

# Gene Section

## Review

### CD38 (CD38 molecule)

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#### Identity

**Other names:** T10

**HGNC (Hugo):** CD38

**Location:** 4p15.32

#### DNA/RNA

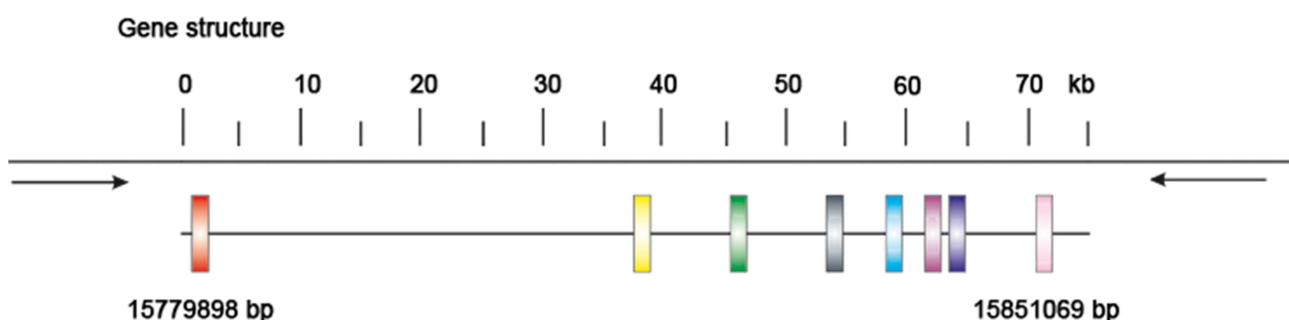
##### Description

The genomic DNA of CD38 extends for 71172 base pairs with 8 exons, starting at 15779898 bp and ending at 15851069 bp. The CD38 gene is located at 4p15.32. The 5'-flanking promoter region of the gene contains a CpG island that is ~900 bp long and includes exon 1 and the 5'-end of the intron 1. This region contains a binding site for the transcription factor Sp1 and several potential binding for other factors such as interleukins, interferon and hormones. A critical region in the CD38 gene is the retinoic acid responsive element (RARE)

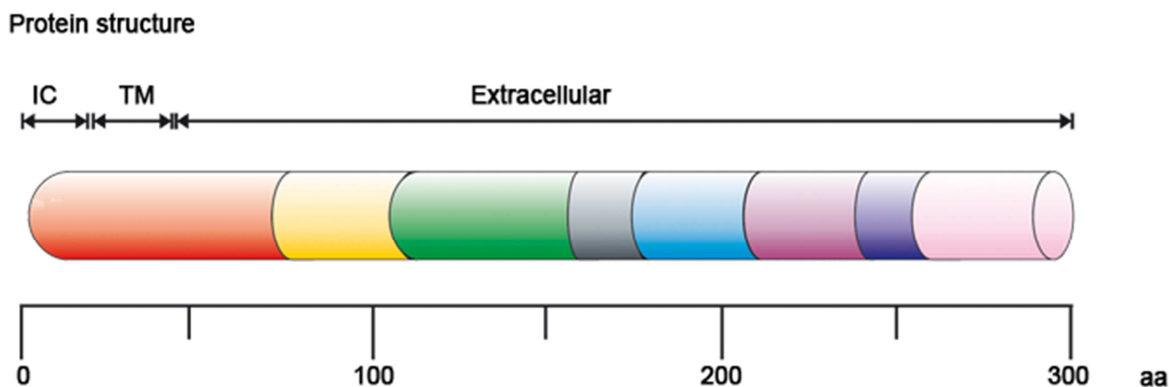
responsible for the upregulation of CD38 expression induced by all-trans retinoic acid (Nata et al., 1997; Ferrero and Malavasi, 1999). The 5'-end of the intron 1 contains also a C → G single nucleotide polymorphism (SNP), rs6449182, that leads to the presence or absence of a PvuII restriction site (see below). The SNP is located within a putative E-box, a region of binding of the E proteins with a consequent regulation of gene transcription. In the B cell compartment a relevant role is played by E2A, that controls the expression of several B lineage genes. E2A was demonstrated to bind to the E-box of the CD38 gene, regulating its expression, and the binding of the protein is influenced by the CD38 genotype, with the G allele resulting in a stronger binding of E2A (Saborit-Villarroya et al., 2011).

##### Transcription

The mRNA of CD38 (NM\_001775.2) contains 1494 bp.



**Gene structure of CD38.** Colored boxes represent the 8 exons; the total length, the starting and ending base pair of the gene are indicated.



**CD38 protein structure.** CD38 is a transmembrane molecule of 300 aa. The intracellular (IC), the transmembrane (TM) and the extracellular domains are indicated in the diagram. The different portions of the aminoacidic chain are shown as coded by the different exons.

## Protein

### Description

Human CD38 is made up of a single chain of 300 aa with a corresponding molecular weight of approximately 45 kDa. It is characterized by a short cytoplasmic tail (21 aa), a small transmembrane domain (23 aa) and a large extracellular domain (256 aa). CD38 is a glycoprotein comprising 2 to 4 N-linked oligosaccharide chains containing sialic acid residues. The overall structure of the CD38 molecule is stabilized by six pairs of disulphide bonds.

Besides the monomeric membrane-bound form of CD38, a soluble form of CD38 of approximately 78 kDa (p78) (Mallone et al., 1998) and a high-molecular weight form of 190 kDa (p190) (Umar et al., 1996), have been described. The latter fits with a tetrameric conformation of the molecule, both displaying enzymatic activities.

The carboxyl-terminal of the molecule harbors the catalytic site (CD38 is defined as an ecto-enzyme) and the binding site for CD31, the non-substrate CD38 ligand (Deaglio et al., 1998).

The overall structure of the CD38 molecule, obtained by crystallographic analyses, is "L"-shaped and can be divided into two separate domains. The N-terminal domain, formed by a bundle of  $\alpha$  helices ( $\alpha 1$ ,  $\alpha 2$ ,  $\alpha 3$ ,  $\alpha 5$ ,  $\alpha 6$ ) and two short  $\beta$  strands ( $\beta 1$ ,  $\beta 3$ ), and the C-terminal domain, formed by four-stranded parallel  $\beta$  sheet ( $\beta 2$ ,  $\beta 4$ ,  $\beta 5$ , and  $\beta 6$ ) surrounded by two long ( $\alpha 8$  and  $\alpha 9$ ) and two short  $\alpha$  helices ( $\alpha 4$  and  $\alpha 7$ ). These two distinct domains are connected by a hinge region composed of three peptide chains. The enzyme's overall topology is similar to the related proteins CD157 and the *Aplysia* ADP-ribosyl cyclase, with the exception of important structural changes at the two termini. The extended positively charged N terminus has lateral associations with the other CD38 molecule in the crystallographic asymmetric unit. The analysis of the CD38 substrate binding models revealed three key residues that may be critical in controlling CD38

enzymatic functions. Indeed, the positions of residues Glu226, Trp125, and Trp189, which are essential for the enzyme's catalytic activity are highly conserved; Trp125 and Trp189 are suggested as the residues for recognizing and positioning the substrate by hydrophobic interactions, while Glu226 is the catalytic residue that takes part in the formation of the catalytic intermediate) (Munshi et al., 2000; Liu et al., 2005).

### Expression

Human CD38 is surface expressed by various cells of both hematopoietic and non-hematopoietic lineages. In the T cell compartment, CD38 is expressed by a significant fraction of human thymocytes, mainly at the double-positive stage. In B cells, the expression is tightly regulated during cell ontogenesis, being present at high levels in bone marrow precursors and in terminally differentiated plasma cells. CD38 is expressed also in circulating monocytes, but not in resident macrophages, and in circulating and residential NK cells and granulocytes.

CD38 is also present in many tissues other than haematopoietic cells, including normal prostatic epithelial cells, pancreatic islet cells and the brain, where it is detected in perikarya and dendrites of many neurons, such as the cerebellar Purkinje cells, in rat astrocytes and in perivascular autonomic nerve terminals. Other CD38<sup>+</sup> cells include smooth and striated muscle cells, renal tubules, retinal gangliar cells and cornea (Malavasi et al., 2008).

### Localisation

CD38 is a type II transmembrane protein expressed on plasma and nuclear membranes.

### Function

CD38 is a multifunctional ecto-enzyme involved in signal transduction, cell adhesion and calcium signaling. The binding to the ligand CD31, initiates a signaling cascade that includes phosphorylation of sequential intracellular targets and increases cytoplasmic Ca<sup>2+</sup> levels, mediating different biological

events depending on the cells type (e.g., activation, proliferation, apoptosis, cytokines secretion and homing). As an enzyme, CD38 metabolizes  $\text{NAD}^+/\text{NADP}^+$ , generating cADPR, ADP-ribose and NAADP (Lee, 2006). These products bind different receptors and channels ( $\text{IP}_3$  receptors  $\text{IP}_3\text{R}$ , Ryanodine receptor RyR and Transient receptor potential cation channel subfamily M member 2 TRPM2) and are involved in the regulation of intracellular  $\text{Ca}^{2+}$  and activation of critical signaling pathways connected to the control of cell metabolism, genomic stability, apoptosis, cell signaling, inflammatory response and stress tolerance (Guse, 2005).

### Homology

The CD38 gene is conserved in human, chimpanzee, dog, mouse, rat and chicken. Human CD38 shares a 25-30% homology in amino acid sequence to the Aplysia ADP ribosyl cyclase and it is highly homologous to CD157 (BST-1), originated by gene duplication (Ferrero and Malavasi, 1997; Ferrero and Malavasi, 1999).

## Mutations

### Germinal

Not yet reported.

## Implicated in

### Chronic lymphocytic leukemia (CLL)

#### Disease

CLL is the most common adult leukemia in the United States and Europe that results from the accumulation of small B lymphocytes expressing CD19/CD5/CD23 in blood, bone marrow, lymph nodes and other lymphoid tissues (Chiorazzi and Ferrarini, 2003). The latter districts represent permissive niches where lymphocytes can proliferate in response to microenvironmental signals (Malavasi et al., 2011). The incidence rates in men are nearly twice as high as women and it is less common among people of African or Asian origin. Advanced age and a family history of leukemia and lymphoma are additional risk factors (Dores, 2007).

#### Prognosis

CLL is currently categorized into prognostic groups based on the clinical staging systems developed by Rai and Binet (Rai et al., 1975; Binet et al., 1981). The disease is heterogenous from the clinical point of view with at least three group of patients. Approximately one-third of CLL patients are affected by an indolent form of disease that does not require treatment. Another third of patients presents with a leukemia that will require iterative therapies, affecting their quality and length of life. A small fraction of CLL patients will develop Richter syndrome (RS), represented in most cases by diffuse large B-cell lymphoma (DLBCL)

arising from the transformation of the original CLL clone. RS is a highly aggressive syndrome with a median overall survival of 5 to 8 months (Hallek et al., 2008). Several molecular markers have been identified with a prognostic significance to distinguish among the different groups of patients. The most credited molecular indicators are the absence of mutations in the IgVH genes and the expression of CD38 and Zap70 (Cramer and Hallek, 2011).

### Cytogenetics

CLL is associated with chromosomal deletions and amplifications: the most frequent is trisomy of chromosome 12 (+12; 16%) and deletion of chromosomal regions 11q (18%), 17p (7%) and 13q14 (55%). The molecular consequences of trisomy 12 are unknown, but probably related to an elevated gene dosage of a proto-oncogene. Del(11)(q22-q23) comprise ataxia teleangiectasia (ATM) gene, a gene related to genomic instability and DNA-repair and associated with a predisposition to lymphoid malignancies. The inability to repair DNA-damage due to ATM-deficiency contributes to CLL pathogenesis, allowing accumulation of additional genetic mutations during cellular proliferation. A similar pathogenetic mechanism occurs in CLL with del(17p13) that include the TP53 tumor suppressor gene. The del(13q14) mono- or bi-allelic involves two microRNAs, miR-15a and miR16-1, that can be two potential candidate tumor suppressor genes, even though their targets are still unknown (Klein and Dalla-Favera, 2010; Zenz et al., 2010).

### Oncogenesis

In CLL, elevated expression of CD38 is associated with several adverse prognostic factors such as advanced disease stage, higher incidence of lymphadenopathy, high-risk cytogenetics, shorter lymphocytes doubling time (LDT), shorter time to initiation of first treatment (TFT) and poorer response to therapy. Besides being a prognostic marker, CD38 is a key element in the pathogenesis of CLL, as a component of a molecular network delivering growth and survival signals to CLL cells (Deaglio et al., 2005). CD38 performs as a receptor on leukemic cells following the binding to its ligand CD31 and the signals are mediated by Zap70, another negative prognosticator for the disease and a limiting factor for the activation of the CD38-mediated pathway (Deaglio et al., 2003; Deaglio et al., 2007). CD38 can work in association with chemokines and their receptors, mainly CXCL12/CXCR4, influencing the migratory responses and contributing to the recirculation of neoplastic cells from blood to lymphoid organs (Vaisitti et al., 2010) and with specific adhesion molecules, belonging to the integrin family (Zucchetto et al., 2009; Zucchetto et al., 2012). An important role in the oncogenesis of CLL is likely by the CD38 SNP (see above) that has been recently described as an independent risk factor for Richter syndrome (RS) transformation. The frequency of the G allele is

significantly higher in a subset of CLL patients characterized by clinical and molecular markers of poor prognosis, with the highest allele frequency scored by patients with RS (Aydin, 2008). The same G allele was independently reported as a susceptibility factor for CLL development in a Polish population (Jamrozniak et al., 2009). The presence of the rare G allele is not correlated to a higher expression of CD38 by CLL cells, but is responsible for the ability to modulate CD38 expression in response to environmental signals.

## **Multiple myeloma (MM)**

### **Disease**

Multiple myeloma is a malignancy of the immune system characterized by accumulation of plasma cells in the bone marrow (BM), by a high concentration of monoclonal Ig in serum or urine and lytic bone lesions arising from osteolytic activity of plasma cell-activated osteoclasts. The proliferation of plasma cells in MM may interfere with the normal production of blood cells, resulting in leukopenia, anemia and thrombocytopenia. The aberrant antibodies that are produced lead to impaired humoral immunity and patients have a high prevalence of infection. It is diagnosed with blood tests, microscopic examination of the bone marrow (bone marrow biopsy) and radiographs of commonly involved bones.

### **Prognosis**

MM is characterized by neoplastic proliferation of plasma cells involving more than 10% of the BM. Increasing evidence suggests that the BM microenvironment of tumor cells plays a pivotal role in the pathogenesis of myeloma. MM is a heterogeneous disease, with survival ranging from 1 year to more than 10 years. The 5-year relative survival rate is around 40%. Survival is higher in younger people. The tumor burden (based on C-reactive protein CRP and beta-2-microglobulin  $\beta_2m$ ) and the proliferation rate are the two key indicators for the prognosis in patients with MM (Palumbo and Anderson, 2011).

### **Cytogenetics**

MM is characterized by very complex cytogenetic and molecular genetic aberrations. The chromosome number is usually either hyperdiploid with multiple trisomies or hypodiploid with one of several types of immunoglobulin heavy chain (Ig) translocations. The chromosome status and Ig rearrangements are two genetic criteria to stratify patients into a specific prognostic group. The malignant cells of MM are the most mature cells of the B lineage. B cell maturation is associated with a programmed rearrangement of DNA sequence in the process encoding the structure of mature immunoglobulins. Indeed, MM is characterized by over-production of monoclonal immunoglobulin G (IgG), IgA and/or light chains. Rearrangements involving the switch regions of immunoglobulin heavy chain (IgH) gene at the 14q32 with various partner genes (t(4;14), t(14;16), t(11;14)) represent the most

common structural abnormalities in MM. Several chromosomal aberrations are acquired during disease progression, involving MYC rearrangements, chromosome 13 (del(13q)), 17 (del(17p)) and 1p deletions. These chromosomal abnormalities are associated to specific oncogenes, such as c-myc that develop early in the course of plasma cell tumors, while changes in other oncogenes such as N-ras and K-ras are more often found in MM after BM relapse. Abnormalities are also described for tumor suppressor genes such as TP53, associated with spread to other organs. (Sawyer, 2011).

### **Oncogenesis**

CD38 is predominantly expressed by BM precursor cells and terminally differentiated plasma cells. MM cells show moderate to high expression levels of CD38. The need for improved MM therapy has stimulated the development of monoclonal antibodies (mAbs) targeting either MM cells or cells of the BM microenvironment. CD38 is one of the candidates: recently, a human anti-CD38 (HuMax-CD38 or Daratumumab) antibody was generated and preclinical studies indicated that it is highly effective in killing primary CD38<sup>+</sup>CD138<sup>+</sup> patients MM cells and a range of MM/lymphoid cell lines by both Antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Moreover, in a SCID mouse animal model, this antibody inhibited CD38<sup>+</sup> tumor cell growth (Stevenson et al., 2006; de Weers et al., 2011; Tai and Anderson, 2011). Another fully human anti-CD38 mAb (MorphoSysAG) was reported to efficiently trigger ADCC against CD38<sup>+</sup> MM cell lines and patients MM cells in vitro as well as in vivo in a xenograft mouse model (Stevenson et al., 2006).

## **Acute myeloid leukemia (AML)**

### **Disease**

Acute myelogenous leukemia (AML) is a cancer of the myeloid lineage, characterized by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells (maturational arrest of bone marrow cells in the earliest stages of development due to the activation of abnormal genes through chromosomal translocations and other genetic abnormalities).

### **Prognosis**

AML has several subtypes: 5-year survival rates vary from 15% to 70% and relapse rates vary from 33 to 78% depending on subtype. The French-American-British (FAB) classification system divides AML into 8 subtypes, M0 through M7, based on the type of cell from which the leukemia developed and its degree of maturation (morphology of the neoplastic cells and cytogenetic analysis to characterize chromosomal abnormalities). The M3 subtype, also known as acute promyelocytic leukemia (APL), is caused by an arrest of leukocyte differentiation at the promyelocyte stage.

Various clinical regimens combining anthracyclines, retinoic acid (RA), that induces APL differentiation, and arsenic trioxide, that triggers apoptosis and differentiation, results in a remission of 80-90% of patients (de Thé and Chen, 2010; Kamimura et al., 2011).

### Cytogenetics

Cytogenetics is the single most important prognostic factor in AML. About 50% of AML patients have a normal cytogenetics; certain cytogenetic abnormalities are associated with good outcomes (t(15;17) in acute promyelocytic leukemia), while other cytogenetic abnormalities are associated with a poor prognosis and a high risk of relapse after treatment. APL is characterized by a reciprocal translocation, t(15;17), that results in a fusion oncogene, PML (promyelocytic leukemia)-RAR $\alpha$  (retinoic acid receptor  $\alpha$ ) with a consequent block of the normal myeloid differentiation program and increased self-renewal of leukemic progenitors cells.

### Oncogenesis

Retinoic acid (RA), the vitamin A derivative plays a critical role during the differentiation of myeloid progenitors towards the neutrophil lineage. This role is primarily mediated by binding of RA to RAR $\alpha$  (RAR $\alpha$ , a nuclear receptor that modulates the expression of multiple downstream targets via retinoic acid response elements. Biochemical evidence suggests RAR $\alpha$  performs two opposing functions, one as a repressor of gene expression in the absence of ligand, the second as a transcriptional activator in the presence of ligand, each controlled by multimeric complexes of transcription corepressors and coactivators. The fusion gene product PML-RAR $\alpha$  causes the chimeric receptor to bind more tightly to the nuclear corepressor factor. Therefore, the gene cannot be activated with physiologic doses of retinoic acid. RA induces the differentiation of leukemic cells into mature granulocytes and complete remissions in a majority of patients with APL. Although well tolerated, this therapeutic regimen may be associated with a toxic side effect known as retinoic acid syndrome (RAS), characterized by fever, dyspnea, pulmonary edema and infiltrates. The increased production of inflammatory cytokines (IFN- $\gamma$  and IL-1 $\beta$ ) by myeloid cells and an aberrant interaction between maturing granulocytes and host tissues contribute to RAS pathogenesis. Normal granulocytes do not express CD38, while RA-treated APL/AML cells express high amounts of this molecule (Drach et al., 1994; Mehta and Cheema, 1999). The aberrant expression of CD38 on leukemic cells enhances their propensity to interact with CD31, expressed by lung endothelial cells, resulting in a local production of inflammatory cytokines, apoptosis of endothelial cells and development of RAS (Gao et al., 2007).

## To be noted

### Note

The human CD38 gene contains a well defined bi-allelic polymorphism that can be identified by the restriction endonuclease PvuII (PvuII site: CAGCTG). The polymorphic site is located at the 5' end of the first intron of the CD38 gene and marks a C $\rightarrow$ G variation at position 184. The gene frequencies in the healthy population are 0,78 and 0,22 for the C and G allele respectively (CC 61%, GC 33% and GG 6%). The analysis of this polymorphism in a large cohort of CLL patients indicate that the G allele is significantly associated with molecular markers of unfavourable prognosis and represents a significant risk factor for RS transformation (Aydin et al., 2008). The correlation between this polymorphism and genetic susceptibility has been studied also for other diseases, including Systemic Lupus Erythematosus (SLE), where the CC genotype causes susceptibility and the CG genotype confers protection for discoid rash development (Gonzales-Escribano et al., 2004). Recently, a role for CD38 in mediating oxytocin (OT) release in the brain has been described (Jin et al., 2007). Mice deficient in CD38 lack short term social memory, a defect that has been associated to the autism spectrum disorders (ASD) in humans. Several polymorphism across CD38 gene (rs6449197, rs3796863 and rs1800561) are associated with ASD (Lerer et al., 2010; Muniesue et al., 2010) and a correlation between CD38 expression and measure of social function in ASD observed (Riebold et al., 2011). Indeed, a reduced expression of CD38 in lymphoblast from ASD patients compared to parental lymphoblastoid cell lines has been reported. Lower CD38 expression and consequently lower level of activation of its enzymatic functions in ASD can be linked to a dysfunction in OT transmission in this disorder (Higashida et al., 2007; Salmina et al., 2010; Higashida et al., 2010).

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