growth. Removing the feedback from IGFBP2 to HIF1α results in the inhibition of cell growth (49). Foulstone *et al* found a positive feedback

loop between IGFBP2 and ER-α, which could stimulate IGFBP2 expression. IGFBP2 also could increase the expression of ER-α in breast cancer cells, and the crosstalk between IGFBP2/ER-α may contribute to the growth and survival of breast cancer cells (97). IGFBP2 significantly upregulates the expression of hTERT and stimulates activity of telomerase in the absence of androgens, which plays a role in prostate cancer cell immortality (53). Furthermore, the IGFBP2 function that triggers pro-carcinogenic effects in prostate cancer appears to be in part mediated by the MAP-kinase and PI3-kinase pathways (53).

4. Expression of IGFBP2 as a diagnostic/prognostic biomarker for multiple cancers

IGFBP2 is one of the most common and abundant members of the IGFBP family in numerous human cancers. It became evident that IGFBP2 exerts important roles in growth, metabolism and cancer development (6). Additionally, aberrant overexpression of IGFBP2 is intimately associated with adverse cancer-associated clinical parameters (6). Centered on several malignancies, the expression of IGFBP2 in cancer is elaborated in Table II, as is IGFBP2 expression as a diagnostic/prognostic biomarker in different tumor types.

Glioma. Previous studies based on gene expression profiling showed that the *IGFBP2* gene was significantly and differentially overexpressed in human glioma (10,113). High expression of the *IGFBP2* gene may possess potential prognostic value in glioma, and co-overexpression of the *IGFBP2*, *EGFR* and *HIF-2A* genes is remarkably correlated with a less than 2-year survival compared with the expression of each individual gene alone (95). Yuan *et al* (98) investigated the relationship between expression of IGFBP2 mRNA and clinical characteristics in glioblastoma. They found that IGFBP2 mRNA is highly overexpressed in glioblastoma tissues compared to normal tissues, and is associated with shorter survival of patients. Moreover, the combination of IGFBP2 mRNA expression and TERT promoter status could better predict the prognosis of patients.

As a malignancy-associated secreted protein, high IGFBP2 protein expression is detected both in tissues and blood of glioma patients, and is positively correlated with tumor grade (12,79). Moreover, higher plasma IGFBP2 protein expression is significantly associated with poorer disease-free survival and recurrence after surgery in patients with GBM (12). In addition, high expression of tissue IGFBP2 protein may serve as an independent poor prognosis biomarker in patients with GBM (11). In fact, except for the two above-mentioned studies, the prognostic value of IGFBP2 protein has also been assessed in other several studies, as shown in Table II. From these studies, it can be gleaned that a high expression of IGFBP2 protein is a usable predictor for the progression and unfavorable outcome in patients with glioma. In addition, tumor-specific immunity against IGFBP2 has been reported in glioma. Li *et al* (76) were, to the best of our knowledge, the first to evaluate the diagnostic value of serum IGFBP2 antibodies in early detection of glioma. They ultimately found that high IGFBP2 antibody expression distinguished patients with grade II and III gliomas from normal controls, and the combination of serum IGFBP2 and IGFBP2 antibodies improved the diagnostic power for glioma.

Breast cancer. IGFBP2 is consistently highly expressed in breast cancer tissue compared with benign lesions in tissue microarray analysis. In addition, increased IGFBP2 expression may be a useful marker to predict lymph node metastasis in patients with T1 invasive breast carcinoma (31). The expression of IGFBP2 is strongly correlated with the grade of mammary neoplasms, as shown in a study by Busund *et al*, where the expression of IGFBP2 increases in a step-wise manner from hyperplasia, atypical hyperplasia, and carcinoma *in situ* to invasive breast carcinoma (28). Additionally, the prognostic value of IGFBP2 for breast cancer patients has been shown in numerous reports (Table II). A prospective cohort study showed that patients with higher pre-diagnostic serum levels of IGFBP2 are more likely to have higher breast cancer-specific mortality within 5 years of follow up (102). Moreover, IGFBP2 serves as a predictive factor for recurrence-free survival (RFS) risk in patients with residual triple receptor-negative breast cancer (TNBC) after neoadjuvant chemotherapy (NCT) (103). Notably, IGFBP2 expression is an independent predictor of shorter overall survival, and the prognostic relevance of IGFBP2 partly is associated with hormonal status and body weight in breast cancer (104). Similarly, a similar finding from So *et al* showed that high IGFBP2 expression is related to poorer disease-specific survival in patients with hormone receptor-negative invasive breast cancer, but not in patients with hormone receptor-positive tumors (101). Since breast cancer patients easily become resistant to antiestrogen treatment, it may be a strong clinical challenge to cure these hormone-resistant tumors. IGFBP2 is a potential marker for antiestrogen treatment response in breast cancer, as both high IGFBP2 protein and mRNA levels can be examined for resistance to antiestrogens such as tamoxifen, ICI 182,780 and RU 58668 (114).

Prostate cancer. Increasing studies over the past decades has investigated the expression of IGFBP2 with malignant prostate disease. Elevated levels of serum IGFBP2 are detected in patients with prostate cancer (24), and are positively associated with high serum levels of prostate-specific antigen (PSA) (23). In addition, high serum IGFBP2 is an important risk factor for low-grade prostate cancer (115). Both IGFBP2 protein and mRNA expression are increased in high-grade prostate intraepithelial neoplasia (PIN) tissues, and even further elevated in malignant adenocarcinoma tissues, when compared to normal epithelium (116). Subsequently, Richardsen *et al* reported that overexpression of IGFBP2 in prostate tissue is a useful marker for malignant transformation of prostate epithelium, and may be a potential auxiliary tool in the diagnosis of prostate cancer. Immunohistochemical detection of IGFBP2 expression is negative or very weakly positive in normal prostate epithelium or benign prostatic hyperplasia (BPH) tissue, but increased extent and intensity of IGFBP2 staining can be observed in prostatic intraepithelial neoplasia (PIN) and carcinoma (105). IGFBP2 expression also appears to be involved in the development of hormone-refractory prostate cancer. Immunohistochemical analysis revealed that IGFBP2 protein is significantly overexpressed in 100% of hormone-refractory

Table II. IGFBP2 as a diagnostic and prognostic biomarker in different cancers.

Tumor type	Authors	Sample type	Patient number	Methods	Diagnosis/prognosis
Glioma	Scrideli *et al* (95)	Tissues	84	RT-qPCR	Decreased survival
	Yuan *et al* (98)	Tissues	180	TMA, RNA-scope	Decreased survival
	Han *et al* (99)	Plasma	83	ELISA	Decreased survival
	Gállego Pérez-Larraya *et al* (100)	Plasma	111	ELISA	Decreased survival
	Lin *et al* (12)	Plasma	196	ELISA	Decreased survival and increased recurrence
	Mcdonald *et al* (11)	Tissues	143	TMA, IHC	Decreased survival
	Patil *et al* (51)	Tissues	112	TMA, IHC	Decreased survival
	Li *et al* (76)	Serum	145	ELISA	Diagnostic biomarker
Breast cancer	So *et al* (101)	Tissues	4186	TMA, IHC	Decreased survival
	Wang *et al* (31)	Tissues	164	TMA, IHC	Decreased survival
	Kalledsøe *et al* (102)	Serum	412	RIA	Decreased survival
	Sohn *et al* (103)	Tissues	54	RPPAs	Decreased survival
	Probst-Hensch *et al* (104)	Tissues	885	TMA, IHC	Decreased survival
Prostate cancer	Richardsen *et al* (105)	Tissues	193	IHC	Auxiliary diagnosis
	Mita *et al* (106)	Tissues	24	RT-qPCR	Decreased survival
Ovarian cancer	Baron-Hay *et al* (20)	Serum	99	RIA	Decreased survival and increased recurrence
	Russell *et al* (21)	Serum	482	ELISA	Diagnostic biomarker
	Lancaster *et al* (107)	Serum	110	RIA	Diagnostic biomarker
	Huang *et al* (108)	Serum	128	ELISA	Decreased survival
Lung cancer	Zhang *et al* (109)	Serum	294	ELISA	Diagnostic biomarker
	Guo *et al* (33)	Plasma	80	ELISA	Decreased survival
Colorectal cancer	Liou *et al* (35)	Plasma	162	ELISA	Diagnostic biomarker and Decreased survival
	Li *et al* (76)	Serum	70	ELISA	Diagnostic biomarker
Pancreatic cancer	Kendrick *et al* (26)	Serum	84	ELISA	Diagnostic biomarker
	Yoneyama *et al* (27)	Plasma	164	RPPAs	Diagnostic biomarker
	Gao *et al* (9)	Tissues	80	IHC	Decreased survival
Gastric cancer	Hur *et al* (110)	Serum	118	ELISA	Decreased survival
Esophageal cancer	Warnecke-Eberz *et al* (111)	Tissues	40	Whole genome profiling, RT-qPCR	Diagnostic candidate marker
	Myers *et al* (112)	Tissues	30	RT-qPCR, IHC	Decreased survival

TMA, tissue microarray; IHC, immunohistochemistry; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay; RIA, radio immunoassay; RPPAs, reverse phase protein arrays.

prostate cancers, and in 36% of primary tumors, but not in normal specimens (117). Similarly, increased expression of IGFBP2 plays a role in lymph node metastasis of prostate cancer after hormone therapy, and is a potential prognostic indicator in hormone-treated prostate cancer patients (106).

Ovarian cancer. IGFBP2 is overexpressed in ovarian cancer tissues, serum and cyst fluids, and has a key role in the regulation of human ovarian cancer progression (19,118,119). There are histological differences of IGFBP2 expression in ovarian cancer. This was further substantiated by Wang *et al*, using tissue microarray analysis, who revealed that the expression of IGFBP2 was more often higher in high-grade serous carcinoma, malignant-mixed Mullerian tumors (MMMT), and undifferentiated carcinoma, but frequently expressed at low levels or not at all in clear cell and mucinous carcinoma (18). Moreover, IGFBP2 expression is closely correlated with tumor grade and aggressiveness of ovarian carcinoma. IGFBP2 is

also highly expressed in invasive carcinomas compared to borderline tumors (17,18).

Most importantly, IGFBP2 is a potential serum biomarker in the detection and monitoring of epithelial ovarian cancer (EOC) (107). Increased levels of serum IGFBP2 are positively correlated with expression of the ovarian tumor marker CA125 in patients with EOC (16), and the combination of IGFBP2 and CA125 may improve the sensitivity of CA125 alone for the early detection of ovarian cancer (21). High serum IGFBP2 levels are closely correlated with increased risk of mortality and poorer responses to chemotherapy, indicating that IGFBP2 is an early predictor of EOC-related mortality and chemotherapeutic response in EOC (108). Moreover, patients with higher preoperative serum levels of IGFBP2 have a significantly higher risk of relapse and worse overall survival (20).

Lung cancer. High blood and tissue levels of IGFBP2 can be found in patients with lung cancer (33,120). Increased plasma IGFBP2 expression is positively associated with tumor size and tumor stage, and patients with higher IGFBP2 levels have shorter overall survival, suggesting that IGFBP2 may be a useful prognostic biomarker in lung cancer (33). In addition, tissue IGFBP2 overexpression is correlated with lymph node metastasis and dasatinib resistance in non-small cell lung cancer (NSCLC) (58,120). A study by Migita *et al*, using immunohistochemical analysis, found that high IGFBP2 expression is inversely correlated with procaspase-3 expression, and may be an anti-apoptotic biomarker for lung adenocarcinoma (LUAD) (32). Interestingly, it can be found that high serum anti-IGFBP2 antibodies show diagnostic relevance for early-stage lung cancer, and the combination of serum IGFBP2 and anti-IGFBP2 antibodies can be more effective for lung cancer diagnosis (109).

Although these findings show that a high IGFBP2 expression is associated with poor prognosis in lung cancer, conflicting results have also been reported. Bioinformatics analysis by Wang *et al* showed that increased IGFBP2 mRNA levels are correlated with unfavorable OS in patients with NSCLC, but with favorable OS in patients with lung squamous cell carcinoma (LUSC) (121). Similarly, an investigation *in vitro* revealed that the overexpression of IGFBP2 may contribute to inhibitory effects on cell growth in small cell lung cancer (SCLC) (122). As mentioned above, these findings highlight the paradoxical role of IGFBP2 in different subtypes of lung cancer. Therefore, further research is required to explore the role of IGFBP2 and its exact regulatory mechanism in different subtypes of lung cancer. As a matter of fact, it has been reported that IGFBP2 functions as a tumor suppressor in some tumors. Mechanistically, it has been proposed that the suppressive/oncogenic role of IGFBP2 in carcinogenesis may be associated with the cleaved status of IGFBP2. Protease-resistant IGFBP2 is both able to suppress tumor growth *in vitro* and *in vivo* when compared with wild-type IGFBP2 (123).

Gastrointestinal cancer. Circulating IGFBP2 expression shows a close relationship with the malignant development of patients with CRC. For instance, serum IGFBP2 expression increases from Dukes B and C to advanced cancer, and is highly associated with tumor load (35,36). Plasma IGFBP2 levels can discriminate between advanced colon polyps and CRC, and higher plasma IGFBP2 expression at diagnosis correlates with worse overall survival in patients with CRC, suggesting that high plasma IGFBP2 expression may serve as a valuable diagnostic and prognostic biomarker in CRC (35). Also, Li *et al* (76) reported that serum IGFBP2 antibody levels can discriminate patients with CRC I-II from normal controls, and the combination of serum IGFBP2 and IGFBP2 antibodies are more effective for early cancer detection of CRC.

The diagnosis and management of pancreatic cancer remains a great challenge due to the lack of effective biomarkers. Quantitative proteomics analysis by Chen *et al* identified that IGFBP2 is aberrantly highly expressed in the pancreatic juice and tumor tissue of pancreatic cancer patients compared to patients with chronic pancreatitis (124). Furthermore, IGFBP2 also appears to be elevated in riskier diseases of pancreatic malignancy, such as intraductal papillary mucinous neoplasms (IPMNs). Kendrick *et al* (26) reported that a high serum IGFBP2 expression is directly correlated with tumor burden, and may serve as a potential diagnostic biomarker for PDAC. The expression of IGFBP2 can distinguish early stage invasive ductal adenocarcinoma of the pancreas (IDACP) patients from normal controls, and the use of IGFBP2 with the CA19-9 biomarker may be more effective for the diagnosis of IDACP (27). Additionally, an *in vivo* model and clinical findings also showed that IGFBP2 overexpression in primary tumors is more likely to increase the risk of lymph node metastasis and is correlated with shorter survival in patients with PDAC, suggesting that IGFBP2 may be a valuable biomarker for evaluating prognosis in PDAC (9).

Previous findings have shown that the IGF-IGFBP system may play an important role in gastric cancer development. For example, IGFBP2 can be detected in all gastric cancer cell lines, and the ubiquitous expression pattern of IGFBP2 suggests that IGFBP2 may confer some growth advantage to the tumor cells (125). High IGFBP2 expression can be found in gastric carcinoma tissues, compared with normal gastric mucosa, and participates in the malignant progression of gastric carcinoma (42). Immunohistochemical staining demonstrated that the expression of IGFBP2 shows a positive correlation with Ki-67 expression, suggesting that IGFBP2 may participate in carcinogenesis and progression of gastric carcinoma by promoting cell proliferation. Additionally, IGFBP2 expression is greatly elevated from early gastric carcinoma to advanced gastric carcinoma, and is positively correlated with lymph node metastasis and clinical stage of the tumor (41,42). Patients with higher serum IGFBP2 levels are more likely to have a lower 5-year overall survival rate, indicating that serum IGFBP2 may be a potential biomarker predicting prognosis for patients with gastric cancer (110).

Recently, researchers have shown an increasing interest in the role of IGFBP2 for esophageal cancer development. Gene expression profiling has shown that the IGFBP2 gene is highly expressed in early tumor stages (pT1-2) of esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma compared to normal tissues, and is a potential diagnostic candidate marker for esophageal cancer (111), but more clinical studies are needed to determine its diagnostic impact. Interestingly, a high expression of IGFBP2 may be an important predictive factor for recurrence and chemoresistance

in patients with EAC after chemotherapy following esophagectomy (112). In fact, few studies have investigated the relationship between IGFBP2 with esophageal cancer development. Therefore, more studies are needed to elaborate the role of IGFBP2 in esophageal cancer.

5. Conclusion and perspectives

The purpose of this review was to summarize recent insights on the role of IGFBP2 and its underlying regulatory mechanisms in the development and progression of different tumors. To the best of our knowledge, there is compelling evidence suggesting that IGFBP2 has pivotal tumorigenic functions in a great majority of human cancers, but these findings are contradictory in a few tumors, including LUSC and SCLC. According to these reports, IGFBP2 can have both stimulatory and inhibitory effects on tumor cell growth and survival, and these discrepancies may be ascribed to the diversity of IGFBP2 functions in different cancers. A large number of reports support the viewpoint that the oncogenic properties of IGFBP2 are more likely to be IGF-independent, but the exact mechanisms of how the IGFBP2 plays a role in different tumors remains not fully elucidated. At present, IGFBP2 has received more interest as a potential therapeutic target in multiple cancers. However, there is no IGFBP2 inhibitor for clinical application. In addition, the diagnostic or prognostic relevance of IGFBP2 has been evaluated in a wide variety of human cancers. Nevertheless, it has yet to provide diagnostic value for clinical use. Undoubtedly, more studies are in great need to expound the underlying mechanisms of IGFBP2 in detail, and improve the understanding of IGFBP2 as a tumor biomarker and as a potent therapeutic target for better clinical management of patients with malignant tumors.

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Authors' contributions

Draft preparation, writing, and editing of the review was carried out by LFW, XFW, XCH, HPG, YHP and YWX. HPG, YHP and YWX drafted the review or revised it critically for important intellectual content. All authors have read and agreed to the published version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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