Transforming Growth Factor-β Superfamily in Meningiomas: Targets for Novel Therapy in Meningiomas?

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Abstract

Meningiomas are central nervous system tumors with a high recurrence rate. In the absence of effective chemotherapies, inoperable, recurrent and metastatic tumors remain a therapeutic challenge. Members of the TGF-β super-family play an integral role in the development, progression and metastases of many malignancies yet may be underappreciated participants in the biology of meningiomas. This paper reviews the common abnormalities in TGF-β or BMP signaling in neoplasias with a focus on meningiomas. Sites of potential targeting for new chemotherapies are also noted.

Keywords: Meningioma; TGF-β receptors; TGF-β; BMP; SMAD

1. Introduction

Meningiomas represent a common primary brain tumor in adults (Perry et al., 1997; Mawrin and Perry, 2010). Although the majority are benign, approximately 20% are World Health Organization (WHO) grade II with a recurrence rate approaching 40% at 5 years after gross total resection (Perry et al. 1997; Mawrin and Perry, 2010). Metastases also occur in grade II tumors with an underestimated frequency (Surov et al., 2013, Forest et al., 2014). Anaplastic, WHO grade III meningiomas, approximately 3-5% of tumors, have an even higher recurrence rate and metastatic potential. Moreover, the mortality rate of anaplastic meningiomas is 20% at 2 years (Forest et al., 2014; Yamaguchi et al., 2014). Thus, while surgical resection is possible for many WHO grade I and II tumors, growth at inaccessible sites complicates management of some. Stereotactic radiotherapy is a treatment option and effective in many cases (Sheehan et al., 2010, Komotar et al., 2012, Starke et al., 2012) but the high rate of recurrence and resistance to radiation over time complicates this
management and underscores the need for an effective chemotherapy (Wen et al., 2010; Chamberlain, 2012). The absence of viable chemotherapies has prompted the search for novel therapies targeting growth regulatory cytokines. Of these, members of transforming growth factor beta (TGF-B) super-family may be particularly relevant.

2. TGF-β

2a. TGF-β synthesis and latency

Fig. 1. TGF-β and BMP signaling in meningiomas.

Multiple sites in these receptors and signaling pathways have been identified in malignancies including meningiomas.

The transforming growth factor-βs (TGF-β) represent an important family of numerous peptides including the TGFB1, 2, 3 and bone morphogenetic proteins (BMPs). TGF-βs are synthesized as prohormones. Pro- TGF-β1, 2 or 3, 75 kDa homodimers, are cleaved in the Golgi apparatus to form 25 kDa homodimers (Barnard et al., 1990; Shi and Massague, 2003). The mature homodimers associate with latency associated proteins to form latency complexes (Barnard et al., 1990; Rifkin, 2005). These are further processed in the cells endoplasmic reticulum where disulfide bonds are
formed between the latency binding protein and TGF-β to form larger latent complexes. The larger complexes are secreted to the extracellular matrix where they anchor to cell membrane components such as fibronectin and remain inactive (Taiple et al., 1994; Isogai et al., 2003). Anchored latent TGF-β is cleaved by several proteinases such as thrombospondin and metalloproteinase MMP2, integrins and changes in pH to form the active TGF-β monomer which, in turn, binds by sulfides to become functional TGF-β (Barcellos-Hoff and Dix, 1990; Schultz-Cherry S and Murphy-Ulrich JE, 1993; Munger, J.S. et al., 1999; Jenkins, 2008).

In terms of growth regulatory effects on normal cells, TGF-β is largely inhibitory. In fact, TGF-βs inhibit proliferation of nearly all normal epithelial cells, mesenchymal cells and cells from some low grade neoplasias (Piel and Roberts, 2001; Millet and Zhang, 2007; Massague, 2008; Massague, 2012). TGF-β effects are largely transduced through binding to the TGF-β type II receptor (TGF-βRII) that then complexes with the TGF-β type I receptor phosphorylating and activating its serine/threonine kinase (TGF-βRI) (Massague, 1992). TGF-βRII i.e. betaglycan, is a membrane glycoprotein which facilitates TGF-β binding to the TGF-βRII (Massague, 1992). The activated TGF-βRI receptor phosphorylates a number of membrane/cytoplasmic proteins which transduce growth regulatory signals to the nucleus (Massague, 1992; Massague, 2012) (Figure 1).

2b. TGF-β signaling

The main signal effectors for TGF-β are the SMADs 2 and 3 (Zhang et al., 1996; Zhang and Derynk, 1999). Activation of the type I receptor cytoplasmic domain phosphorylates the carboxyterminal domain of SMAD 2 and SMAD 3 resulting in their heteromerization with SMAD 4 in the cytoplasm. The activated SMAD 2, 3 and 4 complex translocates to the nucleus where they interact with and stabilize transcriptional complexes of numerous transcription factors (Zhang et al., 1996; Zhang and Derynk, 1999; Massague, 2012) (Figure 1). Under some circumstances, TGF-β also utilizes other signaling pathways including the RAF-MAPK/Erk kinase-1(MEK-1)-mitogen-activated protein kinase (MAPK) pathway (Yan et al., 1994; Kawabata et al., 1995; Mucasi et al., 1996; Frey and Mulder, 1997; Lewis et al., 1998; Mulder, 2000; Javelaud and Mauviel, 2005). This may be by direct TGFBR1 activation of Ras then downstream RAF, MEK-1 and p44/42MAPK (Mulder, 2000; Javelaud and Mauviel, 2005). This activation may be part of a tightly regulated feedback loop in some tumors such as prostatic carcinoma cells where constitutively activated MAPK induces TGFβ synthesis (Yu et al., 2010). Nonetheless, at higher levels TGF-β may attenuate p44/42 MAPK activation by recruiting and activating phosphatase PP2a which dephosphorylates MAPK (Yu et al., 2010). TGFβs also signal via the phosphoinositide 3 kinase (PI3K)-protein kinase B/Akt - p70^S6K (Kawabata et al., 1995; Lewis et al., 1998; Higaki and Shimmkado, 1999; Vicancano and Sawyers, 2002) and p38-JNK pathways (Frey and Mulder 1997, Ravanti et al 1999).

2c. TGF-β expression and meningiomas

Altered expression of, or sensitivity to TGF-β has been identified in several malignancies where reduction of TGF-βs inhibitory effects are thought to contribute to their development. The role of TGF-βs in meningioma development is likely specific to degree of differentiation and target cells. TGF-β1, 2 and 3 as well as TGF-β receptors I, II and III are expressed in human leptomeninges and in varying levels depending on the grade in meningiomas (Johnson et al., 1992a; Johnson et al.,
1992b; Johnson et al., 2004; Johnson et al., 2011). Both precursor leptomeningeal cells and menigioma cells synthesize and release all three (presumably latent) TGF-β isoforms in vitro (Johnson et al. 1992a; Johnson et al. 1992b; Johnson et al. 2004; Johnson et al. 2011). At least in vitro, TGF-β1 reduces basal proliferation in half of WHO grade I meningioma cell cultures (Johnson et al., 1992a; Johnson et al., 2004) and attenuates epidermal growth factor induced proliferation in 80% of meningiomas (Johnson et al., 1992a). Thus, paracrine TGF-β1 effects from leptomeningeal cells may tonically suppress growth of human leptomeningeal and WHO grade I menigioma cells (Johnson et al. 1992, Johnson et al., 2004). Autocrine TGF-β1 may also restrain grade I meningioma proliferation (Johnson et al., 1992a; Johnson et al., 2004). In WHO grade I meningioma cells this inhibitory TGF-β signaling is associated with TGF-β1 activation/phosphorylation of SMAD 2/3 (Johnson et al., 2004). In contrast, the p44/42 MAPK pathway does not appear activated by TGF-β1 in WHO grade I meningiomas (Johnson et al., 2004).

In contrast, the p44/42 MAPK pathway, which is mitogenic to meningioma cells (Johnson et al., 2001; Johnson et al., 2002; Mawrin et al., 2005) is activated by TGF-β1 that stimulates phosphorylation of p44/42 MAPK in some meningioma cell cultures from grade II meningiomas. Thus, p44/42 MAPK may transduce some TGF-β effects in higher grade meningioma cells with low, but still partially functional receptors (Johnson et al., 2011). As meningiomas progress and TGF-β RII levels decline, non-SMAD, non-inhibitory pathways may participate in meningioma biology.

2d. Loss of TGF-β inhibition and meningiomas

A reduction in sensitivity to TGF-β’s peptide’s growth inhibition may facilitate development of several malignancies (Glick et al., 1994 Fan et al., 1989). For example, disruption of TGF-β promotes progression in squamous cell carcinoma (Glick et al., 1994). This scenario is also seen in astrocytes and low grade astrocytoma cells that secrete TGF-β1 and 2 and are inhibited by exogenous TGF-β (Jennings et al., 1991). However, anaplastic astrocytoma cells become progressively resistant to the growth inhibitory effects of TGF-β as they evolve into malignant gliomas (Jennings et al., 1991). Similarly, intestinal epithelium and benign adenoma cells are also inhibited by TGF-β but become progressively resistant to TGF-β as adenoma cells dedifferentiate into carcinomas (Manning et al., 1991; Principe et al., 2014). Paracrine TGF-β1 from leptomeningeal cells may tonically suppress growth of human leptomeningeal and WHO grade I menigioma cells (Johnson et al., 1992a, 1992b, 2004). Autocrine TGF-β1 may also restrain grade I meningioma proliferation (Johnson et al., 2004). In WHO grade I meningioma cells this inhibitory TGF-β signaling is associated with TGF-β1 activation/phosphorylation of SMAD 2/3 (Johnson et al., 2004). In contrast, TGF-β inhibition is not detected in most WHO grade II and III meningiomas (Johnson et al., 2011). Thus, loss of sensitivity to TGF-β’s inhibitory effects may also occur in higher grade meningiomas as well as other tumors.

2e. TGF-β immunosupression in meningiomas

Immunomodulation is a central role of TGF-β1 which has potent immunosuppressive effects on natural killer and cytotoxic T cells (Shull et al., 1999). In many neoplasms, TGF-β suppression of the body’s immunosurveillance is thought to contribute to the progression and metastases of malignancies (Massague, 2008). Inflammatory infiltrates have been described at the invading edge
of meningiomas (Grund et al., 2009). Nonetheless, the role of the immune system in limiting the meningioma invasion and metastases has not been extensively studied. Future studies may clarify the importance of inflammatory and TGF-β immunomodulatory effects on meningioma invasion, spread and recurrence.

2f. Alterations in TGF-β receptors in neoplasms including meningiomas

Loss of TGF-βRs has been described in numerous other malignancies. Missense or frameshift mutations in the TGF-βRI has been demonstrated in breast, ovarian, esophageal and head and neck carcinomas (Ohue et al. 1996; Chen et al., 1998; Kretzschmar 2000; Knobloch et al., 2001; Wang et al., 2007; Xu and Pasche et al., 2007; Jin et al. 2008; Massague, 2008; Massague, 2012; Chen et al., 2011). Epigenetic decreased expression in TGF-βRII has been found in gastric carcinoma (Massague, 2008). Inactivating mutations in TGF-βRI, often in tumors with microsatellite instability, has been found in breast, ovarian, esophageal and head and neck carcinomas (Chen et al., 1999 and Chen et al., 2001). Mutations in TGF-βRII have been found in pulmonary, biliary, gastric, colonic and ovarian carcinomas (Ohue et al., 1996; Chen et al., 1998; Kretzschmar, 2000; Matsushita et al., 2005; Wang et al., 2007; Xu and Pasche, 2007; Jin et al., 2008; Chen et al., 2011). Loss or down regulation of the TGF-βRII may be even more common in malignancies having been identified in prostatic and non-small cell carcinoma, neuroblastomas, ovarian, endometrial and renal cancers (Iolascon et al. 2000; Copland et al. 2003; Florio et al., 2005; Hempel et al., 2007; Sharfi et al., 2007; Turley et. al, 2007; Finger et al. 2008; Bilandzic et al. 2009;). Loss of TGF-βRIII may also permit progression of breast cancer (Dong et al., 2007). The role of altered TGF-βR expression in the pathogenesis of meningiomas is not fully understood. TGF-βRII protein is reduced or undetectable in the majority of grade II and III meningiomas. TGF-βRIII mRNA is significantly reduced in WHO grade III compared to lower grade meningiomas. In addition, TGF-β1 inhibition of leptomeningeal and WHO grade I meningioma cell growth, (Johnson et al., 1992a; Johnson et al., 2004; Johnson et al., 2011), is not detected in nearly all WHO grade II and the grade III tumor cells. Recent, comparative genomic hybridization has also identified a 2.3 fold reduction in TGF-βRIII gene copy in "high proliferative" meningiomas (Carvalho et al., 2007). Thus, because TGF-β effects are initiated by binding to the TGF-β type II and III receptors, a genetic or epigenetic reduction in the concentration of receptors likely results in attenuated TGF-β growth inhibition. This may permit less restrained growth of higher grade meningiomas.

2g. SMAD 7 inhibition of TGF-β signaling in meningiomas

SMAD 7 is a natural inhibitor of TGF-β signaling and part of complex feedback loops regulating TGF-β effects (Kleef et al., 1999; Massague, 2008; Massague, 2012). It has been hypothesized that SMAD 7 might increase in higher grade meningiomas as another mechanism of escape from TGFβ inhibitory effects. Overexpression of SMAD 7, attenuating TGF-β inhibitory effects, has been found in endometrial and thyroid carcinomas (Nakano et al., 1997; Cerutti et al., 2003; Dowdy et al., 2005). EGF also increases SMAD 7 which is inhibitory to SMAD 2/3 signaling (Dowdy, 2006). Nonetheless, SMAD 7 expression is not increased or significantly different between meningioma grades (Johnson et al., 2011). Moreover, a recent comparative genomic hybridization analysis has found a 3 fold reduction rather than increase in SMAD 7 gene expression in high grade compared to low grade meningiomas (Carvalho et al., 2007).
2h. Alterations in TGF-β signaling in meningiomas

Loss of sensitivity to the inhibitory effects of TGF-β in meningiomas may also be downstream from alterations in receptor activation, SMAD or MAPK signaling. Mutations in Smad 4 have been identified in pancreatic carcinoma and murine adenocarcinoma of the colon (Luttges et al., 2001; Xu et al., 2007). Reduced Smad signaling has also been associated with development of carcinomas of the head and neck and metastatic potential (Xie et al., 2003a; Xie et al., 2003b). LMO4, which influences TGF-β signaling by interactions with SMAD signaling, represent a downstream site where inhibitory TGF-β signaling may be altered (Lu et al., 2006). Moreover, this appears to be in concert with mitogenic signals from other growth factors. For example, activation of mitogenic EGF receptor tyrosine kinases (present on meningioma cells) activate MAPK/Erk kinase which hyperphosphorylates SMAD 2 and 3 preventing their movement into the nucleus and TGF-β signaling (Principe et al., 2014). TGF-β1 also influences cell proliferation by alternately reducing p44/42 MAPK (erk) phosphorylation at high concentrations while increasing phosphorylation/activation at lower concentrations particularly in higher grade tumors (Principe et al., 2014; Zhang et al., 2014). In our studies, TGF-β1 increased p44/42MAPK phosphorylation in the majority of higher grade i.e. grade II meningiomas (Johnson et al., 2011). This regulation appears to be by influencing the activation of protein phosphatase 2a (PP2A) which can alter p-44/42MAPK phosphorylation status (Lu et al., 2006). Thus, early in the development of meningiomas, other factors may slowly override any tonic inhibitory effects on meningioma cell proliferation.

Higher grade, particularly anaplastic meningiomas have the highest recurrence rate and the least response to any current therapy. Our findings suggest that restoring TGF-β inhibitory signaling pathways may be an important component to the development of effective chemotherapies for meningiomas.

2i. Cerebrospinal fluid and TGF-β signaling in meningiomas

TGF-β1 is present in human cerebrospinal fluid at concentrations that may activate TGF-β receptors (Vawter et al., 1996; Johnson et al., 1992b; Johnson et al., 2004). Nonetheless, its' influence on meningioma cell growth appears complex. Cerebrospinal fluid, from patients without neurological disease, is a potent mitogen for meningioma cells of all grades in vitro (Johnson et al., 2012). In this context, TGF-β1 in cerebrospinal fluid appears to limit grade I meningioma cell proliferation in vitro. For example, adding TGF-β1 neutralizing antibodies to cerebrospinal fluid potentiates the cerebrospinal fluid’s mitogenic effects in some meningioma cells (Johnson et al. 2004). Cerebrospinal fluid effects on TGF-β isoforms and TGF-β receptors have not been reported. However, screening of a limited number of meningiomas in vitro found that cerebrospinal fluid (from patients without neurological disease of inflammation) had no effect on the TGF-β precursor protein levels in cells from 5 human meningiomas (Johnson et al., unpublished). In these same cells, cerebrospinal fluid had no effect on protein levels of the TGF-β antagonist, SMAD 7. However, intriguingly, exogenous platelet derived growth factor-BB (PDGF-BB), which is also in cerebrospinal fluid and released by meningioma cells, increased SMAD 7 levels in meningioma cells (Johnson et al., unpublished). This raises the possibility that cerebrospinal fluid’s mitogenic effects
on meningioma cells may, in part, be via induction of SMAD 7 expression which could counteract TGF-β’s inhibitory autocrine or paracrine effects.

2j. TGF-β and Merlin in Meningiomas

Expression of TGF-β, TGF-βRs, SMAD 7 and phosphorylation of SMAD 3 do not correlate with the presence or absence of Merlin protein, the tumor suppressor protein encoded by the NF2 gene (Gusella et al., 1999; Perry et al., 2004, Riemenschneider et al., 2006) in any grade of meningiomas. Consequently, Merlin doesn’t appear to regulate TGF-β, TGF-βRs or SMAD 3 phosphorylation.

3. BMPs

The bone morphogenic proteins (BMP) include 20 dimers that are part of the larger transforming growth factor beta (TGF-β) superfamily (Chen et al., 2004; Herpin and Cunningham, 2007). While BMPs were originally identified as proteins inducing bone formation, it is now recognized that they influence multiple functions including cell proliferation, apoptosis, angiogenesis, differentiation and extra cellular matrix formation (Chen et al., 2004; Herpin and Cunningham, 2007). BMP4 is synthesized as a large precursor peptide which is subsequently cleaved to form the active carboxyl terminus protein and secreted as a dimer (Chen et al., 2004; Herpin and Cunningham, 2007). BMPs signal through binding and coupling of two BMP type II and type I receptor serine/threonine kinases forming a heterotetracomplex. The activated BMPRII receptors transphosphorylate the type I receptors which, in turn, phosphorylate intracellular substrates including Smad 1, p38 MAPK and other signaling proteins (Chen et al., 2004; Herpin and Cunningham, 2007).

3a. BMP signaling

BMP4 influences cellular function by binding cooperatively to the BMPRI and II, forming a heterotetraplex of 2 BMPRIIs and 2 BMPRIs. The constitutively active type II receptors transphosphorylate and activate the type I receptor serine/threonine kinases (Miyazono et al., 2005; Herpin and Cunningham, 2007). Major signaling is thru phosphorylation of Smad 1, 5 and 8 which form a heterocomplex with Smad4 and enter the nucleus where they directly regulate or couple with Co-Smads to regulate transcription factors influencing target gene transcription (Miyazono et al., 2005; Herpin and Cunningham, 2007). BMP4 also signals by activation of non-SMAD pathways such as the p 38 MAPK, p44/42 MAPK and JNK pathways (Herpin and Miyazono et al., 2005; Jeffrey et al., 2005; Beck et al., 2007; Cunningham, 2007).

3b. BMP effects on leptomeningeal and other central nervous system cells

Evaluation of the effects of BMPs in the leptomeninges has focused on BMP4 and BMP7, the main BMPs isolated there. BMP4 and 7 are inhibitory to many normal cell types (Kallionemi, 2012). The role of BMP4 and BMP7 in regulating leptomeningeal cell proliferation appears complex. BMP4, BMP7, BMP R1a and BMPRIIa are expressed in human fetal and adult leptomeningeal cells (Johnson et al., unpublished data). However, levels of these BMPs may be low as neither BMP4 nor BMP7 can be detected in media conditioned by fetal leptomeningeal cells. Similarly, BMPR2 and BMP4 have been detected in the mouse leptomeninges (Ikeda et al., 1996). Exogenous BMP4 has no effect on
basal leptomeningeal cell proliferation but inhibits some fetal leptomeningeal cell proliferation in PDGF-BB stimulated cells in vitro. In contrast, BMP7 stimulates some fetal leptomeningeal cell proliferation in vitro (Johnson et al., unpublished data).

Paracrine effects of BMP 4 or 7 released form the pia, arachnoid and dura also appear to have major effects on overlying and subjacent tissues. In the brain, BMP4 and 7 inhibit growth and promote differentiation, at least in neuronal and astrocytic lineages (Mabie et al., 1999; Dorsky et al., 2000; Yabe et al., 2002; Gomes et al., 2003; Segkia et al., 2012; Choe et al., 2012; Choe et al., 2013). With regard development of the overlying calvarium, several studies have shown that BMP4 promotes osteoblast and chondrocyte differentiation (Nishimura et al., 2008; Shen et al., 2009; Chen et al., 2012; Nishimura et al., 2012).

BMPs also influence angiogenesis in many tissues, in part, by influencing VEGF and VEGF receptor expression. BMP4 reduces VEGF expression in the second and third trimester human fetal leptomeninges (Johnson et al. unpublished observations). Similarly, BMP9 reduces VEGF expression in endothelial cells (Shao et al., 2009). In contrast, BMP4 stimulates VEGFA expression in developing tissues and during neoplastic transformation appears to be via activation of SMAD1/5/8 and downstream activation of VEGF family and its receptors (Lowery and de Caestecker, 2010; Farnsworth et al., 2011).

Regarding the leptomeninges, BMP effects on VEGF receptors are also isoform dependent. BMP4 has no effect on leptomeningeal VEGFR expression (Johnson et al. unpublished observations). However in endothelial cells, BMP4 increases VEGFR (Suzuki et al., 2008). In contrast, BMP7 increases VEGFR expression in fetal leptomeninges and this is potentiated PDGFs effects on stimulation (Johnson et al. unpublished observations). To our knowledge, this has not been previously described but may reflect another important role for BMP7 in leptomeningeal development.

3c. BMP expression in meningiomas

BMP4 expression has been demonstrated in meningiomas (Johnson et al., 2009) and BMP4 mRNA has been reported in 6 of 7 uncharacterized meningiomas of unknown subtype and grade (Hirota et al., 1995). In WHO grade I tumors, expression is detected in meningothelial, transitional and fibrous meningiomas and not restricted to a specific subtype. BMP4 has also been detected in media conditioned by WHO grade I and II meningiomas (Johnson et al., 2009). In higher grade meningiomas, expression was detected in only fibrous and transitional (Hirota et al., 1995). PCR analysis of low and high grade meningiomas has also found reduced median BMP4, Smad7, Smad 9 and TGF-ß R III expression in grade III compared with grade I meningiomas (Carvalho et al., 2007). Thus, reduced BMP4 gene expression may also be a feature of some higher grade meningiomas possibly contributing to the pathogenesis of these meningiomas.

3d. BMP regulation of proliferation in neoplasia including meningiomas

BMPs appear to have more complex effects on cell proliferation and progression of many neoplasms. BMP4 is inhibitory to myeloma, pulmonary adenocarcinoma, breast, gastric and
pancreatic cancer cells (Hjertner, O. et al. 2001, Buckley, S. et al. 2004; Ketolainen, J.M. et al. 2010, Shirai, Y.T. et al. 2011; Virtanen, S. et al. 2011 ). However, BMP4 has also been implicated in promotion of invasion and/or metastases of many tumors such as breast, colon, and pancreatic carcinoma cells (Deng, H. et al. 2007; Kallioniemi, A. 2012). Of particular note, BMP4 gene variants increasing BMP4 have also been associated with increased risk of developing cancer of the colon and rectum (Houlston, R.S. et al. 2008; Lubbe, S.J. et al. 2012; Slattery, M.L. et al. 2012 ).

This complexity also applies to cell proliferation in central nervous system and pituitary tumors. BMPs have been either inhibitory or stimulatory in central nervous system-associated tissues. BMP4 inhibits glioma stem cell proliferation (Zhou et al., 2011; Kallionemi, 2012) but stimulates pituitary adenoma cells and inhibits primitive neuroectodermal cell apoptosis (Intoska, et al., 1999; Paez-Pereda et al., 2003,). BMP4 stimulation of other select mesodermal and epithelial cells has also been described (Yang et al., 2007, Montesano et al., 2008).

In meningiomas, BMP4 potentiates DNA/cell proliferation when added to fetal bovine serum. This raises the possibility that BMP4 may potentiate proliferative effects of other growth factors released by meningioma cells or present in cerebrospinal fluid (Johnson et al., 2009). Meningioma cell release of BMP4 raises the possibility of complex interactions between this cytokine, other members of the TGF-β superfamily (Johnson et al., 2005) and other growth regulatory cytokines secreted by meningioma cells or in the cerebrospinal fluid.

4. Targeting TGF-β and BMP Signaling Alterations in Meningiomas

Disrupting alterations in TGF-β or BMP signaling in malignancies depends on the site and nature of the defect. To date, direct therapeutic options are limited, in part, due to toxicities associated with disrupting TGF-β signaling. Nonetheless, in many malignancies where TGF-β switches from inhibitory effects to promotion of tumor progression, TGF-β signaling may be blocked small molecule inhibitors of the TGF-β type I receptor (Dituri et al., 2013). Preliminary studies suggest LY 2157229 is effective in blocking TGF-β effects. At least in initial human toxicity studies, when carefully dosed, LY 2157229 may have limited cardiac toxicity (Rodon, J et al., 2014). Because TGF-β induces retinoic acid which may mediate some signaling thru retinoic acid receptors, targeting the RA signaling pathways may bypass defects in TGF-β R III loss in progressively malignant meningiomas (Xu and Kopp, 2012).

The role of BMP4 and 7 in treatment of meningiomas is likely to be multifaceted. One potential target might be the disfiguring hyperostosis of the skull overlying sites of meningioma growth. Hyperostosis is a common morbidity associated with meningiomas especially in the calvarium (Goyal et al. 2012) and may require extensive bone resection (Bikmaz K et al. 2007). A similar reaction has been demonstrated in prostate carcinoma cells that stimulate bone formation via secretion of BMP4. Treatment with monoclonal antibodies to BMP4 and small molecule inhibitors to BMP4 blocked this osteoblastic reaction (Lee et al., 2012). This study raises the possibility that local administration of anti-BMP4 may suppress hyperostosis around meningiomas as well.
5. Conclusions

Loss of TGF-β and BMP inhibition of cell proliferation may be central to the development of meningoimias. Alterations in TGF-β and BMP signaling pathways may also influence progression, invasion metastasis and immunosurveillance against the development of meningioma cells. Clarification of the multiple sites where TGF-β superfamily members affect meningioma biology may facilitate development of novel therapies against these frequently recurrent tumors.

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