

Cluster of Differentiation (CD)

Ma Hongbao ¹, Margaret Young ², Yang Yan ¹

¹ Brookdale Hospital, Brooklyn, New York 11212, USA; ² Cambridge, MA 02138, USA
ma8080@gmail.com

Abstract: The cluster of differentiation (or cluster of designation or classification determinant, abbreviated as CD) is a group of cell surface molecules providing targets for immunophenotyping of cells. CD can act as receptors or ligands to play the functions as cell signaling and cell adhesion etc. Human CD number is up to 364. In the animal the CD system is normally play a role as cell marker in immune purpose to recognize the molecules in the cells' surface. Several markers combine is a normal condition in the immune reaction.

[Ma H, Young M, Yang Y. **Cluster of Differentiation (CD)**. *N Y Sci J* 2015;8(7):49-53]. (ISSN: 1554-0200).
<http://www.sciencepub.net/newyork>. 8

Key words: cluster of differentiation (CD); life; cell

1. Introduction

The cluster of differentiation (CD) is a group of cell surface molecules providing targets for immunophenotyping of cells. CD can act as receptors or ligands to play the functions as cell signaling and cell adhesion etc. There are 364 Human CDs discovered up to now. In the animal the CD system normally plays a role as a cell marker in immune purpose to recognize the molecules in the cells' surface. Several markers combine is a normal condition in the immune reaction.

CD3 is initially expressed in the cytoplasm of pro-thymocytes, the stem cells from which T-cells arise in the thymus. The pro-thymocytes differentiate into common thymocytes, and then into medullary thymocytes, and it is at this latter stage that CD3 antigen begins to migrate to the cell membrane. The antigen is found bound to the membranes of all mature T-cells, and in virtually no other cell type, although it does appear to be present in small amounts in Purkinje cells. This high specificity, combined with the presence of CD3 at all stages of T-cell development, makes it a useful immunohistochemical marker for T-cells in tissue sections. The antigen remains present in almost all T-cell lymphomas and leukaemias, and can therefore be used to distinguish them from superficially similar B-cell and myeloid neoplasms.

CD4 is a glycoprotein on the surface of immune cells such as T helper cells, monocytes, macrophages, and dendritic cells. CD4⁺ T helper cells are white blood cells as an essential part of the human immune system, which are often referred to as CD4 cells, T-helper cells or T4 cells. They are called helper cells because one of their main roles is to send signals to other types of immune cells, including CD8 killer cells, which then destroy the infectious particle. If CD4 cells become depleted, for example in untreated HIV infection, or following immune suppression prior to a transplant, the body is left vulnerable to a wide

range of infections that it would otherwise have been able to fight. CD4 is a co-receptor assisting T cell receptor (TCR) in communicating with an antigen-presenting cell. HIV-1 uses CD4 to entry into host T-cells and achieves this through its viral envelope protein gp120. The binding to CD4 creates a shift in the conformation of gp120 allowing HIV-1 to bind to a co-receptor expressed on the host cell. These co-receptors are chemokine receptors CCR5 or CXCR4. Following a structural change in another viral protein (gp41), HIV inserts a fusion peptide into the host cell that allows the outer membrane of the virus to fuse with the cell membrane. HIV infection leads to a progressive reduction in the number of T cells expressing CD4. Medical professionals refer to the CD4 count to decide when to begin treatment during HIV infection. A CD4 count measures the number of T cells expressing CD4. While CD4 counts are not a direct HIV test--e.g. they do not check the presence of viral DNA, or specific antibodies against HIV--they are used to assess the immune system of a patient. Patients often undergo treatments when the CD4 counts reach a level of 350 cells per microliter in Europe but usually around 500cpm in the US; people with less than 200 cells per microliter are at high risk of contracting AIDS defined illnesses. National Institute of Health guidelines recommend treatment of any HIV-positive individuals, regardless of CD4 count medical professionals also refer to CD4 tests to determine efficacy of treatment.

CD4 and CD8 play roles in antigen recognition. CD4 and CD8 are normally used as markers for helper and cytotoxic T cells. Human immunodeficiency virus (HIV) binds CD4 on the surface of a T helper cell to enter the cell. The level of CD4 and CD8 T cells in blood is used to monitor the HIV infection condition.

CD14 exists in two forms, one is in the membrane by a glycosylphosphatidylinositol tail (mCD14), and the other is a soluble form (sCD14).

CD14 acts as a co-receptor (along with the Toll-like receptor TLR 4 and MD-2) for the detection of bacterial lipopolysaccharide (LPS). CD14 can bind LPS only in the presence of lipopolysaccharide-binding protein (LBP). Although LPS is considered its main ligand, CD14 also recognizes other pathogen-associated molecular patterns such as lipoteichoic acid. CD14 is expressed mainly by macrophages and neutrophils. It is also expressed by dendritic cells. The soluble form of the receptor (sCD14) is secreted by the liver and monocytes and is sufficient in low concentrations to confer LPS-responsiveness to cells not expressing CD14. mCD14 and sCD14 are also present on enterocytes. sCD14 is also present in human milk, where it is believed to regulate microbial growth in the infant gut. CD14⁺ monocytes can differentiate into a host of different cells, including dendritic cells, a differentiation pathway encouraged by cytokines, including GM-CSF and IL-4. CD14 has been shown to interact with lipopolysaccharide-binding protein.

CD15 mediates phagocytosis and chemotaxis, found on neutrophils; expressed in patients with Hodgkin disease, some B-cell chronic lymphocytic leukemias, acute lymphoblastic leukemias, and most acute nonlymphocytic leukemias. It is also called Lewis x and SSEA-1 (stage-specific embryonic antigen 1) and represents a marker for murine pluripotent stem cells, in which it plays an important role in adhesion and migration of the cells in the preimplantation embryo. It is synthesized by FUT4 (fucosyltransferase 4) and FUT9.

CD16 has been identified as Fc receptors FcγRIIIa (CD16a) and FcγRIIIb (CD16b). These receptors bind to the Fc portion of IgG antibodies which then activates the NK cell for antibody-dependent cell-mediated cytotoxicity. A lack of CD16 in a given population of neutrophils may indicate prematurity, as could be caused by a left-shift due to neutrophilic leukocytosis induced by tissue necrosis or bacterial infection.

The CD19 gene encodes a cell surface molecule that assembles with the antigen receptor of B lymphocytes in order to decrease the threshold for antigen receptor-dependent stimulation. CD19 is expressed on follicular dendritic cells and B cells. In fact, it is present on B cells from earliest recognizable B-lineage cells during development to B-cell blasts but is lost on maturation to plasma cells. It primarily acts as a B cell co-receptor in conjunction with CD21 and CD81. Upon activation, the cytoplasmic tail of CD19 becomes phosphorylated, which leads to binding by Src-family kinases and recruitment of PI-3 kinase. As on T cells, several surface molecules form the antigen receptor and form a complex on B lymphocytes. The (almost) B cell-specific CD19

phosphoglycoprotein is one of these molecules. The others are CD21 and CD81. These surface immunoglobulin (sIg)-associated molecules facilitate signal transduction. On living B cells, anti-immunoglobulin antibody mimicking exogenous antigen causes CD19 to bind to sIg and internalize with it. The reverse process has not been demonstrated, suggesting that formation of this receptor complex is antigen-induced. This molecular association has been confirmed by chemical studies.

CD20 is an activated-glycosylated phosphoprotein expressed on the surface of all B-cells beginning at the pro-B phase (CD45R⁺, CD117⁺) and progressively increasing in concentration until maturity. In humans CD20 is encoded by the MS4A1 gene. This gene encodes a member of the membrane-spanning 4A gene family. Members of this nascent protein family are characterized by common structural features and similar intron/exon splice boundaries and display unique expression patterns among hematopoietic cells and nonlymphoid tissues. This gene encodes a B-lymphocyte surface molecule that plays a role in the development and differentiation of B-cells into plasma cells. This family member is localized to 11q12, among a cluster of family members. Alternative splicing of this gene results in two transcript variants that encode the same protein. The protein has no known natural ligand and its function is to enable optimal B-cell immune response, specifically against T-independent antigens. It is suspected that it acts as a calcium channel in the cell membrane.

CD22 is a sugar binding transmembrane protein, which specifically binds sialic acid with an immunoglobulin (Ig) domain located at its N-terminus. The presence of Ig domains makes CD22 a member of the immunoglobulin superfamily. CD22 functions as an inhibitory receptor for B cell receptor (BCR) signaling. It is also involved in the B cell trafficking to Peyer's patches in mice. An immunotoxin, BL22, that targets this receptor is being tested at the NIH.

CD24 is a glycoprotein expressed at the surface of most B lymphocytes and differentiating neuroblasts. This gene encodes a sialoglycoprotein that is expressed on mature granulocytes and in many B cells. The encoded protein is anchored via a glycosyl phosphatidylinositol (GPI) link to the cell surface. CD24 gene is found on chromosome 6 (6q21). An alignment of this gene's sequence finds genomic locations with similarity on chromosomes 1p36, 3p26, 15q21.3, 20q11.2 and Yq11.222. Whether transcription, and corresponding translation, occurs at each of these other genomic locations needs to be experimentally determined.

CD25 is the alpha chain of the IL-2 receptor. It is a type I transmembrane protein present on activated

T cells, activated B cells, some thymocytes, myeloid precursors, and oligodendrocytes that associates with CD122 to form a heterodimer that can act as a high-affinity receptor for IL-2. Though CD25 has been used as a marker to identify CD4+FoxP3+ regulatory T cells in mice, it has been found that a large proportion of resting memory T cells constitutively express CD25 in humans. CD25 is expressed in most B-cell neoplasms, some acute nonlymphocytic leukemias, neuroblastomas, and tumor infiltrating lymphocytes. Its soluble form, called sIL-2R may be elevated in these diseases and is occasionally used to track disease progression.

CD30, also known as TNFRSF8, is a cell membrane protein of the tumor necrosis factor receptor family and tumor marker. This receptor is expressed by activated, but not by resting, T and B cells. TRAF2 and TRAF5 can interact with this receptor, and mediate the signal transduction that leads to the activation of NF-kappaB. It is a positive regulator of apoptosis, and also has been shown to limit the proliferative potential of autoreactive CD8 effector T cells and protect the body against autoimmunity. Two alternatively spliced transcript variants of this gene encoding distinct isoforms have been reported.

Platelet endothelial cell adhesion molecule (PECAM-1) also known as cluster of differentiation 31 (CD31) is a protein that in humans is encoded by the PECAM1 gene found on chromosome 17. PECAM-1 plays a key role in removing aged neutrophils from the body. PECAM-1 is found on the surface of platelets, monocytes, neutrophils, and some types of T-cells, and makes up a large portion of endothelial cell intercellular junctions. The encoded protein is a member of the immunoglobulin superfamily and is likely involved in leukocyte transmigration, angiogenesis, and integrin activation.

Hematopoietic progenitor cell antigen CD34 is a cluster of differentiation in the cell surface glycoprotein and functions as a cell-cell adhesion factor. It mediates the attachment of stem cells to bone marrow extracellular matrix or directly to stromal cells. CD34 is an important adhesion molecule and is required for T cells to enter lymph nodes. It is expressed on lymph node endothelia. CD34 plays a selective role in chemokine-dependent migration of eosinophils and dendritic cell precursors. The CD34 (CD34+ cell) are normally expressed in the umbilical cord and bone marrow of cells such as hematopoietic cells, mesenchymal stem cells, endothelial progenitor cells, endothelial cells of blood vessels, mast cells, a sub-population dendritic cells in the interstitium and around the adnexa of dermis of skin, soft tissue tumors, etc. The presence of CD34 on non-hematopoietic cells in various tissues has been linked to progenitor and

adult stem cell phenotypes. CD34+ cells can be isolated from blood samples using immunomagnetic or immunofluorescent methods. To quantify and purify hematopoietic progenitor stem cells the antibodies can be used. Injection of CD34+ hematopoietic stem cells has been clinically applied to treat various diseases including spinal cord injury, liver cirrhosis and peripheral vascular disease, etc. CD34 interacts with L-selectin to play a role in inflammation.

CD38 (cluster of differentiation 38), also known as cyclic ADP ribose hydrolase is a glycoprotein found on the surface of many immune cells (white blood cells), including CD4+, CD8+, B lymphocytes and natural killer cells. CD38 also functions in cell adhesion, signal transduction and calcium signaling. In humans, the CD38 protein is encoded by the CD38 gene which located on chromosome 4. CD38 is a multifunctional ectoenzyme that catalyzes the synthesis and hydrolysis of cyclic ADP-ribose (cADPR) from NAD+ to ADP-ribose. These reaction products are essential for the regulation of intracellular Ca²⁺.

Protein tyrosine phosphatase, receptor type, C also known as PTPRC is an enzyme that, in humans, is encoded by the PTPRC gene. PTPRC is also known as CD45 antigen (CD stands for cluster of differentiation), which was originally called leukocyte common antigen (LCA). The protein encoded by this gene is a member of the protein tyrosine phosphatase (PTP) family. PTPs are known to be signaling molecules that regulate a variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation. This PTP contains an extracellular domain, a single transmembrane segment and two tandem intracytoplasmic catalytic domains, and thus belongs to receptor type PTP. This gene is specifically expressed in hematopoietic cells. This PTP has been shown to be an essential regulator of T- and B-cell antigen receptor signaling. It functions through either direct interaction with components of the antigen receptor complexes or by activating various Src family kinases required for the antigen receptor signaling. This PTP also suppresses JAK kinases, and, thus, functions as a negative regulator of cytokine receptor signaling. Four alternatively spliced transcripts variants of this gene, which encode distinct isoforms, have been reported. It is a type I transmembrane protein that is in various forms present on all differentiated hematopoietic cells, except erythrocytes and plasma cells, that assists in the activation of those cells (a form of co-stimulation). It is expressed in lymphomas, B-cell chronic lymphocytic leukemia, hairy cell leukemia, and acute nonlymphocytic leukemia. A monoclonal antibody to CD45 is used in routine immunohistochemistry to

differentiate between histological sections from lymphomas and carcinomas.

Neural cell adhesion molecule (NCAM), also called CD56, is a homophilic binding glycoprotein expressed on the surface of neurons, glia, skeletal muscle and natural killer cells. NCAM has been implicated as having a role in cell-cell adhesion, neurite outgrowth, synaptic plasticity, and learning and memory. NCAM is a glycoprotein of Immunoglobulin (Ig) superfamily. At least 27 alternatively spliced NCAM mRNAs are produced, giving a wide diversity of NCAM isoforms. The extracellular domain of NCAM consists of five immunoglobulin-like (Ig) domains followed by two fibronectin type III (FNIII) domains. The different domains of NCAM have been shown to have different roles, with the Ig domains being involved in homophilic binding to NCAM, and the FNIII domains being involved signaling leading to neurite outgrowth. Homophilic binding occurs between NCAM molecules on opposing surfaces (trans-) and NCAM molecules on the same surface (cis-)¹. There is much controversy as to how exactly NCAM homophilic binding is arranged both in trans- and cis-. Current models suggest trans- homophilic binding occurs between two NCAM molecules binding antiparallel between all five Ig domains or just IgI and IgII. cis-homophilic binding is thought to occur by interactions between both IgI and IgII, and IgI and IgIII, forming a higher order NCAM multimer. Both cis- and trans-NCAM homophilic binding have been shown to be important in NCAM "activation" leading to neurite outgrowth.

CD114 is a protein that in humans is encoded by the CSF3R gene. G-CSF-R is a cell-surface receptor for the granulocyte colony-stimulating factor (G-CSF). The G-CSF receptors belongs to a family of cytokine receptors known as the hematopoietin receptor family. The granulocyte colony-stimulating factor receptor is present on precursor cells in the bone marrow, and, in response to stimulation by G-CSF, initiates cell proliferation and differentiation into mature neutrophilic granulocytes and macrophages. The G-CSF-R is a transmembrane receptor that consists of an extracellular ligand-binding portion, a transmembrane domain, and the cytoplasmic portion that is responsible for signal transduction. GCSF-R ligand-binding is associated with dimerization of the receptor and signal transduction through proteins including Jak, Lyn, STAT, and Erk1/2.

CD117 is a cytokine receptor expressed on the surface of hematopoietic stem cells as well as other cell types. Altered forms of this receptor may be associated with some types of cancer. CD117 is a receptor tyrosine kinase type III, which binds to stem cell factor (a substance that causes certain types of

cells to grow), also known as "steel factor" or "c-kit ligand". When this receptor binds to stem cell factor (SCF) it forms a dimer that activates its intrinsic tyrosine kinase activity, that in turn phosphorylates and activates signal transduction molecules that propagate the signal in the cell. Signalling through CD117 plays a role in cell survival, proliferation, and differentiation. Hematopoietic progenitor cells are normally present in the blood at low levels. Mobilization is the process by which progenitors are made to migrate from the bone marrow into the bloodstream, thus increasing their numbers in the blood. Mobilization is used clinically as a source of hematopoietic stem cells for hematopoietic stem cell transplantation (HSCT). Signaling through CD117 has been implicated in mobilization. At the current time, G-CSF is the main drug used for mobilization. G-CSF indirectly activates CD117. Plerixafor (an antagonist of CXCR4-SDF1) in combination with G-CSF, is also being used for mobilization of hematopoietic progenitor cells. Direct CD117 agonists are currently being developed as mobilization agents. Activating mutations in this gene are associated with gastrointestinal stromal tumors, testicular seminoma, mast cell disease, melanoma, acute myeloid leukemia, while inactivating mutations are associated with the genetic defect piebaldism. CD117 is a proto-oncogene, meaning that overexpression or mutations of this protein can lead to cancer. Seminomas, a subtype of testicular germ cell tumors, frequently have activating mutations in exon 17 of CD117. In addition, the gene encoding CD117 is frequently overexpressed and amplified in this tumor type, most commonly occurring as a single gene amplicon. Mutations of CD117 have also been implicated in leukemia, a cancer of hematopoietic progenitors, melanoma, mast cell disease, and gastrointestinal stromal tumors (GISTs). The efficacy of imatinib (trade name Gleevec), a CD117 inhibitor, is determined by the mutation status of CD117. When the mutation has occurred in exon 11 (as is the case many times in GISTs), the tumors are responsive to imatinib. However, if the mutation occurs in exon 17 (as is often the case in seminomas and leukemia), the receptor is not inhibited by imatinib. In those cases other inhibitors such as dasatinib and nilotinib can be used. Antibodies to CD117 are widely used in immunohistochemistry to help distinguish particular types of tumour in histological tissue sections. It is used primarily in the diagnosis of GISTs, which are positive for CD117, but negative for markers such as desmin and S-100, which are positive in smooth muscle and neural tumors, which have a similar appearance. In GISTs, CD117 staining is typically cytoplasmic, with stronger accentuation along the cell membranes. CD117 antibodies can also be used in the

diagnosis of mast cell tumours and in distinguishing seminomas from embryonal carcinomas.

CD135 play roles as cell surface receptor for growth factors. CD13 is a marker for kidney disorder as the aminopeptidase N plays. Aminopeptidase N is located in the small-intestinal and renal microvillar membrane, and also in other plasma membranes. In the small intestine aminopeptidase N plays a role in the final digestion of peptides generated from hydrolysis of proteins by gastric and pancreatic proteases. The large extracellular carboxyterminal domain contains a pentapeptide consensus sequence characteristic of members of the zinc-binding metalloproteinase superfamily. Sequence comparisons with known enzymes of this class showed that CD13 and aminopeptidase N are identical. The latter enzyme was thought to be involved in the metabolism of regulatory peptides by diverse cell types, including small intestinal and renal tubular epithelial cells, macrophages, granulocytes, and synaptic membranes from the CNS. Human aminopeptidase N is a receptor for one strain of human coronavirus that is an important cause of upper respiratory tract infections. Defects in this gene appear to be a cause of various types of leukemia or lymphoma (Entrez Gene, 2015).

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

References

1. Entrez Gene: ANPEP alanyl (membrane) aminopeptidase (aminopeptidase N, aminopeptidase M, microsomal aminopeptidase, CD13, p150). <http://www.ncbi.nlm.nih.gov/gene?Db=gene&Cd=ShowDetailView&TermToSearch=290>. 2015.
2. <https://en.wikipedia.org/wiki/CD13>. 2015
3. [https://en.wikipedia.org/wiki/CD3_\(immunology\)](https://en.wikipedia.org/wiki/CD3_(immunology)). 2015
4. <https://en.wikipedia.org/wiki/CD34>. 2015
5. https://en.wikipedia.org/wiki/Cluster_of_differentiation. 2015
6. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92.
7. Ma H, Cheng S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96.
8. Ma H, Cheng S. Nature of Life. Life Science Journal 2005;2(1):7 - 15.
9. Ma H, Yang Y. Turritopsis nutricula. Nature and Science 2010;8(2):15-20. http://www.sciencepub.net/nature/ns0802/03_127_9_hongbao_turritopsis_ns0802_15_20.pdf.
10. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11. Nature and science 2007;5(1):81-96.
11. National Center for Biotechnology Information, U.S. National Library of Medicine. <http://www.ncbi.nlm.nih.gov/pubmed>. 2015.
12. Wikipedia. The free encyclopedia. <http://en.wikipedia.org>. 2015.

7/15/2015