

Gene Section

Review

CD59 (CD59 molecule, complement regulatory protein)

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Identity

Other names: 16.3A5, 1F5, EJ16, EJ30, EL32, G344, HRF-20, HRF20, MAC-IP, MACIF, MEM43, MIC11, MIN1, MIN2, MIN3, MIRL, MSK21, p18-20

HGNC (Hugo): CD59

Location: 11p13

Local order: FBOX3, CD59, C11orf91.

Note

CD59 gene encodes a ubiquitously expressed membrane-bound glycoprotein which inhibits complement system. More specifically, CD59 binds complement C8 and/or C9 during the assembly of the membrane attack complex, thus protecting self-cells from damage caused by the activation of the terminal pathway of complement cascade (Bubeck et al., 2011; Walport, 2001).

DNA/RNA

Description

NCBI Reference Sequence: NG_008057.1.

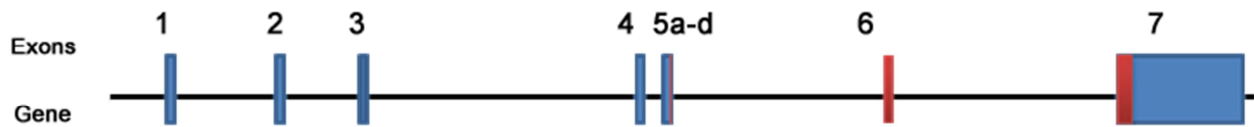
Transcription

- Total range: NG_008057.1
- exon 1: (1..98); total length: 98; strand: plus
- exon 2: (2870..2985); total length: 116; strand: plus
- exon 3: (5012..5056); total length: 45; strand: plus
- exon 4: (13528..13563); total length: 36; strand: plus
- exon 5a: (13753..13844); total length: 92; strand: plus
- exon 5b : (13753..13909); total length: 157; strand: plus
- exon 5c: (13753..14101); total length: 349; strand: plus
- exon 5d: (14017..14101); total length: 85; strand: plus
- exon 6: (19009..19110); total length: 102; strand: plus
- exon 7: (26137..33470); total length: 7,334; strand: plus.

Transcription results in 22 different mRNAs (20 alternatively spliced variants and 2 unspliced forms). Despite the very high number of different CD59 transcripts, most of them vary at their 5' and/or 3' ends and encode a unique CD59 protein. However, different splicing variants have alternative promoters and stabilising sequences which is likely to affect the expression level of the protein.



Red line marks the position of the CD59 gene in chromosome 11, p13.



CD59 gene consists of 7 exons and 6 introns spanning 1 to 33470bp of DNA (NCBI Reference Sequence: NG_008057.1) from 11p13 and includes a 5'-/3'- non-coding regions. The position of exons is: 1..98 (exon 1), 2870..2985 (exon 2), 5012..5056 (exon 3), 13528..13563 (exon 4), 13753..13844 (exon 5a), 13753..13909 (exon 5b), 13753..14101 (exon 5c), 14017..14101 (exon 5d), 19009..19110 (exon 6), and 26137..33470 (exon 7). Highlighted in red is the protein coding sequence from exons 5c/5d, 6 and 7 (14035..26354).

mgiiqggsvifgllilvavfChsgshsqCyncpnptadCktavnCssdfdaClitkagllqvynkOwkfehCnfnvdttrfreneltyyCCkddlCnfneqlenggttslsekvtllvtpflaaawshp

Sequence of CD59 protein. CD59 contains 10 cystein residues involved in 5 disulphide bonds creating 5 loop structures. First three helical loops at the N-terminus form the hydrophobic core of CD59. Detailed information on CD59 protein structure can be obtained in works published by Bubeck et al. (Bubeck et al., 2011) and Huang et al. (Huang et al., 2007).

Protein

Description

CD59 is a 128aa-long protein. No polymorphisms have been described in the protein coding sequence of the CD59 gene. All transcription variants of CD59 result in the synthesis of a single CD59 protein with molecular mass between 18 and 22 kDa, depending on the level of glycosylation. CD59 has sites for both N- and O-glycosylation.

Expression

CD59 is expressed in all organs and in almost all cell types. It is essential to protect cells from self-destruction by complement-mediated lysis. The highest expression in humans has been detected in cardiomyocytes and smooth muscles (Su et al., 2004). Some nucleated blood cells (CD14 monocytes, T cells) either lack CD59 expression or express it very low which makes them highly susceptible to complement lysis.

Localisation

CD59 is expressed on the surface of cells. It is attached to the cellular membrane via a glycosylphosphatidylinositol tail (GPI-anchored molecule). In urine, CD59 can be found as soluble protein.

Function

The major and well-studied role of CD59 protein is to protect cells from self-destruction by our complement system. CD59 is the only membrane-bound inhibitor of the terminal pathway of complement cascade.

However, in more recent years, some other functions of CD59 were described. CD59 was found to attenuate angiogenesis by preventing the complement-mediated lysis of newly grown blood vessels (Ekdahl et al., 2006). In addition, it was found that via CD59, the LPS signal is transduced into the nucleus via NF-kappaB

activation inducing cytokine generation (Yamamoto et al., 2003).

Homology

CD59 protein does not show significant homology with other proteins. However, there is a high cross-primates homology for CD59. Human CD59 has 84% homology with CD59 in *Macaca fascicularis* and 91% homology in *Pongo abelii* (BLAST search). Homology between human CD59 protein and CD59 in rodents, however, is less than 50% (BLAST analysis).

Mutations

Somatic

No polymorphisms have been described for CD59 gene which affect the protein sequence. However, analysis of the sequence of the human CD59 gene revealed the presence of a (GT)₁₉ dinucleotide repeat ~800bp upstream from exon 1 (Nöthen and Dewald, 1995). This polymorphism might affect expression and/or stability of CD59 transcripts, however, there is no experimental information on this matter.

A mutation in another gene, PIGA gene, however, indirectly results in lack of CD59 on red blood cells (RBCs). This condition is called paroxysmal nocturnal haemoglobinuria (PNH) and is a clonal disorder of RBCs. As a result of defective PIGA function, affected RBCs lack all GPI-linked membrane proteins, including CD59. The lack of CD59 renders PNH-RBCs susceptible to autologous complement lysis (Botto et al., 2009).

Implicated in

Paroxysmal nocturnal hemoglobinuria (PNH)

Note

Decrease or absence of glycosylphosphatidylinositol-anchored molecules from the surface of the affected

cells, such as CD59 (and CD55), resulting in chronic intravascular hemolysis, cytopenia and increased tendency to thrombosis, venous thrombosis, deficient hematopoiesis and, rarely, leukemic conversion.

Disease

PNH involves the defective synthesis of a glycosylphosphatidylinositol (GPI) anchor that is used by certain surface proteins for tethering to the cell membrane, such as CD59 (Meri and Jarva, 1998). Somatic mutations in the X-linked gene PIGA (GPI complementation group A) which encodes a protein required in the biosynthesis of GPI molecules, have been strongly implicated in the pathogenesis of PNH (Rosti, 2000).

Prognosis

Poor.

Oncogenesis

Possible association between paroxysmal nocturnal hemoglobinuria phenotype and lymphoproliferative syndromes (Meletis et al., 2001).

Alzheimer's disease (AD)

Note

It was demonstrated at both protein and mRNA levels that CD59 expression in frontal cortex and hippocampus in AD brains was significantly decreased when compared with normal age matched non-demented individuals, supporting the hypothesis that AD brains are particularly vulnerable to complement-mediated neuronal death (Yang et al., 2000).

Disease

AD is a neurodegenerative disease that causes changes in brain function.

AD usually affects people over the age of 65 years, with a progressive decline in memory, thinking, language and learning capacity. Age is the strongest predictor for the development and progression of AD (Tanna, 2004).

Prognosis

AD is incurable. It leads to death within an average of eight years after diagnosis, the last three of which are typically spent in an institution.

Cytogenetics

The molecular mechanisms and hypotheses of AD can be incredibly complex.

One of the key events leading to AD appears to be the formation of a peptide (protein) known as amyloid beta (beta amyloid, A β), which clusters into amyloid plaques (senile plaques) on the blood vessels and on the outside surface of neurons of the brain.

This plaques have been shown to activate the complement system (Kolev et al., 2009).

Breast cancer

Disease

Human breast cancer cells are protected from complement-dependent lysis (CDC) by overexpression

of CD59 (Yu et al., 1999). It has been shown in numerous studies that inhibition/neutralization of CD59 on breast tumour cells increases tumour killing by complement system both in vivo and in vitro.

Prognosis

A recent comparative proteomics study provided novel insights into key proteins associated with the metastatic potential of breast cancer cells and identified CD59 as a marker for breast cancer aggressiveness (Terp et al., 2012).

Oncogenesis

Overexpression of CD59 on the surface of tumour cells confers resistance to CDC which has been suggested to result in tumour growth (Chen et al., 2000; Donev et al., 2006).

Ovarian cancer

Disease

CD59 is strongly expressed in the ovarian tumor tissues and their associated cell lines cells in all 28 benign and malignant tumors examined (Björge et al., 1997).

Neutralization of CD59 with an anti-CD59 monoclonal antibody or inhibition of cd59 expression by siRNA significantly enhances CDC of the ovarian cell lines (Kolev et al., 2011).

Prognosis

Significant reduced levels of CD59 were detected in the urine of patients with ovarian carcinoma compared to the control subjects (Abdullah-Soheimi et al., 2010).

Thus, CD59 can be used as a biomarker in the development of noninvasive assays for diagnosis and screening for ovarian carcinoma.

Oncogenesis

It has been demonstrated that overexpression of CD59 on cancer cell surface promotes tumour growth in vitro and in vivo by protecting them from complement lysis (Chen et al., 2000; Donev et al., 2006).

Various cancers

Note

Complement is one of the main mediators of antibody-based cancer therapy via the CDC effect. Tumour cells overexpress CD59 which plays a critical role in resistance to CDC and monoclonal antibody-therapy for treatment of cancer (Juhl et al., 1997; Yan et al., 2008).

Disease

CD59 is overexpressed on the surface of different tumour types and their associated cell lines – colorectal cancer (Thorsteinsson et al., 1998), B-cell leukemias (Treon et al., 2001), neuroblastoma (Donev et al., 2008), prostate cancer (Jarvis et al., 1997), malignant melanoma (Weichenthal et al., 1999), lung carcinoma (Varsano et al., 1998), etc.

Prognosis

In general, overexpression of CD59 on tumour surface is associated with poor prognosis.

Oncogenesis

It has been demonstrated that overexpression of CD59 on cell surface promotes tumour growth in vitro and in vivo by protecting them from complement lysis (Chen et al., 2000; Donev et al., 2006).

Diabetes**Note**

Glycation was shown to inhibit CD59 function. In presence of glycation on CD59 it loses its MAC-inhibitory function and results in vascular proliferative complications like diabetes (Davies et al., 2005). Loss of functional CD59 in hyperglycaemics contributes to their susceptibility to lysis by complement. Thus, it was suggested that glycation-induced inactivation of CD59 is a factor contributing to anaemia in type I diabetes. It is hypothesized that glycation near residue K41 and W40, two highly conserved amino acids essential for the CD59 function, inhibits CD59 function (Davies et al., 2005).

Disease

Diabetes is a disease due to an increased level in glucose, which results in glycation and impairment of protein function. Glycation is when a sugar molecule binds a protein or a lipid molecule without the control of an enzyme.

Age-related macular degeneration (AMD)**Note**

Immunohistochemical studies have localized activated complement components, including the membrane attack complex (MAC) in retinal pigment epithelium (RPE) and drusen in the eyes of patients with AMD (Johnson et al., 2000). CD59 protects autologous cell killing by preventing the formation of lytic MAC on the cell membrane (Meri et al., 1990).

The expression of CD59 was found to be significantly lower on CD14(+) monocytes in patients with neovascular AMD compared with controls (Singh et al., 2012). Introduction of human CD59 using adenoviral vectors as a possible therapeutic strategy has been proposed (Ramo et al., 2008).

Disease

Molecular basis for AMD is not well understood, a growing body of evidence has recently implicated inflammatory processes, specifically the complement system, in the pathogenesis of this disease (Johnson et al., 2000).

Prognosis

AMD is the leading cause of blindness among the elderly in industrialized nations (Klein et al., 2008).

Major depression**Note**

Expression of CD59 has been found significantly inhibited in an animal model of major depression (Pajer

et al., 2012). This suggests that neurons become more susceptible to complement-mediated damage.

Disease

Early-onset major depressive disorder (MDD) is a serious psychiatric condition occurring in people under 25 years of age. Early onset of MDD predicts greater familial risk, suggesting a substantial genetic etiology. Approximately 1% of the population of 12 years has MDD, but rates increase to 17-25% by late adolescence and young adulthood (Pajer et al., 2012).

Breakpoints**Note**

Chromosomal in situ hybridization and pulsed field gel electrophoresis mapped the CD59 gene to 11p13, distal to the breakpoint of acute TCL2 (T-Cell Leukemia) and proximal to the Wilms tumor gene (WT1) (Heckl-Ostreicher et al., 1993).

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