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Gene Section
Review

MUC5AC (mucin 5AC, oligomeric mucus/gel-forming)

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Identity

Other names: LeB; MUC5; mucin 5AC; TBM

HGNC (Hugo): MUC5AC

Location: 11p15.5

DNA/RNA

Description

MUC5AC gene approximately extends 150 kb-long on the chromosome 11 in the region p15.5. The central region has sequences repeated in tandem (TR) with a consensus motif composed of 24 bp. The variable number of TR (VNTR) polymorphism is low compared with MUC2 and MUC6. The MUC5AC alleles present small differences in length, but the tandem repeat sequence is highly polymorphic and differs in length by 0.5-1 kb.

Transcription

To date, there is a discrepancy regarding the total number of exons present in MUC5AC gene.

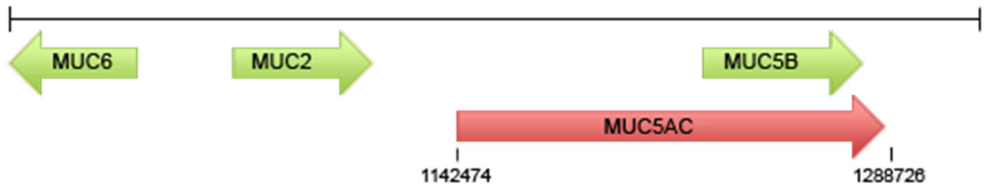
The full size 5' UTR of MUC5AC has not been yet determined, but it is estimated that the mRNA length is approximately 17.5 kb.

The 4 kb fragment upstream is essential for the cell-specific expression of MUC5AC. It contains a TATA box at -29/-23 and potential transcription factor binding sites are described for NFkappaB, Sp-1, GRE and AP-2. One CACCC box able to bind SP1 and initiate transcription has been identified.

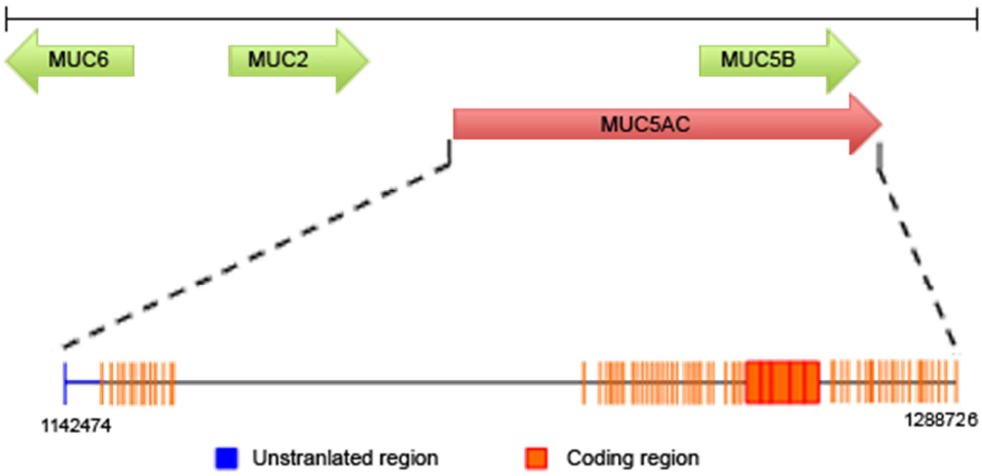
At present no splice variant forms have been reported.

The MUC5AC promoter has lower number of CpG dinucleotides compared to the other mucin genes located at 11p15, and no silencing of this gene could be explained by methylation.

Several factors have been shown to induce the transcription of MUC5AC such as cytokines, inflammatory mediators, growth factors, some bacterial exproducts and toxic agents like tobacco smoke and pollutants. Furthermore, it is reported that glucocorticoids downregulate MUC5AC expression.



Location of MUC5AC gene.



Genomic organization of MUC5AC gene (not to scale).

Protein

Note

MUC5AC is a secreted, gel-forming mucin with a high molecular weight (approximately 641 kDa). Up to 80% of the total weight is due to the large number of O-glycosilated chains attached to Thr and Ser residues in the TR sequence.

Description

MUC5AC is a polymeric mucin with a N-terminal region, a central region, and a C-terminal region.

At the N-terminal region, D1, D2, D' and D3 cysteine-rich domains (Cys) similar to von Willebrand factor (vWF) are present, and are responsible for the disulfide-mediated polymer formation.

At the central region, coded by a single large exon, nine Cys domains are located: Cys1 to Cys5 are interspersed by domains rich in Ser, Thr and Pro (STP) with no repetitive sequences, whereas Cys5 to Cys9 domains are interspersed by four TR domains. The consensus repetitive sequence most frequent is TTSTTSAP containing a high number of potential O-glycosilation sites. The C-terminal region has the cysteine-rich vWF-like domains D4, B, C and CK. The CK domain mediates the formation of disulfide-linked dimmers by an autocatalytic process. Towards the C-terminus, contains an autocatalytic protein-cleavage site at the motif GDPH.

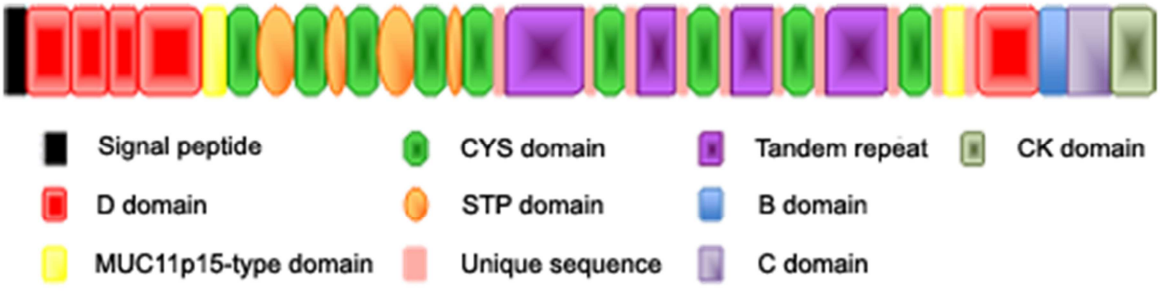
Expression

MUC5AC was initially isolated from a human tracheobronchial cDNA library, and it is highly expressed in the goblet cells of the respiratory epithelium. MUC5AC is also highly detected in the superficial gastric epithelium, and it is also expressed in pancreas, endocervix and gallbladder.

Under pathological conditions, MUC5AC expression can be altered, as it is reported below. The changes associated with neoplastic transformation and inflammatory diseases, can be induced by the activation of signaling pathways in response to several factors such as inflammatory cytokines, growth factors, and bacterial products.

Function

MUC5AC is a gel-forming mucin and it is a major constituent of the mucus lining mainly the respiratory tract and the stomach. In the surface of the normal respiratory epithelium, MUC5AC is one of the major contributors to the rheological properties of the mucus that has a critical role in the defense against pathogenic and environmental challenges. In the gastric mucosa, MUC5AC and MUC6 are the main components of the protective layer over the surface, and act as a selective diffusion barrier for HCl. MUC5AC also protect the gastric epithelium from Helicobacter pylori, and the glycan structures on MUC5AC, Le^b and sialyl Le^x, act as ligands for the bacterium competing with the ligands located on the epithelial cell surface.



Schematic representation of MUC5AC peptide structure (not to scale).

Homology

Several orthologues of MUC5AC have been identified in Mus musculus, Rattus norvegicus, Canis lupus familiaris, Equus caballus and Pan troglodytes. The chicken, horse and mouse Muc5AC have a similar domain structure. Murine N-terminal and C-terminal regions showed striking similarities with human MUC5AC, whereas the TSP domains are specific for species. Furthermore, MUC5AC tissue-specific expression is conserved in murine and equine organisms.

Implicated in

Gastric cancer

Disease

Gastric cancer remains the second leading cause of cancer related deaths and the fourth most common cancer in the world, although its incidence is gradually decreasing.

Prognosis

Gastric neoplastic transformation is associated with a decreased expression of MUC5AC. MUC5AC is used as a marker of gastric phenotype in stomach tumours, and its expression is associated with antral carcinomas. MUC5AC expression have been also related to tumour stage: it is expressed in early carcinomas while advanced gastric cancers present reduced levels of MUC5AC.

Colon cancer

Disease

Colorectal cancer is one of the commonest cancers and the third leading cause of cancer death. However, its incidence has decreased due to a most effective intervention and life-style changes in the western countries.

Prognosis

MUC5AC has been detected in precancerous lesions as well as in colon cancer, and this ectopic expression may represent a nonspecific repair function of the colon cells to compensate for damage to barrier function.

Endometrial adenocarcinoma

Disease

Endometrial adenocarcinoma is the most common malignant neoplasm of the female genital tract in developed countries, and it occurs predominantly after menopause.

Prognosis

Increased levels of MUC5AC have been found in endometrial adenocarcinoma compared to normal endometrium and endometrial hyperplasia, suggesting a potential role for MUC5AC as a marker of endometrial neoplastic transformation.

Pancreatic cancer

Disease

Pancreas cancer is a very aggressive tumor with a 5-year survival of less than 5%, and approximately 85% of them correspond to ductal adenocarcinomas.

Prognosis

The ectopic expression of MUC5AC in pancreas ductal adenocarcinomas is an early event, already detected in the PanIN1A (pancreatic intraepithelial neoplasia 1A) stage. The MUC5AC expression is maintained to reach 85% of the pancreatic tumors.

Biliary tract cancer

Disease

Biliary tract carcinomas are uncommon tumors that includes cholangiocarcinomas and gallbladder carcinomas. These tumors has a poor prognosis: more than 80% of the patients are unresectable with a 6-9 month survival, and this rate is increased to 5-year after surgery.

Prognosis

MUC5AC is detected at very low levels in biliary tract carcinomas and its expression do not correlate with the clinical stage of the tumor. However, the detection of MUC5AC in sera from biliary tract carcinoma patients, associated to the MUC4 expression in the tumor, have been suggested as a highly specific markers for this neoplasia.

Airways pathologies: asthma, cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) and nasal polyps (NP) in upper airways

Disease

Asthma has grown, particularly among children, in prevalence and it is characterized by an airflow obstruction caused by inflammation-induced changes in airway smooth muscle contraction and by mucus hypersecretion.

CF is characterized by impaired mucociliary clearance, leading to chronic airflow obstruction and to recurrent infections.

COPD is the fourth leading cause of death in the U.S. and Europe. Submucosal gland hypertrophy and airway surface metaplasia are the hallmarks of COPD.

NP is an inflammatory disease whose aetiology is still unknown and affects 2-4% of general population.

Prognosis

MUC5AC levels have been found to be increased in asthma, CF and COPD that alter the transport properties of the mucus gel and provide a favourable environment for pathogens. In NP a decrease of MUC5AC levels are detected.

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