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/CFB, 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, CTNNBL1, 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 glutamic 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.
- Strutural domains:
  - Aspartate domain - amino acid sequence Asp86-Asp89
  - RGD sequence - amino acid sequence Arg159-Asp159
  - SVVYGLR sequence - amino acid sequence Ser162-Ser169
  - Calcium binding domain - amino acid sequence Asp216-Ser228

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 metrial gland cells, vascular tissues and cytrophoblasts 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 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 (TGFalpha/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 metastatize. 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**


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


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