Atlas of Genetics and Cytogenetics in Oncology and Haematology

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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.

References

Urist MR. Bone: formation by autoinduction. Science. 1965 Nov 12;150(3698):893-9

Wozney JM, Rosen V, Celeste AJ, Mitsock LM, Whitters MJ, Kriz RW, Hewick RM, Wang EA. Novel regulators of bone formation: molecular clones and activities. Science. 1988 Dec 16;242(4885):1528-34

Bennett CP, Betts DR, Seller MJ. Deletion 14q (q22q23) associated with anophthalmia, absent pituitary, and other abnormalities. J Med Genet. 1991 Apr;28(4):280-1

Jones CM, Lyons KM, Lapan PM, Wright CV, Hogan BL. DVR-4 (bone morphogenetic protein-4) as a posterior-ventralizing factor in Xenopus mesoderm induction. Development. 1992 Jun;115(2):639-47

Elliott J, Maltby EL, Reynolds B. A case of deletion 14(q22.1-->q22.3) associated with anophthalmia and pituitary abnormalities. J Med Genet. 1993 Mar;30(3):251-2

Kurihara T, Kitamura K, Takaoka K, Nakazato H. Murine bone morphogenetic protein-4 gene: existence of multiple promoters and exons for the 5'-untranslated region. Biochem Biophys Res Commun. 1993 May 14;192(3):1049-56

Jones WK, Richmond EA, White K, Sasak H, Kusmik W, Smart J, Oppermann H, Rueger DC, Tucker RF. Osteogenic protein-1 (OP-1) expression and processing in Chinese hamster ovary cells: isolation of a soluble complex containing the mature and pro-domains of OP-1. Growth Factors. 1994;11(3):215-25

Phadke SR, Sharma AK, Agarwal SS. Anophthalmia with cleft palate and micrognathia: a new syndrome? J Med Genet. 1994 Dec;31(12):960-1

Castilla EE, Martínez-Frías ML. Congenital healed cleft lip. Am J Med Genet. 1995 Aug 28;58(2):106-12

Feng JQ, Chen D, Cooney AJ, Tsai MJ, Harris MA, Tsai SY, Feng M, Mundy GR, Harris SE. The mouse bone morphogenetic protein-4 gene. Analysis of promoter utilization in fetal rat calvarial osteoblasts and regulation by COUP-TFI orphan receptor. J Biol Chem. 1995 Nov 24;270(47):28364-73

Oida S, Iimura T, Maruoka Y, Takeda K, Sasaki S. Cloning and sequence of bone morphogenetic protein 4 (BMP-4) from a human placental cDNA library. DNA Seq. 1995;5(5):273-5

Onichtchouk D, Gawantka V, Dosch R, Delius H, Hirschfeld K, Blumenstock C, Niehrs C. The Xvent-2 homeobox gene is part of the BMP-4 signalling pathway controlling [correction of controling] dorsoventral patterning of Xenopus mesoderm. Development. 1996 Oct;122(10):3045-53

Schmidt JE, von Dassow G, Kimelman D. Regulation of dorsal-ventral patterning: the ventralizing effects of the novel Xenopus homeobox gene Vox. Development. 1996 Jun;122(6):1711-21

Shafritz AB, Shore EM, Gannon FH, Zasloff MA, Taub R, Muenke M, Kaplan FS. Overexpression of an osteogenic morphogen in fibrodysplasia ossificans progressiva. N Engl J Med. 1996 Aug 22;335(8):555-61

van den Wijngaard A, van Kraay M, van Zoelen EJ, Olijve W, Boersma CJ. Genomic organization of the human bone morphogenetic protein-4 gene: molecular basis for multiple transcripts. Biochem Biophys Res Commun. 1996 Feb 27;219(3):789-94

Ebara S, Kawasaki S, Nakamura I, Tsutsumimoto T, Nakayama K, Nikaido T, Takaoka K. Transcriptional regulation of the mBMP-4 gene through an E-box in the 5'-flanking promoter region involving USF. Biochem Biophys Res Commun. 1997 Nov 7;240(1):136-41

Gannon FH, Kaplan FS, Olmsted E, Finkel GC, Zasloff MA, Shore E. Bone morphogenetic protein 2/4 in early fibromatous lesions of fibrodysplasia ossificans progressiva. Hum Pathol. 1997 Mar;28(3):339-43

Cui Y, Jean F, Thomas G, Christian JL. BMP-4 is proteolytically activated by furin and/or PC6 during vertebrate embryonic development. EMBO J. 1998 Aug 17;17(16):4735-43

Kawabata M, Imamura T, Miyazono K. Signal transduction by bone morphogenetic proteins. Cytokine Growth Factor Rev. 1998 Mar;9(1):49-61

Kim J, Ault KT, Chen HD, Xu RH, Roh DH, Lin MC, Park MJ, Kung HF. Transcriptional regulation of BMP-4 in the Xenopus embryo: analysis of genomic BMP-4 and its promoter. Biochem Biophys Res Commun. 1998 Sep 18;250(2):516-30

Lemyre E, Lemieux N, Décarie JC, Lambert M. Del(14)(q22.1q23.2) in a patient with anophthalmia and pituitary hypoplasia. Am J Med Genet. 1998 May 1;77(2):162-5

Shore EM, Xu M, Shah PB, Janoff HB, Hahn GV, Deardorff MA, Sovinsky L, Spinner NB, Zasloff MA, Wozney JM, Kaplan FS. The human bone morphogenetic protein 4 (BMP-4) gene: molecular structure and transcriptional regulation. Calcif Tissue Int. 1998 Sep;63(3):221-9

Iantosca MR, McPherson CE, Ho SY, Maxwell GD. Bone morphogenetic proteins-2 and -4 attenuate apoptosis in a cerebellar primitive neuroectodermal tumor cell line. J Neurosci Res. 1999 May 1;56(3):248-58

Onichtchouk D, Chen YG, Dosch R, Gawantka V, Delius H, Massagué J, Niehrs C. Silencing of TGF-beta signalling by the pseudoreceptor BAMBI. Nature. 1999 Sep 30;401(6752):480-5

Attisano L, Wrana JL. Smads as transcriptional co-modulators. Curr Opin Cell Biol. 2000 Apr;12(2):235-43

Helvering LM, Sharp RL, Ou X, Geiser AG. Regulation of the promoters for the human bone morphogenetic protein 2 and 4 genes. Gene. 2000 Oct 3;256(1-2):123-38

Xu MQ, Feldman G, Le Merrer M, Shugart YY, Glaser DL, Urtizberea JA, Fardeau M, Connor JM, Triffitt J, Smith R, Shore EM, Kaplan FS. Linkage exclusion and mutational analysis of the noggin gene in patients with fibrodysplasia ossificans progressiva (FOP). Clin Genet. 2000 Oct;58(4):291-8

Hjertner O, Hjorth-Hansen H, Börset M, Seidel C, Waage A, Sundan A. Bone morphogenetic protein-4 inhibits proliferation and induces apoptosis of multiple myeloma cells. Blood. 2001 Jan 15;97(2):516-22

Ahmad ME, Dada R, Dada T, Kucheria K. 14q(22) deletion in a familial case of anophthalmia with polydactyly. Am J Med Genet A. 2003 Jul 1;120A(1):117-22

Nemer G, Nemer M. Transcriptional activation of BMP-4 and regulation of mammalian organogenesis by GATA-4 and -6. Dev Biol. 2003 Feb 1;254(1):131-48

Paez-Pereda M, Giacomini D, Refojo D, Nagashima AC, Hopfner U, Grubler Y, Chervin A, Goldberg V, Goya R, Hentges ST, Low MJ, Holsboer F, Stalla GK, Arzt E. Involvement of bone morphogenetic protein 4 (BMP-4) in pituitary prolactinoma pathogenesis through a Smad/estrogen receptor crosstalk. Proc Natl Acad Sci U S A. 2003 Feb 4;100(3):1034-9

Shepherd TG, Nachtigal MW. Identification of a putative autocrine bone morphogenetic protein-signaling pathway in human ovarian surface epithelium and ovarian cancer cells. Endocrinology. 2003 Aug;144(8):3306-14

Shmueli O, Horn-Saban S, Chalifa-Caspi V, Shmoish M, Ophir R, Benjamin-Rodrig H, Safran M, Domany E, Lancet D. GeneNote: whole genome expression profiles in normal human tissues. C R Biol. 2003 Oct-Nov;326(10-11):1067-72

ten Dijke P, Korchynskyi O, Valdimarsdottir G, Goumans MJ. Controlling cell fate by bone morphogenetic protein receptors. Mol Cell Endocrinol. 2003 Dec 15;211(1-2):105-13

Brubaker KD, Corey E, Brown LG, Vessella RL. Bone morphogenetic protein signaling in prostate cancer cell lines. J Cell Biochem. 2004 Jan 1;91(1):151-60

Buckley S, Shi W, Driscoll B, Ferrario A, Anderson K, Warburton D. BMP4 signaling induces senescence and modulates the oncogenic phenotype of A549 lung adenocarcinoma cells. Am J Physiol Lung Cell Mol Physiol. 2004 Jan;286(1):L81-6

Chen D, Zhao M, Mundy GR. Bone morphogenetic proteins. Growth Factors. 2004 Dec;22(4):233-41

Kim IY, Lee DH, Lee DK, Kim WJ, Kim MM, Morton RA, Lerner SP, Kim SJ. Restoration of bone morphogenetic protein receptor type II expression leads to a decreased rate of tumor growth in bladder transitional cell carcinoma cell line TSU-Pr1. Cancer Res. 2004 Oct 15;64(20):7355-60

Nohe A, Keating E, Knaus P, Petersen NO. Signal transduction of bone morphogenetic protein receptors. Cell Signal. 2004 Mar;16(3):291-9

Shimasaki S, Moore RK, Otsuka F, Erickson GF. The bone morphogenetic protein system in mammalian reproduction. Endocr Rev. 2004 Feb;25(1):72-101

Feeley BT, Gamradt SC, Hsu WK, Liu N, Krenek L, Robbins P, Huard J, Lieberman JR. Influence of BMPs on the formation of osteoblastic lesions in metastatic prostate cancer. J Bone Miner Res. 2005 Dec;20(12):2189-99

Feng XH, Derynck R. Specificity and versatility in tgf-beta signaling through Smads. Annu Rev Cell Dev Biol. 2005;21:659-93

Nowak NJ, Gaile D, Conroy JM, McQuaid D, Cowell J, Carter R, Goggins MG, Hruban RH, Maitra A. Genome-wide aberrations in pancreatic adenocarcinoma. Cancer Genet Cytogenet. 2005 Aug;161(1):36-50

Rothhammer T, Poser I, Soncin F, Bataille F, Moser M, Bosserhoff AK. Bone morphogenic proteins are overexpressed in malignant melanoma and promote cell invasion and migration. Cancer Res. 2005 Jan 15;65(2):448-56

Yanai I, Benjamin H, Shmoish M, Chalifa-Caspi V, Shklar M, Ophir R, Bar-Even A, Horn-Saban S, Safran M, Domany E, Lancet D, Shmueli O. Genome-wide midrange transcription profiles reveal expression level relationships in human tissue specification. Bioinformatics. 2005 Mar 1;21(5):650-9

Giacomini D, Páez-Pereda M, Theodoropoulou M, Labeur M, Refojo D, Gerez J, Chervin A, Berner S, Losa M, Buchfelder M, Renner U, Stalla GK, Arzt E. Bone morphogenetic protein-4 inhibits corticotroph tumor cells: involvement in the retinoic acid inhibitory action. Endocrinology. 2006 Jan;147(1):247-56

Goldman DC, Hackenmiller R, Nakayama T, Sopory S, Wong C, Kulessa H, Christian JL. Mutation of an upstream cleavage site in the BMP4 prodomain leads to tissue-specific loss of activity. Development. 2006 May;133(10):1933-42

Piccirillo SG, Reynolds BA, Zanetti N, Lamorte G, Binda E, Broggi G, Brem H, Olivi A, Dimeco F, Vescovi AL. Bone morphogenetic proteins inhibit the tumorigenic potential of human brain tumour-initiating cells. Nature. 2006 Dec 7;444(7120):761-5

Shore EM, Xu M, Feldman GJ, Fenstermacher DA, Cho TJ, Choi IH, Connor JM, Delai P, Glaser DL, LeMerrer M, Morhart R, Rogers JG, Smith R, Triffitt JT, Urtizberea JA, Zasloff M, Brown MA, Kaplan FS. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. Nat Genet. 2006 May;38(5):525-7

Sneddon JB, Zhen HH, Montgomery K, van de Rijn M, Tward AD, West R, Gladstone H, Chang HY, Morganroth GS, Oro AE, Brown PO. Bone morphogenetic protein antagonist gremlin 1 is widely expressed by cancer-associated stromal cells and can promote tumor cell proliferation. Proc Natl Acad Sci U S A. 2006 Oct 3;103(40):14842-7

Alarmo EL, Kuukasjärvi T, Karhu R, Kallioniemi A. A comprehensive expression survey of bone morphogenetic proteins in breast cancer highlights the importance of BMP4 and BMP7. Breast Cancer Res Treat. 2007 Jun;103(2):239-46

Deng H, Makizumi R, Ravikumar TS, Dong H, Yang W, Yang WL. Bone morphogenetic protein-4 is overexpressed in colonic adenocarcinomas and promotes migration and invasion of HCT116 cells. Exp Cell Res. 2007 Mar 10;313(5):1033-44

Deng H, Ravikumar TS, Yang WL. Bone morphogenetic protein-4 inhibits heat-induced apoptosis by modulating MAPK pathways in human colon cancer HCT116 cells. Cancer Lett. 2007 Oct 28;256(2):207-17

Hamada S, Satoh K, Hirota M, Kimura K, Kanno A, Masamune A, Shimosegawa T. Bone morphogenetic protein 4 induces epithelial-mesenchymal transition through MSX2 induction on pancreatic cancer cell line. J Cell Physiol. 2007 Dec;213(3):768-74

Kwak C, Park YH, Kim IY, Moon KC, Ku JH. Expression of bone morphogenetic proteins, the subfamily of the transforming growth factor-beta superfamily, in renal cell carcinoma. J Urol. 2007 Sep;178(3 Pt 1):1062-7

Montesano R. Bone morphogenetic protein-4 abrogates lumen formation by mammary epithelial cells and promotes invasive growth. Biochem Biophys Res Commun. 2007 Feb 16;353(3):817-22

Rothhammer T, Bataille F, Spruss T, Eissner G, Bosserhoff AK. Functional implication of BMP4 expression on angiogenesis in malignant melanoma. Oncogene. 2007 Jun 14;26(28):4158-70

Thériault BL, Shepherd TG, Mujoomdar ML, Nachtigal MW. BMP4 induces EMT and Rho GTPase activation in human ovarian cancer cells. Carcinogenesis. 2007 Jun;28(6):1153-62

Bakrania P, Efthymiou M, Klein JC, Salt A, Bunyan DJ, Wyatt A, Ponting CP, Martin A, Williams S, Lindley V, Gilmore J, Restori M, Robson AG, Neveu MM, Holder GE, Collin JR, Robinson DO, Farndon P, Johansen-Berg H, Gerrelli D, Ragge NK. Mutations in BMP4 cause eye, brain, and digit developmental anomalies: overlap between the BMP4 and

hedgehog signaling pathways. Am J Hum Genet. 2008 Feb;82(2):304-19

Davies SR, Watkins G, Douglas-Jones A, Mansel RE, Jiang WG. Bone morphogenetic proteins 1 to 7 in human breast cancer, expression pattern and clinical/prognostic relevance. J Exp Ther Oncol. 2008;7(4):327-38

Houlston RS, Webb E, Broderick P, Pittman AM, Di Bernardo MC, Lubbe S, Chandler I, Vijayakrishnan J, Sullivan K, Penegar S, Carvajal-Carmona L, Howarth K, Jaeger E, Spain SL, Walther A, Barclay E, Martin L, Gorman M, Domingo E, Teixeira AS, Kerr D, Cazier JB, Niittymäki I, Tuupanen S, Karhu A, Aaltonen LA, Tomlinson IP, Farrington SM, Tenesa A, Prendergast JG, Barnetson RA, Cetnarskyj R, Porteous ME, Pharoah PD, Koessler T, Hampe J, Buch S, Schafmayer C, Tepel J, Schreiber S, Völzke H, Chang-Claude J, Hoffmeister M, Brenner H, Zanke BW, Montpetit A, Hudson TJ, Gallinger S, Campbell H, Dunlop MG. Meta-analysis of genome-wide association data identifies four new susceptibility loci for colorectal cancer. Nat Genet. 2008 Dec;40(12):1426-35

Montesano R, Sarközi R, Schramek H. Bone morphogenetic protein-4 strongly potentiates growth factor-induced proliferation of mammary epithelial cells. Biochem Biophys Res Commun. 2008 Sep 12;374(1):164-8

Wamstad JA, Corcoran CM, Keating AM, Bardwell VJ. Role of the transcriptional corepressor Bcor in embryonic stem cell differentiation and early embryonic development. PLoS One. 2008 Jul 30;3(7):e2814

Zhao H, Ayrault O, Zindy F, Kim JH, Roussel MF. Post-transcriptional down-regulation of Atoh1/Math1 by bone morphogenic proteins suppresses medulloblastoma development. Genes Dev. 2008 Mar 15;22(6):722-7

Capasso M, Ayala F, Russo R, Avvisati RA, Asci R, Iolascon A. A predicted functional single-nucleotide polymorphism of bone morphogenetic protein-4 gene affects mRNA expression and shows a significant association with cutaneous melanoma in Southern Italian population. J Cancer Res Clin Oncol. 2009 Dec;135(12):1799-807

Chandler KJ, Chandler RL, Mortlock DP. Identification of an ancient Bmp4 mesoderm enhancer located 46 kb from the promoter. Dev Biol. 2009 Mar 15;327(2):590-602

Deng H, Ravikumar TS, Yang WL. Overexpression of bone morphogenetic protein 4 enhances the invasiveness of Smad4-deficient human colorectal cancer cells. Cancer Lett. 2009 Aug 28;281(2):220-31

Gordon KJ, Kirkbride KC, How T, Blobe GC. Bone morphogenetic proteins induce pancreatic cancer cell invasiveness through a Smad1-dependent mechanism that involves matrix metalloproteinase-2. Carcinogenesis. 2009 Feb;30(2):238-48

Hartmann O, Spyratos F, Harbeck N, Dietrich D, Fassbender A, Schmitt M, Eppenberger-Castori S, Vuaroqueaux V, Lerebours F, Welzel K, Maier S, Plum A, Niemann S, Foekens JA, Lesche R, Martens JW. DNA methylation markers predict outcome in node-positive, estrogen receptor-positive breast cancer with adjuvant anthracycline-based chemotherapy. Clin Cancer Res. 2009 Jan 1;15(1):315-23

Johnson MD, O'Connell MJ, Vito F, Pilcher W. Bone morphogenetic protein 4 and its receptors are expressed in the leptomeninges and meningiomas and signal via the Smad pathway. J Neuropathol Exp Neurol. 2009 Nov;68(11):1177-83

Kelley R, Ren R, Pi X, Wu Y, Moreno I, Willis M, Moser M, Ross M, Podkowa M, Attisano L, Patterson C. A concentration-dependent endocytic trap and sink mechanism converts Bmper from an activator to an inhibitor of Bmp signaling. J Cell Biol. 2009 Feb 23;184(4):597-609

Maegdefrau U, Amann T, Winklmeier A, Braig S, Schubert T, Weiss TS, Schardt K, Warnecke C, Hellerbrand C, Bosserhoff AK. Bone morphogenetic protein 4 is induced in hepatocellular carcinoma by hypoxia and promotes tumour progression. J Pathol. 2009 Aug;218(4):520-9

Pregizer S, Mortlock DP. Control of BMP gene expression by long-range regulatory elements. Cytokine Growth Factor Rev. 2009 Oct-Dec;20(5-6):509-15

Shon SK, Kim A, Kim JY, Kim KI, Yang Y, Lim JS. Bone morphogenetic protein-4 induced by NDRG2 expression inhibits MMP-9 activity in breast cancer cells. Biochem Biophys Res Commun. 2009 Jul 24;385(2):198-203

Su D, Zhu S, Han X, Feng Y, Huang H, Ren G, Pan L, Zhang Y, Lu J, Huang B. BMP4-Smad signaling pathway mediates adriamycin-induced premature senescence in lung cancer cells. J Biol Chem. 2009 May 1;284(18):12153-64

Suzuki S, Marazita ML, Cooper ME, Miwa N, Hing A, Jugessur A, Natsume N, Shimozato K, Ohbayashi N, Suzuki Y, Niimi T, Minami K, Yamamoto M, Altannamar TJ, Erkhembaatar T, Furukawa H, Daack-Hirsch S, L'heureux J, Brandon CA, Weinberg SM, Neiswanger K, Deleyiannis FW, de Salamanca JE, Vieira AR, Lidral AC, Martin JF, Murray JC. Mutations in BMP4 are associated with subepithelial, microform, and overt cleft lip. Am J Hum Genet. 2009 Mar;84(3):406-11

Grcević D, Kusec R, Kovacić N, Lukić A, Lukić IK, Ivcević S, Nemet D, Seiwerth RS, Ostojić SK, Croucher PI, Marusić A. Bone morphogenetic proteins and receptors are over-expressed in bone-marrow cells of multiple myeloma patients and support myeloma cells by inducing ID genes. Leuk Res. 2010 Jun;34(6):742-51

Haubold M, Weise A, Stephan H, Dünker N. Bone morphogenetic protein 4 (BMP4) signaling in retinoblastoma cells. Int J Biol Sci. 2010 Nov 24;6(7):700-15

Ketolainen JM, Alarmo EL, Tuominen VJ, Kallioniemi A. Parallel inhibition of cell growth and induction of cell migration and invasion in breast cancer cells by bone morphogenetic protein 4. Breast Cancer Res Treat. 2010 Nov;124(2):377-86

Labeur M, Páez-Pereda M, Haedo M, Arzt E, Stalla GK. Pituitary tumors: cell type-specific roles for BMP-4. Mol Cell Endocrinol. 2010 Sep 15;326(1-2):85-8

Liu B, Tian D, Yi W, Wu L, Cai Q, Dong H, Shen H, Ji B, Wang L, Zhang S, Ruan D, Chen Q. Effect of bone morphogenetic protein 4 in the human brain glioma cell line U251. Cell Biochem Biophys. 2010 Nov;58(2):91-6

Miyazono K, Kamiya Y, Morikawa M. Bone morphogenetic protein receptors and signal transduction. J Biochem. 2010 Jan;147(1):35-51

Murohashi M, Nakamura T, Tanaka S, Ichise T, Yoshida N, Yamamoto T, Shibuya M, Schlessinger J, Gotoh N. An FGF4-FRS2alpha-Cdx2 axis in trophoblast stem cells induces Bmp4 to regulate proper growth of early mouse embryos. Stem Cells. 2010 Jan;28(1):113-21

Puskaric S, Schmitteckert S, Mori AD, Glaser A, Schneider KU, Bruneau BG, Blaschke RJ, Steinbeisser H, Rappold G. Shox2 mediates Tbx5 activity by regulating Bmp4 in the pacemaker region of the developing heart. Hum Mol Genet. 2010 Dec 1;19(23):4625-33

Shaw A, Gipp J, Bushman W. Exploration of Shh and BMP paracrine signaling in a prostate cancer xenograft. Differentiation. 2010 Jan;79(1):41-7

Spanjol J, Djordjević G, Markić D, Klarić M, Fuckar D, Bobinac D. Role of bone morphogenetic proteins in human prostate cancer pathogenesis and development of bone metastases:

immunohistochemical study. Coll Antropol. 2010 Apr;34 Suppl 2:119-25

Wu DC, Paulson RF. Hypoxia regulates BMP4 expression in the murine spleen during the recovery from acute anemia. PLoS One. 2010 Jun 24;5(6):e11303

Wu X, Rauch TA, Zhong X, Bennett WP, Latif F, Krex D, Pfeifer GP. CpG island hypermethylation in human astrocytomas. Cancer Res. 2010 Apr 1;70(7):2718-27

Bragdon B, Moseychuk O, Saldanha S, King D, Julian J, Nohe A. Bone morphogenetic proteins: a critical review. Cell Signal. 2011 Apr;23(4):609-20

Duerr EM, Mizukami Y, Moriichi K, Gala M, Jo WS, Kikuchi H, Xavier RJ, Chung DC. Oncogenic KRAS regulates BMP4 expression in colon cancer cell lines. Am J Physiol Gastrointest Liver Physiol. 2012 May 15;302(10):G1223-30

Kim SG, Park HR, Min SK, Choi JY, Koh SH, Kim JW, Lee HW. Expression of bone morphogenic protein-4 is inversely related to prevalence of lymph node metastasis in gastric adenocarcinoma. Surg Today. 2011 May;41(5):688-92

Kim W, Bennett EJ, Huttlin EL, Guo A, Li J, Possemato A, Sowa ME, Rad R, Rush J, Comb MJ, Harper JW, Gygi SP. Systematic and quantitative assessment of the ubiquitin-modified proteome. Mol Cell. 2011 Oct 21;44(2):325-40

Laatio L, Myllynen P, Serpi R, Rysä J, Ilves M, Lappi-Blanco E, Ruskoaho H, Vähäkangas K, Puistola U. BMP-4 expression has prognostic significance in advanced serous ovarian carcinoma and is affected by cisplatin in OVCAR-3 cells. Tumour Biol. 2011 Oct;32(5):985-95

Lee YC, Cheng CJ, Bilen MA, Lu JF, Satcher RL, Yu-Lee LY, Gallick GE, Maity SN, Lin SH. BMP4 promotes prostate tumor growth in bone through osteogenesis. Cancer Res. 2011 Aug 1;71(15):5194-203

Lombardo Y, Scopelliti A, Cammareri P, Todaro M, Iovino F, Ricci-Vitiani L, Gulotta G, Dieli F, de Maria R, Stassi G. Bone morphogenetic protein 4 induces differentiation of colorectal cancer stem cells and increases their response to chemotherapy in mice. Gastroenterology. 2011 Jan;140(1):297-309

Lubbe SJ, Pittman AM, Matijssen C, Twiss P, Olver B, Lloyd A, Qureshi M, Brown N, Nye E, Stamp G, Blagg J, Houlston RS. Evaluation of germline BMP4 mutation as a cause of colorectal cancer. Hum Mutat. 2011 Jan;32(1):E1928-38

Markić D, Ćelić T, Gršković A, Španjol J, Fučkar Ž, Grahovac B, Dorđević G, Bobinac D. mRNA expression of bone morphogenetic proteins and their receptors in human renal cell carcinoma. Urol Int. 2011;87(3):353-8

McLean K, Gong Y, Choi Y, Deng N, Yang K, Bai S, Cabrera L, Keller E, McCauley L, Cho KR, Buckanovich RJ. Human ovarian carcinoma–associated mesenchymal stem cells regulate cancer stem cells and tumorigenesis via altered BMP production. J Clin Invest. 2011 Aug;121(8):3206-19

Rodriguez-Martinez A, Alarmo EL, Saarinen L, Ketolainen J, Nousiainen K, Hautaniemi S, Kallioniemi A. Analysis of BMP4 and BMP7 signaling in breast cancer cells unveils time-dependent transcription patterns and highlights a common synexpression group of genes. BMC Med Genomics. 2011 Nov 25;4:80

Shirai YT, Ehata S, Yashiro M, Yanagihara K, Hirakawa K, Miyazono K. Bone morphogenetic protein-2 and -4 play tumor suppressive roles in human diffuse-type gastric carcinoma. Am J Pathol. 2011 Dec;179(6):2920-30

Su D, Peng X, Zhu S, Huang Y, Dong Z, Zhang Y, Zhang J, Liang Q, Lu J, Huang B. Role of p38 MAPK pathway in BMP4-mediated Smad-dependent premature senescence in lung cancer cells. Biochem J. 2011 Jan 15;433(2):333-43

Thériault BL, Nachtigal MW. Human ovarian cancer cell morphology, motility, and proliferation are differentially influenced by autocrine TGFβ superfamily signalling. Cancer Lett. 2011 Dec 26;313(1):108-21

Tomlinson IP, Carvajal-Carmona LG, Dobbins SE, Tenesa A, Jones AM, Howarth K, Palles C, Broderick P, Jaeger EE, Farrington S, Lewis A, Prendergast JG, Pittman AM, Theodoratou E, Olver B, Walker M, Penegar S, Barclay E, Whiffin N, Martin L, Ballereau S, Lloyd A, Gorman M, Lubbe S, Howie B, Marchini J, Ruiz-Ponte C, Fernandez-Rozadilla C, Castells A, Carracedo A, Castellvi-Bel S, Duggan D, Conti D, Cazier JB, Campbell H, Sieber O, Lipton L, Gibbs P, Martin NG, Montgomery GW, Young J, Baird PN, Gallinger S, Newcomb P, Hopper J, Jenkins MA, Aaltonen LA, Kerr DJ, Cheadle J, Pharoah P, Casey G, Houlston RS, Dunlop MG. Multiple common susceptibility variants near BMP pathway loci GREM1, BMP4, and BMP2 explain part of the missing heritability of colorectal cancer. PLoS Genet. 2011 Jun;7(6):e1002105

Virtanen S, Alarmo EL, Sandström S, Ampuja M, Kallioniemi A. Bone morphogenetic protein -4 and -5 in pancreatic cancer--novel bidirectional players. Exp Cell Res. 2011 Sep 10;317(15):2136-46

Xu J, Zhu D, He S, Spee C, Ryan SJ, Hinton DR. Transcriptional regulation of bone morphogenetic protein 4 by tumor necrosis factor and its relationship with age-related macular degeneration. FASEB J. 2011 Jul;25(7):2221-33

Xu T, Yu CY, Sun JJ, Liu Y, Wang XW, Pi LM, Tian YQ, Zhang X. Bone morphogenetic protein-4-induced epithelial-mesenchymal transition and invasiveness through Smad1-mediated signal pathway in squamous cell carcinoma of the head and neck. Arch Med Res. 2011 Feb;42(2):128-37

Zaravinos A, Lambrou GI, Boulalas I, Delakas D, Spandidos DA. Identification of common differentially expressed genes in urinary bladder cancer. PLoS One. 2011 Apr 4;6(4):e18135

Zhou Z, Sun L, Wang Y, Wu Z, Geng J, Miu W, Pu Y, You Y, Yang Z, Liu N. Bone morphogenetic protein 4 inhibits cell proliferation and induces apoptosis in glioma stem cells. Cancer Biother Radiopharm. 2011 Feb;26(1):77-83

Barbieri CE, Baca SC, Lawrence MS, Demichelis F, Blattner M, Theurillat JP, White TA, Stojanov P, Van Allen E, Stransky N, Nickerson E, Chae SS, Boysen G, Auclair D, Onofrio RC, Park K, Kitabayashi N, MacDonald TY, Sheikh K, Vuong T, Guiducci C, Cibulskis K, Sivachenko A, Carter SL, Saksena G, Voet D, Hussain WM, Ramos AH, Winckler W, Redman MC, Ardlie K, Tewari AK, Mosquera JM, Rupp N, Wild PJ, Moch H, Morrissey C, Nelson PS, Kantoff PW, Gabriel SB, Golub TR, Meyerson M, Lander ES, Getz G, Rubin MA, Garraway LA. Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer. Nat Genet. 2012 May 20;44(6):685-9

. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012 Jul 18;487(7407):330-7

Chiu CY, Kuo KK, Kuo TL, Lee KT, Cheng KH. The activation of MEK/ERK signaling pathway by bone morphogenetic protein 4 to increase hepatocellular carcinoma cell proliferation and migration. Mol Cancer Res. 2012 Mar;10(3):415-27

Grasso CS, Wu YM, Robinson DR, Cao X, Dhanasekaran SM, Khan AP, Quist MJ, Jing X, Lonigro RJ, Brenner JC, Asangani IA, Ateeq B, Chun SY, Siddiqui J, Sam L, Anstett M, Mehra R, Prensner JR, Palanisamy N, Ryslik GA, Vandin F, Raphael BJ, Kunju LP, Rhodes DR, Pienta KJ, Chinnaiyan AM, Tomlins SA. The mutational landscape of lethal castration-resistant prostate cancer. Nature. 2012 Jul 12;487(7406):239-43

Guo D, Huang J, Gong J. Bone morphogenetic protein 4 (BMP4) is required for migration and invasion of breast cancer. Mol Cell Biochem. 2012 Apr;363(1-2):179-90

Guo X, Xiong L, Zou L, Zhao J. Upregulation of bone morphogenetic protein 4 is associated with poor prognosis in patients with hepatocellular carcinoma. Pathol Oncol Res. 2012 Jul;18(3):635-40

Holien T, Våtsveen TK, Hella H, Rampa C, Brede G, Grøseth LA, Rekvig M, Børset M, Standal T, Waage A, Sundan A. Bone morphogenetic proteins induce apoptosis in multiple myeloma cells by Smad-dependent repression of MYC. Leukemia. 2012 May;26(5):1073-80

Jumlongras D, Lachke SA, O'Connell DJ, Aboukhalil A, Li X, Choe SE, Ho JW, Turbe-Doan A, Robertson EA, Olsen BR, Bulyk ML, Amendt BA, Maas RL. An evolutionarily conserved enhancer regulates Bmp4 expression in developing incisor and limb bud. PLoS One. 2012;7(6):e38568

Kallioniemi A. Bone morphogenetic protein 4-a fascinating regulator of cancer cell behavior. Cancer Genet. 2012 Jun;205(6):267-77

Lubbe SJ, Pittman AM, Olver B, Lloyd A, Vijayakrishnan J, Naranjo S, Dobbins S, Broderick P, Gómez-Skarmeta JL, Houlston RS. The 14q22.2 colorectal cancer variant rs4444235 shows cis-acting regulation of BMP4. Oncogene. 2012 Aug 16;31(33):3777-84

Rankin SA, Gallas AL, Neto A, Gómez-Skarmeta JL, Zorn AM. Suppression of Bmp4 signaling by the zinc-finger repressors Osr1 and Osr2 is required for Wnt/β-catenin-mediated lung specification in Xenopus. Development. 2012 Aug;139(16):3010-20

Ricketts CJ, Morris MR, Gentle D, Brown M, Wake N, Woodward ER, Clarke N, Latif F, Maher ER. Genome-wide CpG island methylation analysis implicates novel genes in the pathogenesis of renal cell carcinoma. Epigenetics. 2012 Mar;7(3):278-90

Slattery ML, Lundgreen A, Herrick JS, Kadlubar S, Caan BJ, Potter JD, Wolff RK. Genetic variation in bone morphogenetic protein and colon and rectal cancer. Int J Cancer. 2012 Feb 1;130(3):653-64

Theodoratou E, Montazeri Z, Hawken S, Allum GC, Gong J, Tait V, Kirac I, Tazari M, Farrington SM, Demarsh A, Zgaga L, Landry D, Benson HE, Read SH, Rudan I, Tenesa A, Dunlop MG, Campbell H, Little J. Systematic meta-analyses and field synopsis of genetic association studies in colorectal cancer. J Natl Cancer Inst. 2012 Oct 3;104(19):1433-57

Zhou Z, Chen ZW, Yang XH, Shen L, Ai XH, Lu S, Luo QQ. Establishment of a biomarker model for predicting bone metastasis in resected stage III non-small cell lung cancer. J Exp Clin Cancer Res. 2012 Apr 26;31:34

Alarmo EL, Huhtala H, Korhonen T, Pylkkänen L, Holli K, Kuukasjärvi T, Parkkila S, Kallioniemi A. Bone morphogenetic protein 4 expression in multiple normal and tumor tissues reveals its importance beyond development. Mod Pathol. 2013 Jan;26(1):10-21

Ivanova T, Zouridis H, Wu Y, Cheng LL, Tan IB, Gopalakrishnan V, Ooi CH, Lee J, Qin L, Wu J, Lee M, Rha SY, Huang D, Liem N, Yeoh KG, Yong WP, Teh BT, Tan P. Integrated epigenomics identifies BMP4 as a modulator of cisplatin sensitivity in gastric cancer. Gut. 2013 Jan;62(1):22-33

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