

Gene Section

Short Communication

OSGIN1 (oxidative stress induced growth inhibitor 1)

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Abstract

Review on OSGIN1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: BDGI, OKL38

HGNC (Hugo): OSGIN1

Location: 16q23.3

DNA/RNA

Note

Human OSGIN1 is located on chromosome 16 in the region of q23.3.

Description

Human OSGIN1 gene is 13111 bp in length, composed of 6 exons and 5 introns, and located at chromosome 16q23.3.

Transcription

OSGIN1 transcript contains 6 exons. ORF is 1434 bp, which expands from exon 2 to exon 6. And exon 6 also contributes to 371 bp 3'UTR.

Protein

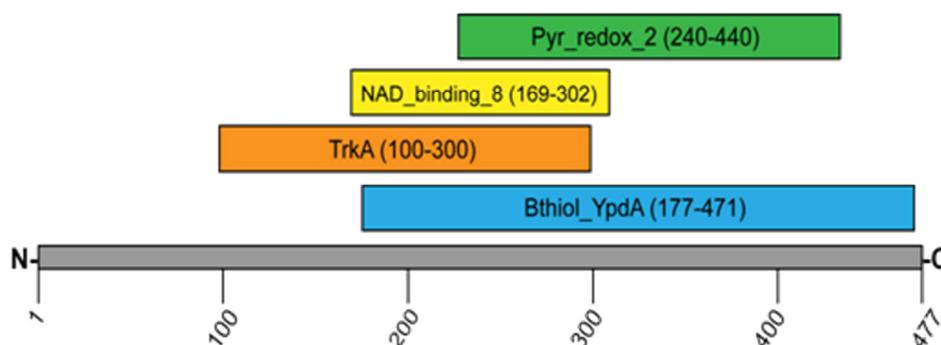
Note

Human OSGIN1/BDGI has a dominant isoform containing 477 amino acids with calculated 52 kDa molecular weight (derived from transcript variants HuOKL38-1a/2a).

Besides, there are a 61 kDa longer isoform of OSGIN1 with 560 amino acids (transcribed from variant HuOKL38-2b), a 59 kDa longer isoform of OSGIN1 with 560 amino acids (transcribed from variant HuOKL38-2c), and a 34 kDa shorter isoform with 317 amino acids, which was the first one to identify in 2001 and might be generated by internal transcription start codon within ORF or cleaved from longer isoforms.



OSGIN1 genomic organization and transcript. The schematic representation of human OSGIN1 gene and its transcript. ATG: translation start codon; TAA: translation stop codon; UTR: untranslated region; ORF: open reading frame (according to Ref-seq).



The predicted OSGIN1 structure contains a potential flavoprotein involved in K⁺ transport domain (TrkA) (201 aa), a potential NAD(P)-binding Rossmann-like domain (NAD_binding_8) (134 aa), a potential pyridine nucleotide-disulphide oxidoreductase domain (Pyr_redox_2) (201 aa) and a potential putative bacillithiol system oxidoreductase, YpdA family domain (Bthiol_YpdA) (295 aa).

Description

OSGIN1, described as a pregnancy-induced growth inhibitor, belongs to OKL38 protein family.

Expression

OSGIN1 gene was identified in rat mammary secretory epithelial cells, which was up-regulated significantly in mammary gland during pregnancy and lactation. In various human normal tissues, OSGIN1 transcripts are observed with basal levels, but increase remarkably in liver, followed by kidney, ovary, testis, and spleen especially. On the contrary, OSGIN1 show low or undetectable mRNA expression in liver, kidney, ovary tumor tissues compared to their paired normal counterparts. Similarly, it is rarely expressed in many cancer cell lines, including HepG2, SL, NIH, U2OS, MCF-7.

Localisation

Nucleus and mitochondria.

Function

OSGIN1 was first discovered in 2001 as a pregnancy-induced growth inhibitor. It is highly expressed in ovary, kidney and liver. Stable expression of OSGIN1 is characterized by relatively low proliferative rate and extensive differentiation. Conversely, loss of OKL38 activity leads to a disruption in the balance between cell growth, cell proliferation and cell death, and is associated with rapid tumor growth. OSGIN1 is inducible by distinct stress signals in multiple cell types. Oxidative stress induced by oxidized phospholipids (OxPAPC and its component lipid PEIPC) mediates expression of OSGIN1 regulated via Nox/Nrf2 pathway. After DNA damage treatment in cancer cells such as MCF-7 and U2OS,

OSGIN1 is also up-regulated by p53, and then triggers apoptosis by changing mitochondrial morphology, elevating ROS levels and inducing cytochrome c release. Thus, OKL38 likely plays a critical role in multiple tissues to guard against tumorigenesis.

Homology

An alignment of the amino acid sequences in ClustalW showed that OSGIN1 and OSGIN2, another member of OKL38 family, share 49% sequence identity, especially in C-terminal region of the two proteins.

However, the biological function of OSGIN2 remains unclear so far, which may be implicated in Nijmegen breakage syndrome and gastric cancer.

Mutations

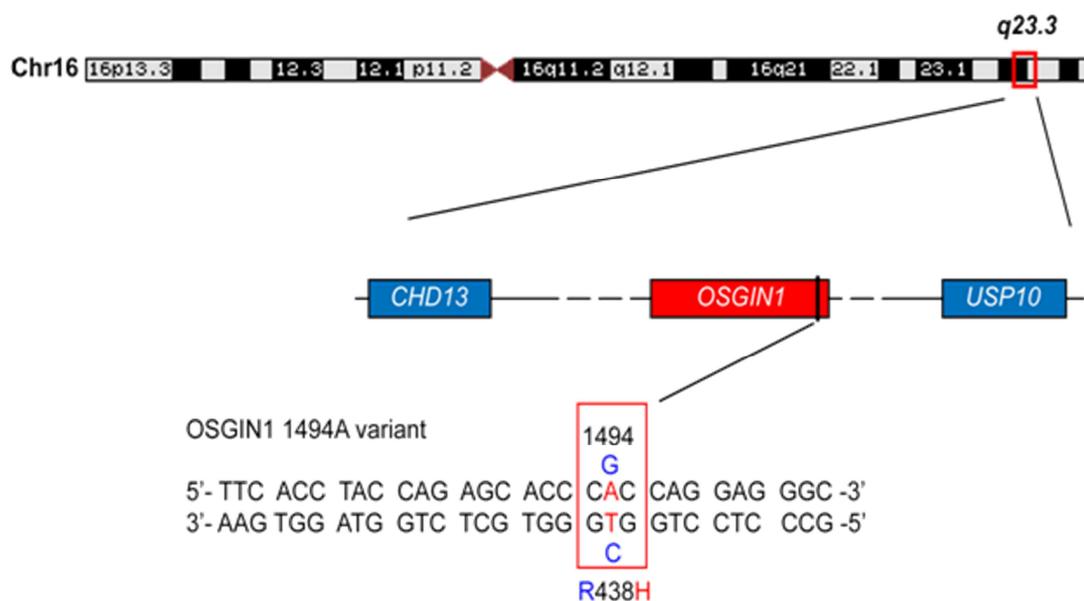
Somatic

Based on analysis of tumor and adjacent noncancerous tissues from total 400 patients of hepatocellular carcinoma (HCC), a single-nucleotide variation from G to A at nt 1494 of OSGIN1 was identified, resulting in an amino acid substitution R438H at codon region.

Although OSGIN1 1494A variant appears in both tumor and noncancerous tissues, it shows higher occurrence in the tumor tissues than the common variant 1494G.

And the allele-specific imbalance of OSGIN1 at nt1494 is highly possible due to its localization at chromosome 16q23.3, which is prone to loss of heterozygosity in a variety of cancers.

Functional studies revealed that OSGIN1 1494A variant may have defects in translocation to mitochondria and apoptosis.



Implicated in

Hepatocellular carcinoma (HCC)

Disease

HCC is the most common type of liver cancer and one of the top human malignances worldwide. Generally, chronic liver injury by cirrhosis and infection of hepatitis viruses are two major causes of HCC. HCC also show higher incidence in population of Asia/Africa than North America/Western Europe, suggesting a variety of underlying genetic and environmental factors.

Prognosis

OSGIN1 expression analysis between tumor and paired noncancerous tissues from 89 HCC patients with clinicopathological data indicated the patients with less OSGIN1 transcripts and higher occupancy of OSGIN1 1494A variant have more sever symptoms and shorter survival time. Thus, quantitation of OSGIN1 expression and presence of OSGIN1 1494A variant may help diagnose HCC patients at early clinical trail and their responses after chemotherapy.

Oncogenesis

OSGIN1 expression is higher in immortal liver cell lines (LO2 and Miha) that that in HCC cell lines (PLC8024 and Hep3B). Loss of wild-type OSGIN1 in HCC tumors at higher stages and HCC cell lines may be due to its 5' untranslated region (5'UTR)-regulated mRNA translation suppression. And OSGIN1 1494A variant coded protein is less capable to translocate from nucleus to mitochondria and induce apoptosis compared to its wide-type protein, suggesting its impaired role as tumor suppressor.

Renal cell carcinoma (RCC)

Disease

Renal cell carcinoma (RCC) is the primary type of the adult kidney cancer. In contrast to HCC, RCC incidence rates are higher in North America/Western Europe region but lower in Asia/Africa region. The causes of RCC are complicated, probably due to lifestyle-related and/or hereditary factors.

Prognosis

Both OKL38 transcripts and protein levels are low or undetected in majority of the kidney tumors examined compared to patient's corresponding normal adjacent tissues using cancer profiling assay, western blot assay and immunohistological analysis.

Oncogenesis

Forced overexpression of OSGIN1 in human kidney cancer cell A498 inhibits cell growth and stimulates cell death.

Breast cancer

Disease

Breast cancer is the most common cancer and the second top cause of cancer death among women. The American Cancer Society's estimates about 232670 new cases of invasive breast cancer will be diagnosed in women in the US for 2014. Risk factors associated with breast cancer include age, geography, family history and so on. Especially, genetic risk factors with mutations in some signature genes (e.g. BRCA1 and BRCA2) have been studied well for prognosis and treatment of breast cancer. Interestingly, some particular reproductive factors like earlier age at first full-term

pregnancy and higher number of pregnancies can reduce breast cancer significantly.

Oncogenesis

Overexpression of OSGIN1 in MCF-7 human breast adenocarcinoma cells decreases their in vitro metastatic activity and in vivo tumor formation. The mechanistic study found that high expression of OSGIN1 may direct cell cycle arrested in S phase, and induce apoptosis further.

These data suggest a potential correlation between OSGIN1 and the reduction in breast cancer risk observed in pregnancy-associated cases.

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