

Gene Section

Review

CEACAM19 (carcinoembryonic antigen related cell adhesion molecule 19)

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Abstract

CEACAM19 is a member of the CEACAM subfamily of genes, described for the first time by Scorilas et al. (2003). Very few studies have been conducted so far concerning the CEACAM19 gene. Consequently, very little is known about it, and its function in either physiological or pathological cellular processes remains poorly elucidated. Here, we present a review on the DNA, mRNA and protein level of the gene and on its implication in various types of human malignancies.

Keywords

Carcinoembryonic antigen; Immunoglobulin superfamily; ovarian cancer; breast cancer; gastric cancer; penile cancer; lung adenocarcinoma.

Identity

Other names

CEACM19, CEAL1

HGNC (Hugo): CEACAM19

Location: 19q13.31

Local order: Centromere to telomere

DNA/RNA

Description

The CEACAM19 gene belongs to the CEACAM subfamily of the CEA gene family, which in turn belongs to the Immunoglobulin Superfamily (IgS) (Scorilas et al., 2003). It has a total length of 12,904 nucleotides and consists of 8 exons and 7 intervening introns (Scorilas et al., 2003). It is located

downstream of the PVR gene (poliovirus receptor cell adhesion molecule) and upstream of the CEACAM16 gene at the chromosomal location 19q13.31.

Transcription

CEACAM19 pre-mRNA is subjected to alternative splicing. According to UniProt, three main splice variants of the gene have been described. The first one, which is referred to as the "canonical" one, consists of 903 nt and encodes for a 300-amino-acid (aa) polypeptide chain (Scorilas et al., 2003). The second splice variant contains one more exon (exon 3) of 134 bp and encodes for a polypeptide chain of 142 aa residues (Scorilas et al., 2003). The third splice variant consists of 900 nt and encodes for a polypeptide chain of 299 aa residues. However, according to the Human Protein Atlas, another five splice variants have also been described.

Pseudogene

Not identified so far.

Protein

Description

The canonical polypeptide isoform that is encoded by the CEACAM19 gene (isoform 1) consists of 300 aa residues and has a putative molecular weight of 32.6 kDa. (Scorilas et al., 2003). This polypeptide corresponds to a protein with an N-terminal extracellular domain consisting of the aa residues 33-157 and one Ig-like helical transmembrane domain, similar to other members of the same gene family (CEA family), composed of the aa residues 158-178 (Scorilas et al., 2003). The protein carries a

hydrophobic N-terminal sequence, which is thought to act as a signal peptide and which is comprised on its whole of the aa residues 1-32 (Scorilas et al., 2003). The signal peptide of the protein is removed. aa residues 179-300 represent the cytoplasmic part of this protein (Figure 1). The CEACAM19 protein bears no constant C2-like domains like the ones seen in other members of the same family (Beauchemin et al., 2013). The protein bears a 9-aa sequence (SAMGQRDIV - from position 92 to 100) that is present in the eIF5A domain of a variety of transcription factors in eukaryotes (Scorilas et al., 2003). Moreover, the CEACAM19 polypeptide is a heavily glycosylated glycoprotein, which carries an ITAM motif (Immunoreceptor Tyrosine-based Activation Motif) in its cytoplasmic tail (as most of the members of the same subfamily) (Beauchemin et al., 2013). Moreover, several putative sites for post-translational modifications, such as O-/N-glycosylation, phosphorylation, N-myristoylation, have been described (Scorilas et al., 2003). The alternative splicing of CEACAM19 pre-mRNA leads to the production of two other protein isoforms. As described previously, the second splice variant encodes for a polypeptide of 142 aa residues, shorter than the one described as the canonical form of the protein. Besides the fact that the aa residues from position 143 to 300 are missing, this isoform also differs from the canonical one in that the glutamic acid residue in position 142 is replaced by an aspartic acid residue. The third

protein isoform is derived from a splice variant of 900 nt and consists of 299 aa residues. In this case, the glutamine residue in position 282 of the canonical form is missing.

As described above, the Human Protein Atlas mentions the existence of another five splice variants of the CEACAM19 gene, which encode for secreted polypeptides and not transmembrane ones (contrary to the three main isoforms described earlier). Four of these polypeptides consist of 56 aa residues and share a common molecular weight of 6.1 kDa each, while one of them consists of 54 amino acids and has a molecular weight of 6 kDa. All these polypeptide chains bear a signal peptide consisting of the amino acids 1-33.

Expression

The CEACAM19 gene is widely expressed in a variety of tissues. Based on RNA-seq experiments (Fagerberg et al., 2014), higher expression levels are mainly seen in skin and testis. However, moderate to high expression levels have also been described in the prostate, adrenal gland, endometrium, lung, and ovary.

Localisation

The three main CEACAM19 protein isoforms that bear a transmembrane domain are characterized as single-pass type-I membrane proteins. These are proteins that traverse the membrane only once with their N-terminal domain on the extracellular side of it and their signal peptide being removed.



Figure 1. Alignment of the three main protein isoforms (CLUSTAL O 1.2.4) that arise as a result of the CEACAM19 pre-mRNA alternative splicing procedure. The N-terminal signal peptide and the eIF5A domain that are present in all three protein isoforms are shown in red and light blue, respectively. The Ig-like transmembrane domain is underlined. The ITAM motif present in the two of the three isoforms is shown in green

However, according to the Human Protein Atlas, the rest of the protein isoforms, which lack transmembrane domains, are predicted to be secreted.

Function

The functions of the CEACAM19 protein (either physiological or pathological) have not been elucidated, yet.

Implicated in

Ovarian cancer

Prognosis

CEACAM19 mRNA expression is higher in ovarian cancer tissues, particularly in patients with late stage (stage III) of the disease and patients having been subjected to suboptimal cytoreduction. The sizes of the residual tumors were found to present a statistically significant difference between CEACAM19 mRNA-positive and -negative tumors, with the positive ones exhibiting larger dimensions. No statically significant association has been observed between the expression status of CEACAM19 and patients' age (Scorilas et al., 2003).

Breast cancer

Prognosis

CEACAM19 has been shown to be overexpressed in malignant breast tissue sections, compared to normal counterparts derived from the same patients (Michaelidou et al., 2013), and in breast tumor samples compared to samples derived from normal individuals (Estiar et al., 2016). Furthermore, higher mRNA levels of CEACAM19 have been associated with increased risk of breast cancer in women. The association between CEACAM19 mRNA expression and various clinicopathological parameters linked to aggressive tumor behavior and poor prognosis has also been examined in the aforementioned study. In particular, elevated expression levels have been observed in higher grade (grade III) tumors and those with a high proliferation index. Moreover, it has been shown that the expression of CEACAM19 is elevated in estrogen receptor (ER)-negative tumors and those of premenopausal patients; both these features are associated with poor prognosis (Michaelidou et al., 2013). On the other hand, another study by Estiar et al. (2016) did not support the positive association between CEACAM19 expression and tumor grade, observed by Michaelidou et al. (2013), as described above. In the study of Estiar et al., no significant association was shown between CEACAM19 mRNA expression status and tumor grade. Moreover, the study of Estiar et al. revealed a statistically significant difference in the expression of CEACAM19 between ER/PR-positive and -

negative breast cancer patients, with higher mRNA levels in the latter (Estiar et al., 2016).

Gastric cancer

Prognosis

It has been shown that CEACAM19 protein levels are significantly elevated in gastric cancer tissues and cancerous cell lines, compared to normal ones. Similarly, the same study showed that the expression of matrix metalloproteinases 2 and 9 (MMP2 and MMP9) was also upregulated in gastric cancer cell lines and that knockdown of CEACAM19 via siRNA in the same cells led to the inhibition of their expression. Knockdown of CEACAM19 was also shown to lead to a decrease in proliferation, invasion, and migration of gastric cancer cells. Furthermore, it has been suggested that knockdown of CEACAM19 leads to the inactivation of PI3K/Akt and NF- κ B signaling pathways and to the inhibition of tumor growth *in vivo*, as measured by xenograft experiments in mice (Zhao et al., 2018).

Penile cancer

Prognosis

Differential expression levels of CEACAM19 have been shown in penile cancer cases, with some cancerous tissues exhibiting low and others exhibiting higher expression levels, compared to normal ones. Overexpression of CEACAM19 has been associated with distant and lymph node metastasis in penile cancer and with unfavorable cancer-specific survival of patients, but its prognostic significance is not independent from other predictors of survival. Moreover, it has been shown that knockdown of CEACAM19 in penile cancer cell lines leads to decreased cell growth and that it suppresses colony formation. CEACAM19 knockdown has also been related to the decrease of SMAD2/3 signaling pathway activity and inhibition of MMP2 and MMP9 secretion, which are both associated with invasion and metastasis. Consequently, it has been observed that migration and invasion abilities of the Pen11 cancerous cells were suppressed after CEACAM19 knockdown (Hu et al., 2019).

Lung adenocarcinoma

Prognosis

Kobayashi et al. (2012) examined whether some members of the CEACAM gene family could be used as surrogate markers for tyrosine kinase inhibitor (TKI) sensitivity in lung adenocarcinoma patients. The examined members of the family included CEACAM3, CEACAM5, CEACAM6, CEACAM7, and CEACAM19. The expression patterns of all these genes were found to be associated with TKI sensitivity, in microarray analysis. Moreover, the immunoreactivity of the CEACAMs examined was shown to be significantly

higher in patients carrying EGFR mutations than in those carrying the wild-type gene. CEACAM19 immunoreactivity was not found to present statistically significant association with clinicopathological parameters of lung adenocarcinoma patients, such as age, sex, tumor size, stage of the disease, and lymph node metastasis.

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