

Gene Section

Mini Review

SPP1 (secreted phosphoprotein 1)

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Identity

Other names: BNSP, BSPI, ETA-1, MGC110940, Nephropontin, OPN, SPP-1, Uropontin, osteopontin
HGNC (Hugo): SPP1

Location: 4q22.1

Note: Gene type: protein coding.

DNA/RNA

Note

Genes encompassed within a 600 kb region on human chromosome 4 encode several noncollagenous bone and dentin proteins. They include osteopontin, bone sialoprotein, dentin matrix protein I, and dentin sialophosphoprotein, all of which have been categorized as members of the small integrin-binding ligand N-linked glycoprotein (SIBLING) family-related proteins. The 4 proteins are somewhat similar being secreted, sialylated, phosphorylated, and acidic in nature.

Description

- Osteopontin is encoded by a single copy gene

located on the human chromosome 4; 7 exons.

- Codon triplets are not interrupted by introns, and consequently, exon skipping will not affect the codon triplets in the remaining exons.

- The human gene sequence spans ~9 kb and the open reading frame consists of 942 nucleotides from the start codon (in exon 2) to the stop codon (in exon 7).

Transcription

- The 5'-untranslated region includes exon 1, which starts a transcription initiation site (AGC).

- The 3'-untranslated region consists of the last part of exon 7, which includes three potential polyadenylation attachment signals (AATAA).

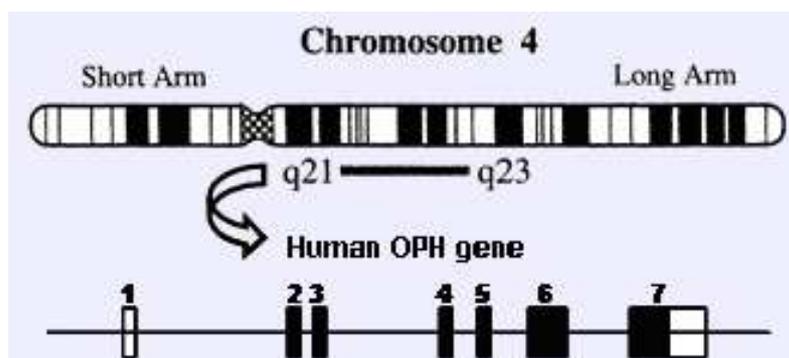
- Exon 2 encodes the signal peptide and the first two amino acids in the mature protein.

- Exon 3 and 5, the two characteristic Ser-Ser-Glu-Glu phosphorylation sequences.

- Exon 4, the two transglutaminase-reactive glutamine residues.

- Exon 6, the aspartic-rich sequence.

- Exon 7 is the largest exon encoding approximately half of the proteins including the RGD motif and the central thrombin cleavage site.



The gene structure of human osteopontin. Exons are boxed, filled boxes are coding regions and open boxes are untranslated regions.



Structure of human osteopontin protein indicating selected structural domains.

- There are 3 transcripts for osteopontin splice variants that are OPN-a, OPN-b and OPN-c. Alternative splicing occurs in a region of the molecule that is upstream of the central integrin binding domain and the C-terminal CD44 binding domain. OPN-b lacks exon 5 and OPN-c lacks exon 4.

- Transcriptional regulation is complex and involves multiple pathways including AP-1, Myc, v-Src, RunX/CBF, TGF-B/BMPS/Smad/Hox and Wnt/b-catenin/APC/GSK-3b/Tcf-4.

Protein

Note

Osteopontin serves as a substrate for thrombin and matrix metalloproteinases (MMP2, MMP3, MMP7, MMP9 and MMP12), can bind to the extracellular matrix proteins fibronectin and collagen, and interacts with integrins alphaV (beta1, beta2 or beta5) and (alpha4, alpha5, alpha8 or alpha9) beta1 surface receptors through an Arg-Gly-Asp (RGD) sequence.

Secreted phosphoprotein 1 (or osteopontin) was identified with 7 protein interactions: ITGAV, IGFBP5, PDLIM7, CD44, ITGA5, CTNBL1, SGTA.

Description

- Recommended name: osteopontin.
 - Osteopontin is 314 amino acids in length.
 - The molecular weight of osteopontin and associated isoforms are measured between 41 and 75 kDa. Post-translational modifications leading to cell-type and condition-specific variations may account for this variability in molecular weight.

- Osteopontin is extremely hydrophilic with a low isoelectric point (3.5).

- It displays an unusual amino acid composition with 42 serine, 48 aspartic acid and 27 glutamine acid residues. It is important to notice that 27 out of the 42 serine residues are phosphorylated.

- The predicted secondary structure of osteopontin consists of eight alpha-helices and six beta-sheet segments.

- Structural domains:

Aspartate domain - amino acid sequence Asp86-Asp89
 - binds hydroxyapatite,

RGD sequence - amino acid sequence Arg159-Asp159
 - binds alphaVbeta3, alphaVbeta1, alphaVbeta5 and alpha5beta1 integrins,

SVVYGLR sequence - amino acid sequence Ser162-Arg168 - binds alpha9beta1 and alpha1beta1 integrins,

Thrombin cleavage site - amino acid sequence Arg168-Ser169 - displays RGD sequence,

Calcium binding domain - amino acid sequence Asp216-Ser228 - calcium binding,

Heparin binding domain - amino acid sequence Asp290-Ile305 - mediates CD44v3 binding.

- Post-translational modifications:

Extensively phosphorylated on clustered serine residues,

N- and O-glycosylated.

Expression

Osteopontin is expressed by cells in a variety of tissues, including bone, dentin, cementum, hypertrophic cartilage, kidney, brain, bone-marrow-derived stromal cells, vascular tissues and cytotrophoblasts of the chorionic villus in the uterus and decidua, ganglia of the inner ear, brain cells and specialized epithelia found in mammary, salivary, and sweat glands, in bile and pancreatic ducts, and in distal renal tubules and in the gut, as well as in activated macrophages and lymphocytes.

Cell types which express osteopontin: osteoclasts, osteoblasts, kidney, breast and skin epithelial cells, nerve cells, vascular smooth muscle cells and endothelial cells. Activated immune cells (T-cells, NK cells, macrophages and Kupffer cells) also express osteopontin.

Localisation

It is predominantly secreted but its intracellular form has also been described.

Function

- Binds tightly to hydroxyapatite. Appears to form an integral part of the mineralized matrix. Probably important to cell-matrix interaction.

- Acts as a cytokine involved in enhancing production of interferon-gamma and interleukin-12 and reducing production of interleukin-10 and is essential in the pathway that leads to type I immunity.

- Participates in bone remodelling, inflammation, cancer and immunity to infection disease.

- Regulates the formation and growth of calcium phosphate and oxalate crystals.

- Is involved in cell attachment and signalling through integrins.

- Is involved in cell attachment and signalling through CD44.

Homology

The amino acid sequence of osteopontin is nowadays available for several species, such as rat, mouse, human, pig, rabbit and cow. The referenced mammalian osteopontin sequences are identical in ~33% of the residues, and in addition, many similar amino acids are conserved between the sequences. Identical residues are scattered in clusters. More

specifically, the larger clusters are located in the hydrophobic leader sequence (the first 16 residues), in a potential site for N-linked glycosylation, and in several sites for O-linked glycosylation and phosphorylation. A stretch of consecutive aspartic acid residues was also found in all species, as well as a cell attachment RGD motif almost immediately followed by a thrombin cleavage site.

Implicated in

Multiple cancers

Note

The ability of osteopontin to interact with a diverse range of factors including cell surface receptors (integrins, CD44), secreted proteases (matrix metalloproteinases, urokinase plasminogen activator) and growth factor/receptor pathways (TGF α /EGFR, HGF/MET) is central to its role in malignancy.

Changes in gene expression implies alterations in cell properties involved in malignancy such as adhesion, migration, invasion, enhanced tumour survival, tumour angiogenesis, and metastasis.

Disease

Multiple cancers such as breast, thyroid, cervical, prostate, lung, gastric, liver and colon.

At present, it is fully accepted that osteopontin expressed by tumour cells alters their malignant properties, specifically by affecting their ability to grow, invade, and metastasize. However, it is important to notice that osteopontin is expressed both in normal and malignant tissues. Recent studies suggest that osteopontin levels in the blood or tumours of patients with cancer may provide useful clinical information on patient prognoses.

Prognosis

Elevated osteopontin expression correlate with tumour invasion, progression or metastasis in multiple cancers (thyroid, cervical, breast, prostate, lung, gastric, liver and colon). Osteopontin expression is associated with disease progression in patients, with higher levels of osteopontin produced by cancer cells associated with a poorer patient survival.

Oncogenesis

Osteopontin is believed to be an effector of activated oncogenes functioning to facilitate tumour growth and metastasis.

References

Butler WT. The nature and significance of osteopontin. *Connect Tissue Res.* 1989;23(2-3):123-36

Kiefer MC, Bauer DM, Barr PJ. The cDNA and derived amino acid sequence for human osteopontin. *Nucleic Acids Res.* 1989 Apr 25;17(8):3306

Brown LF, Berse B, Van de Water L, Papadopoulos-Sergiou A, Perruzzi CA, Manseau EJ, Dvorak HF, Senger DR. Expression

and distribution of osteopontin in human tissues: widespread association with luminal epithelial surfaces. *Mol Biol Cell.* 1992 Oct;3(10):1169-80

Denhardt DT, Guo X. Osteopontin: a protein with diverse functions. *FASEB J.* 1993 Dec;7(15):1475-82

Brown LF, Papadopoulos-Sergiou A, Berse B, Manseau EJ, Tognazzi K, Perruzzi CA, Dvorak HF, Senger DR. Osteopontin expression and distribution in human carcinomas. *Am J Pathol.* 1994 Sep;145(3):610-23

Hijiya N, Setoguchi M, Matsuura K, Higuchi Y, Akizuki S, Yamamoto S. Cloning and characterization of the human osteopontin gene and its promoter. *Biochem J.* 1994 Oct 1;303 (Pt 1):255-62

Oates AJ, Barraclough R, Rudland PS. The role of osteopontin in tumorigenesis and metastasis. *Invasion Metastasis.* 1997;17(1):1-15

Rittling SR, Novick KE. Osteopontin expression in mammary gland development and tumorigenesis. *Cell Growth Differ.* 1997 Oct;8(10):1061-9

Sodek J, Ganss B, McKee MD. Osteopontin. *Crit Rev Oral Biol Med.* 2000;11(3):279-303

Furger KA, Menon RK, Tuck AB, Bramwell VH, Chambers AF. The functional and clinical roles of osteopontin in cancer and metastasis. *Curr Mol Med.* 2001 Nov;1(5):621-32

Weber GF. The metastasis gene osteopontin: a candidate target for cancer therapy. *Biochim Biophys Acta.* 2001 Dec 28;1552(2):61-85

Kim JH, Skates SJ, Uede T, Wong KK, Schorge JO, Feltmate CM, Berkowitz RS, Cramer DW, Mok SC. Osteopontin as a potential diagnostic biomarker for ovarian cancer. *JAMA.* 2002 Apr 3;287(13):1671-9

Mazzali M, Kipari T, Ophascharoensuk V, Wesson JA, Johnson R, Hughes J. Osteopontin--a molecule for all seasons. *QJM.* 2002 Jan;95(1):3-13

Brakora KA, Lee H, Yusuf R, Sullivan L, Harris A, Colella T, Seiden MV. Utility of osteopontin as a biomarker in recurrent epithelial ovarian cancer. *Gynecol Oncol.* 2004 May;93(2):361-5

Christensen B, Nielsen MS, Haselmann KF, Petersen TE, Sørensen ES. Post-translationally modified residues of native human osteopontin are located in clusters: identification of 36 phosphorylation and five O-glycosylation sites and their biological implications. *Biochem J.* 2005 Aug 15;390(Pt 1):285-92

Rodrigues LR, Teixeira JA, Schmitt FL, Paulsson M, Lindmark-Månsson H. The role of osteopontin in tumor progression and metastasis in breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2007 Jun;16(6):1087-97

Tuck AB, Chambers AF, Allan AL. Osteopontin overexpression in breast cancer: knowledge gained and possible implications for clinical management. *J Cell Biochem.* 2007 Nov 1;102(4):859-68

Chakraborty G, Jain S, Kundu GC. Osteopontin promotes vascular endothelial growth factor-dependent breast tumor growth and angiogenesis via autocrine and paracrine mechanisms. *Cancer Res.* 2008 Jan 1;68(1):152-61

Hedley BD, Welch DR, Allan AL, Al-Katib W, Dales DW, Postenka CO, Casey G, Macdonald IC, Chambers AF. Downregulation of osteopontin contributes to metastasis suppression by breast cancer metastasis suppressor 1. *Int J Cancer.* 2008 Aug 1;123(3):526-34

Mirza M, Shaughnessy E, Hurley JK, Vanpatten KA, Pestano GA, He B, Weber GF. Osteopontin-c is a selective marker of breast cancer. *Int J Cancer*. 2008 Feb 15;122(4):889-97

Partridge CR, He Q, Brun M, Ramos KS. Genetic networks of cooperative redox regulation of osteopontin. *Matrix Biol*. 2008 Jun;27(5):462-74

Wai PY, Kuo PC. Osteopontin: regulation in tumor metastasis. *Cancer Metastasis Rev*. 2008 Mar;27(1):103-18

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