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Gene Section
Review

PERP (PERP, TP53 apoptosis effector)

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Abstract

PERP is a p53/p63-regulated gene encoding a desmosomal protein that plays a critical role in stratified epithelial development, cell adhesion and tumor suppression.

Keywords
PERP, p53-dependent apoptosis, PMP-22, p63, epithelial development, cell-cell adhesion, cell junction, desmosomal protein.

Identity

Other names: KCP1, KRTCAP1, PIGPC1, THW, dJ496H19.1

HGNC (Hugo): PERP

Location: 6q23.3

Local order
From centromere to telomere: LOC100130476, TNFAIP3, RPSAP42, PERP, KIAA1244, PBOV1, MARCKSL1P2.

DNA/RNA

Description

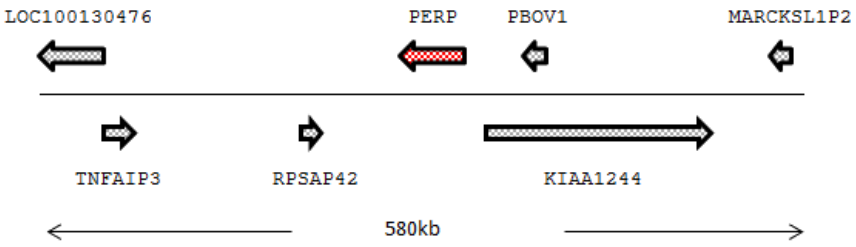
The PERP gene is of 19019 bases and localized on the minus strand. PERP encompasses three exons (NCBI, 2014).

Transcription

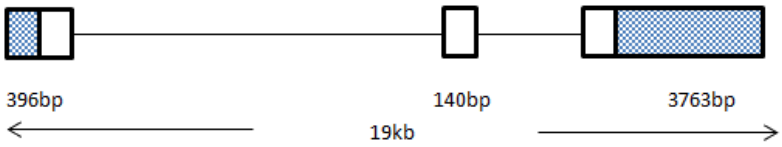
4319 bp long mRNA; 582 bp long open reading frame (NM_022121.4).

Pseudogene

No reported pseudogenes.



Local order of PERP is shown together with leading and subsequent genes on chromosome 6. The direction of arrows indicates transcriptional directions on the chromosome and arrow sizes approximate gene sizes.



Boxes are exons. The lines are introns. Unshaded parts of the exon boxes are coding regions.

Protein

Description

PERP encodes a 193 amino acid long tetraspan membrane protein (Attardi et al., 2000). Perp has a molecular mass of 21 kDa with an isoelectric point of 6.68 (Franke et al., 2013).

Expression

PERP is expressed in the tongue mucosa, cornea, heart, lung (Chen et al., 2011) simple, columnar, complex, transitional and stratified epithelia of human, bovine, porcine and murine (Franke et al., 2013) and teeth (Jheon et al., 2011; Neupane et al., 2014). PERP is also expressed in the primary choroidal melanoma (Paraoan et al., 2006) and in cell lines derived from breast, prostate, colon, cervix and pancreas tumors (Hildebrandt et al., 2001).

Localisation

Perp exhibits a punctuated pattern of localization at the plasma membrane and interdesmosomal regions (Franke et al., 2013) and colocalizes with desmosomal components (Attardi et al., 2000; Davies et al., 2009; Singaravelu et al., 2009). Perp is also suggested to localize at the perinuclear region and endoplasmic reticulum/golgi apparatus in primary uveal melanoma (UM) cells (Davies et al., 2009).

Function

PERP is a transcriptional target of p53 and p63 transcription factors acting alone or in concert to homeodynamically modulate cellular responses. The expression of PERP appears to be independent of p53 in embryogenesis but is dependent upon p63. The interaction of p53 or p63 with several response elements of varying affinities on the PERP locus is responsible for the PERP expression. The regulation of PERP transcription by p63 in epithelial-specific manner during embryogenesis is critical for the stratified epithelial development through functions of Perp at desmosomes (Attardi et al., 2000; Ihrie et al., 2005). The absence of Perp as studied in a PERP knockout mouse model is manifested as defects in the assembly and maintenance of desmosomes (Ihrie et al., 2005). Perp is also shown to participate in skin and notochord development of zebrafish (Nowak et al., 2005). The mediation of PERP expression by p53 results in apoptosis independent of cell cycle arrest. The expression of PERP is shown to increase during apoptosis, but not upon induced G1 arrest in mouse embryonic fibroblasts (Attardi et al., 2000). Induction of PERP expression induces apoptosis through the activation of caspase-8 in primary UM cell lines (Davies et al., 2009). Similarly, the overexpression of PERP at the outer medullary proximal tubular cells of ischemic kidneys in response to hypoxia appears to augment apoptosis by inducing mitochondrial permeability and cytochrome c release as well as by activating apoptosis-inducing factor (AIF) and caspase 9 proteins (Singaravelu et al., 2009).

These findings collectively indicate that Perp is an important mediator of stratified epithelial development, cell adhesion and apoptosis through desmosomal activities.

Homology

Perp shares amino acid sequence similarities with peripheral myelin protein 22/growth arrest specific 3 (PMP-22/gas3) tetraspan membrane protein family, which is associated with growth regulation (Attardi et al., 2000).

Implicated in

Papilloma

Note

Papilloma refers to an exophytically growing benign epithelial tumor. In studies using a two-step skin carcinogenesis mice model system, it was shown that mice lacking PERP expression in the skin are resistant to papilloma development. It appears that the lack of Perp impairs cell adhesion as a result of aberrant desmosome assembly, thereby diminishing tumor development (Marques et al., 2005).

Breast cancer

Note

Using a laser capture microdissection approach in tumor stroma from primary breast tumors, it was reported that PERP is one of repressed genes in samples of the poor outcome cohort (Finak et al., 2008).

This is consistent with findings that the expression of PERP is reduced in breast cancer cell lines. Experimental studies using a mouse mammary cancer model further reveal that Perp plays an important role in mammary gland homeostasis by affecting desmosome numbers and/or integrity in the

mammary epithelium and in mammary tumor suppression by modulating microenvironment (Dusek et al., 2012).

Squamous cell carcinoma (SCC)

Note

The SCC, the second-most common skin cancer, is a malignant proliferation of the keratinocyte of the epidermis (Schwartz, 1988). It was reported that the expression of PERP is downregulated during SCC progression. Moreover, Perp deficiency appeared to promote SCC in a PERP knockout mouse model for human SCC (Beaudry et al., 2010). Consistent with these observations, the loss of PERP expression is reported to correlate with the progression of oral cavity SCC with increased local relapse (Kong et al., 2013).

Primary uveal melanoma

Note

The PERP gene expression was reported to be downregulated in uveal melanomas with high risk of metastasis (Paraoan et al., 2006).

Lung cancer

Note

It was shown that the PERP gene introduction as a gene therapy approach induces apoptosis in lung cancer xenografts in mice by reducing xenograft volume and preventing angiogenesis through the activation of pro-apoptotic caspase-3 cascade and the suppression of vascular endothelial growth factor expression. The introduction of PERP was also observed to lead to an enhanced activity of the second mitochondria-derived activator of caspase (Smac) cascade (Chen et al., 2011).

Rheumatoid arthritis (RA)

Note

It was reported that PERP mRNA levels in peripheral blood mononuclear cells from patients with RA are significantly lower than those of healthy subjects (Du et al., 2013).

Renal ischemia

Note

It was shown that Perp mediates apoptosis in renal ischemia cells of mice models (Singaravelu et al., 2009).

Pemphigus vulgaris (PV)

Note

PV is an autoimmune disease with the loss of cell-cell adhesion in the epidermis induced by desmoglein (a desmosomal protein)-specific autoantibodies (Bektas and Rubenstein, 2009). In studies using human keratinocyte cultures, it was demonstrated that PV autoantibodies hinder the localization of Perp at the membrane and induce its internalization with desmosomal cadherin desmoglein 3 (DSG3) through an endosomal pathway resulting in Perp degradation. Furthermore, PERP deficiency in PERP-/- keratinocytes was found to enhance pathogenic effects of PV autoantibodies (Nguyen et al., 2009).

Ankyloblepharon ectodermal dysplasia and cleft lip/palate (AEC) or Hay-Wells syndrome

Note

AEC is an autosomal dominant disorder characterized by the abnormal development of ectodermal tissues including the skin, hair, nails, teeth, and sweat glands. A subset of AEC patients was found to show an aberrant PERP expression in skin biopsies. This finding suggests that dysregulation of the PERP gene expression contributes to the pathogenesis of AEC (Beaudry et al., 2009).

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