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Review Article

Disease evidence for IGFBP-2 as a key player in prostate cancer progression and development of osteosclerotic lesions

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Abstract: Accumulating evidence indicates that alterations in the IGF axis contribute to the development of chemo- and radio-resistant, advanced-stage cancers. Additionally, they contribute to hormonal insensitivity in adenocarcinomas such as those derived from prostate and breast. The ligands, IGF-I and IGF-II, along with their receptors, IGF-IR and IGF-IIR, have been implicated in a wide range of disease. Activation and subsequent signal transduction through the receptors is attenuated, and/or potentiated, by the interactions of IGF axis ligands, IGF-I/II, with the high affinity IGF-binding proteins 1 to 6 (IGFBP1-6). New evidence indicates that the IGFBPs, irrespective of ligand interactions, correlate with the development and metastatic behavior of several cancers. Increased expression of insulin-like growth factor binding protein 2 (IGFBP-2) is found in advanced cancers of the ovary, breast, stomach, adrenal gland, bladder, CNS, and prostate. Further, IGFBP-2 seemingly has ligand-independent effects that participate in the development and dissemination of advanced cancer cells. As such, IGFBP-2 can assist in the development of the lethal phenotype for some cancers. While several reports have shown an important role for IGFBP-2 in the development of androgen insensitivity and the proliferation of AI PCa cells in vivo, these studies have not tested a role for IGFBP-2 in the metastatic spread of AI PCa cells. Additionally, the mechanism of IGFBP-2 action in these events has not been elucidated. The redundancy and abundance of the IGFBPs have precluded a clear understanding of the means by which IGFBP-2 signals. Components of these signaling pathways, particularly IGFBP-2, are being evaluated currently in clinical trials.

Key Words: Insulin-like growth factor, IGF; prostate cancer, PCa; androgen insensitivity, AI; androgen sensitive, AS; neoplasm, bone, metastasis

Introduction

It has been recognized for some time that steroid hormones contribute, either directly or by a poorly defined contributory manner, to the initiation, promotion, and progression of tumors to an advanced, more aggressive, and malignant state [1, 2]. It was realized that certain tumors are hormone-sensitive. This was exploited for the design of the first effective clinical treatments for advanced breast and prostate cancers (PCa). [3-9]. The presence of steroid hormone receptors is the most widely used prognostic marker for breast cancer responsiveness to anti-estrogen therapy. Indeed, more than 60 years ago Charles Huggins proposed and espoused hormone ablation as an effective therapy for men with advanced PCa. Prevailingly for patients, this extended lifespan and reduced metastasis-associated pain [10, 11]. Huggins' approach evolved into some version of hormone blockade or ablation, now the mainstay clinical treatment for advanced, metastatic PCa [12]. Unfortunately, chemical/surgical castration or combined androgen blockade eventually results in the development of hormonally insensitive, very aggressive PCa. Thus, a search continues for new molecular targets of which can be exploited for slowing progression to an advanced, androgen insensitive (AI) state.

The members of growth hormone (GH)-insulin-like growth factor (IGF) axis possess pleotropic actions in cell proliferation [13, 14], growth [15-18], survival [17-23], angiogenesis [18, 23, 24], chemoresistance [25] and signaling cross-talk to both steroid hormone receptors and other growth factor receptor signaling cascades [3, 13, 19, 24, 26-30]. In the proper context, these molecules are central to disregulated processes in the development and progression of neoplasias from a wide array of tissues. The IGF axis consists of two ligands (IGF-I and IGF-II), two receptors (IGF1R and IGF2R), as well as a family of closely related IGF binding proteins (IGFBP 1-6) of which are distinct from the CCN proteins [31]. Altered expression in IGF axis members is generally considered associated with the development of several cancers including prostate [13, 32]. Elevated serum levels of IGF-1 have been associated with increased risk for developing breast cancer in women [28, 33-35], colorectal cancer [36-39], and prostate cancers [36, 40-45], as well as enhancing the likelihood of developing additional primary tumors from head and neck cancer [46, 47]. In breast cancer patients, decreased serum ratios of free/total IGF-II correlated with primary tumor size [48], further implicating the more stable, complexed form of the ligand as the critical compound. The ligands, IGF-I and -II show similar evidence of altered expression in both prostate cancer tissues and cell lines [49]. Generally speaking, the level of IGF ligands appears to increase in carcinoma cell lines with aggressiveness [50, 51]. In normal tissue, the expression pattern of these ligands is predominately stromal, but in cancer their stromal expression is enhanced, combined with some epithelial expression [13, 49]. In the isogenic cell lines of the LNCaP human PCa progression model, IGF-II secretion increases from LNCaP to C4-2 and remains stable in the bone-adapted cell line, C4-2B4 [50]. However, IGF-I expression is not detected in LNCaP to C4-2 while C4-2B4 cells express significantly detectable IGF-I [51]. Furthermore, in both the LNCaP and LAPC-9 xenograft models, succession from AS to AI is accompanied by a dramatic increase in IGF-I and IGF-IR, as well as alterations in additional IGF-axis members [52]. Elevated IGF-II levels increase aggressiveness of MCF-7 cells both in vitro and in vivo [48, 53-56]. Synonymously, reduced IGF-1 and II levels inhibit PC-3 prostate cancer cell growth [57-59].

Based upon the co-expression of IGFBPs, IGFs, and steroid hormone receptors [19, 20, 35, 54, 60, 61] the role of the IGF type I receptor (IGF1R) in cancer development and progression is tissue dependent as well as contextually dependent. In part this is because the receptor has a dual role of controlling cell proliferation or cell differentiation. The IGF1R is at least somewhat produced in almost all expression studies for human benign and malignant tissues, and is infrequently lost.

Insulin-Like Growth Factor Binding Protein-2 (IGFBP-2) has garnered interest as a candidate target/molecule for PCa development and progression [62]. In addition to the possible targeting of IGFBP-2 to prevent the progression to AI PCa, IGFBP-2 may have utility in clinical screening for the detection of both advanced PCa and AI PCa. Herein we briefly summarize the evidence for ligand-independent effects of IGFBPs with an emphasis on the role of IGFBP-2 in cancer progression. Based on the literature and personal experience, we describe the ability of IGFBP-2 (1) to promote the survival of PCa cells in a castrate environment, (2) to facilitate progression to AI, and (3) to possibly enhance the aggressive behavior of AI PCa cells. By this, IGFBP-2 maybe an important driving force in the development of metastatic, hormonally refractive, bone-colonizing PCa.

IGFBPs

Six well characterized IGFBPs (1-6) are known, ranging in molecular weights from 24 kDa (IGFBP-4) to 45 kDa (IGFBP-3). All six IGFBPs have affinities for IGF-I and IGF-II in the same order of magnitude as the ligands have for IGFIR [63-69]. The IGFBPs are best understood to regulate IGF bioavailability and to maintain the half-life of circulating IGF-I/II in all tissues, including that of the prostate [70]. Based on physiological context (i.e. cell type, growth factor milieu present, etc), individual IGFBPs may act to either attenuate or potentiate IGF signaling. Thus, the action of IGFBPs is described classically as "IGF-dependent". Via poorly understood mechanisms, IGFBPs clearly extend the serum half-life of IGFs and their resulting presentation to cognate receptors [63, 71, 72]. This can result in pleiotropic but tissue specific signaling cascades and effects

observed for the IGFs [63, 71, 72]. In contrast to their involvement in signal promotion, some evidence indicates that IGFBPs participate in the scavenging of free, bioactive IGFs thereby dampening the signaling responses [65, 73, 74].

Ligand-dependent Actions of IGFBPs and Cancer

Although its expression is not detected in PCa tissue [75], serum IGFBP-1 levels are significantly greater in patients with PCa (mean = 23.7ng/mL) as compared to healthy individuals of related age (mean = 14.4ng/mL) [76]. Interestingly, however, IGFBP-1 has been shown to modulate the bioavailability of IGF-I and decreases LNCaP cell growth in vitro [16]. Because IGFBP-1 is nutritionally regulated [77], the physical condition of the patients from which the sera was derived in the prior study may be the cause for this discrepancy. Here, patients in a fasting, or nutritionally poor, condition would allow for misinterpretation. Its potential inhibitory effects displayed in Ngo et al. proffer a therapeutic role for IGFBP-1, but there is no evidence for its expression in the prostate or prostate cancer [75]. Additional evidence for a disease-inhibitory role of IGFBP-1 extends beyond PCa. The risk of colorectal cancer is inversely correlated with increased IGFBP-1 levels [78].

As discussed above, the expression of IGFBP-2 increases during prostate disease progression from benign prostatic hyperplasia (BPH) to metastatic prostate cancer [79]. This trend continues with increased IGFBP-2 expression in AI PCa [80]. IGFBP-2 promotes glioma cell invasion [14] and increased IGFBP-2 levels are found in the sera of patients with aggressive ovarian cancer [81]. Elevated IGFBP-2 levels positively correlate with the presence of cancer antigen 125 (CA 125), a putative cancer biomarker [81]. In this regard, IGFBP-2 holds promise as a potential biomarker for the screening of such cancers. By contrast, IGFBP-2 also may have anti-tumorigenic properties. Elevated IGFBP-2 levels were inversely correlated with the risk of colorectal cancer [78] as well as primate mammary epithelial cell proliferation and survival [82, 83].

IGFBP-3 expression decreases during the progression from BPH to metastatic PCa [79]. IGF/IGFBP-3 ratios indicate a man's relative risk for developing prostate cancer [36, 41], while plasma concentrations of IGFBP-3 hold promise as a predictor of advanced stage disease [84]. Since the risk for non-small cell lung cancer (NSCLC) is correlated to a particular polymorphic variation in the IGFBP-3 gene [85], genetic polymorphisms may explain its role in the development of cancer. In contrast to PCa, increased serum levels of IGFBP-3 portend a higher risk of developing breast cancer (BCa) in premenopausal women [34, 82, 86-88]; were positively correlated with BCa tumor size and increased in ER/PR-negative patients [88]; and finally, were reported in patients diagnosed with colorectal cancer [89]. This is controversial for colorectal malignancies however, as other groups report an inverse correlation between IGFBP-3 levels and disease risk [32]. It has been suggested that the discrepancies between these data resulted from differential techniques in assaying for intact and/or proteolytically cleaved IGFBP-3 [78]. The discrepancy may also be the result of the actual IGFBP-3 levels in patients at risk versus those with colon cancer.

IGFBP-4 has been detected in endothelial cells [90], spinal cord [91], bone mesenchyme [92-95], and human fibroblasts [96-98], but seems to be absent in the normal protate [99-101]. Tennant et al. detected IGFBP-4 in prostate epithelial cell primary cultures and observed a decrease in expression in the more aggressively tumorigenic derivative cell lines [102]. However, other groups reported LNCaP cells display no IGFBP-4 protein and low mRNA expression [103, 104]. Prostatic stromal cell primary cultures have shown some expression of IGFBP-4 [105]. IGFBP-4 expression is seen in a variety of cancers including neuroblastoma [106, 107], osteosarcoma [95, 108], and that of the breast [109], lung [110], and prostate [100-102, 104, 111, 112]. In vitro studies indicate an IGF-inhibitory action for IGFBP-4 [65, 77, 113-115]. In an IGF-dependent manner, IGFBP-4 was also shown to inhibit the invasion and proliferation of colon cancer cells [116], osteosacroma growth [117], and delayed the onset of prostate tumor formation [15]. These data strongly implicate IGFBP-4 as a negative modulator for PCa growth.

IGFBP-5 is expressed in various cell types including human fibroblasts [118], ovarian

granulose cells [50], and articular chondrocytes [119]. Further, expression of IGFBP-5 has been found in the rat ventral prostate, as well as various PCa model systems including LNCaP cells [120], PC3 cells [120], and CWR22 human prostate xenografts [49]. IGFBP-5 has been found to inhibit the actions of IGF-I in osteosarcoma [121] and smooth muscle cells [122]. However it appears to potentiate the effects of IGF-I in prostatic disease, consistently [118, 123]. It mimics IGFBP-2 expression as it increases with the progression of prostatic disease from BPH to metastatic PCa [49, 102, 111, 112, 123]. Through IGF-I, IGFBP-5 accelerates the progression of prostate cancer cells to AI [124]. Interestingly, the expression of IGFBP-5 appears to be stromally derived and not a direct result of PCa expression [102]. Therefore, the generation of a reactive stroma or microenvironment rich in IGFBP-5 may be a prerequisite for rapid PCa establishment and growth.

Seemingly, IGFBP-6 possesses an initial anti-proliferative role that is altered during disease progression to become an opposite stimulatory role. Although mechanistically unclear, IGFBP-6 can stimulate osteosarcoma cell growth and survival [125], while it hinders IGF-2 signaling in healthy tissue [107, 126], likely reducing cell growth. The aggressive nature of P69 cell lines is inversely correlated with IGFBP-6 expression [127]. P69, PC-3, ALVA-31, and DU145 prostate cancer cell lines all make IGFBP-6 [103, 127, 128] while LNCaP cells do not [103, 104]. IGFBP-6 is present in ovarian tissue [64], fibroblasts [126], primary cultures of prostate epithelial cells [127], and osteoblasts [129, 130]. Cancers including osteosarcoma [125], neuroblastoma [106, 107], and that of the breast [109] and prostate [104, 111, 127, 128, 131] produce IGFBP-6.

The molecular context in which the cancer lays includes the dynamic interplay between the tumor cells and the neighboring microenvironment. Perhaps the functions of IGFBP-2, along with the actions of other IGF-axis members, depend more on this context than previously thought.

Ligand-independent actions of IGFBPs and Cancers

IGFBPs also act in manners that have no obligatory requirement for ligand or, at least, signal transduction through the IGFIR. Accordingly, the ability of IGFBPs to act via these non-classical pathways is referred to as IGF-, IGFIR-, or ligand-independent. Autocrine production of IGF axis members in cancer cells complicates the analysis of IGFBP ligand-independent effects. Nonetheless, evidence supports the ability of IGFBPs to act through non-IGFIR mediated pathways that alter cell extracellular matrix (ECM) production and cell surface interactions [132-134], nuclear localization [135], apoptosis [136], growth [136], and the modulation of transcriptional activity [137].

Frommer et al. showed that exogenously added recombinant IGFBP-2 induced apoptosis in the IGFIR-null human BCa cell line (Hs578T). Microarray and RT-PCR data generated by the same group indicates that IGFBP-2 induces the expression of genes that regulate cellular proliferation, adhesion, and apoptosis [138]. Butt et al. [63] demonstrated that IGFBP-3 induced growth inhibition and apoptosis of human breast cancer cells even when blocking signal transduction through the IGF-IR. Additional data suggests the presence of IGFBP-3 specific membrane receptors on the surfaces of some cell types, including human breast cancer epithelial cells [139], human airway smooth muscle cells (ASMs) [136], and prostate cancer epithelial cells [140]. Interestingly, the TGFβ type V receptor can seemingly interact with both TGF-β1 and IGFBP-3 [141-143]. In the absence of IGFs, IGFBP-4 inhibits anchorage-independent colony formation of colon cancer cells [116]. Furthermore, data to supports that bone formation is stimulated by IGFBP-5 in an IGF-independent fashion [144].

Ligand-independent actions of IGFBPs and PCa

Normally, post-translational modifications of IGFBPs alter their interaction with ligand, however, this may also change the ligand independent functions of the IGFBPs. Such modifications include phosphorylation (IGFBP-1, -3, and –5), N-glycosylation (IGFBP-3, and –4), and proteolysis (IGFBP1-6). Of these modifications, IGFBP proteolysis may be the most crucial as it acts to (1) decrease the magnitude of intact IGFBP present [145], (2) decrease the affinity of a given IGFBP for IGF-I and/or IGF-II (thus increasing the concentration of free, bioactive IGFs) [77],

and/or (3) liberate otherwise cryptic domains, resulting in additional IGF-independent effects not observed in intact IGFBPs [146, 147]. Thus, the ability of IGFBPs to undergo regulated proteolysis has important implications regarding their ability to act in both an IGF-dependent and IGF-independent manner. Moreover, the inability to regulate levels of free, bioactive IGFs via IGFBP proteolysis, or the inability to produce bioactive IGFBP fragments, may have important consequences in regard to disease progression.

As an example and introduction to this topic we use IGFBP-3, which has been studied extensively in this context. Independent of ligand, IGFBP-3 has been shown to induce apoptosis in PC-3 cells in a [148]. In support this ligand independent action, ligand binding mutants still demonstrated IGFBP-3-induced apoptosis [59]. As previously eluded to, IGFBP-3 maybe signaling through the TGFβ type V receptor [140], and possibly via other specific, yet unidentified cell surface proteins [136, 139, 140]. Rajah et al. showed that the pro-apoptotic effects of TGF-β1 in PCa required IGFBP-3 stimulation, and that IGFBP-3 still induced apoptosis in IGF-receptor null mouse fibroblasts [140]. Other IGF-independent growth effects of IGFBP-3 occur via the RXR nuclear receptor and what maybe a IGFBP-3-specific cell surface receptor [63]. Cathepsins [120], matrix metalloproteinases [149], and PSA [150] are all proteases of which cleave IGFBP-3 at various sites. The proteolysis results in the production of lower molecular weight fragments that have a decreased affinity for ligand [151]. In this way, proteolysis may lead to the increased availability of IGFs to interact with their receptors.

IGFBP-2 and progression to AI PCa

It remains to be determined whether increased IGFBP-2 expression drives progression to AI-PCa or is an adaptive response to an androgen depleted environment. A comparison of the androgen sensitive CWR22 and androgen insensitive CWR22R xenograft tissues provided the early evidence for a role of IGFBP-2 in progression to AI-PCa. In these tumor xenografts IGFBP-2 was over-expressed greater than two fold in the CWR22R tumors [152]. Here, patient samples expressed strong IGFBP-2 staining in 100% of hormone refractory PCa versus 36% of primary PCa and in 0% of benign prostatic hyperplasia specimens. Subsequent studies validated these findings [62, 80, 153-155], thereby supporting that increased IGFBP-2 expression is associated with progression to AI. Tissue microarray data from repeated biopsies of intermittent androgen ablation trials indicated that IGFBP-2 protein levels are increased with time and number of cycles following androgen ablation, especially in samples derived from patients converting to AI PCa [80]. Furthermore, IGFBP-2 mRNA levels were increased in both castrated rats [99] and in rats undergoing chemical castration using 10 mg/kg bicalutamide [52]. In these studies the highest levels of IGFBP-2 mRNA were coincident with peak levels of apoptosis, suggesting that increased IGFBP-2 expression is important for the expansion of AI clones in a castrate environment. This assertion is supported by a report indicating that IGFBP-2 stimulates the proliferation of AI PCa cells [154]. Also, tumors derived from LNCaP cells selected to overexpress IGFBP-2 displayed enhanced rebound following castration as well as increased tumor size and PSA levels post-castration [80]. Treatment of mice bearing LNCaP tumors with IGFBP-2 anti-sense oligonucleotides (ASOs) resulted in decreased PSA levels and tumor volumes in the castrate environment. This lends support to the idea that the tumor cells have adapted or acquired a dependence upon the expression of IGFBP-2. Thus, it appears that IGFBP-2, in addition to promoting progression to AI, may be an excellent molecular target for preventing this deadly process. However, the actual molecular mechanism by which IGFBP-2 acts in the genesis of AI-PCa is unclear. Elucidation of this adaptive or promotional pathway may provide other significant targets for therapeutic development.

A role for IGFBP-2 in the metastatic phenotype of AI PCa?

Classically, IGFBP-2 functions to modulate of IGF-I and IGF-II induced cell signaling. Evidence indicates that increased levels of IGFBP-2 are correlated both with the presence of advanced disease and may promote several steps of the metastatic process (see **table**). For example, invasive breast cancer was shown to express higher amounts of IGFBP-2 compared to carcinomas in situ [156] and IGFBP-2 facilitates the migration of breast

Table 1: Evidence Relating IGFBP-2 to Advanced Cancer

	In vitro	*In vivo*
Adrenal Cancer	no reports	Increased in the serum of patients [165] Increased expression in malignant vs. benign human tumors [166]
Bladder Cancer	Increased invasion of bladder cancer cells [167]	Increased expression in invasive disease [168]
Breast Cancer	Denotes anti-estrogen resistant BCa cell lines [169]	Increased expression in invasive disease [156]
CNS cancers	Increased migration of SHEP cells [14] Increases glioma cell invasion [170] Assoc. with expression of Invasion genes [159]	Correlated with decreased survival [171] Increased with tumor grade [172] Increased with progression [173]
Gastric Cancer	Expressed in multiple cancer cell lines [174] Associated with increased proliferation [175]	Increased in peritoneal metastasis [176] Associated with advanced disease [137]
Ovarian Cancer	Increased invasion [175]	Increased in serum of ovarian cancer patients [177] Increased in ovarian tissue during progression [178] Increased in, and associated with increased risk of advanced disease [175] [179]
Prostate Cancer	Increased in metastatic, AI PCa cell lines [51] Loss of proteolytic degradation in AI PCa [145] Decreased time to attain AI [80]	Serum levels have inverse correlation to advanced disease [180] Increased expression in AI PCa [75]

cancer cells in response to IGF signaling [157]. Similarly, IGFBP-2 over expression is positively associated with advanced gastric [29] and ovarian cancers [158]. In vitro, the invasive capability of glioblastoma [159] and ovarian cancer cells [158] is increased significantly with over expression of IGFBP-2.

Finally, IGFBP-2 negatively modulates cell adhesion [133], perhaps facilitating the entry of metastatic cells into a distal site. In contrast to these reports, there are examples of IGFBP-2 negatively regulating the malignant behavior of breast cancer cells [132, 157]. This supports the pleiotropic and tissue-specific functions of IGFBPs as described previously [64, 72, 77, 160]. These data notwithstanding, the molecular determinants associated with the metastatic process, which clearly vary by cellular context, are only starting to be elucidated. To date, however, the majority of accumulated data strongly implies that increased production and/or accumulation of IGFBP-2 is associated with the presence of more clinically aggressive cancers and increased metastatic phenotype in vitro.

Data published recently from our laboratory suggests that IGFBP-2 is proteolyzed by AS PCa cells in the presence of androgen. Therefore, a consequence of castration may be to increase the levels of intact IGFBP-2 [145]. Furthermore, the ability of PCa cells to proteolyze IGFBP-2 in the presence of androgen is lost during progression to AI

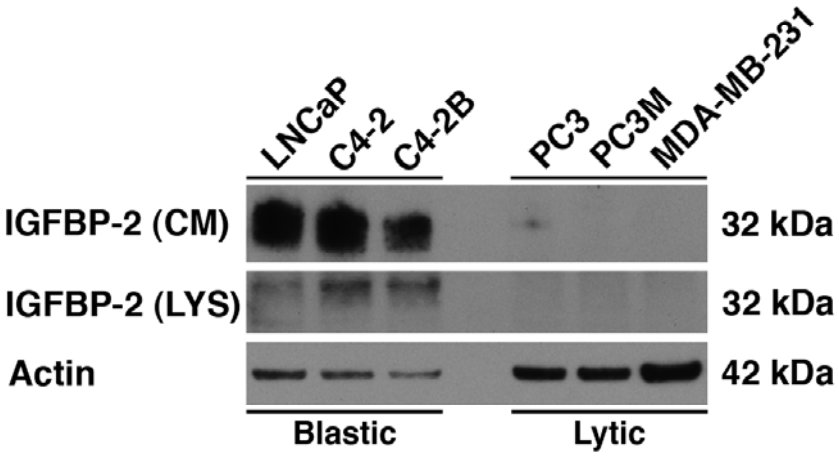

Figure 1. Western blot analysis for IGFBP-2 in both the whole cell lysate (WCL) and conditioned media (CM) of osteoblastic and osteolytic cancer cell lines. Actin served as a loading control for WCL only. Cell lines were cultured in 5% FBS and serum starved for 48hrs before lysis. IGFBP-2 is present in the osteoblastic/sclerotic prostate cancer cell lines (LNCaP, C4-2, and C4-2B4) while absent in the osteolytic prostate cancer cell lines (PC3 and PC3M) and breast cancer cell line (MDA-MB-231).

[145]. The post-castration loss of IGFBP-2 proteolysis would result in increased levels of IGFBP-2, thus providing a local microenvironment suitable for PCa adaptation to high levels of IGFBP-2. This would lead to the aforementioned increased proliferation of PCa cells in an androgen depleted environment [154], and facilitate the subsequent clonal expansion and development of AI PCa [80]. Our work and that of others [51] has shown that AI PCa cells isolated from the bone microenvironment produce higher levels of IGFBP-2. This all argues strongly that IGFBP-2 plays a major role in the development of both AI PCa as well as metastasis to bone.

Yet still unclear are the mechanisms involved by which PCa cells promote the formation of osteosclerotic lesions in bone. IGFBP-2 may be correlated with the extent of how osteoblastic or osteolytic these lesions become. In vitro data from our lab suggests that IGFBP-2 is present in both the cell lysate and culture media of osteoblastic prostate cancer cell lines while absent from that of osteolytic cancer cell lines (**Figure 1**). The presence of IGFBP-2 possibly possesses a causal relationship for the difference in bone turnover among different forms of advanced disease.

Any role that IGFBP-2 has in facilitating dissemination of metastatic cancer cells almost certainly arises from the combination of ligand dependent and independent actions. It is well known that increased IGF signaling can stimulate the aggressive behavior of a variety of cancer cells, including neuroblastoma [161] and PCa [162, 163], as well as numerous others. Indeed, prostate cancer cells of the LNCaP progression series express progressively more IGF-II [164] and begin to express IGF-I following bone adaptation [51]. Further, we have shown that expression of IGF ligands increases the survival of AI-PCa cells in an androgen receptor independent manner [19]. So, in the cases where increased IGFBP-2 production/activity facilitates IGF signaling, it is conceptually straightforward to conceive how this would contribute to metastasis. On the other hand, the mechanism by which IGFBP-2 acts independently of IGF signaling to facilitate metastasis is not well understood, but may be rooted in the presence of a putative heparin-

binding domain [14], as well as an RGD sequence in the C-terminus of IGFBP-2. These two domains were critical for the ability of IGFBP-2 to interact with ECM components [14] and cell surface integrins [132, 133]. Therefore, these two domains may allow IGFBP-2 to act as a molecular "bridge" between the cell surface and the ECM. Increased expression/accumulation of IGFBP-2 may result in the increased ability of a metastatic cell to interact with the local environment, thus facilitating the aggressive behavior of metastatic cells.

Future studies on the role of IGFBP-2 in PCa metastases

Currently, studies are needed to determine (1) if increased levels of IGFBP-2 promote the selection of or adaptation of AI PCa cells, (2) if IGFBP-2 selectively promotes the growth of AI-PCa cells, (3) if IGFBP-2 operates in an IGF-dependent and/or IGF-independent manner to facilitate the metastasis of AI PCa cells, (4) the cell signaling pathways activated by IGFBP-2 binding, (5) if the action of IGFBP-2 in the context of androgen is altered in a castrate environment, (6) the molecular basis for IGFBP-2 induced migration, metastasis, and invasion, and (7) better therapeutic targets for AI PCa and PCa metastasis.

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