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Gene Section
Review

PRDX4 (peroxiredoxin 4)

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Identity

Other names: AOE37-2, PRX-4

HGNC (Hugo): PRDX4

Location: Xp22.11

DNA/RNA

Note

Prdx4 gene is ubiquitously expressed in various strata of life in which more than 40 species has been sequenced.

Description

Human PRDX4 gene is located on X chromosome at p22 location.

Transcription

Transcription of PRDX4 gene generates 5 different transcripts and the length of the longest is 1005 bp containing 7 exons.

Pseudogene

PRDX4P1, PRDX4P2.

Protein

Note

Human PRDX4 gene encodes 271 amino acids. It may present in biological system as dimeric and decameric state. The presence of dimeric or decameric state of Prx-4 may be redox regulated (Wood et al., 2002).

The crystal structure of the decameric Prx-4 has been resolved. It is also noteworthy that Prx-4 forms heterodimer or multimer with other Prx isoforms.

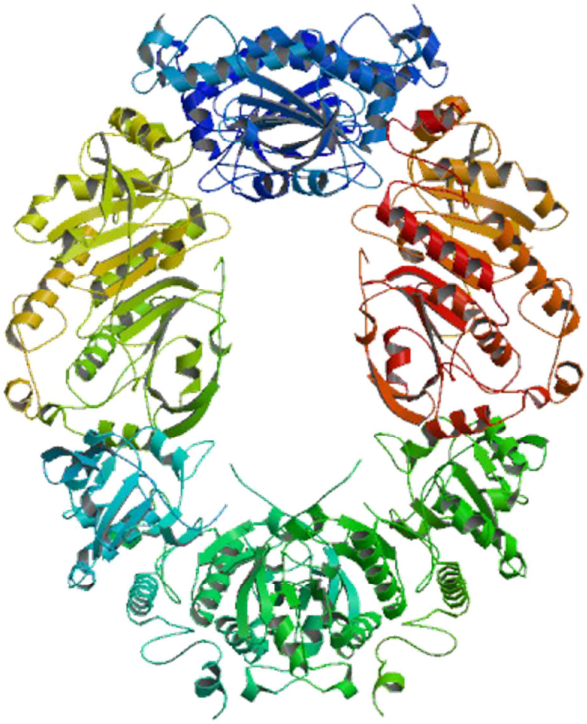
Description

Peroxiredoxin 4 is an antioxidant enzyme that belongs to the peroxiredoxin family. The peroxiredoxin family of proteins scavenges hydrogen peroxide and plays a critical role in cellular response to oxidative stress and intracellular signal transduction.

Expression

Peroxiredoxin 4 is abundantly expressed in pancreas, liver and heart.

Map of X-chromosome showing location of PRDX4 gene.



Crystal structure of human peroxiredoxin 4 (PDB 2PN8).

Localisation

Prx-4 is mainly localized in the endoplasmic reticulum (ER), but is also present in the cytosol, lysosome, nucleus, or secreted (Leyens et al., 2003).

Function

The antioxidant property of Prx-4 may play an essential role in the redox balance in the ER. The Cysteine residue of Prx-4 is first oxidized to sulfenic acid form and then forms intermolecular disulfide bond with another Prx molecule, which can be reversed by the reducing activity of the thioredoxin-thioredoxin reductase system. Under oxidative stress conditions, however, the Cysteine of Prx-4 undergoes further oxidation to sulfinic/sulfonic acid forms which can only be reduced by sulfiredoxin (Jeong et al., 2012). The hyperoxidized (or overoxidized) form of Prx-4 loses its antioxidant property but may function as molecular chaperone to facilitate protein folding (Rhee and Woo, 2011; Zito et al., 2010). The Prx-4 has also been shown to mediate multiple cell signaling pathways including the phosphorylation of p38α, JNK1/JNK2, GSK3α/GSK3β, MEK1/MEK2, MSK1/MSK2, AMPKα, HSP27, Src, Fyn, etc.

Homology

As in other typical 2-Cys peroxiredoxins, Prdx4 also contains a peroxidatic Cysteine and a resolving Cysteine that is separated by 121 amino acids. The overall sequence homology of Prx-4 with other 2-Cys Prx is at least 56% or higher. In particular, sequences surrounding both cysteine residues are highly conserved which may indicate the importance of those motifs for the activity of Prx family of proteins.

Implicated in

Lung cancer

Note

Prx-4 along with sulfiredoxin plays very important role in tumor progression and metastasis in lung cancer. The expression of Prx-4 is at least 1.5 fold higher in tumor cells compared to control and this finding applies most frequently to adenocarcinoma and to little bit modestly to squamous cell carcinoma (Lehtonen et al., 2004). Alteration in expression of Prx-4 results in alteration in rate of tumor progression and metastasis which is indicated by anchorage independent colony formation, cell migration and invasion of human lung cancer cells (Wei et al., 2011). This ability of Prx-4 to promote tumor progression and metastasis is supposed to be due to its antioxidant properties. Same study has also shown role of Srx-Prx-4 axis in activation of intracellular phosphokinase signaling including AP-1/MMP-9 axis and MAPK signaling.

Leukemia

Note

Alteration of Prx-4 expression is proposed to play a role in development of different types of leukemia. In acute myeloid leukemia (AML) patients, the PRDX4 gene is fused with the AML1 gene between exon 5 and 6 of AML1 and exon 2 of Prdx4 (Zhang et al., 2004). This fusion of AML1 gene with the Prdx4 gene is

supposed to play a role in altered expression of Prdx 4 in acute myeloid leukemia. In another study, researchers have found that the alteration in genomic sequence and expression level of Prdx4 is rare in acute myeloid leukemia but have found strong reduction in Prdx4 expression in acute promyelocytic leukemia (APL) (Palande et al., 2011). This study has suggested that due to alteration in Prdx4 expression, the signal transduction from a myeloid growth factor receptor i.e. the granulocyte colony stimulating factor receptor is affected. This study have also found the role of histone methylation in transcriptional silencing of Prdx4 in APL.

Glioblastoma multiforme (GBM)

Note

Prx-4 is supposed to play a role in most aggressive primary brain malignancy i.e. glioblastoma multiforme (Kim et al., 2012). Kim TH et al. have found in this study that the knockdown of Prx-4 results in reduced cell growth and radiation resistance along with increase ROS level, DNA damage and apoptosis in in-vitro models. This study suggests the importance of Prx-4 in radiation resistance and tumor maintenance of GBM. It also proposes the Prx-4 as an important therapeutic target in this disorder which can be persuaded for drug discovery and may result in development of some anti-GBM chemotherapeutic drug in future.

Oral cavity squamous cell carcinoma (OSCC)

Note

Prx-4 is also studied for its role in tumor progression, cell migration and invasiveness in oral cavity squamous cell carcinoma (Chang et al., 2011). This study proposes that the Prx-4 can act as a good tumor prognostic factor as it is highly overexpressed in OSCC. Along with the prognostic value of Prx-4 suggested in paper, the Prx-4 can also be a good therapeutic target in OSCC by virtue of its ability to mediate cell migration and/or metastasis. The attributes of Prx-4 leading to OSCC should at least be partially due its ability to manage oxidative stress.

Cardiovascular diseases

Note

Oxidative stress is considered to play major role in the pathological remodeling of arterial wall (Martin-Ventura et al., 2012). As it is an antioxidant protein, the Prx-4 expression level increases in variety of oxidative stress conditions. Also, Prx-4 is secreted into extracellular environment; therefore, its plasma concentration may be used as a molecular indicator of various cardiovascular disease and other disorders involving oxidative stress. The increased serum
Prx-4 concentration is considered as a good indicator of risk to cardiovascular disease (Abbasi et al., 2012) because cardiovascular disease have higher level of oxidative stress and Prx-4 is over-expressed in these conditions.

Hepatic disease

Note

Prx-4 has the ability to act as a hepato-protective protein due to its ability to act as an antioxidant protein, by virtue of which Prx-4 can protect the hepatic tissue against the Hydrogen peroxide as well as other reactive oxygen species causing oxidative stress. A study in rat model of Wilson's disease has demonstrated that this disease have lower level of Prx-4 expression as compared to normal (Ito et al., 2012). The same study has proposed that Prx-4 can be used as a potential biomarker of hepatic diseases as the Prx-4 serum concentration in this model was found to be quite low.

Non-canonical scurvy

Note

Genomic loss of Prx-4 in mice results in testicular atrophy due to elevated spermatogenic cell death (Iuchi et al., 2009).
Depletion of Prx-4 along with ER specific thiol oxidases ERO1α and ERO1β lead to non-canonical scurvy in mice (Zito et al., 2012), which suggests that Prx-4 and other ER thiol oxidases may be critical for protein folding and disulfide bond formation in the ER. In this sense, Prx-4 may also be considered as an alternative to ERO1α and ERO1β in higher organisms (Zito et al., 2010).

Inflammatory disease

Note

Prx-4 is a secretory antioxidant protein which can be detected in plasma.
By virtue of its antioxidant activity, the extracellular Prx-4 can protect the vascular tissue against reactive oxygen species and hence, it has ability to inhibit the oxidative stress induced inflammation in various tissues and it can also reduce the chances of oxidative stress induced diabetes mellitus in animal models (Yamada et al., 2012).

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