

Gene Section

Review

SEPP1 (selenoprotein P, plasma, 1)

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Identity

Other names: SELP; SeP

HGNC (Hugo): SEPP1

Location: 5p12

Local order: According to NCBI Map Viewer, SEPP1 gene is located between: LOC100420450, GHR, CCDC152 (in telomeric position) and LOC100420275, LOC402213 (in centromeric position).

DNA/RNA

Description

The genomic DNA of SEPP1 spans about 12 kb. SEPP1 consists of 6 exons.

Transcription

3 alternative mRNAs exist encoding 2 different isoforms of selenoprotein P. Transcript variants 1 and 2 encode isoform 1 and transcript variant 3 encodes isoform 2.

Protein

Note

SEPP1 belongs to selenoproteins, all of which contain selenium in the form of selenocysteine (SeC) and are being synthesized in the presence of UGA codon, specific stem loop structure in 3' UTR of mRNA called SECIS (Selenocysteine Insertion Sequence) and other specific factors. Selenoprotein P is a glycoprotein present mainly in plasma, where it accounts for 40 - 65% of total selenium in this blood compartment. Plasma SEPP1 concentration is regarded as a functional biomarker of human selenium status (Saito and Takahashi, 2002; Méplan et al., 2009; Xia et al., 2010).

Description

Selenoprotein P consists of 381 amino acids and contains ten selenocysteines: nine are located in Sec-rich C-terminal domain (suggested as the region responsible for selenium delivery) and one is present in N-terminal domain (region with redox properties responsible for enzymatic activity of the protein). Two protein isoforms were identified in human plasma: 50 kDa and 60 kDa (Méplan et al., 2007; Méplan et al., 2009).

Expression

SEPP1 is expressed mainly in the liver, from where it is exported to plasma and other tissues. Other organs expressing the protein include mainly brain, thyroid gland, prostate and mammary gland. Its expression has been found to be significantly reduced in cancer, including prostate, colon and lung (Gonzalez-Moreno et al., 2010).

SEPP1 expression is downregulated by different cytokines (Al-Taie et al., 2002). Also hepatic factors such as insulin and glucocorticoids may regulate SEPP1 expression (Speckmann et al., 2008).

Localisation

Plasma.

Function

It is supposed that SeP is responsible for the transport of selenium within body and delivering the microelement to the cells. In brain and testis (organs, in which selenium plays an important role), SEPP1 uptake is mediated by apolipoprotein E receptor-2 (apoER2). In kidneys, the uptake is regulated by another receptor, called megalin (Burk and Hill, 2009) (figure 1).

Additionally, SEPP1 is involved in the reduction of oxidative stress due to its redox properties (Saito et al., 2004).

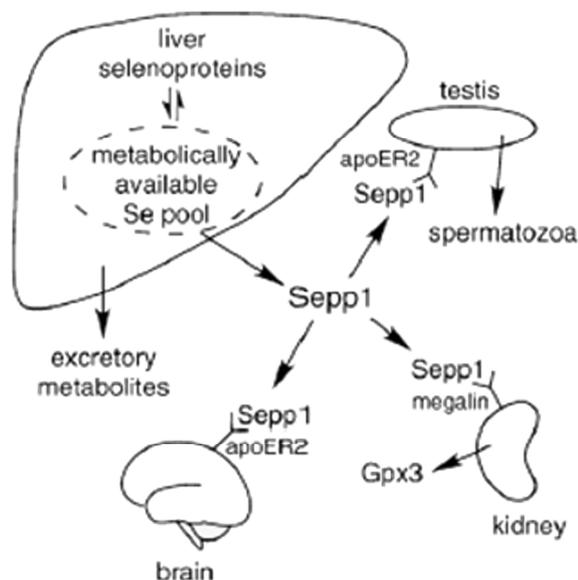


Figure 1. SEPP1 in selenium homeostasis and transport to the testis, brain and kidney. Whole - body selenium excretion is controlled by selenium excretion in the urine. SEPP1 and selenium excretory metabolites compete for metabolically available selenium in the liver, determining urinary selenium excretion. The lipoprotein receptor apoER2 binds SEPP1 and facilitates its uptake into the testis where selenium is incorporated into spermatozoa. ApoER2 also maintains brain selenium. SEPP1 is filtered by the kidney into the glomerular filtrate and binds to megalin in the brush border of proximal convoluted tubules. Those cells endocytose the SEPP1 bound to megalin and presumably use its selenium to synthesize plasma glutathione peroxidase (GPx3) (adapted from Burk and Hill, 2009, with the authors' permission).

Homology

SEPP1 is conserved in chimpanzee, dog, cow, mouse, rat and zebrafish.

Mutations

Note

No mutations in SEPP1 gene have been identified yet. Genetic variations: several SNPs were identified.

Most often studied polymorphisms within SEPP1:

- Ala234Thr (rs 3877899) - associated with a G/A transition at position 24731 of mRNA, with the amino acid change from alanine to threonine in the codon 234. This polymorphism influences the SePP1 isoform pattern. Using Western blot analysis, it was shown that in the individuals possessing Ala/Ala genotype, 60 kDa protein was a dominating isoform, whereas in those with Ala/Thr genotype, the band for 50 kDa isoform was stronger (Thr/Thr genotype was not analyzed in this study). It was also observed, that within Ala/Ala and Ala/Thr individuals, males had less 60 kDa isoform as compared to females (Méplan et al., 2009).

- r25191g/a (rs 7579) - G/A transition at position 25191 within 3'-UTR. Similarly as rs 3877899 SNP, this SNP

seems to influence the proportion of SEPP1 isoforms. Individuals with GG genotype had lower proportion of 60 kDa isoform as compared to those with GA or AA genotype (Méplan et al., 2009).

- (TC)₅/(TC)₃ repeats at promoter region. It was shown in in vitro study that TC₃ allele reduced the promoter activity of reporter gene constructs in HepG2 cells (Al-Taie et al., 2002).

Implicated in

Cancer

Note

Persson-Moschos et al. (2000) conducted a nested case control study, in which 12500 middle aged men were enrolled and the follow up time was between 1974-1988. Within the studied cohort, SEPP1 plasma concentration was significantly lower in the individuals who were diagnosed with cancer during the follow up (and whose plasma samples were available for analysis, n=302) as compared to control subjects (n=604). The authors of this study suggested that plasma SEPP1 level is associated with higher risk of cancer of respiratory and digestive tract.

Colon cancer

Note

Decreased expression of SePP1 mRNA was observed in colorectal cancer tissue as compared with normal colon mucosa (Al-Taie et al., 2004).

The study of 196 cases and 239 controls revealed no association between polymorphism at SEPP1 promoter region (TC)₅/(TC)₃ repeats and colon cancer risk. However, authors of the study observed genomic instability of Poly-(T)-single nucleotide repeat motif present in the SEPP1 promoter sequence in the colon cancer tissues as compared to normal colon mucosa from the same patients. This instability was observed in 10 out of 51 cases possessing two (TC)₅ alleles (no instability was observed in 5 cases with (TC)₅/(TC)₃ genotype; (TC)₃/(TC)₃ homozygotes were not present in the studied group) (Al-Taie et al., 2002).

Other study, involving 772 cases and 777 controls, revealed that four SNPs within SEPP1 gene were significantly associated with risk of colorectal adenoma. The SNPs were: SEPP1 -4166G, rs12055266, rs3797310, rs2972994 (Peters et al., 2008).

In the study by Méplan et al. (2009), in which plasma samples from 20 colon cancer patients and 21 healthy individuals were analyzed, significantly lower proportion of 60 kDa isoform was observed in cases with SEPP1 GG genotype of rs 3877899 as compared to controls with the same genotype. Similar (statistically significant) difference between cases and controls was also indicated within individuals possessing GA genotype of rs7579.

Prostate cancer

Note

Expression of SEPP1 mRNA was down regulated in human prostate tumours as well as prostate carcinoma cell lines (Calvo et al., 2002).

Further investigation revealed that down-regulation of SEPP1 in prostate cancer cells leads to an increased production of reactive oxygen species (Gonzalez-Moreno et al., 2010).

In the study conducted on 90 males with prostate cancer and 100 control men, it was observed that protein's concentration measured in serum was lower in cases as compared to controls (Meyer et al., 2009).

The interaction between polymorphic variants of SePP1 and SOD2 genes in prostate cancer risk was found by Cooper et al. (2008). According to the results based on CAPS study (Prostate Cancer in Sweden), males being homozygous for SEPP1 Ala234 allele (rs 3877899) and who possessed at least one SOD2 Ala16 allele (rs 4880), were at significantly higher risk of prostate cancer.

In a study of 248 prostate cancer cases and 492 controls, borderline significant association between prostate cancer risk and SEPP1 polymorphism (rs 7579) was found (Steinbrecher et al., 2010).

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