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Gene Section

Review

BMP4 (bone morphogenetic protein 4)

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Identity

Other names: BMP2B, BMP2B1, MCOPS6, OFC11, ZYME

HGNC (Hugo): BMP4

Location: 14q22.2

Local order: Genes flanking BMP4 at 14q22.2 are (centromeric to telomeric): MIR5580 (microRNA 5580), **BMP4**, ATP5C1P1 (ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide 1 pseudogene 1).

DNA/RNA

Description

Gene spans approximately 9 kbp on the minus strand at 14q22.2.

Transcription

Alternative splicing in the 5'UTR gives rise to 3 transcript variants, all encoding an identical protein. Transcript variant 1 is 1917 bp in length with 4 exons (2 coding exons), transcript variant 2 is 1708 bp in length with 4 exons (2 coding exons), and transcript variant 3 is 1705 bp in length with 3 exons (2 coding exons).

In Xenopus embryos, BMP4 itself, along with the homeobox genes Vox, X-vent1, X-vent2, GATA-1, GATA-2 and AP-1 were found to induce the expression of BMP4 and control dorsoventral patterning in the mesoderm (Jones et al., 1992; Kim et al., 1998; Onichtchouk et al., 1996; Schmidt et al., 1996), whereas organizer signals, chordin and noggin, and X-lim1 negatively regulate BMP4 transcription (Kim et al., 1998). Lung specification in Xenopus depends on the suppression of BMP4 expression by zinc-finger transcriptional repressors Osr1 and Osr2 (Rankin et al., 2012).

Analysis of the mouse BMP4 gene identified 2 G-C rich Sp1 binding motifs proximal to the transcriptional start sites for exons I and II (Kurihara et al., 1993). The presence of dual promoter regions flanking exons I and II were later confirmed in human cancer cell lines (van den Wijngaard et al., 1996). Mouse BMP4 is negatively regulated by direct binding of chicken ovalbumin upstream-transcription factor I (COUP-TF1) to the proximal promoter of exon I (Feng et al., 1995). Deletion analysis of the mouse BMP4 promoter in MC3T3E1 cells identified a cis-acting E-box element proximal to the transcriptional start site that is bound by upstream regulatory factor (USF), a member of the helix-loop-helix family of regulatory proteins (Ebara et al., 1997). In mouse development, GATA-4 and -GATA-6 were found to specifically regulate BMP4 transcription to mediate endoderm-mesoderm signalling and early vasculogenesis (Nemer et al., 2003).

Similarly, analysis of mouse embryonic stem cells identified the transcriptional corepressor Bcor as an important regulator of ES cell differentiation into mesoderm, ectoderm and hematopoietic lineages through regulating developmental genes including BMP4 expression (Wamstad et al., 2008). Furthermore, the transcription factor Cdx2 has been shown to directly regulate BMP4 expression in mouse trophoblast cells to promote early mouse embryogenesis (Murohashi et al., 2010), while Shox2 regulates BMP4 expression to promote pacemaker development in the murine heart (Puskaric et al., 2010).

Analysis of the human BMP4 promoter in U2OS and SaOS2 cells identified the lack of a proximal TATA box, while sharing similar transcriptional start sites and regulatory elements with the mouse BMP4 promoter

(Helvering et al., 2000; Shore et al., 1998). Putative binding motifs for AP1, Sp1, CRE, Cfab1 were identified, and direct binding of Cfab1 to the BMP4 promoter was confirmed, along with transcriptional upregulation of BMP4 by osteogenic compounds such as retinoic acid and the phorbol ester PMA (Helvering et al., 2000).
Transcriptional control of BMP4 is also important in diseased states. During recovery from acute anemia, hypoxia induces BMP4 expression and subsequent erythropoiesis in the murine spleen through direct binding of HIF2alpha to the BMP4 promoter (Wu et al., 2010). In retinal pigment epithelium cells of patients suffering from the wet form, but not the dry form, of macular degeneration, TNFalpha represses BMP4 transcription through phosphorylation of the transcription factor Sp1, demonstrating a BMP4 expression-dependent molecular switch (Xu et al., 2011).
In hepatocellular carcinoma cells, Ets-1 was demonstrated to directly regulate hypoxia-induced BMP4 transcription to promote tumorigenesis (Maegdefrau et al., 2009). In colorectal cancer cells, oncogenic KRAS can repress BMP4 expression through a novel ras-responsive region (Duerr et al., 2012).
In addition to many proximal regulatory sites, the BMP4 gene, along with many other BMP family genes, resides within a conserved gene desert, which contains many additional distal cis-regulatory regions (located over 30 kbp from coding sequences) that control BMP4 expression in a spatiotemporal and tissue-dependent manner (Chandler et al., 2009; Pregizer et al., 2009). For example, an evolutionarily conserved distal enhancer site, 46 kb upstream of the transcriptional start site, is bound by Pitx2 and likely participates in tooth and limb morphogenesis (Jumlongras et al., 2012). Furthermore, a common polymorphism found within the distal BMP4 promoter (17kb upstream) acts as a cis-acting enhancer of BMP4 transcription, and is significantly associated with colorectal cancer risk (Lubbe et al., 2012).

Pseudogene

None annotated.

Protein

Description

BMP4, a member of the TGFbeta superfamily of signalling molecules, is a 46.5 kDa, 408 aa protein that is translated as a precursor containing a signal peptide (aa 1 - 19), a prodomain (aa 20 - 292) and a mature domain (aa 293 - 408).
After the BMP signal peptide has been removed, dimerization of the proproteins proceeds.
Proprotein cleavage is achieved by the candidate serine endoproteases Furin, PCSK5, PCSK6, or PCSK7 at the consensus sequence RXXR, resulting in the generation and secretion of biologically active molecules (Bragdon et al., 2011; Cui et al., 1998; Goldman et al., 2006; Shimasaki et al., 2004). As with other TGFbeta family members, BMP4 is a cysteine knot-containing, disulfide-linked dimer (Jones et al., 1994; Shimasaki et al., 2004), containing a conserved TGF-beta propeptide domain (pfam00668) and transforming growth factor beta like domain (cl02510). One high-throughput study has identified a ubiquitination site at Lys-185 (Kim et al., 2011).

Expression

The amino acid sequence for BMP4 was first derived from an isolated preparation of bovine bone (Wozney et al., 1988). Human BMP4 was cloned from a placental cDNA library (Oida et al., 1995). Apart from its high expression in developing embryonic tissues (Chen et al., 2004), BMP4 was determined by microarray analysis to be highly expressed in adult tissues such as the thymus, spleen, brain, heart, muscle, kidney, lung, liver, pancreas, and prostate (Schmueli et al., 2003; Yanai et al., 2005).
Immunohistochemical analysis of adult tissues shows high expression in epithelial cells of the skin, bladder and stomach (Alarmo et al., 2012). In tumors, BMP4 is expressed in melanoma, ovarian, gastric, basal cell, renal and squamous carcinomas of the head and neck (Chiu et al., 2012; Deng et al., 2007; Davies et al., 2008; Giacomini et al., 2006; Johnson et al., 2009; Kim et al., 2011; Kwak et al., 2007; Laatio et al., 2011; Lombardo et al., 2011; Sneddon et al., 2006; Rothhammer et al., 2005; Xu et al., 2011). Overexpression of BMP4 in comparison to normal tissues is observed in breast, ovarian, gastric, hepatocellular and colorectal carcinomas (Alarmo et al., 2012; Chiu et al., 2012; Deng et al., 2007; Kim et al., 2011).

Localisation

BMP4 is a secreted protein localized within the extracellular milieu (Chen et al., 2004), but has also been shown to localize within the cytoplasm in vesicles directed for lysosomal degradation, in order to tightly mitigate BMP4 signalling (Kelley et al., 2009).

Function

BMP4 is a member of the bone morphogenetic protein family, which is part of the transforming growth factor-beta superfamily of growth and differentiation factors.
Bone morphogenetic proteins were originally identified by an ability of demineralized bone extract to induce endochondral osteogenesis in vivo in an extraskeletal site (Urist, 1965), but are now considered essential factors with varying roles during embryogenesis, skeletal formation, hematopoiesis and neurogenesis (Bragdon et al., 2001; Chen et al., 2004; Kallioniemi, 2012). In adult tissues, BMP4 signalling can control many cellular behaviours including differentiation, proliferation, apoptosis, and motility (Kallioniemi, 2012).

The mature BMP4 dimer binds to type I and II serine-threonine kinase receptors, and the constitutively active BMP type II receptor will phosphorylate the type I receptor upon ligand binding (Miyazono et al., 2010; Nohe et al., 2004). The activated type I BMP receptor is then able to phosphorylate the cytosolic receptor-regulated SMAD proteins (Attisano et al., 2000; Bragdon et al., 2001; Miyazono et al., 2010), which will then form a complex with the common SMAD4, translocate to the nucleus to regulate gene transcription (Feng et al., 2005; ten Dijke et al., 2003). In addition to this canonical SMAD-dependent signaling pathway, BMP4 can signal through SMAD-independent means to directly induce ERK and p38 MAPKs, JNK, NFkB, PI3K, PKA, PKC and PKD signaling pathways affecting cell survival, apoptosis, migration and differentiation (Bragdon et al., 2011). In addition to intracellular regulation, BMP4 signals can be modulated at the receptor level through interaction with three different type I (BMPR1A [ALK3], BMPR1B [ALK6], and ACVR1A [ALK2]) and type II (BMPR2, ACVR2A [Act-RII], and ACVR2B [Act-RIIB]) receptors (Kawabata et al., 1998; Miyazono et al., 2010; Nohe et al., 2004), and negatively regulated by interaction with the pseudoreceptor BAMBI (Onichtchouk et al., 1999). BMP4 signalling can also be regulated at the extracellular level through binding to the endogenous inhibitors tsg (Twisted gastrulation) and Follistatin, and those belonging to the Dan family (Dan, Gremlin, Gremlin2, Cerberus, Coco, Caronte, Ectodin, and Sclerostin), and the Chordin family (Chordin, Chordin-like-2, Noggin) of BMP antagonists (Bragdon et al., 2011).

Homology

There are BMP4 homologs in several vertebrate species, including chimpanzee, rhesus monkey, dog, cow, chicken, rat, mouse, lizard, frog (Xenopus laevis), and zebrafish (Danio rerio) and in invertebrates such as the fruit fly (Drosophila melanogaster) and the worm (Caenorhabditis elegans).

Mutations

Germinal

Heterozygous mutations in exons 3 and 4 of the BMP4 gene resulting in decreased expression were found in children with cleft lip and cleft palate (Suzuki et al., 2009), including: a 1037C-T transition resulting in an A346V substitution; a 271A-T transversion resulting in a S91C substitution; a 860G-A transition resulting in an R287H substitution; and a 592C-T transition resulting in an R198X substitution.

Three pathogenic germline mutations were identified in a cohort of 504 genetically enriched colorectal cancer cases. p.R286X (g.8330C>T) localizes to the N-terminal of the prodomain truncating the protein prior to the active domain; p.W325C (g.8449G>T) and p.C373S (g.8592G>C) mutations are predicted from protein homology modelling with BMP2 to impact deleteriously on BMP4 function; and p.C373S (g.8592G>C) segregates with adenoma and hyperplastic polyps in first-degree relatives, suggesting this germline mutation may confer a juvenile polyposis-type phenotype (Lubbe et al., 2011).

Somatic

Four substitution missense mutations have been identified: two mutations were detected in two different single prostate tumors (c.344A>T, p.N115I (Grasso et al., 2012), c.857G>A, p.R286Q (Barbieri et al., 2012), and two in two different large intestinal carcinoma tumors (c.631C>T, p.R211W, and c.1222C>T, p.R408C)) (The Cancer Genome Atlas Network, 2012).

Implicated in

Fibrodysplasia ossificans progressiva (FOP)

Prognosis

Fibrodysplasia ossificans progressiva (FOP) is an extremely rare and disabling autosomal dominant genetic disorder with complete penetrance characterized by congenital malformations of the great toes and by progressive heterotopic endochondral ossification in predictable anatomical patterns. Ectopic expression of BMP-4 was found in FOP patients (Gannon et al., 1997; Xu et al., 2000).

Cytogenetics

Overexpression of BMP4 mRNA was found in FOP patients (Shafritz et al., 1996), in addition a heterozygous activating mutation found in the ACVR1 gene (Shore et al., 2006).

Microphthalmia, syndromic 6 (MCOPS6)

Prognosis

A loss of BMP4 expression can lead to the heritable disorder microphthalmia syndromic type 6 (MCOPS6); also known as microphthalmia and pituitary anomalies or microphthalmia with brain and digit developmental anomalies. Microphthalmia is a clinically heterogeneous disorder of eye formation, ranging from small size of a single eye to complete bilateral absence of ocular tissues (anophthalmia). MCOPS6 is characterized by microphthalmia/anophthalmia associated with facial, genital, skeletal, neurologic and endocrine anomalies. (Bakrania et al., 2008; Bennett et al., 1991; Elliott et al., 1993; Lemyre et al., 1998; Phadke et al., 1994).

Cytogenetics

Deletions in 14q22-q23 are associated with anophthalmia-microphthalmia, brain, pituitary, and ear anomalies including structural defects and hearing loss, hypothyroidism, poly- and/or syndactyly, clinodactyly, high arched palate, cryptorchidism, and developmental delay (Ahmad et al., 2003; Bennett et al., 1991).

Oral Facial Cleft 11 (OFC11)

Prognosis

Mutations in the BMP4 gene during development can result in congenital 'healed' cleft lip (CHCL), an unusual heritable anomaly consisting of a paramedian 'scar' of the upper lip with an appearance suggesting that a typical cleft lip was corrected in utero. The CHCL is frequently associated with an ipsilateral notch in the vermilion border and a 'collapsed' nostril (Castilla et al., 1995).

Cytogenetics

Missense and nonsense mutations in the BMP4 gene resulting in decreased expression were found in children with cleft lip and cleft palate (Suzuki et al., 2009).

Basal-cell carcinoma

Oncogenesis

BMP4 treatment of primary cultures of basal carcinoma cells reduces cell growth and induces the expression of keratinocyte differentiation markers, which can be antagonized by the BMP inhibitor gremlin1 (Sneddon et al., 2006).

Bladder cancer

Oncogenesis

BMP4 inhibits growth in the RT4 cell line, but no effect is seen in TCC-Sup or TSU-Pr1 cells; expression of BMPR2 in TSU-Pr1 cells restores the growth-inhibitory effect of BMP4 treatment in nude mice (Kim et al., 2004). Through the mining of publicly available whole genome microarray datasets, BMP4 was identified within a set of 17 differentially expressed genes to be downregulated in bladder cancers (Zaravinos et al., 2011).

Brain cancers

Oncogenesis

BMP4 increased growth and reduced apoptosis of the neuroectodermal tumor cell line DAOY (Iantosca et al., 1999). Treatment of glioblastoma stem cells with BMP4 decreased proliferation and induced differentiation in GBM cells (Piccirillo et al., 2006), cerebellar granule neuron progenitors (GNPs) and primary GNP-like medulloblastoma cells (Zhao et al., 2008), and inhibited glioma stem cell proliferation via G1 arrest and CCND1 while enhancing apoptosis through induction of Bax and inhibition of Bcl-2 and Bcl-xL (Zhou et al., 2011). BMP4-dependent growth inhibitory effects were also seen in the brain glioma cell line U251 (Liu et al., 2011). BMP4 is expressed in meningiomas, and stimulates the proliferative capacity of primary meningioma cell cultures via phosphorylation of Smad 1, but not p38 MAPK (Johnson et al., 2009). Human astrocytomas were found to have methylation of the BMP4 promoter (Wu et al., 2010).

Breast cancer

Prognosis

BMP4 is highly expressed in primary breast cancer tumors and cell lines (Alarmo et al., 2007), and strong immunohistochemical expression of BMP4 correlates significantly with reduced proliferation and increased rates of recurrence (Alarmo et al., 2012). Methylation of the BMP4 promoter, combined within a four-gene methylation signature, was found predictive of outcome in steroid receptor-positive, node-negative, HER-2 negative breast cancer patients treated with anthracycline (Hartmann et al., 2009).

Oncogenesis

Exogenous treatment of BMP4 abrogates lumen formation in mammary epithelial cells and promotes invasive growth (Montesano, 2007). BMP4 treatment did not affect the proliferative capacity of immortalized mammary epithelial cells, however BMP4 potentiates growth factor-induced proliferation (Montesano et al., 2008). BMP4 treatment of MDA-MB-231 and MCF-7 breast carcinoma cells inhibited MMP expression and activity, decreasing their metastatic potential (Shon et al., 2009). In nine breast cancer cell lines, BMP4 treatment induced growth suppression via G1 arrest, while stimulating cell migration and invasion in a SMAD-dependent manner (Ketolainen et al., 2010). BMP4 treatment of MDA-MB-231 and MCF-7 breast cancer cell lines induced migration and invasion phenotypes via the upregulation of MMP-1 and CXCR4 that could be abrogated by either anti-BMP4 siRNA or Noggin treatment (Guo et al., 2012). BMP4 treatment of multiple breast cancer cell lines and analysis using a whole genome oligo microarray revealed a strong transcriptional response for genes involved in cellular differentiation and transcriptional activity (Rodriguez-Martinez et al., 2011).

Colorectal carcinoma (CRC)

Prognosis

Three germline pathogenic mutations of BMP4, p.R286X (g.8330C>T), p.W325C (g.8449G>T) and p.C373S (g.8592G>C) were suggested to be causal for colorectal cancer (Lubbe et al., 2011). Three common variants (rs4444235, rs17563, and rs1957636) at the BMP4 locus have been associated with elevated risk of colorectal cancer (Houlston et al., 2008; Lubbe et al., 2012; Slattery et al., 2012; Theodoratou et al., 2012; Tomlinson et al., 2011). Immunohistochemical and real-time mRNA expression analysis of BMP4 in primary tumors correlated strongly with advanced stage and liver metastases (Deng et al., 2007).

Oncogenesis

Germline BMP4 mutations were found to be deleterious to the BMP4 protein in colorectal cancers (Lubbe et al., 2011). Furthermore, a common polymorphism found within the distal BMP4 promoter (17 kb upstream) acts as a cis-acting enhancer of BMP4

transcription, leading to enhanced expression, which is significantly associated with colorectal cancer risk (Lubbe et al., 2012).
Overexpression of BMP4 in HCT116 human colorectal cancer cell line promotes in vitro migration and invasion (Deng et al., 2007). In colorectal stem cells isolated from primary tumors, BMP4 treatment induced terminal differentiation, apoptosis and chemosensitization in vitro and in tumour xenografts (Lombardo et al., 2011). BMP4 signalling has been shown to protect HCT116 cells from heat-induced apoptosis by modulating MAPK pathways (Deng et al., 2007), and overexpression of BMP4 can enhance the invasiveness of CRC cells independent of Smad4 activity (Deng et al., 2009).

Gastric cancer (GC)

Prognosis

Expression of BMP4 is inversely related to prevalence of lymph node metastasis in gastric adenocarcinomas (Kim et al., 2011). BMP4 mRNA was significantly overexpressed in gastric cancers relative to mucosal controls and negatively correlated with BMP4 promoter methylation, while high expression of BMP4 predicted poor outcome (Ivanova et al., 2012).

Oncogenesis

Immunocytochemical analysis of primary gastric tumors revealed that BMP4 was significantly overexpressed in comparison to normal mucosa, and correlated with Helicobater pylori infection. However, the expression of BMP4 negatively correlated with the presence of lymph node metastases and tumor invasiveness (Kim et al., 2011). BMP4 is highly expressed in cisplatin-resistant cell lines, and overexpression induced GC cell line tumorigenicity in vitro, while shRNA-mediated knockdown decreased proliferation, colony formation and restored cisplatin sensitivity (Ivanova et al., 2012). In diffuse-type gastric carcinoma cells lines in vitro, BMP4 acted as a tumor suppressor by inducing cell cycle arrest in these cells via p21 induction through the SMAD pathway (Shirai et al., 2011).

Hepatocellular carcinoma (HCC)

Prognosis

BMP4 is significantly overexpressed in 60% of primary HCC tumors (Chiu et al., 2012). BMP4 immunohistochemical expression significantly correlated with increased tumor nodules, increasing TMN stage, vascular invasion and tumor invasiveness, and was an independent predictor of disease-free and overall survival in HCC patients (Guo et al., 2012).

Oncogenesis

BMP4 promotes the growth and migration of HCC cell lines in vitro, and BMP4 can induce cyclin-dependent kinase 1 (CDK1) and cyclin B1 upregulation to accelerate cell-cycle progression and metastasis in HCC cells through MEK-ERK signaling (Chiu et al., 2012).
In HCC cell lines, BMP4 expression was shown to be induced by hypoxia to promote in vitro migration, invasion, anchorage-independence and tube formation to promote tumor progression (Maegdefrau et al., 2009).

Lung cancer

Prognosis

Combined with 3 other biomarkers, immunohistochemical expression of BMP4 was shown to predict the risk of bone metastasis in stage III resected non-small cell lung carcinoma (Zhou et al., 2012).

Oncogenesis

Treatment of lung cancer cell line A549 with BMP4 induced a senescent phenotype, characterized by reduced growth, increased size, reduced invasion, and expression of senescence-associated beta-galactosidase. BMP4-treated A549 cells also exhibited decreased growth in mouse xenograft models (Buckley et al., 2004). BMP4 via Smad signalling has also been shown to mediate adriamycin-induced premature senescence in multiple lung carcinoma cell lines (Su et al., 2009). A later study found that cooperativity between p38 MAPK and Smad pathways is required for BMP4-induced senescence (Su et al., 2011).

Melanoma

Prognosis

Bioinformatics analyses identified polymorphisms within the BMP4 gene (SNPs 6007 C/T (rs17563) and 3445 T/G (rs4898820)) affecting mRNA expression and shows a significant association with cutaneous melanoma (Capasso et al., 2009).

Oncogenesis

BMP4 was found to be overexpressed in melanoma cell lines, and primary and metastatic melanomas compared to nevi. Although no effect was seen on proliferation, BMP4 signalling significanctly increased migration and invasion in melanoma cell lines (Rothhammer et al., 2005). BMP4 was later shown to stimulate angiogenesis in malignant melanomas by inducing tube formation as well as the migratory efficiency of microvascular endothelial cells (Rothhammer et al., 2007).

Multiple myeloma

Oncogenesis

BMP4 inhibited DNA synthesis and induced G1 arrest and/or apoptosis in OH-2, IH-1 and ANBL-6 cell lines (Hjertner et al., 2001), and induced apoptosis in multiple myeloma cell lines via Smad-dependent down-regulation of MYC (Holien et al., 2012).
However, BMP4 was shown to be overexpressed in bone marrow cells derived from multiple myeloma

patients, and partially protected myeloma cells from apoptosis induced by the anti-myeloma drug bortezomib (a proteosome inhibitor) (Grcevic et al., 2010).

Ovarian cancer

Prognosis

One study identified via immunohistochemistry that high BMP4 expression in primary serous ovarian cancer tumors was an independent prognostic factor for longer progression-free survival time and overall survival prior to administration of chemotherapy (Laatio et al., 2011).

Oncogenesis

An autocrine BMP signalling pathway was identified in primary human ovarian surface epithelial cells and primary ovarian cancer cells. Treatment of primary ovarian cancer cells with BMP4 had no effect on proliferative capacity, but long-term cultures showed decreased cell density and increased cell spreading and adherence (Shepherd et al., 2003).

Treatment of primary ovarian cancer cells with exogenous BMP4 produced morphological alterations and increased cellular adhesion, motility and invasion, which could be inhibited by Noggin, while primary ovarian surface epithelial cells showed no response to these ligands (Thériault et al., 2007). BMP4 treatment also altered the EMT markers Snail, Slug and E-cadherin, along with an increase in activation of Rho-GTPases, suggesting that ovarian cancer agressive cellular behaviours may be mediated through autocrine BMP4 signalling (Thériault et al., 2007). These BMP4-induced changes in cellular morphology and motility were later found to be Smad-dependent (é et al., 2011).

Ovarian cancer tumor-associated mesenchymal stem cells were found to have overexpression of BMP4, suggesting BMP4 may have a role in modulation of the tumor microenvironment to promote tumorigenesis (McLean et al., 2011).

Pancreatic cancer

Cytogenetics

A CGH study of pancreatic primary tumors, cell lines and xenografts determined a significant recurrent low-level gain of chromosome 14q22.2 in these samples (Nowak, et al., 2005).

Oncogenesis

BMP4 demonstrates overexpression at the mRNA level in 25% of 16 established pancreatic cell lines compared to normal tissues. Treatment of 5 cell lines with BMP4 induced growth suppression via G1 arrest, but significantly increased the migratory and invasive phenotypes of pancreatic cell lines (3 out of 5) in vitro via SMAD-dependent signalling (Virtanen et al., 2011).

BMP4 treatment of Panc-1 cells induced an EMT response characterized by increased migration mediated by MSX2 induction (Hamada et al., 2007), while another study demonstrated BMP4 treatment of Panc-1 cells also resulted in an EMT response involving MMP2 activity that was Smad1-dependent (Gordon et al., 2009).

Prostate cancer

Prognosis

Immunohistochemical analysis of primary prostate cancer tumors and bone metastases revealed that BMP4 was overexpressed in the metastatic deposits, but not the primary tumors suggesting a role for BMP4 expression in promoting prostate cancer metastasis (Spanjol et al., 2010).

Oncogenesis

Treatment of LNCaP cells with BMP4 inhibited proliferation through G1 arrest and induction of p21, however no effect on growth was seen in PC-3 cells (Brubaker et al., 2004).

Another study confirmed the growth inhibitory effect of BMP4 on LNCaP cells and found the effect could be abrogated by Noggin treatment (Shaw et al., 2010).

In LAPC-4 cells, BMP4 treatment showed no effect on cellular proliferation, migration or invasion (Feeley et al., 2005).

However a later study found that BMP4 could promote prostate tumor growth in bone through osteogenesis in the xenograft cell line MDA-PCa-118b (Lee et al., 2011).

Pituitary tumors

Oncogenesis

BMP4 has cell-type specific effects on pituitary cells (Labeur et al., 2010). BMP4 signalling was determined to stimulate proliferation and MYC expression in pituitary prolactinomas but not in other pituitary tumors, along with promoting tumorigenic growth of rat GH3 cells in nude mice (Paez-Pereda et al., 2003).

BMP4 expression is reduced in corticotrophinomas from Cushing's

patients in comparison to normal corticotroph cells, while BMP4 treatment of mouse AtT-20 corticotroph cells showed no effect on proliferation, but transfection of the BMP4 inhibitor Noggin stimulated tumorigenic growth in nude mice (Giacomini et al., 2006).

Renal cell carcinoma (RCC)

Prognosis

Immunohistochemical analysis of RCC tumors demonstrated BMP4 overexpression in 44%, however no prognostic value could be associated with BMP4 expression (Kwak et al., 2007). BMP4 mRNA expression was significantly higher in non-clear cell RCCs than clear cell RCCs, however no association of BMP4 expression with survival was found (Markic et al., 2011).

Oncogenesis

The BMP4 promoter was hypermethylated, resulting in downregulated expression in 35% of primary RCC tumors tested (Ricketts et al., 2012).

Retinoblastoma

Oncogenesis

BMP4 signalling was intact, and exogenous treatment increased caspase-independent apoptosis in the RB1-deficient cell line WERI-Rb1, while no effect on proliferation was seen (Haubold et al., 2010).

Various cancers

Note

Numerous microarray studies indexed in Oncomine (oncomine.org) document altered expression of BMP4 in other cancers, including head and neck cancers, cervical cancers and lymphomas and sarcomas.

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