

## Gene Section

### Review

# CEACAM5 (carcinoembryonic antigen-related cell adhesion molecule 5 (carcinoembryonic antigen)

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## Abstract

The CEACAM5 gene encodes carcinoembryonic antigen (CEA), which was first identified as an oncofetal antigen in 1965 in human colon cancer tissue extracts. CEA is a heavily glycosylated protein that belongs to the CEA-related cell adhesion molecule (CEACAM) family of the immunoglobulin (Ig) gene superfamily. CEA is closely related to CEACAM1, CEACAM3, CEACAM4, CEACAM5, CEACAM6, CEACAM7, and CEACAM8. CEA is also expressed at low levels in normal tissues of epithelial origin in a polarized manner and found only at the luminal portion of the cell, but not at the basolateral surface. CEA in normal tissues is now considered to protect the luminal organs of the body from microbial infection by binding and trapping infectious microorganisms. In contrast, the expression of CEA is frequently high in various carcinomas. Cancer cells not only lose polarized expression of CEA, but also actively cleave CEA from their surface by phospholipases, resulting in increased serum concentrations of CEA. The serum CEA levels may be monitored to detect a response to cancer therapy or disease recurrence and serve as a prognostic indicator in patients with various cancers, where

elevated levels indicate a poor prognosis and correlate with a reduced overall survival. Cell-bound CEA has served as a target for tumor imaging and various cancer therapies.

### Keywords

CEACAM5, CEA, CEA gene family, CD66e, tumor marker

## Identity

**Other names:** CEA, CD66e

**HGNC (Hugo):** CEACAM5

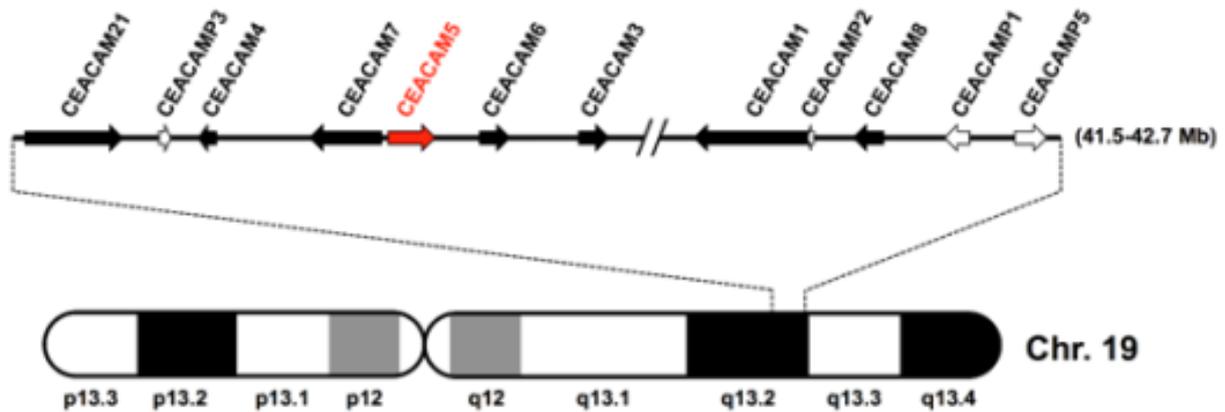
**Location:** 19q13.2

### Local order

cent ---- CEACAM21 - CEACAMP3 - CEACAM4 - CEACAM7 - CEACAM5 - CEACAM6 - CEACAM3 - CEACAM1 - CEACAMP2 - CEACAM8 - CEACAMP1 - CEACAMP5 ---- qter

### Note

The CEACAM5 gene is classified as a member of the CEACAM family (24 genes), which belongs to the CEA gene family (35 genes) together with the pregnancy-specific glycoprotein (PSG) family (11 genes). The CEA gene family is a member of the immunoglobulin (Ig) supergene family (Thompson et al., 1991; Pavlopoulou and Scorilas, 2014).



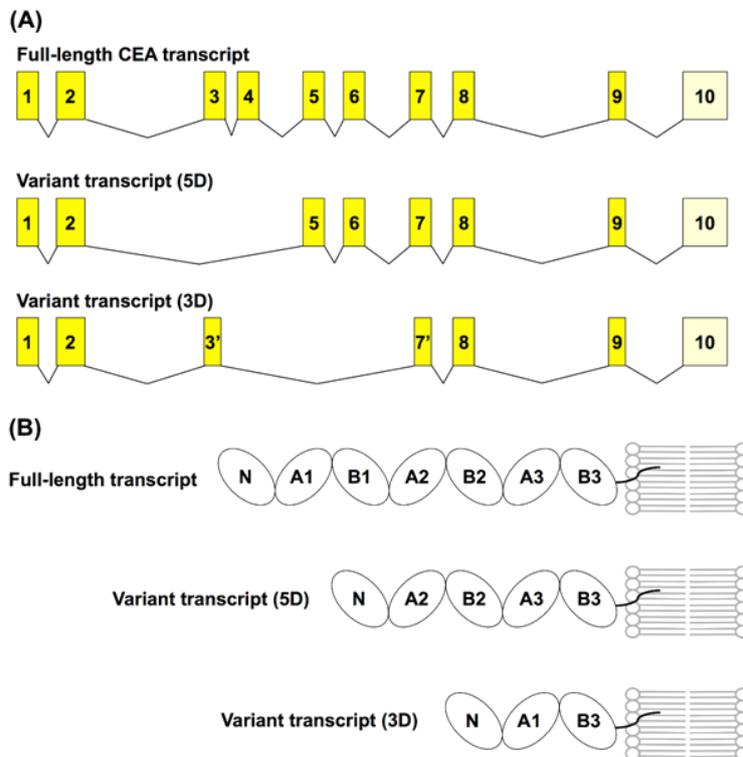
A schematic representation of the chromosomal arrangement of the CEACAM family genes. Main members (CEACAM1, CEACAM3, CEACAM4, CEACAM5, CEACAM6, CEACAM7 and CEACAM8) of the CEACAM family are localized in the region of the chromosome 19q13.2.

## DNA/RNA

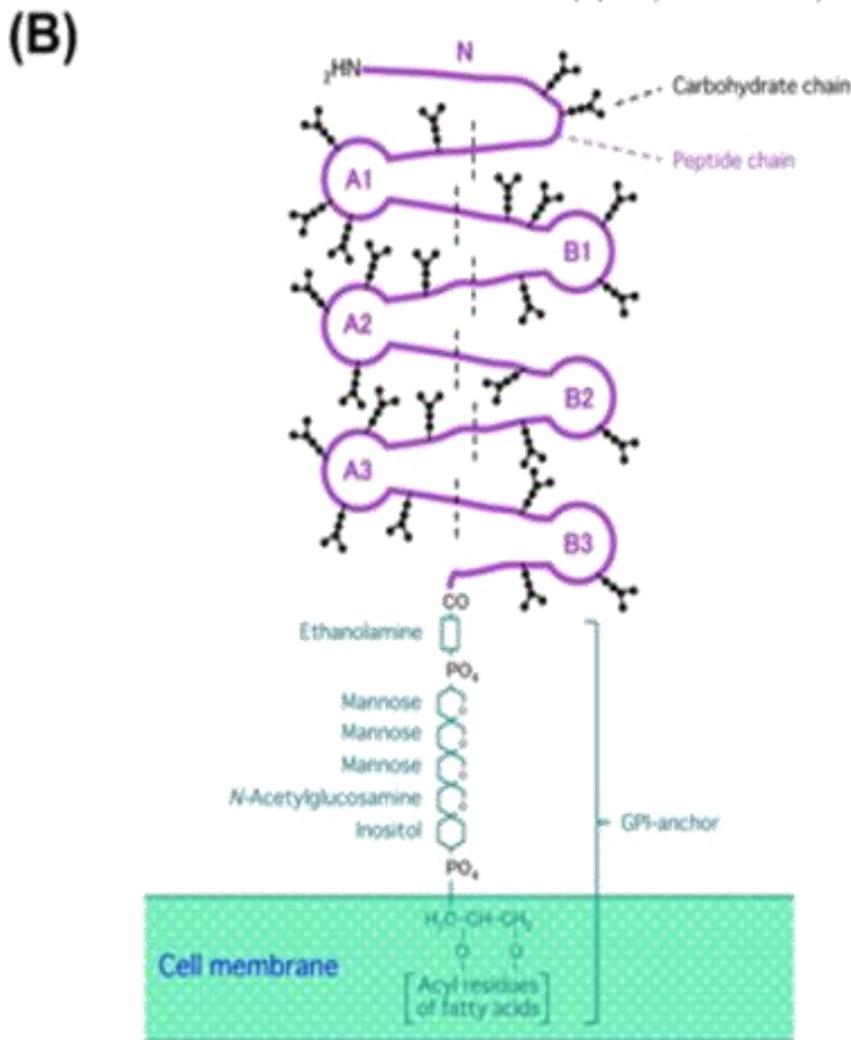
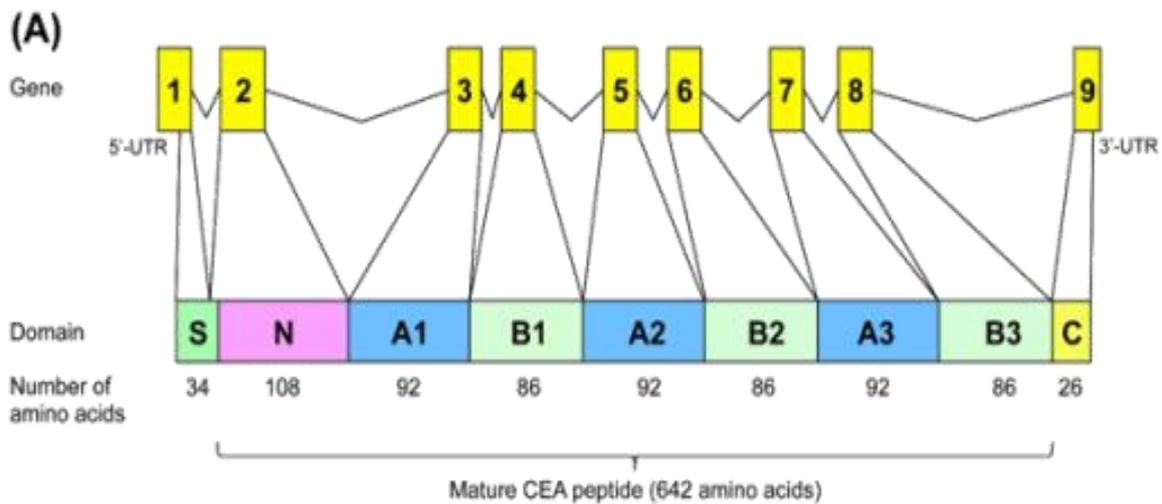
Out of 24 CEACAM family genes, twelve members (i.e., CEACAM1, CEACAM3, CEACAM4, CEACAM5, CEACAM6, CEACAM7, CEACAM8, CEACAM16, CEACAM18, CEACAM19, CEACAM20 and CEACAM21) are expressed while the other 12 genes are pseudogenes (Pavlopoulou and Scorilas, 2014). All the CEACAM family genes are localized in the 19q13.2-19q13.4 region. Although the newly given

protein names encoded by those active genes are the same as the gene names (Beauchemin et al., 1999), that of CEACAM5 is still CEA because the name of CEA has clinically been widely used for a long time.

Splice variants isoforms of CEACAM/CEA have been detected, and the resulting protein isoforms were not only co-expressed with full-length CEA but also co-secreted into the culture medium by gastrointestinal cancer cell lines (Hatakeyama et al., 2013).



(A) Alternative splicing of CEA precursor mRNA leads to the shorter isoforms with different domain structures. Protein-coding exons (exons 1-9) are shown as yellow boxes; the 3'-untranslated exon 10, the light yellow box. (B) Schematic representations of the protein domain structures of the translated CEA transcripts. The black sigmoidal line attached to the B3 IgC-like domain indicates a glycosylphosphatidylinositol (GPI) anchor to the plasma membrane (see below).



**(A)** (A) The gene structure and protein domain model of the CEA molecule. CEA encoded by the CEACAM5 gene is synthesized as a precursor with a signal peptide (S) followed by 668 amino acids of the putative molecule; the first N-terminal domain (N domain) is followed by six IgC-like domains (A1, B1, A2, B2, A3, and B3 domains) and the last C-terminal hydrophobic domain (C domain) (Oikawa et al., 1987). Exons 1 and 9 include a 5'-untranslated region (5'-UTR) and a 3'-untranslated region (3'-UTR), respectively (Schrewe et al., 1990). **(B)** Schematic representation of the CEA protein structure. CEA is finally anchored to the membrane by the simultaneously occurring proteolysis of the C domain and replacement with the GPI anchor immediately after synthesis (Takami et al., 1988).

## Description

The CEACAM5 gene, spanning a length of approximately 21 kb, consists of 9 exons with a 3'-non-coding exon (exon 10).

## Transcription

The primary CEA transcript encodes a protein with an Ig variable region (IgV)-like domain, termed N, followed by six Ig constant region (IgC)-type 2-like domains, termed A1, B1, A2, B2, A3, and B3. In some normal and cancer cells, the transcript is subjected to alternative splicing, resulting in the generation of several CEA isoforms (Hatakeyama et al., 2013). The CEA transcript with skipping of exons 3-4 encodes the variant with a five-domain structure (N-A2-B2-A3-B3 (5D)), while the transcript lacking the sequence from the 3' end of exon 3 to the 5' end of exon 7 relative to the full-length transcript contains only three domains (N-A1-B3 (3D)).

## Pseudogene

Out of 24 CEACAM family genes, twelve are pseudogenes and have been identified in the CEA family gene cluster (Pavlopoulou and Scorilas, 2014).

## Protein

### Note

The CEACAM5 gene encodes CEA, which is the most widely used tumor marker for the diagnosis and monitoring of various cancers (see below). CEA is composed of 642 amino acids (a molecular mass of approximately 70kDa) and has 28 potential N-linked glycosylation sites (Oikawa et al., 1987; Nicholson and Stanners, 2007). CEA contains 24-26 asparagine-linked sugar chains in one molecule (Yamashita et al., 1987) and its final molecular mass is approximately 180kDa (Thompson et al., 1991).

## Description

Among the main CEACAM family members (CEACAM1, CEACAM3, CEACAM4, CEACAM5, CEACAM6, CEACAM7 and CEACAM8), the genes encoding proteins with transmembrane domains were assigned the CEACAM consecutive numbers 1-4, and the genes encoding GPI-anchored proteins including CEA were assigned the CEACAM numbers 5-8 (Beauchemin et al., 1999).

## Expression

Many CEACAM family proteins, such as CEACAM1, CEACAM8, CEACAM6 and CEACAM3, are known to be expressed in hematopoietic cells (Nagel and Grunert, 1995; Baeclay et al., 1997). In contrast, CEA has not been detected in hematopoietic cells and shows a more

limited tissue localization in normal tissues including the tongue, esophagus, stomach, duodenum, appendix, colon, trachea (Nap et al., 1988; Kuroki et al., 1981) and lung (Nouwen et al., 1986). The CEA expression in those organs starts during the early fetal period (9-14 weeks) and appears to continue throughout one's lifespan (Nap et al., 1988). Increased expression of CEA has also been observed in various cancers including colorectal carcinoma (Jothy et al., 1993), gastric carcinoma (Kinugasa et al., 1998), pancreatic carcinoma (Shi et al., 1994), gall bladder carcinoma (Shi et al., 1994), lung adenocarcinoma (Robbins et al., 1993), small cell lung carcinoma (Kim et al., 1992), breast carcinoma (Cournoyer et al., 1988), urinary bladder carcinoma (Shi et al., 1994), mucinous ovarian carcinoma (Thompson et al., 1994), serous ovarian carcinoma (Thompson et al., 1993) and endometrial adenocarcinoma (Thompson et al., 1993). It is usually expressed in corresponding metastatic lesions as well, due to its involvement in tumor progression and metastasis.

## Localisation

CEA is localized to columnar epithelial cells and goblet cells of the colon, mucous neck cells and pyloric mucous cells of the stomach, squamous epithelial cells of the tongue, esophagus and cervix, secretory epithelia and duct cells of sweat glands and epithelial cells of the prostate (Nap et al., 1988; Kodera et al., 1993; Prall et al., 1996). Studies using immunoelectron microscopy using a specific monoclonal antibody for CEA demonstrate that CEA is specifically localized to the apical surface of mature enterocytes (Ahnen et al., 1982; Baranov et al., 1994; Frångsmyr et al., 1999). No staining is seen at the basolateral surfaces of the enterocytes. The structure that is specifically stained is the apical glycocalyx (= fuzzy coat)/microvillus region of the mature enterocytes. The fuzzy coat is made up of microvesicles and filaments. The microvesicles are formed by the blebbing of microvillus membrane and subsequent pinching off. The finding that CEA in normal colon is released via CEA-coated vesicles agrees with the findings which showed that more than 90% of total CEA in feces exist in a membrane-bound form and that it can be released from the membranes by phosphatidylinositol-specific phospholipase C (Kuroki et al., 1994; Kinugasa et al., 1994).

## Function

In vitro studies with tumor cell lines have demonstrated that CEA, like other CEA gene family members, can act as homophilic and heterophilic adhesion molecules when expressed on the tumor cell surface (Benchimol et al., 1989; Oikawa et al., 1992; Zhou et al., 1993). Therefore, in the tumor environment it is possible that CEA

plays some role as a contact-mediating device when tumor cells are invading new sites. In normal physiology, however, it appears unlikely that CEA is involved in intercellular adhesion due to their apical localization on polarized cells. CEA in normal tissues is now considered to protect the luminal organs of the body from microbial infection by binding and trapping infectious microorganisms. Those organs are the colon and perhaps other areas, such as the upper alimentary tract, the respiratory tract, the urinary bladder, and the skin (sweat glands), where the microbial load is a routine event (Hammarström, 1999).

### Homology

The CEACAM5 gene homologue is present in primates such as chimpanzees, orangutans, macaques and marmosets, but not in rodents such as mice and rats (Pavlopoulou and Scorilas, 2014).

### Mutations

As of July 2015, the 245 single-nucleotide polymorphisms (SNPs) of the CEACAM gene have been included in the NCBI SNP database (dbSNP), and there are 19 independent SNPs located within the coding region. However, to date, no clinical significance of these CEACAM SNPs has been described.

### Implicated in

#### Various cancers

##### Note

As described above, CEA is widely expressed not only on the surface of tumor cells, but also on normal epithelial cells of the luminal organs of the body. These facts demonstrate that CEA is no longer a carcinoembryonic (oncofetal) antigen, rather it should be considered to be a normal tissue component with retained/increased expression in tumors (Kuroki et al., 1988; Hammarström, 1999). The degree of its expression is related to the state of differentiation of the normal or tumor cell; highly differentiated cells express higher levels of CEA (Hammarström, 1999). The localization of CEA in normal adult tissues is, however, restricted to the apical surface of the epithelial cell membranes facing the lumen, so that CEA is not directly exposed to the tissue fluid or blood flow. In contrast, in tumor tissues that no longer conform to the single-layer organization by invading through the basement membrane in multicellular arrays, CEA is typically localized to all sides of the cell surface, directly facing the blood flow or tissue fluid (Hammarström, 1999; Khare et al., 2001). As the tumor size increases, more CEA will accumulate in the blood. Hence, the serum CEA levels may be monitored to detect a response to

anticancer therapy or disease recurrence in various cancers, especially in colorectal cancer (Goldstein Mitchell, 2005; Locker et al., 2006). Immunohistochemical staining of CEA using surgically- or biopsy-removed specimens is also helpful as a diagnostic aid in patients with various cancers (Kuroki et al., 2002).

##### Prognosis

Serum CEA serves as a prognostic indicator in patients with various types of cancer, where elevated levels indicate a poor prognosis and correlate with a reduced overall survival (Duffy, 2001; Locker et al., 2006).

### To be noted

The clear contrast of the CEA localization pattern between normal tissues and tumor tissues suggests that tumor cell-bound CEA may serve as a potential target for tumor imaging (Hong et al., 2008) and various kinds of cancer therapies using anti-CEA monoclonal antibodies or their genes (Khare et al., 2001; Tanaka et al., 2006; Baek et al., 2011; Peng et al., 2012; Kuroki and Shirasu, 2014; Shirasu et al., 2014).

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