INTRODUCTION

Insulin-like growth factor binding protein 2 is a member of the family of six IGF-binding proteins, IGFBP1–6, these proteins bind with high-affinity to IGF1 and IGF2 (1); in addition, there is also a low affinity for insulin (2). Other IGF-binding proteins such as the CCN family retain the name as IGFBPs, although these have ~100-fold lower affinity for IGF1 and IGF2 (1, 3, 4). IGFBP2 has the ability to bind insulin, IGF1 and IGF2 with an increased affinity for the latter (2, 5). IGFBP2 and the other family members have been proposed to suppress tumor development through binding IGFs preventing binding to their receptor and thereby preventing IGF driven tumorigenesis (6). However, despite this suppressive function, there are also studies that demonstrate oncogenic functions including promoting proliferation, driving invasion, and suppressing apoptosis (7). These effects appear to be independent of its ability to bind the IGFs and instead promote invasion and proliferation through interaction with integrins (8, 9).

Insulin-like growth factor binding protein 2 has been proposed as a potential biomarker in various cancer types, including gliomas (10–18), prostate (19–27), ovarian (28–33) colorectal (34–40) and acute myeloid leukemia (13, 41, 42), acute lymphoblastic leukemia (43, 44) pancreatic (45–48), lung (49–52), colorectal (53), breast (54–55) and ovarian (56) cancers to name a few. Other family members have been proposed to suppress tumor development through binding IGFs preventing binding to their receptor and thereby preventing IGF driven tumorigenesis (6). IGFBP2 and the other family members have been proposed to suppress tumor development through binding IGFs preventing binding to their receptor and thereby preventing IGF driven tumorigenesis (6). However, despite this suppressive function, there are also studies that demonstrate oncogenic functions including promoting proliferation, driving invasion, and suppressing apoptosis (7). These effects appear to be independent of its ability to bind the IGFs and instead promote invasion and proliferation through interaction with integrins (8, 9).

The role of insulin-like growth factor binding protein 2 (IGFBP2) in cancer is unclear. In general, IGFBP2 is considered to be oncogenic and its expression is often observed to be elevated in cancer. However, there are a number of conflicting reports in vitro and in vivo where IGFBP2 acts in a tumor suppressor manner. In this mini-review, we discuss the factors influencing the variation in IGFBP2 expression in cancer and our interpretation of these findings.

Keywords: IGF1, IGF1, IGF2, IGFI, IGFBPs, IGFBP2, oncogenes, tumour suppressor
reduced body mass (83) and incidence of colorectal adenomas in experimental models (84).

REGULATION OF IGFBP2 EXPRESSION AT A CELLULAR LEVEL

Given the difficulties in accurately associating plasma levels of IGFBP2 with cancer patient prognosis or disease progression, as well as reports demonstrating a lack of concordance between tumor immunohistochemistry (IHC) and serum levels of IGFBP2 (12, 52, 85–87), it may be more meaningful to assess the expression of IGFBP2 within the tumor itself. IGFBP2 is mainly expressed by the liver, adipose, and reproductive tissues and tissues of the central nervous system (4). However, IGFBP2 is also expressed in a wide range of other tissue types, including both epithelial and mesenchymal cells [see Ref. (88), proteinatlas.org (89), and encode (90)], therefore the local levels of IGFBP2 are likely to play an important part in how the tissue responds to circulating IGFs. Approaches to detect changes in protein or RNA levels of IGFBP2 within tumors have been used to hint at whether IGFBP2 might act in a tumor suppressive or oncogenic manner, however, within a given tumor type the expression of IGFBP2 can vary greatly, so below we examine the mechanisms, which regulate IGFBP2 expression in tumors.

PROMOTER METHYLATION

Promoters, including the IGFBP2 promoter, can become hyper- or hypomethylated relative to the normal state during tumorigenesis. The IGFBP2 promoter has been shown to be hypermethylated, in a subset of tumors, including 8% of small cell lung carcinomas (86), >20% of renal cell carcinomas (91), ~30% squamous cell lung cancers (86), 40% of colorectal cancers (92), >70% lung adenocarcinomas (86), and 75% hepatomas (93). The hypermethylation results in reduced IGFBP2 expression, as demonstrated by Yazawa et al. with good correlation between IGFBP2 promoter methylation and IGFBP2 protein expression detected by IHC (86). The low expression of IGFBP2 observed in some glioblastoma cell lines, is associated with methylation of the IGFBP2 promoter and can be restored with 5-azacytidine treatment suggesting regulation by DNA methyltransferase 1 (DNMT1) (94). Also, DNMT3L knockdown in embryonic stem cells results in elevated IGFBP2 expression (95), suggesting promoter methylation is an important regulator of IGFBP2 expression. The observation that IGFBP2 is hypermethylated in lung and liver cancers is somewhat surprising as elevated plasma levels have been described for these diseases (57, 87); however, the higher plasma levels of IGFBP2 may represent a systemic response to cancer, or the confounding factors described above. Further assessment of the inactivation of the IGFBP2 locus will be greatly aided by The Cancer Genome Atlas project (http://cancergenome.nih.gov/).

NORMAL VERSUS ABERRANT REGULATION

Insulin-like growth factor binding protein 2 expression is greatly influenced by hormonal factors and both positive and negative regulators of IGFBP2 expression have been described, as reviewed in Ref. (88). Interestingly, the same hormone can have differing effects depending upon the tissue. As an example, estradiol (E2) acts on the hippocampus to increase IGFBP2 expression (96) whereas in the cortex IGFBP2 expression is reduced (97). Estradiol also reflects an interesting example of how we interpret the role of IGFBP2 in cancer, as previously described, IGFBP2 is generally considered to be oncogenic in breast cancer; however, IGFBP2 expression, in vivo, is induced by estradiol in normal breast tissue (98), whereas in the rat mammary adenocarcinoma, R3230AC, IGFBP2 expression is reduced following E2 treatment (99). In the breast cancer cell line, MCF7 IGFBP2 expression is also elevated by E2 (100), suggesting that this cell line is responding in the same way as normal tissue. Estrogen receptor (ER) status directly correlates with IGFBP2 expression in breast cancer, with ER-positive cancers having higher levels of IGFBP2 than ER-negative cancers (80, 101, 102), and therefore the high levels of IGFBP2 may simply reflect a functional ER pathway. In order to better understand whether regulation of IGFBP2 expression is de-regulated in cancer, it will be important to further establish how it is regulated in the physiological setting.

REGULATION BY PROTEASES

In addition to the aforementioned disconnect between plasma levels and tumor levels of IGFBP2, there are also reports demonstrating that IGFBP2 mRNA and protein levels do not always correlate (103). Protease cleavage of IGFBP2 could be partially responsible for the lack of association, and also help to explain the differential findings of IGFBP2’s role in cancer. There are a number of proteases, which cleave the mature IGFBP2 peptide, these include calpain (104), pappalysin A (105), kallikrein-2 (106), and MMP7 (107). Plasmin and MMP1 also cleave IGFBP2; however, the cleavage sites have not been defined (108). In addition, IGFBP2 is also cleaved at additional sites; however, the responsible proteases have not been identified (109). IGFBP2 cleavage reduces its affinity for IGF1 and IGF2 (110–112), allowing IGFs to mediate their functions through the IGF1R. Thus, it is important to reflect on the nature of IGFBP2 in carcinogenesis as calpain (113), MMP1 (114), MMP7 (114), and kallikrein-related peptidases (115) have also been described to be elevated or activated in various cancer types and may lead to inactivation of the protein. Many reagents used to detect the IGFBP2 protein are not able to distinguish whether IGFBP2 is in its full-length form. Fragments of IGFBP2 can be detected by the antibodies often used for immunohistochemical detection of IGFBP2 (110). To our knowledge, only one report has assessed IGFBP2 expression with multiple antibodies, targeting the C and N termini of IGFBP2. This work demonstrated a correlation between a cleaved N-terminal fragment of IGFBP2 and the protease ADAMTS1 in glioblastoma (116) suggesting IGFBP2 is not in a full-length form and therefore may be unable to bind IGFs.

Insulin-like growth factor binding protein 2 cleavage may result in enhanced proliferation mediated by IGFs but it has also been proposed that the cleaved fragments of IGFBP2 have additional roles. C-terminal fragments of IGFBP2 are able to promote proliferation of rat chondrocytes (117), and a recent report, which demonstrates that nuclear IGFBP2 can drive VEGF expression demonstrated that a nuclear localization sequence (NLS) is present in the linker region of IGFBP2 (118); interestingly, this region is the site of many cleavage events and may lead to exposure of the NLS. The importance of establishing whether IGFBP2 is cleaved in cancer tissue has recently been demonstrated by Soh et al. (108),...
where a protease-resistant IGFBP2 was more effective at inhibiting IGF1-induced proliferation of the MCF7 cell line than wild-type IGFBP2. Interestingly, protease resistant IGFBP2 was also able to suppress tumor growth in vivo. Furthermore, the MCF7 cell line is known to secrete low levels of full-length IGFBP2 compared to other cancer cell lines even though the mRNA and intracellular protein levels of IGFBP2 are comparable (119), suggesting high levels of proteolytic degradation.

Reflecting on the cleaved status of IGFBP2 in cancer may also help to explain some of the contradictory evidence regarding its tumor suppressive/oncogenic role in carcinogenesis. For example, the elevated expression of the IGFBP2 protein observed in various cancers may represent a response to suppress tumor growth, mediated by IGFs; however, pro-tumorigenic proteases may ultimately inactivate this response. Enhanced proteolysis of IGFBP2 has been described in proliferating cells, and can be inhibited by targeting proteases (120). Therefore, the observation that a protease-resistant IGFBP2 can suppress tumor growth (108) creates the exciting opportunity to target proteases and potentially restore the suppressive actions of IGFBP2.

**INTRA-TUMOR VARIABILITY**

In addition to the variation in IGFBP2 expression between different tumors, there is also further variation in IGFBP2 expression levels, within an individual tumor. While high grade glioblastoma, which are frequently observed to have elevated IGFBP2 level, also have regions of low IGFBP2 expression, which have been shown to be at the invasive front of the tumor (121). Therefore, this data would suggest that IGFBP2 loss correlates with enhanced invasive potential, as observed in other models (59). Interestingly, this is also supported by an in vivo model of malignant brain tumor growth and invasion, where rapidly growing non-invasive tumors have high levels of IGFBP2 compared to invasive tumors, which had low/undetectable IGFBP2 levels (122). Furthermore, the oxygenation of a tumor varies depending on blood supply to different regions of the tumor, hypoxia has been shown to regulate IGFBP2 expression (88, 123–126) and should also be considered when scoring IGFBP2 expression in tumor samples.

**REGULATION OF IGFBP2 EXPRESSION BY TUMOR SUPPRESSORS AND ONCOGENES**

There are a number of additional factors, which are known to influence IGFBP2 expression, and therefore how we evaluate its role in cancer. There are now a number of reports, which demonstrate a connection between PTEN levels and those of IGFBP2 (127–130). PTEN mutation in glioma is associated with high levels of IGFBP2 (130) suggesting that IGFBP2 could be a marker of PTEN mutation. Similarly, mutation of KRAS also induces IGFBP2 expression (131). IGFBP2 expression has also been shown to correlate with TP53 mutational status. While it has been demonstrated that wild-type p53 is required for IGFBP2 induction following irradiation (132), the regulation of IGFBP2 by p53 mutations is, at present, unclear. In breast cancer, p53 mutation is associated with reduced secretion of IGFBP2 (133), whereas in glioblastoma, mutant p53 is associated with high levels of IGFBP2 (94). In addition, Ras mutation, loss of p53 and radiation-induced DNA damage drives a senescence-associated secretory phenotype (SASP), of which, elevated IGFBP2 secretion is a component (134). This is also supported by evidence that mRNA expression is also elevated in senescence (135–137). Together these findings suggest that the variation in IGFBP2 expression in tumors may reflect the status of tumor suppressors, oncogenes, and/or use of radiation therapy, therefore, the tumor suppressive/oncogenic potential of IGFBP2 should now be evaluated in the context of each mutation in order to demonstrate whether or not IGFBP2 has a functional role.

**CORRELATION OF IGFBP2 EXPRESSION WITH CANCER PROGRESSION**

It has been established that enhanced expression of IGFBP2 is associated with the progression of tumorigenesis in prostate (27), breast cancer (138), and glioma (7); however, when the expression of IGFBP2 is examined further it appears that there are certain cancer types or subpopulations of cancers, which develop with little or no expression of IGFBP2. This latter finding goes against the hypothesis of IGFBP2 being a driver of tumorigenesis, and suggests that loss of IGFBP2 may also be an important event in tumors. A detailed examination of ovarian cancers observed that IGFBP2 expression did not correlate with stage of disease (139), with similar proportions of tumors having low or high expression of IGFBP2 at all stages. Interestingly, in the same study, the authors demonstrate that the expression of IGFBP2 is related to the type of ovarian cancer, for example, 80% of serous carcinoma had elevated IGFBP2 whereas 80% of clear cell carcinoma had low IGFBP2 levels. Similarly, in lung cancer, IGFBP2 is found to be overexpressed in the majority of small cell lung carcinomas but reduced in the majority of lung adenocarcinomas (86). Thus, it is important to consider whether these results demonstrate a correlation of IGFBP2 driving tumorigenesis or are, in fact, reflective of tumor stage/subtype. These findings suggest that cancers can develop both in the presence and absence of IGFBP2 and as cancer sub-types become further defined it will be important to evaluate how IGFBP2 expression is regulated among these different groups. Evaluation of IGFBP2’s role in each group will then provide a better understanding of its oncogenic and tumor suppressive potential.

**THERAPEUTIC RESPONSE AND IGFBP2**

Evaluation of IGFBP2 as a biomarker in the treatment of cancer has also generated a dichotomy in how IGFBP2 is perceived. In some cases, IGFBP2 is found to be a marker of response to therapy but then others have demonstrated that high levels confer resistance. In the case of IGF1R targeted therapies, McCaffery et al. (47) demonstrated that there was better response to IGF1R targeted therapy in patients with low IGFBP2 levels, than patients with high IGFBP2 and similar results were found in a mouse model where inhibition with the IGF1R inhibitor BMS-536924, had no effect in reducing growth of cells expressing high levels of IGFBP2 (140). However, down-regulation of IGFBP2 in rhabdomyosarcoma is associated with resistance to IGF1R therapy (141). In response to other therapeutic strategies, tumor samples from patients receiving chemotherapy/radiation therapy have been shown to have elevated IGFBP2 levels and suggest that IGFBP2 is a potential marker of response to these treatments (134) and may be due to a pro-apoptotic function of IGFBP2 (142). However, high levels of
IGFBP2 are also linked with resistance to other therapeutics (143–146) and high levels of IGFBP2 following radio/chemotherapy also correlate with poor survival in elderly patients with glioblastoma (147). Therefore, further evaluation of IGFBP2 in response to therapy is an area, which requires further investigation.

DIFFERENTIAL FUNCTIONS OF IGFBP2

The binding to IGF1 and IGFBP2 is common to in vitro models, which demonstrate either oncogenic or tumor suppressive functions of IGFBP2 (148). In addition to repressing IGF signaling, IGFBP2-dependent functions have also been described. Overexpression or addition of recombinant IGFBP2 activates integrin complexes with integrins α5 and β1 mediating the effects of IGFBP2 (142, 149–151). Through these pathways IGFBP2 reduces adhesion and promotes proliferation and invasion, some of these activities are also observed in cell lines that lack the IGF1-receptor (142) and therefore helps to explain the dichotomy of IGFBP2 functions in vitro and may also explain the association of high levels of IGFBP2 with high grade tumors, despite its inhibitory effect on IGF signaling. It is important to note that these observations have been made following addition of 100–2000 ng/mL recombinant IGFBP2, while these levels are within the physiological range of human plasma these are greater than the levels secreted by cell lines in culture (151).

CONCLUSION

While there is conflicting evidence as to whether IGFBP2 is tumor suppressive or oncogenic, this mini-review highlights a number of factors, which influence our interpretation of these findings. Through detailing factors, which influence IGFBP2 expression alongside measurements in patient samples our current understanding of its role in cancer could be improved. So far, it is through detailing factors, which influence our interpretation of these findings. Through these pathways IGFBP2 reduces adhesion and promotes proliferation and invasion, some of these activities are also observed in cell lines that lack the IGF1-receptor (142) and therefore helps to explain the dichotomy of IGFBP2 functions in vitro and may also explain the association of high levels of IGFBP2 with high grade tumors, despite its inhibitory effect on IGF signaling. It is important to note that these observations have been made following addition of 100–2000 ng/mL recombinant IGFBP2, while these levels are within the physiological range of human plasma these are greater than the levels secreted by cell lines in culture (151).

REFERENCES

1. Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. J Natl Cancer Inst (2000) 92(18):1472–89. doi:10.1093/jnci/92.18.1472
2. Yamanaka Y, Wilson EM, Rosenfeld RG, Oh Y. Inhibition of insulin receptor activation by insulin-like growth factor binding proteins. J Biol Chem (1997) 272(48):30729–34. doi:10.1074/jbc.272.49.30729
3. Holbourn KP, Acharya KR, Perbal B. The CCN family of proteins: structure-function relationships. Trends Biochem Sci (2008) 33(10):461–73. doi:10.1016/j.tibs.2008.07.006
4. Shimasaaki S, Ling N. Identification and molecular characterization of insulin-like growth factor binding proteins (IGFBP-1, -2, -3, -4, -5 and -6). Prog Growth Factor Res (1991) 3(4):243–66. doi:10.1007/9055-2235(91)90003-M
5. Oh Y, Muller HL, Lee DY, Fielder PJ, Rosenfeld RG. Characterization of the affinities of insulin-like growth factor (IGF)-binding proteins 1-4 for IGF-1, IGF-II, IGF1/insulin hybrid, and IGF-1 analogs. Endocrinology (1993) 132(3):1337–44. doi:10.1210/endo.132.3.3767997
6. Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. Nat Rev Cancer (2004) 4(7):505–18. doi:10.1038/nrc1387
7. Fukushima T, Katoaka H. Roles of insulin-like growth factor binding protein-2 (IGFBP-2) in glioblastoma. Anticancer Res (2007) 27(6A):3685–92.
8. Wang GK, Hu L, Fuller GN, Zhang W. An interaction between insulin-like growth factor-binding protein 2 (IGFBP2) and integrin α5 is essential for IGFBP2-induced cell motility. J Biol Chem (2006) 281(20):14085–91. doi:10.1074/jbc.M51366200
9. Oh SH, Lee OH, Schroeder CP, Oh YW, Ke S, Cha HI, et al. Antimetastatic activity of insulin-like growth factor binding protein-3 in lung cancer is mediated by insulin-like growth factor-independent urokinase-type plasminogen activator inhibition. Mol Cancer Ther (2006) 5(11):2685–95. doi:10.1158/1535-7163.MCT-06-0142
10. Scrdeli CA, Carlotti CG, Mata JV, Neder M, Machado HR, Oba-Sinjo SM, et al. Prognostic significance of co-overexpression of the EGRF/IGFBP-2/HIF-2A genes in astrocytomas. J Neurooncol (2007) 83(3):233–9. doi:10.1007/s11060-007-9382-0
11. McDonald KL, O’Sullivan MG, Parkinson JF, Shaw JM, Payne CA, Brewer JM, et al. IQGAP1 and IGFBP2: valuable biomarkers for determining prognosis in glioma patients. J Neuropathol Exp Neurol (2007) 66(5):405–17. doi:10.1097/nen.0b013e3180456767
12. Lin Y, Jiang T, Zhou K, Xu L, Chen B, Li G, et al. Plasma IGFBP-2 levels predict clinical outcomes of patients with high-grade gliomas. Neuro Oncol (2009) 11(5):468–76. doi:10.1215/15228517-2008-114
13. Muller HL, Oh Y, Lehrnbecher T, Blum WF, Rosenfeld RG. Insulin-like growth factor-binding protein-2 concentrations in cerebrospinal fluid and serum of children with malignant solid tumors or acute leukemia. J Clin Endocrinol Metab (1994) 79(2):428–34. doi:10.1210/jcem.79.2.7519190
14. Sontos V, Arivazhagan A, Seekanthredy P, Srinivasan H, Thota B, Srividiya MR, et al. Grade-specific expression of insulin-like growth factor-binding proteins-2, -3, -5 in astrocytomas: IGFBP-3 emerges as a strong predictor of survival in patients with newly diagnosed glioblastoma. Cancer Epidemiol Biomarkers Prev (2010) 19(6):1399–408. doi:10.1158/1055-9965.EPI-09-1213
15. Zhou YH, Hess KR, Liu L, Linkskey ME, Yung WK. Modeling prognosis for patients with malignant astrocytomas: quantifying the expression of multiple genetic markers and clinical variables. Neuro Oncol (2005) 7(4):485–94. doi:10.1215/15228517-2004-00730
16. Muracci G, Morandi I, Magrini E, Farnedi A, Franceschi E, Miglio R, et al. Gene expression profiling in glioblastoma and immunohistochemical evaluation of IGFBP-2 and CD2C0. Virchows Arch (2008) 455(6):599–609. doi:10.1007/s00428-008-0685-7
17. Sandovall JA, Hoelz DJ, Woodruff HA, Powell RL, Jay CL, Grosfeld JL, et al. Novel peptides secreted from human neuroblastoma: useful clinical tools? J Pediatr Surg (2006) 41(1):245–51. doi:10.1016/j.jpedsurg.2005.10.048
18. Nordqvist AC, Peyrard M, Pettersson H, Mathiesen T, Collins VP, Dumanski JP, et al. A high ratio of insulin-like growth factor II/insulin-like growth factor binding protein 2 messenger RNA as a marker for anaplasia in meningiomas. Cancer Res (1997) 57(13):3681–4.
19. Kanety H, Madjar Y, Dagan Y, Levi J, Papa MZ, Pariente C, et al. Serum insulin-like growth factor-binding protein-2 (IGFBP-2) is increased and IGFBP-3 is decreased in patients with prostate cancer: correlation with serum prostate-specific antigen. J Clin Endocrinol Metab (1993) 77(1):229–33. doi:10.1210/jcem.77.1.2669135
20. Tennant MK, Thrasher JB, Twomey PA, Birnbaum RS, Plymate SR. Insulin-like growth factor-binding protein-2 and -3 expression in benign human prostate epithelium, prostate intraepithelial neoplasia, and adenocarcinoma of the prostate. J Clin Endocrinol Metab (1996) 81(1):411–20. doi:10.1210/jcem.81.1.8550786
21. Thrasher JB, Tennant MK, Twomey PA, Hansbery KL, Wettlaufer JN, Plymate SR. Immunohistochemical localization of insulin-like growth factor binding proteins 2 and 3 in prostate tissue: clinical correlations. J Urol (1996) 155(3):999–1003. doi:10.1016/S0022-5347(01)66367-5
22. Ho PJ, Baxter RC. Insulin-like growth factor-binding protein-2 in patients with prostate carcinoma and benign prostatic hyperplasia. Clin Endocrinol (Oxf) (1997) 46(3):333–42. doi:10.1046/j.1365-2265.1997.1100922.x

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23. Yu H, Nicar MR, Shi R, Berkel HJ, Nam R, Trachtenberg J, et al. Levels of insulin-like growth factor I (IGF-I) and IGF binding proteins 2 and 3 in serial preoperative serum samples and risk of prostate cancer recurrence. Urology (2001) 57(3):471–5. doi:10.1006/uros.2000.01033-7

24. Sharati SF, Lamb DJ, Kattan MW, Nguyen C, Kim J, Beck J, et al. Association of preoperative plasma levels of insulin-like growth factor I and insulin-like growth factor binding proteins-2 and -3 with prostate cancer invasion, progression, and metastasis. J Clin Oncol (2002) 20(5):383–41.

doi:10.1021/pr0000650-S00000000112

25. Richardsen E, Ukkonen T, Bjørnsen T, Mortensen E, Egevad L, Busch C. Overexpression of IGFB2 is a marker for malignant transformation in prostate epithelium. Virchows Arch (2003) 442(4):329–35. doi:10.1007/s00428-003-0786-2

26. Inman BA, Harel F, Audet JE, Meyer F, Douville P, Fradet Y, et al. Insulin-like growth factor binding protein 2: an androgen-dependent predictor of prostate cancer survival. Eur Urol (2005) 47(5):695–702. doi:10.1016/j.eururo.2004.12.015

27. Ambrosini-Spaltero A, Farnesi A, Montironi R, Foschini MP. IGFBP2 as an immunohistochemical marker for prostatic adenocarcinoma. Appl Immunohistochem Mol Morphol (2011) 19(4):318–28. doi:10.1097/PINL.0b013e32834f923e

28. Flyvbjerg A, Mogensen O, Mogensen B, Nielsen OS. Elevated serum insulin-like growth factor-binding protein 2 (IGFBP-2) and decreased IGFBP-3 in epithelial ovarian cancer: correlation with cancer antigen 125 and tumor-associated trypsin inhibitor. J Clin Endocrinol Metab (1997) 82(7):2308–13. doi:10.1210/jci.2103.2008

29. Hough CD, Cho KR, Zonderman AB, Schwartz DR, Morin PJ. Coordinately expressed and IGFBP2 is a marker for malignant transformation in prostate cancer. J Clin Endocrinol Metab (2002) 87(10):3744–50. doi:10.1210/jc.2001-023063

30. Baron-Hay S, Boyle F, Ferrier A, Scott C. Elevated serum insulin-like growth factor binding protein-2 as an immunohistochemical marker for prostatic adenocarcinoma. J Transl Med (2014) 12:87. doi:10.1186/1479-5876-12-87

31. Kendrick ZW, Firpo MA, Repko RC, Scaife CL, Adler DG, Boucher KM, et al. Serum IGFBP2 and MSLN as diagnostic and prognostic biomarkers for pancreatic cancer. J Pathol (2014) 233(4):670–6. doi:10.1002/path.41219

32. McCaffrey I, Tudor Y, Deng H, Tang R, Suzuki S, Badao S, et al. Putative predictive biomarkers of survival in patients with metastatic pancreatic adenocarcinoma treated with gemcitabine and ganitumab, an IGFIR inhibitor. Clin Cancer Res (2013) 19(15):4282–9. doi:10.1158/1078-0432.CCR-12-1840

33. Chen R, Brentnall TA, Pan S, Cooke K, Moves KW, Lance Z, et al. Quantitative proteomics analysis reveals that proteins differentially expressed in chronic pancreatitis are also frequently involved in pancreatic cancer. Mol Cell Proteomics (2007) 6(8):1331–42. doi:10.1074/mcp.M700072-MCP200

34. Lee DY, Kim SJ, Lee YC. Serum insulin-like growth factor (IGF)-I and IGF-binding proteins in lung cancer patients. J Korean Med Sci (1999) 14(4):401–4. doi:10.3346/jkms.1999.14.4.401

35. Migita T, Naitia T, Asaka R, Miyagi E, Nagano H, Nomura K, et al. Role of insulin-like growth factor binding protein 2 in lung adenocarcinoma: IGFBP2-related apoptotic effect via caspase-3. Am J Pathol (2010) 176(4):1756–66. doi:10.3533/jpath.2010.090500

36. Yu CJ, Wang CL, Wang CJ, Chen CJ, Dan YM, Wu CC, et al. Comprehensive proteome analysis of malignant pleural effusion for lung cancer biomarker discovery by using multidimensional protein identification technology. J Proteome Res (2011) 10(10):4671–82. doi:10.1021/pr2004743

37. Guo C, Lu H, Gao W, Wang L, Lu K, Wu S, et al. Insulin-like growth factor binding protein-2 level is increased in blood of lung cancer patients and associated with poor survival. PLoS One (2013) 8(9):e74973. doi:10.1371/journal.pone.0074973

38. Kim YW, Bae SM, Park DC, Lee KH, Liu HB, Kim IW, et al. Target-based molecular signature characteristics of cervical adenocarcinoma and squamous cell carcinoma. Int J Oncol (2013) 43(2):539–47. doi:10.3892/ijo.2013.1961

39. Eiseman JL, Guo J, Ramanathan RK, Belani CP, Solit DB, Scher HI, et al. Evaluation of plasma insulin-like growth factor binding protein 2 and Her-2 extracellular domain as biomarkers for 17-allylamino-17-demethoxygeldanamycin treatment of adult patients with advanced solid tumors. Clin Cancer Res (2007) 13(7):2121–7. doi:10.1158/1078-0432.CCR-06-2286

40. Wang H, Arun BK, Fuller GN, Zhang W, Middleton LP, Sahin AA. IGFBP2 and IGFBPS overexpression correlates with the lymph node metastasis in T1 breast carcinomas. Breast J (2008) 14(3):261–7. doi:10.1111/j.1524-4741.2008.00527.x

41. Sohn J, Do KA, Liu S, Chen H, Mills GB, Hottobaygi GN, et al. Functional proteomics characterization of residual triple-negative breast cancer after standard neoadjuvant chemotherapy. Ann Oncol (2013) 24(10):2522–6. doi:10.1093/annonc/mdt488

42. Ranke MB, Kaisen KP, Schweizer R, Stadler B, Schleicher S, Elmlinger MW, et al. Genetic variants, prediagnostic circulating levels of insulin-like growth factor binding protein-2 as indicators of hepatocellular carcinoma. Sichuan Da Xue Xue Bao Yi Xue Ban (2002) 40(4):639–43.

43. Urban N, Thorpe JD, Bergan LA, Forrest RM, Kampani AV, Scholler N, et al. Potential role of IHE4 in multimodal screening for epithelial ovarian cancer. J Natl Cancer Inst (2010) 102(3):1630–4. doi:10.1093/jnci/djp359

44. Ollberding NJ, Cheng I, Willens LR, Henderson BE, Pollak MN, Colonel LN, et al. Genetic variants, predominant circulating levels of insulin-like growth factors, insulin, and glucose and the risk of colorectal cancer: the multiethnic cohort study. Cancer Epidemiol Biomarkers Prev (2012) 21(5):870–10. doi:10.1158/1055-9966.EPI-11-1105

45. Ladd J, Basulad T, Johnson MM, Zhang Q, Pittier SJ, Wang H, et al. Increased plasma levels of the APC-interacting protein MAPRE1, LRG1, and IGFBP2 preceding a diagnosis of colorectal cancer in women. Cancer Prev Res (Phila) (2012) 5(4):655–64. doi:10.1158/1940-6207.CAPR-11-0412

46. Liu JM, Shun CT, Liang JT, Chiu HM, Chen MJ, Chen CC, et al. Plasma insulin-like growth factor-binding protein-2 levels as diagnostic and prognostic biomarker of colorectal cancer. J Clin Endocrinol Metab (2010) 95(4):1717–25. doi:10.1210/jc.2009-2668

47. Lancashire LJ, Roberts DL, Dice R, Rezeli M, Marko-Varga G, et al. The development of composite circulating biomarker models for use in anticancer drug clinical development. Int J Cancer (2011) 128(8):1843–51. doi:10.1002/ijc.25513

48. Renehan AG, Painter JE, O’Halleran D, Atkin WS, Potten CS, O’Dwyer ST, et al. Circulating insulin-like growth factor II and colorectal adenomas. J Clin Endocrinol Metab (2000) 85(9):3402–8. doi:10.1210/jcem.85.9.6770

49. Renehan AG, Jones I, Potten CS, Shalet SM, O’Dwyer ST, Elevated serum insulin-like growth factor (IGF)-II and IGF binding protein-2 in patients with colorectal cancer. Br J Cancer (2000) 83(10):1344–50. doi:10.1054/bjoc.2000.1462

50. el Atiq F, Garrouste F, Remacle-Bennet M, Sastre B, Pommier G. Alterations in serum levels of insulin-like growth factors and insulin-like growth factor-binding proteins in patients with colorectal cancer. Int J Cancer (1994) 57(4):491–7. doi:10.1002/ijc.2910570409
carcinoma tissues. J Exp Clin Cancer Res (2009) 28:122. doi:10.1186/1756-9966-28-122

60. Zhou Q, Mao QJ, Yang WD, Chen YR, Huang RX, Zhou XB, et al. Development of IGF-signaling antibody arrays for the identification of hepatocellular carcinoma biomarkers. PLoS One (2012) 7(10):e46851. doi:10.1371/journal.pone.0046851

61. Matuschek C, Rudoy M, Peiper M, Gerber PA, Hoff NP, Buhren BA, et al. Do insulin-like growth factor associated proteins qualify as a tumor marker? Results of a prospective study in 163 cancer patients. Eur J Med Res (2011) 16(10):451–6. doi:10.1186/2047-835x-16-10-451

62. Tombolan O, Orso F, Guzzardo V, Casara S, Zin A, Bonora M, et al. High IGFBP2 expression correlates with tumor severity in pediatric rhabdomyosarcoma. Am J Pathol (2011) 179(5):2611–24. doi:10.1016/j.ajpath.2011.07.018

63. Fottner C, Sattarova S, Hoffmann K, Spottl G, Weber MM. Elevated serum levels of IGF-binding protein 2 in patients with non-seminomatous germ cell cancer: correlation with tumor markers alpha-fetoprotein and human chorionic gonadotropin. Eur J Endocrinol (2008) 159(3):317–27. doi:10.1530/EJE-08-0033

64. Zhang L, Huang W, Chen J, Zhou X, Lu Z, Zhou H. Expression of IGFBP2 in gastric carcinoma and relationship with clinicopathologic parameters and cell proliferation. Dig Dis Sci (2007) 52(1):248–53. doi:10.1007/s10620-006-9358-x

65. Allander SV, Illei PB, Chen Y, Antonescu CR, Bittner M, Ladanyi M, et al. Expression profiling of synovial sarcoma by cDNA microarrays: association of ERBB2, IGFBP2, and ELFP3 with epithelial differentiation. Am J Pathol (2002) 161(5):1587–95. doi:10.1016/S0002-9440(10)64437-9

66. Boule N, Basudin E, Ciguel C, Logis A, Berthet J, Penfornis A, et al. Evaluation of plasma insulin-like growth factor binding protein-2 as a marker for adenocarcinoma. Eur J Endocrinol (2001) 144(1):29–36. doi:10.1530/eje.0.1440029

67. Zumkeller W, Schwander J, Mitchell CD, Morrell DJ, Schofield PN, Preece MA. CpG methylation profiling in VHL related and VHL unrelated renal cell carcinoma. J Biol Chem (2007) 282(2):e31087. doi:10.1371/journal.pone.0031087

68. Baxter RC. IGF binding proteins in cancer: mechanistic and clinical insights. Endocr Rev (2006) 27(1):90–102. doi:10.1210/endo.2005-1084

69. Wheatcroft SB, Kearney MT. IGF-dependent and IGF-independent actions of IGF-1 in gastric carcinoma tissues. Am J Cancer (1993) 29A(14):1973–7. doi:10.1097/00000984-199309034-00055

70. Baxter RC. IGF binding proteins in cancer: mechanistic and clinical insights. Nat Rev Cancer (2004) 14(5):329–41. doi:10.1038/nrc13720

71. Wheatcroft SB, Kearney MT. IGF-dependent and IGF-independent actions of IGF-binding protein-1 and -2: implications for metabolic homeostasis. Trends Endocrinol Metab (2009) 20(4):153–62. doi:10.1016/j.tem.2009.01.002

72. Ahmed RL, Thomas W, Schmitz KH. Interactions between insulin, body fat, and insulin-like growth factor axis proteins. Cancer Epidemiol Biomarkers Prev (2007) 16(3):593–7. doi:10.1158/1055-9966.EPI-06-0775

73. Carmichael AR. Obesity and prognosis of breast cancer. Obes Rev (2007) 8(4):33–40. doi:10.1111/j.1467-789X.2007.00261.x

74. Mattsson A, Svensson D, Schuett B, Osterziel KJ, Ranke MB. Determinants of circulating IGF-I, IGFBP-2 and IGFBP-3 concentrations -1,-2, -3, C-peptide and risk of postmenopausal breast cancer. J Steroid Biochem Mol Biol (2005) 96(1):113–20. doi:10.1016/j.jsbmb.2004.10.006

75. Gummel D, Oliver SE, Donovan JL, Peters TJ, Gillatt D, Persad R, et al. The effect of an isocaloric low-fat diet on human LAPC-4 prostate cancer xenografts in severe combined immunodeficient mice and the insulin-like growth factor axis. Cancer Res Clin Oncol (2003) 161(6):506–16. doi:10.1007/s00432-003-0505-3

76. He Y, Zhou Z, Hofstetter WL, Zhou Y, Hu W, Guo C, et al. Aberrant expression of proteins involved in signal transduction and DNA repair pathways in lung cancer and their association with clinical parameters. PLoS One (2012) 7(2):e31087. doi:10.1371/journal.pone.0031087

77. Hoeflich A, Wirthgen E, David R, Classen CF, Spitschak M, Brenmoehl J. Control of IGFBP-2 expression by steroids and peptide hormones in vertebrates. Front Endocrinol (Lauzeanne) (2014) 5:45. doi:10.3389/fendo.2014.00043

78. Uhlen M, Oksvold P, Fagerberg L, Lundberg E, Jonasson K, Forsberg M, et al. Towards a knowledge-based human protein atlas. Nat Biotechnol (2010) 28(12):1248–50. doi:10.1038/nbt.12148

79. Consortium EP. An integrated encyclopedia of DNA elements in the human genome. Nature (2012) 489(7411):57–74. doi:10.1038/nature11247

80. McDonald FE, Morris MR, Gentle D, Winchester L, Baban D, Ragoussis J, et al. CpG methylation profiling in VHL related and VHL unrelated renal cell carcinoma. Mol Cancer (2009) 8(1):31. doi:10.1186/1476-4598-8-31

81. Simons CC, van den Brandt PA, Stuiverhoud CD, van Engeland M, Weijenberg MP. Body size, physical activity, early-life energy restriction, and associations with methylated insulin-like growth factor-binding protein-2 gene in colorectal cancer. Cancer Epidemiol Biomarkers Prev (2014) 23(9):1852–62. doi:10.1158/1055-9965.EPI-13-1285

82. Chiba T, Yokosuka O, Fukai K, Hirasawa Y, Tada M, Mikata R, et al. Identification and investigation of methylated genes in hepatoma. J Clin Endocrinol Metab (2005) 41(8):1185–94. doi:10.1210/endo.2005.02014

83. Fukushima T, Tzeka T, Shimomura T, Nakano S, Kataoka H. Silencing of insulin-like growth factor-binding protein-2 in human glioblastoma cells reduces both invasiveness and expression of progression-associated gene CD24. J Biol Chem (2007) 282(25):18634–44. doi:10.1074/jbc.M609567200

84. Neri E, Krepela A, Incarnato D, Maldotti M, Parlati C, Galvagni F, et al. Dnmt3L antagonizes DNA methylation at bivalent promoters and favors DNA methylation at gene bodies in ES cells. Cell (2013) 155(1):121–34. doi:10.1016/j.cell.2013.08.056

85. Takeo C, Ikeda K, Horie-Inoue K, Inoue S. Identification of Igf2, Igfbp2 and Enpp2 as estrogen-responsive genes in rat hippocampus. Endocr J (2006) 53(6):513–20. doi:10.1507/endocrj.K08E.220
Insulin-like growth factor binding protein 2 – oncogene or tumor suppressor?

Kuang Z, Yao S, McNeil KA, Thompson JA, Bach LA, Forbes BE, et al.

Matrix metalloproteases in cancer: their role in tumor progression and therapeutic targets. 

Endocrinology (2010) 151(8):3847–62. doi:10.1210/en.2010-0375

Suzuki A, Uhashi H, Watanabe H, Sato T, Iuchi K, Kobayashi T, et al. 

Comparison of estrogen responsive genes in the mouse uterus, vagina and mammary gland. 

J Vet Med Sci (2007) 69(7):725–31. doi:10.1292/jvms.69.725

Korc-Grodzicki B, Ren N, Hall R. 

Effects of estradiol on the expression and production of IGFBP-2 by R33A/30AC mammary tumor cells. 

Oncol Res (1996) 8(2):473–83.

Martin JL, Baxter RC. 

Expression of insulin-like growth factor binding protein-2 by MCF-7 breast cancer cells is regulated through the phosphatidylinositols 3-kinase/AKT/mammalian target of rapamycin pathway. 

Endocrinology (2007) 148(5):2532–41. doi:10.1210/en.2006-1335

Akraprik M, Nürcici D, Cogdell D, Isi Y, Hategan A, Tabus I, et al. 

Dissection of signaling pathways in fourteen breast cancer cell lines using reverse-phase protein lysate microarray. 

Tecnol Cancer Res Cancer (2006) 5(6):543–51. doi:10.1177/1533340605060006

Maxwell PD, van den Berg HW. 

Changes in the secretion of insulin-like growth factor binding proteins-2 and -4 associated with the development of tamoxifen resistance and estrogen independence in human breast cancer cell lines. 

Cancer Lett (1999) 139(2):121–7. doi:10.1016/S0304-3835(99)00009-9

de Bont JM, van Doorn JR, Reddings RE, Graat GH, Passier MM, den Boer ML, et al. 

Various components of the insulin-like growth factor system in tumor tissue, cerebrospinal fluid and peripheral blood of pediatric medulloblastoma and ependymoma patients. 

Int J Cancer (2008) 123(3):594–600. doi:10.1002/ijc.23558

Berg U, Bang P, Carlsson-Skwirut C. 

Calpain proteolysis of insulin-like growth factor-II via proteinase activity on insulin-like growth factor binding protein-2. 

Biochemistry (2007) 46(10):3292–302. doi:10.1021/bi061231r

Monget P, Mazerozub S, Delpuech T, Maurel MC, Manière S, Zapf I, et al. 

Pregnancy-associated plasma protein-A is involved in insulin-like growth factor binding protein-2 (IGFBP-2) proteolytic degradation in bovine and porcine preovulatory follicles: identification of cleavage site and characterization of IGFBP-2 degradation. 

Bio Reprod (2003) 68(1):77–86. doi:10.1095/biolreprod.102.007690

Rehault S, Monget P, Mazerozub S, Tremblay R, Gutman N, Gauthier F, et al. 

Insulin-like growth factor binding proteins (IGFBPs) as potential physiological substrates for human kallikreins kK2 and kK3. 

Eur J Biochem (2001) 268(10):2960–8. doi:10.1046/j.1432-1327.2001.02185.x

Miyamoto S, Nakamura M, Yano K, Ishii G, Hasebe T, Endoh Y, et al. 

Matrix metalloproteinase-7 triggers the matrikine action of insulin-like growth factor-II via proteinase activity on insulin-like growth factor binding protein-2 in the extracellular matrix. 

Cancer Sci (2007) 98(5):858–91. doi:10.1111/j.1349-7006.2007.00448.x

Soh CL, McNeil K, Owczerek CM, Hardy MP, Fabri LJ, Pearce M, et al. 

Exogenous administration of protease-resistant, non-matrix-binding IGFBP-2 inhibits tumour growth in a murine model of breast cancer. 

Br J Cancer (2014) 110(12):2855–64. doi:10.1038/bjc.2014.232

Forbes BE, McCarthy P, Norton RS. 

Insulin-like growth factor binding protein 2 – a structural perspective. 

Front Endocrinol (Lausanne) (2012) 3:38. doi:10.3389/fendo.2012.00038

Mark S, Kübler B, Honig S, Oesterreicher S, John H, Braulke T, et al. 

Diversity of human insulin-like growth factor (IGF) binding protein-2 fragments in plasma: primary structure, IGF-binding properties, and disulfide bonding patterns. 

Biochemistry (2005) 44(9):3644–52. doi:10.1021/bi047480i

Kuang Z, Yao S, McNeil KA, Thompson JA, Bach LA, Forbes BE, et al. 

Cooperativity of the N- and C-terminal domains of insulin-like growth factor (IGF) binding protein-2 in IGF binding. 

Biochemistry (2007) 46(48):13730–32. doi:10.1021/bi071251d

Kibbey MM, Jameson MJ, Eaton EM, Rosenzweig SA. 

Insulin-like growth factor binding protein-2: contributions of the C-terminal domain to insulin-like growth factor binding and cell growth. 

Med Pharmacol (2006) 69(3):383–45. doi:10.1124/mol.105.016998

Storr SJ, Carragher NO, Frame MC, Parr T, Martin SG. 

The calpain system and cancer. 

Nat Rev Cancer (2011) 11(5):364–74. doi:10.1038/nrc3050

Hladar-Olson E, Winberg JO, Uhlin-Hansen L. 

Matrix metalloproteinases in cancer: their value as diagnostic and prognostic markers and
inhibition of insulin-like growth factor signaling. Cancer Biol Ther (2006) 5(10):1408–14. doi:10.4161/cbt.5.10.3455

133. Milewicz T, Rys J, Wójtowicz A, Stochmal E, Joch R, Krzyziek J, et al. Overexpression of P53 protein and local hGH, IGF-I, IGFBP-3, IGFBP-2 and PRL secretion by human breast cancer explants. Neuropathol Appl Neurobiol (2011) 37(3):328–33.

134. Coppé JP, Patil CK, Rodier F, Sun Y, Muñoz DP, Goldstein J, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol (2008) 6(12):2853–68. doi:10.1371/journal.pbio.0060301

135. Hjelmeland LM, Cristofolo VJ, Funk W, Rakoczy E, Katz ML. Senescence of the retinal pigment epithelium. Mol Vis (1999) 5:33.

136. Matsunaga H, Handa JT, Gelfman CM, Hjelmeland LM. The mRNA phenotype of a human RPE cell line at replicative senescence. Mol Vis (1999) 5:39.

137. Shelton DN, Chang E, Whittier PS, Choi D, Funk WD. Microarray analysis of replicative senescence. Curr Biol (1999) 9(17):939–45. doi:10.1016/S0960-9822(99)80420-5

138. Busund LT, Richardsen E, Busund R, Ukkonen T, Bjørnsen T, Busch C, et al. Significant expression of IGFBP2 in breast cancer compared with benign lesions. J Clin Pathol (2003) 56(4):361–6. doi:10.1136/jcp.2004.020834

139. Wang H, Rosen DG, Fuller GN, Zhang W, Liu J. Insulin-like growth factor-binding protein 2 and 5 are differentially regulated in ovarian cancer of different histologic types. Mod Pathol (2006) 19(9):1149–56. doi:10.1038/modpathol.3800637

140. Villani RM, Adolphe C, Palmer J, Waters MJ, Wainwright BJ. Patched1 inhibits epidermal progenitor cell expansion and basal cell carcinoma formation by limiting Igfbp2 activity. Cancer Prev Res (Phila) (2010) 3(10):1222–34. doi:10.1158/1940-6207.CAPR-10-0082

141. Kang Z, Yu Y, Zhu YJ, Davis S, Walker R, Meltzer PS, et al. Downregulation of IGFBP is associated with resistance to IGFIR therapy in rhabdomyosarcoma. Oncogene (2014) 33(50):5697–705. doi:10.1038/onc.2013.509

142. Frommer KW, Reichenmüller K, Schutt BS, Hoenlich A, Ranke MB, Dödt G, et al. IGF-independent effects of IGFBP-2 on the human breast cancer cell line Hs578T. J Mol Endocrinol (2006) 37(1):13–23. doi:10.1677/jme.1.01955

143. Sakamoto M, Kondo A, Kawasaki K, Goto T, Sakamoto H, Miyake K, et al. Analysis of gene expression profiles associated with cisplatin resistance in human ovarian cancer cell lines and tissues using cDNA microarray. Hum Cell (2001) 14(4):305–15.

144. Lu H, Wang L, Gao W, Meng L, Dai B, Wu S, et al. IGFBP2/FAK pathway is causally associated with dasatinib resistance in non-small cell lung cancer cells. Mol Cancer Ther (2013) 12(12):2864–73. doi:10.1158/1535-7163.MCT-13-0233

145. Biernacka KM, Uzoh CC, Zeng L, Persad RA, Bahl A, Gillatt D, et al. Hyperglycaemia-induced chemoresistance of prostate cancer cells due to IGFBP2. Endocr Relat Cancer (2013) 20(5):741–51. doi:10.1530/ERC-13-0077