

Insulin-Like Growth Factor Binding Protein-2: A Possible Regulator of Invasive Growth in Glioblastoma

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1. Introduction

Glioblastoma is the most common malignant brain tumor and has an extremely lethal course (Clark *et al.*, 2010). Although genetic abnormalities in p53, Akt, phosphatase and tensin homolog deleted from chromosome 10 (PTEN), and epidermal growth factor receptor that are common to various cancers are also found in glioblastoma, the prime cause of glioblastoma's malignant features and conclusive treatment targets have yet to be determined. Better understanding of non-major signal pathways involved in glioblastoma could thus provide breakthroughs in treatment strategies. Insulin-like growth factor binding protein-2 (IGFBP2) was originally reported to be a modulator of the action of insulin-like growth factors (IGFs), but IGF-independent effects of IGFBP2 on cellular proliferation, apoptosis, metabolism, and mobility have since been reported in pathological conditions, including cancers. Recent studies of gene expression microarray revealed that elevated expression of IGFBP2 occurs in gliomas, and is associated with increasing grades of malignancy with significant overexpression in glioblastomas (Fuller *et al.*, 1999; Sallinen *et al.*, 2000). Subsequent studies have suggested that IGFBP2 may be one of the proteins that play an important role in malignant phenotypes of glioblastoma cells (Fukushima & Kataoka, 2007).

This chapter highlights key examples of recent biological and epidemiological research focusing on IGFBP2 in brain tumors and reviews more specialized studies on the fundamental role of IGFBP2 in glioma progression.

2. Structure and physiological functions of IGFBP2

2.1 Human insulin-like growth factor binding proteins (IGFBPs)

IGFBPs are a family of six proteins present in plasma and bodily fluids that bind insulin-like growth factor-I (IGF-I) and IGF-II with high affinity (Table 1) (Hwa *et al.*, 1999; Firth & Baxter, 2002; Fukushima & Kataoka, 2007). By interacting with IGFs, the IGFBPs modulate distribution and activity of IGFs in various tissues and bodily fluids, thereby controlling their biological function *in vivo* (Clemmons 1998; Kelley *et al.*, 2002). IGFBPs in IGFBP/IGF complexes can be cleaved at specific sites by various proteinases (Bunn *et al.*, 2003). This

IGFBP cleavage might be an important regulatory mechanism of pericellular IGF function, as IGFBP proteolysis releases IGF from the IGFBP/IGF complexes (Lee *et al.*, 1996; Bunn *et al.*, 2003; Fowlkes *et al.*, 2004; Mark *et al.*, 2005; Nakamura *et al.*, 2005). Therefore, IGFBPs both positively and negatively regulate IGF function.

	IGFBP1	IGFBP2	IGFBP3	IGFBP4	IGFBP5	IGFBP6
Gene location	7p13-p12	2q33-q34	7p13-p12	17q12-q21.1	2q33-q36	12q13
mRNA (kbp)	1.6	1.4	2.6	2.2	6.3	1
MW (kDa)	25	31	43-45	24	29	28-30
RGD motif	(+)	(+)				
Heparin binding	(+)	(+)	(+)	(+)	(+)	(+)
Phospho. site	(+)		(+)		(+)	
NLS			(+)		(+)	
N-Glycosylation			(+)	(+)		
O-Glycosylation					(+)	(+)

Table 1. Summary of IGFBP family. MW, molecular weight of mature protein. Phospho. site, presumed phosphorylation site. NLS, nuclear localization signal.

2.2 Molecular properties and physiological functions of IGFBP2

2.2.1 Synthesis, structure and distribution of IGFBP2

The IGFBP2 precursor is 36-kDa (328 amino acid residues) in size and consists of a signal peptide and three distinct regions: the highly conserved N-terminal region (IGFBP homolog domain, amino acid residues 43-136); the highly conserved C-terminal region with a thyroglobulin type 1 repeat (amino acid residues 229-309); and an intervening region with four major cleavage sites (Bunn *et al.*, 2003; Mark *et al.*, 2005) (Figure 1). The N-terminal and C-terminal domains are cysteine-rich and globular, both of which have IGF-binding property. Mature IGFBP2 is a 31.4-kDa protein and is the second most abundant IGFBP found in serum.

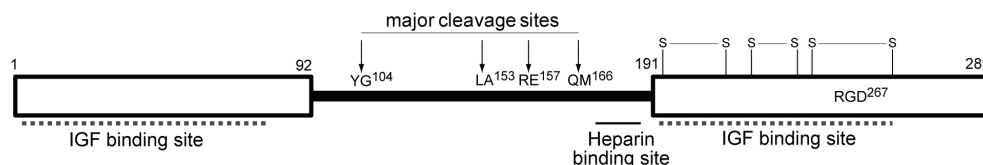


Fig. 1. Molecular structure of human IGFBP2. Amino acid positions of mature IGFBP2 protein are indicated. Integrin binding RGD motif is also shown.

Although IGFBP1, IGFBP3, and IGFBP5 each have phosphorylation sites, IGFBP2 does not. IGFBP2 does, however, have an arginine-glycine-aspartic acid (RGD) motif, which binds to cell surface integrins, and a heparin-binding domain, which facilitates association with extracellular matrices (Figure 1). Both regions are able to localize IGFBP2 and IGFBP2/IGF complexes on/around the cell surface (Schutt *et al.*, 2004; Russo *et al.*, 2005; Wang *et al.*, 2006). Among the six IGFBPs, only IGFBP1 and IGFBP2 possess a RGD motif (Table 1).

IGFBP2 is widely expressed in the fetus where its expression is reported to closely parallel that of IGF-II (Wood *et al.*, 1992, 1993; Lee *et al.*, 1993). IGFBP2 is predominantly expressed in the early post-implantation epiblast, the apical ectodermal ridge, the progenitors of spleen and liver, and fetal astroglial cells (Wood *et al.*, 1992; Lee *et al.*, 1993). Fetal epithelial cells and epidermal progenitor cells abundantly express IGFBP2, which also participates in the regulation of hair follicle development (Harris *et al.*, 2010). The expression of IGFBP2 decreases significantly after birth, but gradually increases again, especially after the age of sixty, and found in plasma, seminal plasma, milk and cerebrospinal fluid (Blum *et al.*, 1993; Schwander & Mary, 1993; van den Beld *et al.*, 2003).

2.2.2 Regulation of IGFBP2 expression

The *IGFBP2* gene is located on chromosome 2q33-q34 near that of IGFBP5 (Garner *et al.*, 2008). The promoter region lacks TATA box and CAAT boxes, but contains GC-rich sequences and therefore putative Sp1 binding sites. Portions of the promoter responsible for dexamethasone-induced transcriptional activity and IGF-induced stimulation of transcription have also been reported (Mouhieddine *et al.*, 1996). Other possibly important promoter regions contain binding sites for AP-4 and nuclear factor κ B (NF- κ B) (Cazals *et al.*, 1999). The relationship between IGFBP2 expression and loss of tumor suppressor gene function has been recently elucidated (Perks *et al.*, 2007; Moore *et al.*, 2009) and hypoxic microenvironment may also upregulate *IGFBP2* gene expression (Feldser *et al.*, 1999). These lines of evidence indicate that upregulated *IGFBP2* gene expression should occur in injured tissue and particularly in tumors.

2.2.3 Proposed physiological functions of IGFBP2

By virtue of its IGF binding capacity, IGFBP2 was initially considered to be an inhibitory factor of IGFs, particularly of IGF-II with K_D values for IGF-I and IGF-II to be 1.14 and 0.37, respectively (Hwa *et al.*, 1999; Russo *et al.*, 2005). However, it was subsequently found to prolong the half-life of IGFs. The binding between IGFs and IGFBP2 is reversible, and IGFs are released when IGFBP2 is processed at its central region cleavage sites by serine proteinases including thrombin and prostate specific antigen (human tissue kallikrein 3) (Clemmons *et al.*, 1998; Cohen *et al.*, 1992; Zheng *et al.*, 1998) or matrix metalloproteinase (MMP) (Nakamura *et al.*, 2005). As IGFBP2 can associate with cell surface integrins via its RGD motif, IGFBP2 could in theory not only be an IGF inhibitor but also provide an IGF reservoir at the cell surface to maintain efficient IGF activity in the pericellular microenvironment. Therefore, interaction between integrins and IGFBP2, cleavage of IGFBPs by proteases, and other factors that could influence the affinity of IGFBP2 for IGFs may be important regulatory mechanisms of pericellular IGF function. On the other hand, IGFBP2 has also been reported in several studies to have a cytosolic or perinuclear localization, suggesting that IGFBP2 may also have IGF-independent functions (Hoeflich *et al.*, 2004; Fukushima & Kataoka, 2007; Migita *et al.*, 2010).

IGFBP2 knockout mice are both viable and fertile, and do not show significant differences in prenatal or postnatal body growth (Wood *et al.*, 1993, 2000). However, detailed analyses of the knockout mice revealed decreased spleen weight and increased liver weight (Wood *et al.*, 2000). Interestingly, male IGFBP2 knockout mice have shorter femurs than their control mouse counterparts, and also have significantly enhanced levels of PTEN in their

osteoblasts and osteoclasts (DeMambro *et al.*, 2008). Recent studies also revealed that IGFBP2 likely has a crucial regulatory role in glucose metabolism as might be expected since IGFBP2 is regulated by leptin, secreted by visceral white adipocytes, and contributes to the prevention of diet-induced obesity as well as having anti-diabetic effects (Hedbacker *et al.*, 2010; Li & Picard, 2010).

3. Roles of IGFBP2 in progression of gliomas

3.1 Expression of IGFBP2 in tumors

3.1.1 Enhanced expression of IGFBP2 in malignancies of various organs

To date, there is accumulating evidence to suggest that IGFBP2 is involved in tumor progression. Increased serum/plasma levels of IGFBP2 are associated with many malignant tumors of various organs, including prostate (Cohen *et al.*, 1993), ovary (Lancaster *et al.*, 2006), colon (Mishra *et al.*, 1998), breast (Busund *et al.*, 2005), lung (Lee *et al.*, 1999), skin (Harris *et al.*, 2010) and the central nervous system (Lin *et al.*, 2009). Upregulated IGFBP2 expression levels have been reported for various tumor tissues as well, and in many instances, these expression levels correlate with the grade of malignancy (Mishra *et al.*, 1998; Pekonen *et al.*, 1992; Fuller *et al.*, 1999; Rickman *et al.*, 2001; Sallinen *et al.*, 2000). Moreover, an inverse correlation between IGFBP2 and tumor suppressor genes, such as *PTEN* and *p16/INK4*, whose loss-of-function is frequently observed in malignant tumors, has also been reported (Perks *et al.*, 2007; Moore *et al.*, 2009). Indeed, induction of *PTEN* downregulates IGFBP2 expression in glioblastoma and prostate cancer cells (Levitt *et al.*, 2005; Mehrian-Shai *et al.*, 2007). On the other hand, the p53 tumor suppressor is suggested to be a transcription factor that stimulates IGFBP2 expression (Grimberg *et al.*, 2006). Hypoxia-induced expression of IGFBP2 mediated by hypoxia inducible factor 1 α (HIF1 α), has also been demonstrated (Feldser *et al.*, 1999). In sum, the expression of IGFBP2 can be significantly influenced by oncogenic genetic alteration and by a hypoxic tumor microenvironment, and many clinicopathological analyses strongly suggest that IGFBP2 participates in tumor progression.

3.1.2 Expression of IGFBP2 in gliomas and its correlation with histological grade

A consistent overexpression of IGFBP2 in glioblastoma was initially reported by Fuller *et al.* (1999) based on a gene expression profiling analysis. This finding has since been confirmed by many researchers and it is now well established that IGFBP2 expression in gliomas increases with tumor grade (Sallinen *et al.*, 2000; Rickman *et al.*, 2001; Elminger *et al.*, 2001; Fukushima & Kataoka, 2007). Indeed, IGFBP2 is one of the most powerful discriminators to distinguish glioblastomas from low-grade gliomas in proteomic analyses (Jiang *et al.*, 2006). Regarding a possible mechanism for IGFBP2 overexpression in glioblastoma, Mehrian-Shai *et al.* (2007) have identified IGFBP2 as the most significant molecular signature for loss of *PTEN* and activation of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway. Notably, glioblastoma is one of the cancers most commonly affected by *PTEN* abnormalities (Sulis & Parsons, 2003). Enhanced activation of NF- κ B signaling pathway in glioblastoma cells (Wang *et al.*, 2004) may also be involved in the upregulation of *IGFBP-2* transcription (Cazals *et al.*, 1999).

The prognostic impact of IGFBPs expression in patients with newly diagnosed glioblastoma was recently reported (Santosh *et al.*, 2010), with protein expression of IGFBP2, IGFBP 3 and

IGFBP5 being significantly associated with shorter survival by univariate Cox regression analysis. However, multivariate Cox proportional hazards model showed that only IGFBP3 had independent prognostic impact. Plasma levels of IGFBP2 can also predict clinical outcomes of patients with glioblastoma (Lin *et al.*, 2009). In that study, preoperative plasma IGFBP2 levels were significantly higher in high-grade glioma patients compared to low-grade glioma patients, and are significantly correlated with recurrence and disease-free survival in glioblastoma patients.

3.1.3 Expression of IGFBP2 in other brain tumors

Analysis of tissue mRNA levels revealed that IGFBP2 expression is indicative of poor prognosis in patients with medulloblastoma (de Bont *et al.*, 2008). IGFBP2 is also expressed by meningiomas, and a high IGF-II/IGFBP2 mRNA ratio is a sign of biologically aggressive behavior in meningiomas (Nordqvist *et al.*, 1997). However, a subsequent study by the same group revealed that IGFBP6 mRNA is more informative than IGFBP2 for the evaluation of meningioma invasiveness (Nordqvist *et al.*, 2002).

3.2 Role of IGFBP2 in malignant progression of gliomas

3.2.1 Role for IGFBP2 in glioma development

As mentioned above, analyses of clinical samples revealed that IGFBP2 expression significantly correlates with disease progression of gliomas, suggesting a role for IGFBP2 in malignant progression. Furthermore, a recent study using a glial-specific transgenic (RCAS/Ntv-a) mouse system indicated that IGFBP2 in combination with platelet-derived growth factor- β (PDGFB) is also an oncogenic factor in glioma development (Dunlap *et al.*, 2007). In this model, the expression of oncogenic IGFBP2 is negatively regulated by *Ink4a-Arf*, and consequently, loss of *Ink4a-Arf* results in enhanced IGFBP2 expression (Moore *et al.*, 2009). Indeed, the *Ink4a-Arf* locus is frequently deleted in human gliomas and IGFBP2 expression is inversely correlated with p16^{INK4a} status (Moore *et al.*, 2009).

Evidence regarding a role for IGFBP2 in glioma development also arose from a recent study of glioma stem cell (GSC) that was found to overexpress IGFBP2, which subsequently promoted GSC expansion and survival (Hsieh *et al.*, 2010). Notably Hedgehog-GLI1 signaling regulates human glioma growth, GSC self-renewal, and tumorigenicity (Clement *et al.*, 2007) and gene expression of IGFs and IGFBPs is upregulated by GLI transcription factors (Villani *et al.*, 2010). Therefore, an autocrine circuit of IGF/IGFBP2- or IGFBP2-induced signaling may be established in GSCs via activation of Hedgehog-GLI1 signaling, which may contribute to the stemness of GSCs.

3.2.2 Roles for IGFBP2 in malignant phenotypes of glioblastoma cells

Glioblastoma is a devastating brain tumor with extremely poor prognosis (Clarke *et al.*, 2010). Significant invasiveness into surrounding brain parenchyma, increased mitotic activity, sustained angiogenesis and necrosis surrounded by palisaded atypical tumor cells are histological hallmarks of this untreatable tumor. The major impediment to successful therapeutic intervention for glioblastomas is their diffuse invasive nature. An *in vitro* study using a human glioblastoma cell line engineered to overexpress IGFBP2 revealed that IGFBP2 enhances glioblastoma cell invasiveness (Wang *et al.*, 2003). Similarly, a study using human glioblastoma cell lines in which IGFBP2 expression was knocked down by consistent

retroviral expression of IGFBP2 short hairpin RNA (shRNA) revealed that silencing of the IGFBP2 gene reduces *in vitro* invasiveness and *in vivo* aggressiveness of the cells (Fukushima *et al.*, 2007). Consistent with these studies, high levels of IGFBP2 expression were detected within the infiltrating tumor cells of human glioblastomas *in vivo* (de Groot *et al.*, 2010). Therefore, IGFBP2 has a crucial role in glioblastoma invasion.

IGFBP2 may also be implicated in glioblastoma angiogenesis. In a cDNA-array analysis of 53 patient biopsies, IGFBP2 was included in a prominent gene cluster that allowed discrimination between primary (*de novo*) and non-primary (secondary) glioblastomas (Godard *et al.*, 2003). This gene cluster is composed mostly of angiogenesis-related genes, including vascular endothelial growth factor (VEGF) and fms-related tyrosine kinase 1. Notably, *in situ* hybridization demonstrates coexpression of IGFBP2 and VEGF in pseudopalisading cells surrounding tumor necrosis, providing evidence for a possible involvement of IGFBP2 in angiogenesis (Godard *et al.*, 2003). It is reasonable to postulate that HIF1 α is responsible for the concomitant expression of VEGF and IGFBP2 (Carmeliet *et al.*, 1998; Feldser *et al.*, 1999). In addition, an anti-apoptotic function of intracellular IGFBP2 was recently reported in lung cancer cells (Migita *et al.*, 2010), which may also have implications for the enhanced expression of IGFBP2 within glioblastoma cells around necrosis.

Taken together, these results strongly indicate that IGFBP2 has significant roles in the development of the malignant phenotypes of glioblastoma.

3.2.3 Potential mechanisms of IGFBP2 action in the invasive growth of glioblastoma cells

Interaction of IGFBP2 with components of the pericellular matrices results in local sequestration of IGFs and then in an enhancement of cellular IGF-induced signaling (Schutt *et al.*, 2004). Experiments using a cultured neuroblastoma cell line showed that the heparin binding domain of IGFBP2 is required for IGFBP2 association to pericellular matrices and for IGFBP2 to promote invasive growth via efficient pericellular localization of IGF-1 (Russo *et al.*, 2005).

However, IGF-independent actions of IGFBP2 may be equally or more important in glioblastoma biology, as has been amply demonstrated by recent research. Interaction of IGFBP2 RGD domain with integrin $\alpha 5$ induces outside-in signaling and may be essential for IGFBP2-induced glioma cell mobility (Wang *et al.*, 2006). Moreover, intracellular localization of IGFBP2 has been shown in glioblastoma cells and other tumor cells such as lung carcinoma, which appears to influence the cellular gene expression signature (Fukushima & Kataoka, 2007; Migita *et al.*, 2010). Overexpression of IGFBP2 in the SNB19 human glioblastoma cell line revealed that IGFBP2 enhances the invasiveness of these cells by up-regulating expression of invasion-associated gene products, such as extracellular matrix-degrading protease, MMP-2 (Wang *et al.*, 2003). We compared the expression profiles of two human glioblastoma cell lines, U251 and YKG-1, in the presence and absence of shRNA-induced silencing of IGFBP2 expression (Fukushima *et al.*, 2007). In both cell lines, expression levels of various genes were altered by IGFBP2 knockdown without apparent alteration of IGF signaling, suggesting that IGFBP2 influences transcriptional regulation of many genes in glioblastoma cells independent of IGF signaling. Among the genes influenced by IGFBP2 silencing, the CD24 gene was identified as a candidate downstream target of IGFBP2-induced signaling, and subsequent analysis revealed that

CD24 is critically involved in the invasiveness of U251 and YKG-1 cells (Fukushima *et al.*, 2007). CD24 is a heavily glycosylated, cell surface, glycosylphosphatidylinositol-anchored protein (Kristiansen *et al.*, 2004). While the precise mechanism by which CD24 induces cellular invasion is unclear, CD24 has been shown to recruit adhesion molecules to lipid rafts, thereby contributing to tumor cell migration, dissemination, and metastasis (Baumann *et al.*, 2005; Runz *et al.*, 2008). Of interest is a recent observation that a splice variant of *GLI1*, truncated *GLI1* (*tGLI1*), which is highly expressed in glioblastoma cells but not in normal cells, induces cellular migratory and invasive capabilities via upregulation of CD24 in U87 glioblastoma cells (Lo *et al.*, 2009). As mentioned above, Hedgehog-GLI1 signaling is involved in glioma cell growth, expansion of GSC and induction of IGFBP2 expression (Clement *et al.*, 2007; Villani *et al.*, 2010). Therefore, Hedgehog-GLI1/IGFBP2/CD24 signaling may play a pivotal role in the invasive growth of glioblastoma cells.

The NF- κ B pathway is another important candidate for the signaling involved in IGFBP2-induced phenotypes. In fact, NF- κ B signaling is activated in glioblastomas and involved in invasion and angiogenesis of glioma cells (Wang *et al.*, 2004; Li *et al.*, 2007). While NF- κ B is suggested to regulate *IGFBP2* gene expression in response to tissue injury (Cazals *et al.*, 1999), intracellular IGFBP2 itself is involved in the regulation of NF- κ B signaling via binding to invasion inhibitory protein 45 (Iip45, also named migration and invasion inhibitor protein MIIP), which was identified by a yeast two-hybrid assay (Song *et al.*, 2003). The *Iip45* gene is located on chromosome 1p36 (Song *et al.*, 2003), a region that is frequently deleted in oligodendrogliomas and occasionally deleted in astrocytomas (Smith *et al.*, 1999). Decreased Iip45/MIIP levels were also observed in 15% of glioblastoma cases (Song *et al.*, 2003). Iip45/MIIP binds to the RGD motif of IGFBP2 and inhibits the interaction between IGFBP2 and integrin, which eventually may inhibit the expression of transcriptional NF- κ B and its downstream genes involved in invasive glioma cell growth (Song *et al.*, 2003). It may be possible that upregulated NF- κ B in the absence of Iip45/MIIP also stimulates IGFBP2 transcription and eventually establishes an autocrine stimulation circuit for invasive growth. Moreover, recent studies have indicated that Iip45/MIIP also interacts with intracellular proteins, such as Cdc20 and histone deacetylase 6 (HDAC6), and inhibits glioma cell proliferation and migration (Ji *et al.*, 2010; Wu *et al.*, 2010). Therefore, interaction between Iip45/MIIP and intracellular IGFBP2 may occur in glioblastoma cells, which may attenuate the function of Iip45/MIIP and thereby may enhance the cellular proliferation and migration.

We summarize hypothetical functions of IGFBP2 in the invasive growth of glioblastoma cells in Figure 2.

3.2.4 IGFBP2 as a therapeutic target for high-grade gliomas

We have shown above that IGFBP2 can provide crucial signaling during glioma development and can exhibit malignant phenotypes of glioblastoma. As such, IGFBP2 and its downstream targets may reasonably serve as novel therapeutic targets for glioblastoma. However, there have been limited attempts to target IGFBP2 for *in vivo* glioblastoma treatments. Moore *et al.* (2009) examined the effect of antisense IGFBP2 *in vivo* using PDGFB-induced glioma in *Ink4a-Arf*-null mice, and found that the inhibition of IGFBP2 expression confers a survival benefit. Therefore, IGFBP2 is a potential therapeutic target for *Ink4a-Arf*-deleted gliomas, such as anaplastic oligodendroglioma and glioblastoma (Moore *et al.*, 2009).

As a downstream molecule of IGFBP2 involved in invasiveness of glioblastoma cells, CD24 may also serve as a molecular target for glioblastoma treatment. Targeting CD24 by monoclonal antibodies, small interfering RNA or shRNA has been reported in xenograft models of human colorectal cancer, pancreatic cancer and ovarian cancer cell lines (Sagiv *et al.*, 2008; Su *et al.*, 2009). In those studies, retardation of tumorigenicity and significant reduction of tumor growth were observed *in vivo*, indicating that CD24 is a promising therapeutic target for treatment of cancer. As glioblastomas abundantly express CD24 as well as IGFBP2 (Fukushima *et al.*, 2007), we suggest that targeting CD24 may be a potential therapeutic approach against glioblastoma.

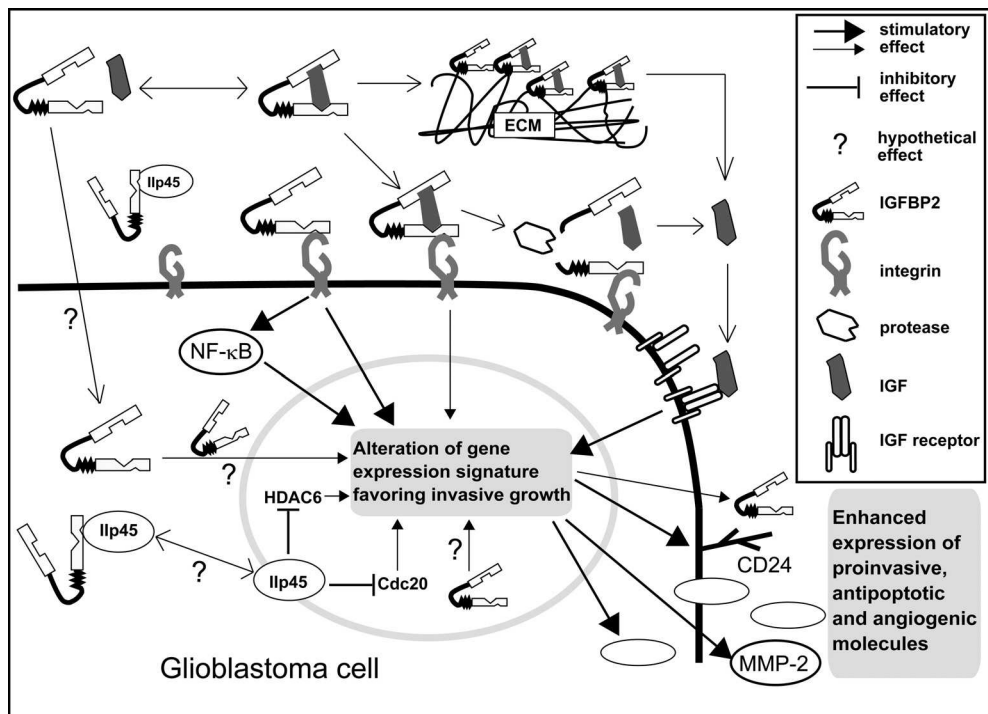


Fig. 2. Roles for IGFBP2 in the establishment of malignant phenotypes of glioblastoma cells. Both IGF-dependent and IGF-independent effects of IGFBP2 have been proposed. Integrin-mediated outside-in signaling and NF- κ B signaling appear to be involved in the IGFBP2-induced effects, which eventually result in enhanced expression of proinvasive molecules, such as CD24 and MMP-2. While IIP45/MIIP may inhibit binding of IGFBP2 to integrin, it is possible to hypothesize that excess intracellular (intranuclear) IGFBP2 may suppress the inhibitory effects of IIP45/MIIP on Cdc20 and/or HDAC6-mediated cellular growth and migration. The upregulated NF- κ B signaling enhances the expression of IGFBP2. Hypoxic microenvironment, loss of PTEN function and Hedgehog-GLI1 signaling might also be involved in the enhanced IGFBP2 expression in glioblastoma cells. Functions of intracellular and intranuclear IGFBP2 remain to be elucidated. ECM, extracellular matrix.

IGFBP2 may also be an attractive marker to influence glioblastoma treatment strategy decisions. Since high IGFBP2 levels serve as a marker for loss of PTEN function and PI3K/Akt activation, the clinical data linking IGFBP2 expression to poor prognosis may be due, at least in part, to the loss of PTEN function, which is well known to lead to aggressive behavior of gliomas (Levitt *et al.*, 2005; Mehrian-Shai, 2007). Therefore, measurements of IGFBP2 expression levels may be useful for estimating the functional PTEN status and PI3K/Akt activation levels in glioma, which in turn may be beneficial for organizing specific treatment strategies for each glioma case (Gonzalez & de Groot, 2008). Moreover, recent study suggests that IGFBP2 expression level may be a marker for DNA hypermethylation profiles in gliomas (Zheng *et al.*, 2011).

4. Conclusion

IGFBP2 is a pleiotropic protein that appears to be involved in many aspects of physiological and pathological processes and shows both positive and negative effects. Even in cancers, opposite effects of IGFBP2 are observed. For example, the growth of colorectal adenomas induced by chemical carcinogens in mice was inhibited upon crossing with IGFBP2 transgenic mice (Diehl *et al.*, 2008). In contrast, IGFBP2 exerts oncogenic effects in brain-specific transgenic mice (Dunlap *et al.*, 2007; Moore *et al.*, 2009). Thus, IGFBP2 shows both negative and positive effects on tumor growth, and these differences are probably dependent on cell type and pericellular environment. Despite the diverse effects of IGFBP2 on the biological behaviors of cancers, it has been clearly demonstrated that IGFBP2 is overexpressed in a wide variety of human malignancies, and evidence is rapidly accumulating to indicate that IGFBP2 is significantly involved in the progression of glioma and confers malignant phenotypes of glioblastoma cells. To clarify the molecular mechanisms underlying the effects of IGFBP2 on gliomas, not only the pericellular IGF-dependent and IGF-independent functions but also the functions of intracellular IGFBP2 should be defined (Figure 2). Additional information concerning the factors that directly regulate IGFBP2 overexpression in gliomas and those that are critically involved in the IGFBP2-mediated malignant features of glioblastoma cells is required and may lead to new therapeutic avenues for one of the most treatment-resistant human tumors.

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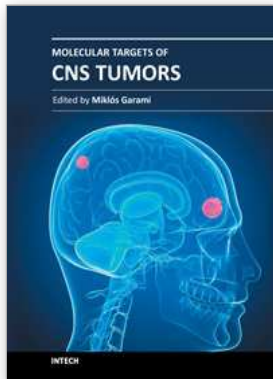
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