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Gene Section
Review

CD81 (Cluster of Differentiation 81)

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Abstract

Cluster of differentiation (CD81) is a type of protein, which is encoded by CD81 gene. Beside that CD81 is also known under other names such as Target of the Antiproliferative Antibody 1 (TAPA-1) and Tetraspanin-28 (TSPAN28). Location of CD81 is known to be on chromosome 11 (11p15.5), where it contains 15-20 bases in length. It is expressed mostly in cells of testis, ovary, endometrium, placenta, bone marrow, smooth muscles and others.
The main function of the CD81 protein is to mediate signal transduction events, which are important for cells' development, activation, growth and motility. The CD81 gene is also known as a candidate for many malignancies because of its location. The characteristic feature of CD81 is that it is highly hydrophobic and contains a short N- and C-terminal cytoplasmic domains together with cytoplasmic cysteines, potential sites of palmitoylation as well as four transmembrane domains where they together hold the protein in a cell membrane. There are two CD81 isoforms, isoform 1 and isoform 2. Isoforms of CD81 are usually found in a tumor-suppressor region where they have a great impact on tumor development. There has always been a high interest in research on CD81 function in viral disease development.
In fact, it is known that CD81 contributes in the development of diseases such as hepatitis C, malaria and various types of cancer.
Since the complete effect of CD81 is unknown, further research and scientific methodology could potentially discover all possible functions and mechanisms regulated by the CD81 protein in human body.

Keywords
CD81, TAPA-1, Tetraspanin-28, malignancies, isoforms, viral disease.

Identity

Other names
TAPA-1; TAPA1; TAPA; CD 81 antigen; CD81 molecule; TSPAN28; TSPAN-28; S5.7; CVID6

HGNC (Hugo): CD81

Location: 11p15.5

DNA/RNA

The highest level of CD81 gene expression is in endometrium (RPKM 241.8), fat (RPKM 237.1), lung (RPKM 191.2) and 24 other tissues in the human body.
Proteins encoded by the CD81 gene are important for transduction of signals, cell development, growth and motility (RefSeq NCBI et al., 2019).

Figure 1. Mapping of CD81 gene on chromosome 11p15.5 (from Ensembl CD81 gene).

Figure 2. Homo sapiens CD81 molecule RefSeqGene (LRG_142) on chromosome 11. (RefSeq NCBI et al., 2019).

Description

Cluster of Differentiation 81 (CD81) is a type of protein, which belongs to tetraspanin family of proteins (Thomas and Mohler, 2011). According to the study, it is an important molecule for the biological system of living organisms that regulates several types of mechanisms in the body (Thomas and Mohler, 2011). The molecule was previously known as TAPA-1 but changed its name to CD81, after the Fifth International Workshop on Human Leukocyte Differentiation Antigens' (IUIS/WHO Subcommittee on CD Nomenclature, 1994).

CD81 gene constitutes a protein coding gene which is located in the chromosomal region 11p15.5 of human genome. Using 5A6 (immunoglobulin- γ1), a monoclonal antiproliferative antibody, Oren et al. (1990) performed the first isolation of cDNAs encoding CD81. The chromosomal localization of CD81 gene in the short arm of chromosome 11 was determined by Andria et al. (1991) in Southern blot experiments in which DNA isolated from somatic cell hybrids was used. In order to assign CD81 gene to a specific region on the chromosome 11, Virtaneva et al. (1994) performed experiments by hybridizing CD81 gene to derivative somatic cell hybrid DNAs of human chromosome 11. The exact location of CD81 gene is shown in the figure 1. To date, 17 transcript variants have been found for this gene.

As indicated by Andria et al. (1991), the 5' untranslated region of the CD81 gene is abundant in CpG islands, which is a common feature observed in many housekeeping genes (Andria et al.,1991; Levy et al., 1998). High content of G + C nucleotides in this region correlates with a high susceptibility to methylation events, which can affect the expression of the receptor (Houldsworth et al., 2013). It also contains a TATA box at -25 position and presumably, binding sites for SP1 transcription factor (Maecker et al., 1997). Additionally, it has been reported that the region in which CD81 gene is located constitutes a tumor-suppressor region, which makes a CD81 gene an important candidate for various malignancies.

Transcription

There are several ongoing studies regarding the CD81 gene due to its transcriptional activity (Hong et al., 2014; Tardif et al., 2005). In an experiment in which promoter analysis was performed, it has been shown that there is an essential role of the SP1 transcription factor in CD81-induced MT1-MMP transcription (Hong et al., 2014). Having CD81 with high MT1-MMP expression levels is of a great importance since it is associated with malignant melanoma development (Hong et al., 2014). The antigen itself is very much vital for the malignancies, primarily due to the location of the CD81 gene in a tumour-suppressor region (Levy et al., 2014). Mature transcript of CD81 is made of eight exons, all of which code information for protein synthesis. The transcript itself is 1,714 bp long.

Protein

Description

CD81 antigen, previously known as TAPA1, constitues a membrane protein of 26-kDa molecular weight, which is expressed in many cell types, including hemopoietic, endothelial as well as epithelial cells. It is a founding member of a highly conserved tetraspan family of transmembrane 4 superfamily, also known as tetraspanin family. Members of this family are expressed not only in mammals, but also in all other multicellular organisms, including insects such as Drosophila, plants as well as fungi. CD81 is a highly hydrophobic protein which contains a short N- and C-terminal cytoplasmic domains with cytoplasmic

cysteins, potential sites of palmitoylation as well as four transmembrane domains (TM 1-4) that hold the protein in a cell membrane. The protein folds itself creating a large extracellular loop (LEL) with CCG motif and two disulfide bridges, small extracellular loop (SEL) and even a smaller loop of intracellular location (Levy, 2014). Unlike many other members of the family, CD81 does not undergo glycosylation. The protein exibits a strong homology with two antigens - CD37 (65% identical) as well as ME491 melanoma-associated antigen (98% identical) also known as CD63 molecule. Originally, CD81 protein was characterized as a target of an antiproliferative antibody that leads to the inhibition of B cell proliferation (Levy, 2014).

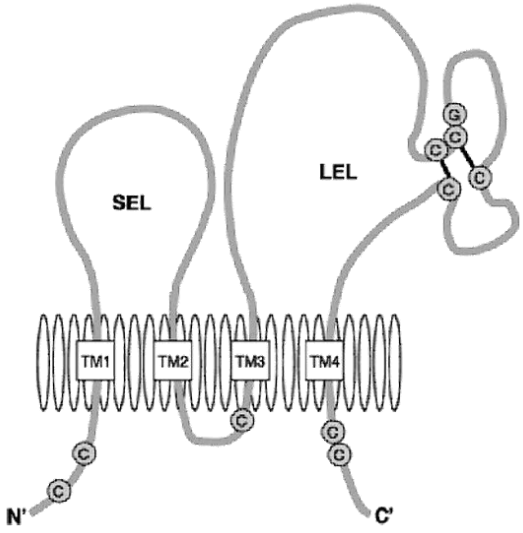

Figure 3. CD81 structure (Levy, 2014).

C According to the Zimmerman et al. (2016), transmembrane parts of CD81 contain two largely disconnected couples of spirals, covered with a bulky extracellular loop at the exterior membrane leaflet. These two sets of coils converge at the position of internal leaflet to generate an intramembrane abridged with supplementary electron concentration corresponding to a cholesterol molecule in a cavity. Molecular subtleties simulation recognizes a supplementary conformation in which extracellular loop splits considerably from the transmembrane domain. Cholesterol binding appears to modulate CD81 activity in cells, signifying a probable mechanism for regulation of tetraspanin occupation.

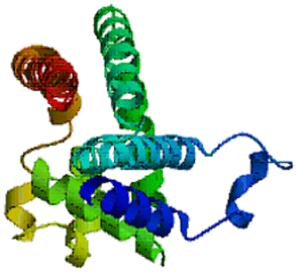

Figure 4. Model of CD81 protein (Source: SWISS-MODEL https://swissmodel.expasy.org/interactive)

Expression

On a protein level the expression of CD81 occurs on B-cells, hepatocytes, monocytes/macrophages and on both naive and memory CD4-positive T cells (Takeda et al., 2003; Silvie et al., 2003; van Zelm et al., 2010; Sagi et al., 2012)

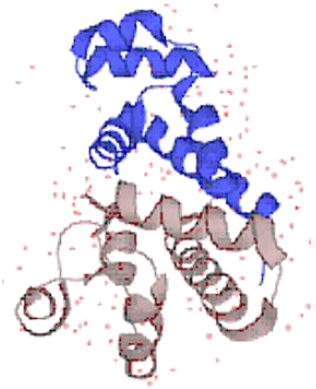

Figure 5. Structure of CD81 protein (Source: UNIPORT https://www.uniprot.org/uniprot/P60033)

Localisation

CD81 gene can be localised in the tumor-suppressor region where two different isoforms can be found.

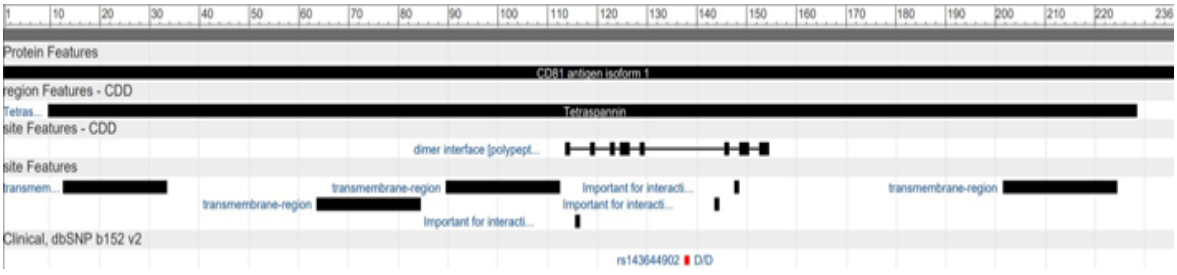

Figure 6. CD81 isoform 1. Location 10-228 (RefSeq NCBI et al., 2019)

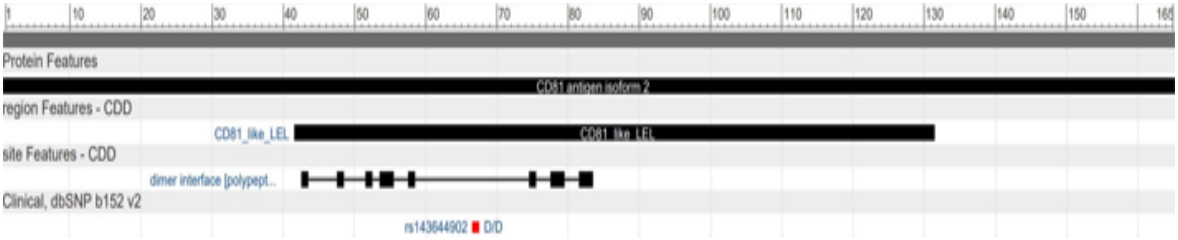

Figure 7. CD81 isoform 2. Location 42-131 (RefSeq NCBI et al., 2019).

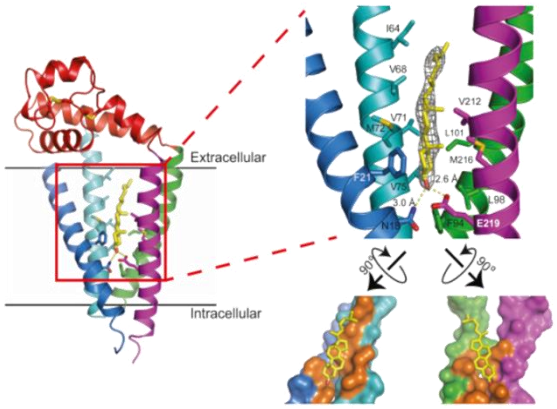

Figure 8. CD81-cholesterol interactions (Zimmerman et al., 2016).

Function

CD 81 plays a significant role in several physiological functions such as regulation of cell activation, development, motility and growth (Fagerberg et al., 2014). It is also involved in signal transduction. CD81 encoded glycoprotein associated with the cell surface is known to create a complex with integrins, which helps to promote fusion of muscle cells as well as maintenance of myotubes.

According to Thomas and Mohler (2011), CD81 is expressed on the surface of oocytes and absence of this molecule is associated with a reduced fertility in the mice system due to egg-sperm fusion defects. On the other hand, Kaji et al. (2002) proved that CD81 and CD9 have corresponding utilities in the egg-sperm fusion. The activity of CD9 is reduced by the absence of the CD81 which was observed in the mice model system. There are several reports available in which it has been proven that CD81 actively prevents development of some viral diseases like hepatitis C virus (Nalesnik and Kanto, 2010). Geisert et al. (2002) showed that CD81 is involved in the development of the central nervous system. According to the experiment, in comparison to normal mice, CD81 mutation in the cells of central nervous system results in the development of 30% larger brains.

When CD81 is increased in the body, it may be promoting breast cancer. Scientific study designed by Zhang et al. (2018) on MDA-MB-435S and MDA-MB-231 human breast cancer cell lines showed that when CD81 expression increases as an effect it can promote breast cancer. Malaria parasite Plasmodium uses CD81 membrane protein to attack liver cells in a human body (Bruening et al., 2018). It is also known that CD81 has an ability to bind to cholesterol where the amount of cholesterol controls the expression of CD81 (van Zelm et al., 2010; Vences-Catalán et al., 2015).

Homology

Highest homology level of CD81 protein can be found between humans and mice (Boismenu et al., 1996). By analysing the homology between human and mouse variants, it has been shown that the transmembrane domain residues are mostly sequentially conserved. Beside that it has been also proven that extracellular domains significantly differ from each other as presented in a figure 9 (Frolikova et al., 2018). The protein exhibits a strong homology with two antigens - CD37 (65% identical) as well as ME491, melanoma-associated antigen (98% identical) also known as CD63 molecule (Levy et al., 2014).

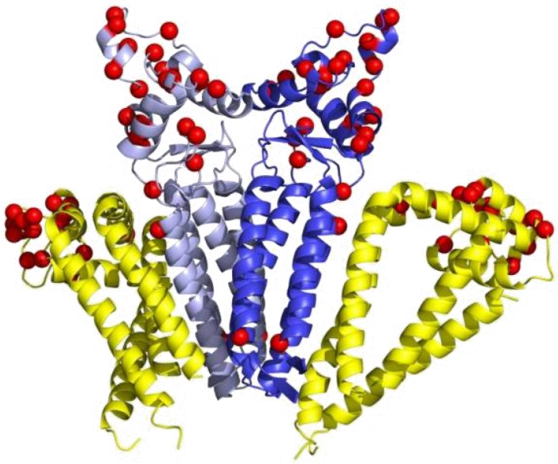

Figure 9. CD81 in human and mouse (Frolikova et al., 2018). Figure 9 presents the transmembrane domain residues and differences between extracellular domains. The whole protein consists of non-identical acids between human and mouse CD81 and CD9 projected onto the model of CD9/CD81 complex. The difference is the amount of amino acids where CD81 contains 17 different amino acids in the extracellular domain while CD9 differs in 25 amino acids on same location (Frolikova et al.,2018).

Mutations

Mutations associated with CD81 are often caused by viral infections such as hepatitis C. According to the study where the hepatitis C virus envelope protein

(E)2 interacts with cellular receptor CD81 it was possible to obtain the modulation of B and T cell function. Despite positive results, the importance of the mutation is unknown even though the mutation was caused by the modulation of these two proteins as well as the effect and the correlation between CD81 and binding regions of HCV Geno/subtypes (Kronenberger B et al., 2004).

Mutations associated with CD81 are often caused by viral infections such as hepatitis C. According to the study where the hepatitis C virus envelope protein (E)2 interacts with cellular receptor CD81 it was possible to obtain the modulation of B and T cell function. Despite positive It is known that CD19 and CD81 depend on each other regardless if the mutation occurs or not. Dependence was described on a group of patients with an increased susceptibility to infection, hypogammaglobulinemia, and normal numbers of mature B cells in blood, but all the patients had a mutation in CD19 in common (van Zelm et al., 2006). Usually, CD81 is expressed on blood cells such as blood lymphocytes, monocytes, basophilic granulocytes, and eosinophils. The absence of CD81 in membrane has never been found in humans before. However, a study performed on B cells from 611 neonatal cord blood samples showed that the absence can occur (Duijts et al., 2009).

Mutations associated with CD81 are often caused by viral infections such as hepatitis C. According to the study where the hepatitis C virus envelope protein (E)2 interacts with cellular receptor CD81 it was possible to obtain the modulation of B and T cell function. Despite positive In a study where a patient had severe nephropathy and profound hypogammaglobulinemia as well as immunodeficiency with decreased memory B cell numbers, with help of DNA sequencing of all 8 exons in which homozygous G>A substitution was found, splice sites were directly identified downstream of exon 6: c.561+1G>A. This kind of exons cause frameshift before the fourth transmembrane domain as well as premature stop (p. Glu188MetfsX13). Because of the mutation, the splice donor site was disrupted and sixth intron in cryptic splice site was used (van Zelm et al., 2010)

Somatic

CD81 also has an ability to regulate CD19 in B-lymphocytes, which can trigger the progression of hepatitis C virus infection in human cells. Scientific research in which human cells underwent a procedure of immunohistological staining proved that normal hematopoietic tissue resulted in a strong staining for CD81 in a normal germinal centre B cell. Another analytical method called high-dimensional flow cytometry confirmed that among B and T cell subsets, germinal centre B cells had the highest level of CD81 expression (Luo et al., 2010). Moreover, scientific study performed on mice showed that there is a correlation between the amount of CD81 and CD9 presented in somatic cells with successful fertilisation of spices..

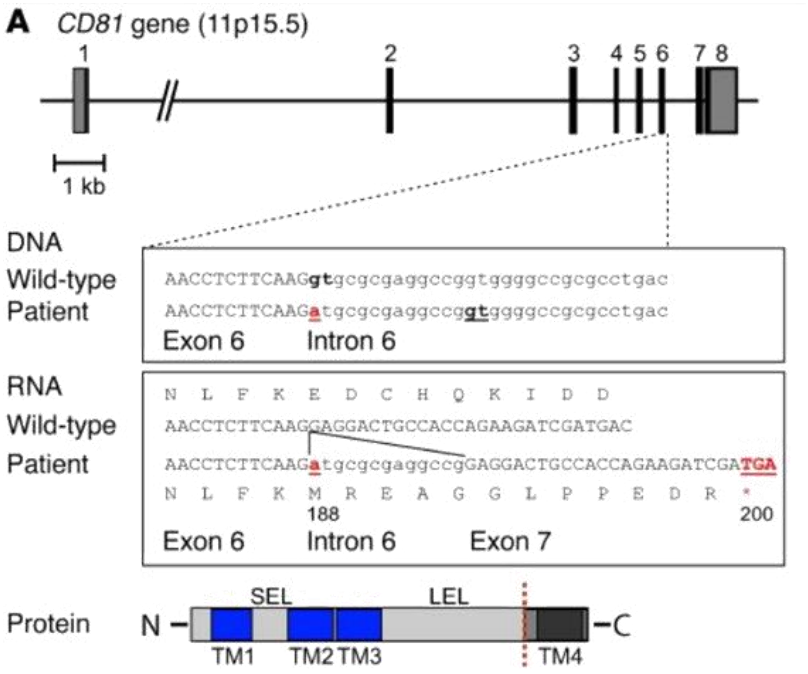

Figure 10. Presentation of the CD81 gene with 8 exons. Patient who participated in the study was homozygous for a splice site mutation downstream of exon 6 (exon6+1 G>A). This is resulting in the usage of a cryptic splice site 13 nucleotides downstream of exon 6. Premature stop codon upstream of the fourth transmembrane domain of the CD81 protein, TM transmembrane domain; SEL, short extracellular loop; LEL, large extracellular loop as well as frameshift are caused by the insertion of the 13-nucleotide region (van Zelm et al., 2010).

It is proven that the lack of CD81 and CD9 leads to a lower chance of successful fertilisation. In somatic cells, CD81 and CD9 associate with each other together with other, non-tetraspanin molecules, creating proteolipid complexes. Artificial removal of CD81 gene in mice leads to 40% reduction of female fertility (Rubinstein et al., 2006).

Epigenetics

Cluster analysis have found 25 types of genes that were hypermethylated and hypomethylated, respectively, in 20% in all of the studies. One of the most frequently hypermethylated genes was CD81. CD81 has been found in larger amounts as target of polycomb repressive complex 2 in embryonic stem cells in a medical condition called Glioblastoma multiforme, a devastating brain tumor in adults. CD81 is a member of membranal-embedded tetraspanin superfamily and it is usually observed in multiple myelomas. Tetraspanin genes associated with signalling proteins modulate fundamental biological functions and can potentially be involved in CD81 gene as a metastasis suppressor (Martinez et al., 2009).

Implicated in

The CD81 protein is a highly involved in the development of several diseases including hepatitis C, malaria, several types of cancer, HIV, fungal diseases, parasites etc. The main mechanism involves CD81 acting as a signalling molecule with a pathogen attached to the extracellular loop of CD81. This means that it acts as a getaway for the infection. It has also been proven that CD81 is important for the immune system due to its close association with CD19 in B cells. Simultaneously, it plays an important role in T cells by acting as a costimulatory agent for CD3 (Vences-Catalán et al., 2015). Presumably, further research on CD81 may provide information on all other possible functions and mechanisms of action of this molecule (Monk and Partridge, 2012).

Hepatitis C

Research on hepatitis C virus and CD81 has always been of a high interest. CD81 is considered to be a central regulator involved in the HCV lifecycle. It has been proven that due to its location in the cell membrane of hepatocytes, CD81 interacts with HCV entry factors and by that it plays a key role in the initiation of infection. The HCV infection begins when viral particles bind to glycosaminoglycans (GAG) as well as Low Density Lipoproteins Receptors (LDL-R), which are non-specific factors located on the cell surface. This stage is then followed by a direct interaction of HCV with an entry factors which are cell specific. Among these factors, CD81 constitutes the most studied and the best characterized entry factor involved in the HCV infection (Pileri et al., 1998; Cormier et al., 2004; Fénéant et al., 2014). Pileri et al. (1998) demonstrated that the virus protein E2 binds large extracellular loop of CD81 protein and that the disruption of the E2-CD81 interaction, results in hindering of the HCV entry and infection.

Malaria

Malaria parasites such as Plasmodium yoelii and Plasmodium falciparum sporozoites are involved in the CD81 expression. In a study where correlation of CD81 and malaria infection has been analysed, direct link between CD81 and cholesterol during the infection of malaria parasites has been shown. Additionally, it has been proven that the loops of these tetraspanins contain a new type of microdomains that potentially could be used by pathogens for infection (Silvie et al., 2006).

Breast cancer

The role of CD81 protein in breast cancer is unknown (Zhang et al., 2018). According to the scientific study the expression of CD81 during breast cancer state is significantly increased compared to the normal breast tissue. The increase of CD81 is associated with lymph node metastasis. (Zhang et al., 2018). It has been concluded that CD81 may be used as a prognostic biomarker associated with poor patient prognosis in breast cancer (Zhang et al., 2018).

Hepatocellular carcinoma

CD81 is known to be a receptor for hepatitis C. This kind of characteristic is a major cause of hepatocellular carcinoma (Charrin et al., 2001).

Acute myeloid leukaemia (AML)

The medical condition AML is known to be heterogeneous disease and lately, novel prognostic factors have been of a great importance in order to propose appropriate therapy. CD81 does have negative impact on survival outcome in AML patients. It is known that CD81 could be used in therapeutic approaches in stating proper AML treatment. Further studies are needed in order to confirm prognostic impact of CD81 and AML (Boyer et al., 2016).

HIV infection

Some reports have indicated that CD81 is associated with CD4, which provides a costimulatory signal that increases HIV-1 gene expression (Gordón-Alonso et al., 2006) CD81 has the ability to deliver a co-signal for T cells. This action triggers cytokine production, which leads to the cellular proliferation. Signalling processes are initiated through the T-cell receptor (TCR)/CD3 complex where coactivator CD28 affects immunodeficiency virus type 1 (HIV-1) gene expression. According to Tardig et al. (2005)

no study has investigated the putative costimulatory activity of CD81 on HIV-1 transcriptional activity.

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