Gene Section

Review

CLEC1B (C-Type Lectin Domain Family 1, Member B)

Katsue Suzuki-Inoue

Department of Clinical and Laboratory Medicine, Faculty of Medicine, University of Yamanashi, 1110 Shimokato, 409-3898 Chuo, Yamanashi, Japan (KSI)

Published in Atlas Database: November 2013


DOI: 10.4267/2042/53964

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2014 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Abstract

Review on CLEC1B, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: 1810061I13Rik, CLEC2, CLEC2B, PRO1384, QDED721
HGNC (Hugo): CLEC1B
Location: 12p13.2

DNA/RNA

Description
The gene is 982 bp in length and contains six exons.

Transcription
In human, mouse, rabbit, rat, and bovine species, transcription produces 2-4 different mRNAs, including alternatively spliced variants and 1 unspliced form.

Pseudogene
No known pseudogenes.

Protein

Description
CLEC-2 is a 32-kDa (229 amino acids) type II trans-membrane receptor that belongs to C-type lectin superfamily. CLEC-2 has 1 C-type lectin-like domain (CTLD) and belongs to the non-classical C-type lectins, which contain a CTLD homologous to a carbohydrate recognition domain but lack the consensus sequence for binding sugars and calcium (Colonna et al., 2000). CLEC-2 has a YxxL motif in its cytoplasmic tail, which is crucial for CLEC-2-mediated signal transduction. This sequence is called hemi-ITAM, since it resembles the immunoreceptor tyrosine-based activation motif (ITAM, YxxL-(X)10-12-YxxL), which includes 2 YxxL motifs. CLEC-2 was first identified through a bioinformatic screen for C-type lectin-like molecules with immune functions. The gene encoding human CLEC-2 is located in the natural killer complex on chromosome 12 along with other C-type lectin-like receptors, including NKG2D, LOX-1, and Dectin-1 (Sobanov et al., 2001).

Expression

Organ: Highly expressed in bone marrow and slightly expressed in liver.
Cell types: CLEC-2 protein is expressed at high levels in platelets/megakaryocytes and at low levels in sinusoidal endothelial cells (Chaipan et al., 2006) and Kupffer cells (Tang et al., 2010) in humans. In mice, CLEC-2 protein is highly expressed in platelets/megakaryocytes, and is slightly expressed in other blood cells, including neutrophils, monocytes, dendritic cells, NK cells, B cells (Chang et al., 2010; Mourao-Sa et al., 2011), and Kupffer cells (Tang et al., 2010).

Localisation
Plasma membrane.
**Function**

**Separation of blood and lymphatic vessels during development**

Podoplanin is also expressed on the surface of lymphatic endothelial cells, but not vascular endothelial cells. During organ development, a cluster of endothelial cells in the cardinal vein is committed to the lymphatic phenotype, and sprouts to form the primary lymphatic sacs from which a portion of the peripheral lymphatic vasculature is generated by further centrifugal growth (Tammela and Alitalo, 2010).

At this stage, platelets are activated by an association between CLEC-2 in the platelets and podoplanin in the lymphatic endothelial cells, which inhibits the growth and migration of lymphatic endothelial cells and facilitates the separation of blood and lymphatic vessels. CLEC-2-deficient mice show blood-filled lymphatic vessels and severe edema due to lymphatic dysfunction (Bertozzi et al., 2010; Suzuki-Inoue et al., 2010; Finney et al., 2011).

One controversial theory proposes that granule contents released from activated platelets inhibit the function of lymphatic endothelial cells (Osada et al., 2012).

**Thrombus formation**

Thrombus formation under flow conditions has been reported to be impaired in CLEC-2-deficient blood. In vivo thrombus formation is also inhibited in antibody-induced CLEC-2-deficient mice (May et al., 2009) or bone marrow chimeric mice deficient in CLEC-2 (Suzuki-Inoue et al., 2010). These findings suggest that CLEC-2 is involved in the stabilization of thrombus formation under flow conditions, although the precise mechanism by which this occurs has not yet been elucidated. Combined in vivo depletion of CLEC-2 and glycoprotein VI (GPVI), a collagen receptor in platelets, severely compromises haemostasis and abrogates arterial thrombosis in mice (Bender et al., 2013). CLEC-2 and GPVI, both of which generate activation signals depending on ITAMs and tyrosine kinases, play a complementary role in thrombosis and haemostasis.

**Maintenance of vascular integrity**

CLEC-2 is involved in maintaining vascular integrity in inflammation (Boulaftali et al., 2013) and high endothelial venules (HEVs) in lymph nodes upon lymphocyte transmigration (Herzog et al., 2013). Podoplanin is expressed on fibroblastic reticular cells, which surround HEVs. Upon lymphocyte transmigration, platelets extravasate to the perivenular space of HEVs and interact with podoplanin.

Local release of sphingosine-1-phosphate after CLEC-2-podoplanin-mediated platelet activation is critical for HEV integrity during immune responses.

**Antigen presentation**

CLEC-2 is also expressed in dendritic cells (DCs) in mice. Associations between CLEC-2 in DCs and podoplanin in lymphatic endothelial and fibroblastic reticular cells in the lymph nodes facilitates DC entry into the lymphatics as well as movement to and within the lymph nodes, thereby reducing T cell priming.

CLEC-2 engagement of podoplanin was found to be necessary for DCs to spread and migrate along stromal surfaces, and was sufficient to induce membrane protrusions through Vav and Rac1 activation (Acton et al., 2012).

**HIV transmission**

Previous reports indicate that platelets capture and transfer infectious HIV-1 via DC-SIGN and CLEC-2, possibly facilitated HIV-1 dissemination in infected patients (Suzuki-Inoue et al., 2011). CLEC-2 does not directly bind to the viral envelope proteins, but to podoplanin incorporated into the
HIV particles released from HEK-293T cells (Chaipan et al., 2010). This mechanism does not seem to be important for viral dispersion in vivo since podoplanin is not expressed on T cells, which are the major HIV target.

**Phagocytosis and cytokine production**

CLEC-2 is expressed in dendritic cells, NK cells, B cells, neutrophils, and monocytes, in addition to platelets (Kerrigan et al., 2009; Chang et al., 2010; Mourao-Sa et al., 2011). Murine CLEC-2 in neutrophils mediates the phagocytosis of anti-CLEC-2 antibody-coated beads. Moreover, neutrophils stimulated by rhodocytin produce proinflammatory cytokines such as TNF-α depending on CLEC-2, but not respiratory burst (Kerrigan et al., 2009). CLEC-2 ligation in macrophages and DCs selectively up-regulates production of IL-10, an anti-inflammatory cytokine, by Toll-like receptor stimulation. Although the physiological relevance of these phenomena has not been determined, CLEC-2 is expressed in myeloid cells and may be able to modulate the inflammatory response in vivo.

**Homology**

Among 226-229 amino acids of 5 species' (human, mouse, rat, rabbit, and bovine) CLEC-2, there are 129 positions with 100% sequence conservation, 36 positions with 80% sequence conservation, and 44 positions with 60% sequence conservation. Human CLEC-2 is 62% identical to mouse CLEC-2, and 70% to rabbit CLEC-2.

**Mutations**

**Note**

No known mutations.

**Implicated in**

**Haematogenous tumour metastasis**

**Note**

CLEC-2 has been identified as a receptor for a platelet activating snake venom, rhodocytin (Suzuki-Inoue et al., 2006). Podoplanin is a type I transmembrane sialomucin-like glycoprotein, and is identified as the endogenous ligand for CLEC-2 (Suzuki-Inoue et al., 2007; Christou et al., 2008). It is expressed on the surface of certain types of tumour cells, where it causes aggregation of platelets in the blood stream, facilitating haematogenous tumour metastasis. Platelet aggregation surrounding tumour cells is considered to protect the tumour cells from shear stress and NK cells (Nieswandt et al., 1999) in the blood stream and provide scaffolding for tumour cell nests. Growth factors released from activated platelets stimulate angiogenesis and/or tumour growth. In an experimental model of metastasis in mice, an anti-podoplanin blocking antibody significantly inhibited the number of tumour-cell containing metastatic lung nodules that expressed podoplanin, implying that CLEC-2/podoplanin may be a promising target protein for anti-metastatic drugs (Kato et al., 2008).

**Various diseases**

**Note**

No implication in any specific diseases in human has been reported.

**References**


Kerrigan AM, Dennehy KM, Mourão-Sá D, Faro-Trindade I, Willment JA, Taylor PR, Eble JA, Reis e Sousa C, Brown GD. CLEC-2 is a phagocytic activation receptor expressed
on murine peripheral blood neutrophils. J Immunol. 2009 Apr 1;182(7):4150-7


This article should be referenced as such: