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Review

LDOC1 (leucine zipper, down-regulated in cancer 1)

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Abstract

LDOC1 (leucine zipper, down-regulated in cancer 1) is expressed by a wide variety of normal human tissues but is downregulated in various kinds of human cancers. Epigenetic silencing by promoter hypermethylation was shown to be an important cause of LDOC1 down-regulation in oral, cervical and ovarian cancers. The normal physiological function of LDOC1 is still not clear. But the ability of LDOC1 to induce apoptosis in various kinds of human cancer cells suggests this gene may act as a tumor suppressor.

Keywords
LDOC1, cancer, methylation

Identity

Other names: BCUR1, Mar7, Mart7

HGNC (Hugo): LDOC1

Location: Xq27

Location (base pair)
starts at 141175745 and ends at 141177214 bp, complement

Local order: from centromere to telomere: SPANXB1, LDOC1, SPANXC

DNA/RNA

Description

The LDOC1 gene includes only one exon.

Transcription

A longer wild type 1376-bp transcript (Nagasaki et al., 1999), and a much shorter 165-bp splice variant LDOC1S (Duzakale et al. 2014) are reported.
The cDNA sequence of wild type LDOC1 contains a 104-bp 5' untranslated region (5'-UTR), a 438-bp open reading frame (ORF), and a 834-bp 3' untranslated region (3'-UTR) including a consensus polyadenylation signal (Nagasaki et al., 1999).

Pseudogene

Not reported.

Protein

Description

The wild type LDOC1 is a 17 kDa protein containing 146 amino acids, with a leucine-zipper like motif at the N-terminal and a proline-rich region that similarity to an Src homolog 3 (SH3)-binding domain (Nagasaki et al., 1999).

A shorter 165-bp splice variant is predicted to translate into a truncated protein of 44 amino acids that contains only the leucine-zipper region of wide type protein (Duzakale et al. 2014).

Expression

LDOC1 is expressed in a wide variety of normal tissues including heart, brain, lung, skeletal muscles, kidney, pancreas, spleen, thymus, prostate, testis, ovary, stomach, small intestine, colon, adrenal medulla, thyroid, adrenal cortex, thymus (Nagasaki et al., 1999). Down-regulation of LDOC1 have been reported in various kinds of human cancer tissues, including oral cancer (Lee et al., 2013), hepatocellular carcinoma (Riordan and Dupuy, 2013), Chronic lymphocytic leukemia (Duzakale et al., 2014), prostate cancer (Camões et al., 2012), as well as in a variety of human cancer cell lines, including pancreatic cancer cell line, gastric cancer cell lines, some breast cancer cell lines (Nagasaki et al., 1999), ovarian cancer cell lines (Buchholtz et al., 2014), cervical cancer cell lines (Buchholtz et al., 2013) and oral cancer cell lines (Lee et al., 2013). Epigenetic silencing by promoter hypermethylation was shown to be an important cause of LDOC1 down-regulation in oral cancer (Lee et al., 2013), cervical cancer (Buchholtz et al., 2013), and ovarian cancer cells (Buchholtz et al., 2014).

Localisation

LDOC1 localizes predominantly in the nucleus (Nagasaki et al., 1999). It may also be retained in cytoplasm through interaction with WAVE3 (Mizutani et al., 2005).

Function

Most reports demonstrated that the biological function of LDOC1 is closely related to modulation of apoptosis. Forced expression of LDOC1 induced apoptosis in Jurkat lymphoma cells, K562 leukemia cells (Inoue et al., 2015), Hela cervical cancer cells (Buchholtz et al., 2013) and oral cancer cells (Lee et al., 2013). Expression of LDOC1 also enhanced TNF-a or phorbol 12-myristate 13-acetate (PMA)-induced anti-proliferative effects in pancreatic cancer cells (Nagasaki et al., 2003). A hematopoietic transcriptional factor (MZF-1) important in regulating myeloid cell differentiation and proliferation may interact with LDOC1 and enhance it apoptosis-inducing function in K562 leukemia cells (Inoue et al., 2015). LDOC1 also induced apoptosis and inhibited degradation of p53, resulting in p53 accumulation in MDCK cells. WAVE3 could interact with LDOC1 with its C-terminal verprolin homolog domain and act as a negative regulator of LDOC1. Forced expression of WAVE3 retained LDOC1 in cytoplasm and attenuated the apoptosis-inducing effect of LDOC1 (Mizutani et al., 2005). Expression of LDOC1 also significantly inhibited the NF-kB reporter activity in LDOC1-negative BxPC-3 pancreatic cancer cells (Nagasaki et al., 2003) and suppressed TNF-a induced activation of NF-kB (Lee et al., 2013). LDOC1 may also interact with CCAAT-enhancer binding protein-a (C/EBPa) (Chih et al., 2004). However, in human intrahepatic biliary epithelial cells, over expression LDOC1 increased the expression of NF-kB (p65), promoted IL-2 and TNF-a secretion and inhibited apoptosis (Song et al., 2013). LDOC1 has recently been reported as a eutherian-specific acquired gene that regulates placental endocrine function (Naruse et al., 2014).

Homology

HomoloGene:32153

Implicated in

Chronic lymphocytic leukemia

Prognosis

Expression of LDOC1 mRNA correlated with prognostic cytogenetic markers of chronic lymphocytic leukemia patients. In primary patients, LDOC1 mRNA-positive group of patients had significantly poorer overall survival compared to LDOC1 mRNA-negative group of patients (Duzakale et al., 2014).

Lymphoma

Oncogenesis

Forced expression of LDOC1 induced apoptosis in Jurkat lymphoma cell lines (Inoue et al., 2015).

Leukemia

Oncogenesis

Forced expression of LDOC1 induced apoptosis in K562 leukemia cell lines (Inoue et al., 2015).

Ovarian cancer

Cytogenetics

No gene deletion was detected in the 7 ovarian cancer cell lines.

Oncogenesis

Three of the 7 ovarian cancer cell lines showed complete loss of LDOC1 transcription, which may due to hypermethylation and inactivation of LDOC1 promoter. Treatment of de-methylation agent (5-aza-2'-deoxycytidine) on ovarian cancer cells induced transcriptional reactivation of LDOC1 gene (Buchholtz et al., 2014).

Cervical cancer

Cytogenetics

No gene deletion was detected in the 6 cervical cancer cell lines.

Oncogenesis

LDOC1 was silenced in 4 of the 6 cervical cancer cell lines. An association of promoter hypermethylation and gene silencing was noted.

Reactivation of LDOC1 gene was noted in Me180 and SiHa cervical cancer cell lines by demethylation agent treatment (5-aza-2'-deoxycytidine). Re-expression of LDOC1induced apoptosis-like cell death in Hela cervical cancer cells (Buchholtz et al., 2013).

Oral cancer

Oncogenesis

Hypermethylation and down-regulation of LDOC1 were consistently noted in oral cancer samples and oral cancer cell lines. Reactivation of LDOC1 gene was noted in oral cancer cells by demethylation agent treatment (5-aza-2'-deoxycytidine). Re-expression of LDOC1suppressed TNF-a induced activation of NF-?B and suppressed the colony forming and in vivo tumorigenic abilities of oral cancer cells. Epigenetic silencing of LDOC1 may contribute to alcohol, betel quid and smoking-associated oral carcinogenesis (Lee et al., 2013).

Prostate cancer

Oncogenesis

LDOC1 was one of the two transcriptional units (LDOC1, HPANXC) mapped in a critical region of HPCX locus linked to prostate cancer susceptibility in Finland (Baffoe-Bonnie et al., 2005). In addition, compared to non-malignant prostate tissue, LDOC1 was under-expressed (1.8 fold decrease) in prostate cancer tissues, although no methylation of LDOC1 promoter was noted in prostate tumor samples (Camões et al., 2012).

Hepato cellular carcinoma

Oncogenesis

LDOC1 was downregulated in 60% (29/48) of hepatic cellular carcinoma samples compared to adjacent non-tumor liver tissues (Riordan and Dupuy, 2013).

Pancreatic cancer

Oncogenesis

Down-regulation of LDOC1 was noted in 8 of 9 pancreatic cancer cell lines except CAPAN2 cell line (Nagasaki et al., 1999). LDOC1 was expressed in normal pancreatic tissue (Nagasaki et al., 2003). Expression of LDOC1 significantly inhibited the NF-kB reporter activity but does not affect p53, AP1 and CRE-dependent reporter gene expression in LDOC1-negative BxPC-3 pancreatic cancer cell line. LDOC1 also enhanced TNF-a or phorbol 12-myristate 13-acetate (PMA)-induced anti-proliferative effects in pancreatic cancer cells (Nagasaki et al., 2003).

Gastric cancer

Oncogenesis

Using northern blot, down-regulation of LDOC1 was noted in 6 (100%) of 6 gastric cancer cell lines. LDOC1 was normally expressed in stomach tissue (Nagasaki et al., 1999).

Lung cancer

Oncogenesis

LDOC1 was differentially expressed in MASPIN-overexpression lung carcinoma cells (LC5) compared to MASPIN-knockdown LC5 cells (Liu et al., 2012).

Esophageal cancer

Oncogenesis

LDOC1 was down-regulated in a radio-sensitive esophageal cancer cell line (TE-11) compared to other relative radio-resistant esophageal cancer cell lines (Ogawa et al., 2008).

Cutaneous malignant melanoma

Oncogenesis

LDOC1 was downregulated in peripheral blood leukocytes from a cutaneous malignant melanoma patient with multiple in-transient metastases, compared to 3 normal controls (Salemi et al., 2010).

Hypertension

LDOC1 gene was consistently influential in a three-endophenotype model for Taiwanese hypertensive males (Lynn et al., 2009).

Premature ovarian failure/insufficiency (POF/POI)

Array comparative genomic hybridization identified a cryptic deletion region of Xq27.2 containing LDOC1 and SPANX genes in a 23-year old woman with premature ovarian failure/insufficiency (Vitek et al., 2012).

Down's syndrome

Gene expression of LDOC1 was increased in peripheral blood leukocytes from 15 (75%) of 20 patients Down's syndrome, as compared to that of 20 age-, sex-matched normal controls (Salemi et al., 2012).

Biliary atresia

Over expression LDOC1 in human intrahepatic biliary epithelial cells increased the expression of NF-kB (p65), promoted IL-2 and TNF-a secretion and inhibited apoptosis of human intrahepatic biliary epithelial cells, which may induce intrahepatic biliary epithelial cell hyperplasia and trigger biliary atresia, bile duct stenosis and hepatic fibrosis (Song et al., 2013).

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