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CD151:

Basis Sequence: Mouse

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Protein Function

CD151 is a member of the Tetraspanin (Tspan) family of transmembrane proteins, which encompasses 33 members in mammals, including CD9 (MRP1), CD63 (LAMP3), CD81 (TAPA1), and CD82 (Kai1). All members of this family possess a common structure containing four membrane-spanning domains arranged in a compact rod-like fashion (Hemler 2005), which leads to the formation of the large and small extracellular loops (LEL and SEL respectively). CD151 functions principally as a transmembrane scaffolding protein. Like most Tspans, CD151 interacts with other transmembrane or membrane-proximal proteins through its LEL and short cytoplasmic tails. Multimerization of the Tspan and its partner proteins leads to the formation of large multimolecular complexes within the membrane. These complexes were originally referred to as the 'tetraspanin web' (Charrin *et al*. 2003; Kovalenko *et al*. 2004; Levy and Shoham 2005); however, the most current literature refers to them as tetraspanin-enriched microdomains (TERMs or TEM; Hemler 2008; Zöller 2009). The LEL contains the majority of amino acids important for interactions with transmembrane and membrane-proximal partners, while the transmembrane regions and cytoplasmic tails are thought to be required for intracellular interactions with Tspan-associated cytoplasmic signaling molecules. Specific partners include integrins α3β1 and α6β4, phosphatidylinositol 4-kinase (PI4 kinase) and protein kinase C α (PKCα). The molecular mechanism(s) by which this Tspan conveys biological activity remains under investigation. CD151 participates in a wide variety of normal physiological processes as well as pathologies, including kidney function, angiogenesis, platelet activation, inflammation, wound healing, tumor invasion, and metastasis (Hemler *et al*. 2003; Lau *et al*. 2004; Kolesnikova *et al*. 2004; Cowin *et al*. 2006; Sachs *et al*. 2006; Sterk *et al*. 2000; Stipp and Hemler 2000; Takeda *et al*. 2007; Wright *et al*. 2004; Yáñez-Mó *et al*. 2008; Zijlstra *et al*. 2008).

Regulation of Activity

Since Tspans are generally expected to function as scaffolding proteins, their activity is defined by their ability to integrate themselves and their partner proteins into macromolecular complexes. This activity of CD151 is primarily regulated post-translationally through modifications of its subcellular distribution or the stability of its interaction with membrane partners. The most common post-translational modification

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involves the palmitoylation of conserved cysteine residues in the transmembrane domains by the palmitoyl-acyl transferase (PAT) DHHC2, one of 23 known mammalian PATs (Sharma *et al*. 2008). Palmitoylation of Tspan proteins such as CD151 affects the assembly and maintenance of TERMS, while also affecting Tspan subcellular distribution, stability during biosynthesis, cell signaling, motility, and morphology. It has also been shown that palmitoylation of CD151 is involved in the regulation of Tspan–Tspan interaction because palmitoylation-deficient CD151 is unable to complex with other Tspan family members (CD9, CD63, CD81) (Berditchevski *et al*. 2002; Kovalenko *et al*. 2004; Yang *et al*. 2002; Yang *et al*. 2004). The importance of this modification has been confirmed both by short interfering RNA (siRNA)-mediated knockdown of expression of DHHC2 as well as the expression of palmitoylation-deficient CD151 mutants. In addition to palmitoylation on conserved cysteine residues, CD151 extracellular domain is routinely glycosylated. While this post-translational modification is important for the modulatory ability of CD151 on α3β1 integrin, it is not required for the formation of the tetraspanin–integrin complex. Furthermore, it has been demonstrated that the loss of CD151 decreases migration on laminin 322, and this effect is reversed with the re-expression of wild-type CD151 but not a glycosylation-deficient CD151 mutant. These findings suggest that the glycosylation state of CD151 modulates integrin activity and function (Baldwin *et al*. 2008). Tspan clustering is the primary mechanism that can influence biological activity of these proteins. Clustering antibodies for CD151 and other Tspans have produced dramatic phenotypes including complete immobilization of tumor cells (Zijlstra *et al*. 2008). These experiments demonstrate that mechanisms capable of regulating Tspan clustering are potent regulators of Tspan activity.

Interactions with Ligands and Other Proteins

CD151 interacts with a large variety of proteins, including integrins, other tetraspanins, proteases, and signaling molecules. Their assembly into TERMs makes it somewhat difficult to evaluate isolated tetraspanin–partner interactions. The associations listed here are confirmed, direct interactions but it has been suggested that Tspans such as CD151 can interact with and regulate the function of many more proteins, directly or indirectly (Hemler 2005; Zöller 2009) and these associations are reviewed by Zijlstra in “Tetraspanins in Cancer”, a chapter in Cell-Extracellular Matrix Interactions in Cancer (DOI: 10.1007/978-1-4419-0814-8_10 (2009)).

Interactions with integrins

The most well studied CD151 interactions are those that involve the laminin-binding integrins α3β1 and α6β1 (Kazarov *et al*. 2002), and these CD151-integrin complexes can regulate cell morphology and migration by controlling adhesion and adhesive strengthening (Sincock *et al*. 1999; Lammerding *et al*. 2003; Geary *et al*. 2008) and cytoplasmic signaling (Alvares *et al*. 2008; Chattopadhyay *et al*. 2003; Yamada *et al*. 2008a; Zhang *et al*. 2001). The nature, stoichiometry, and affinity of tetraspanin–partner interactions have been difficult to assess quantitatively. Direct partners of Tspans are identified through a combination of protein cross-linking, cell-surface biotinylation, differential detergent extraction, and reciprocal immunoprecipitation (Yauch *et al*. 1998; Charrin *et al*. 2003; Chattopadhyay *et*

al. 2003; Yauch *et al*. 2000; Zhang *et al*. 2001). The CD151-α3β1 integrin complex is one of the best defined interactions. This complex can be immunoprecipitated under both mild and stringent detergent extraction conditions indicating a strong, primary interaction that is defined by the specific QRD binding sequence (Kazarov *et al*. 2002; Yamada *et al*. 2008b). The loss of CD151 in human mammary epithelial and carcinoma cells leads to migration deficiencies on laminin-rich matrixes (Novitskaya *et al*. 2010; Winterwood *et al*. 2006; Yang *et al*. 2010). In addition to manipulating the activity of its integrin partners directly, evidence has been presented that the tetraspanin can regulate α3β1 trafficking (Liu *et al*. 2007) and glycosylation (Baldwin *et al*. 2008). Together these observations provide strong support for both physical and functional roles for CD151 in α3β1 biology. The integrins α6β1 and α6β4 are also partners of CD151, although the interaction is not as stable as the CD151-α3 interaction (Sterk *et al*. 2000; Sterk *et al*. 2002). Disruption of CD151-α6 interaction does not alter integrin cell surface expression or cellular adhesion to laminin, but it does diminish α6-dependent cell spreading and integrin-mediated adhesive strengthening (Lammerding *et al*. 2003). The majority of biochemical and functional data have been generated with studies evaluating the ability of CD151 to regulate the functions of laminin-binding integrins α3 and α6. However, CD151 has also been demonstrated to interact with αIIbβ3 in both murine and human platelets under both mild and stringent detergent extraction conditions. The functional significance of this interaction was demonstrated using CD151 null platelets isolated from the CD151 knockout mouse. Characterization of the *in vivo* phenotype of these mice demonstrates a tendency to re-bleed and poor clot retraction. CD151 might therefore be required for potentiation of αIIbβ3 signaling events, but not the cell surface expression of the integrin as the latter is present at equivalent levels in both wild-type and CD151 knockout platelets (as demonstrated by flow cytometry) (Fitter *et al*. 1999; Lau *et al*. 2004). The integrin α5β1, another fibronectin receptor, can be co-immunoprecipitated from human platelets under mild detergent extraction conditions, whereas this complex is lost under stringent detergent extraction conditions. Although this complex is not as stable as the association with α3β1, the loss of CD151 decreases the adherence of human T cells to fibronectin, and anti-CD151 antibody inhibits T cell adherence to fibronectin but not collagen or laminin (Hasegawa *et al*. 1998). The molecular mechanism by which CD151 controls migration remains unknown. *In vivo* work with anti-CD151 antibody indicates, however, that CD151 can have a broad impact on all matrix-binding integrins (Zijlstra *et al*. 2008).

Interactions with signaling molecules

A wealth of literature has suggested that the ability of CD151 to associate with intracellular signaling molecules is required for its ability to interact with and regulate various integrins. CD151 associates with many signaling molecules including PKCα, integrin βII, and PI4 kinase type IIα (Shigeta *et al*. 2003; Yauch *et al*. 1998; Zhang *et al*. 2001), but the importance of these interactions is not fully known. It is reasonable to speculate, however, that the CD151 interactions with these signaling molecules could influence intracellular signaling by incorporating them into the TERM. It has been demonstrated that, in addition to interactions with the above mentioned signaling molecules, some of the proliferative effects associated with CD151 are due to its ability to activate extracellular signal-regulated kinases 1 and 2 (Erk1/2) and protein kinase B (Akt) signaling in non-tumorigenic HB2 mammary

epithelial cells (Novitskaya *et al*. 2010). The loss of CD151 abrogates Erk1/2 and Akt signaling, and additionally rescues the ability of these cells to form luminal-like structures when grown in three-dimensional (3D) cultures, indicating that CD151 might be upstream of Erk1/2 activation. CD151 has been suggested to influence small GTPase activity, including Cdc42 and RhoA activation (Shigeta *et al*. 2003; Johnson *et al*. 2009). In CD151 null carcinoma cells the loss of CD151 leads to an increase in cell migration and a loss of cell–cell adhesion that is independent of the loss of E-cadherin. Re-expression of CD151 promotes the reestablishment of normal cell–cell junctions. Interestingly, this activity is dependent on the CD151/α3β1 complex because in carcinoma cells expressing a CD151 mutant that cannot associate with α3 the cell–cell junctions remain disorganized and E-cadherin is mislocalized (Johnson *et al*. 2009).

Interactions with proteases

Several matrix metalloproteinases have been associated with CD151, including MMP7 (Shiomi *et al*. 2005), MMP14 (Yáñez-Mó *et al*. 2008) and MMP9 (Hong *et al*. 2006). Although the importance of the interactions of CD151 with matrix metalloproteinases is still poorly understood, these studies indicate that the tetraspanin may control activation and localization of these proteases.

The incorporation of CD151 into TERMs is likely to allow it to interact directly and indirectly with a large number of proteins and regulate their function. The extent to which this activity influences biological function will have to be determined for each individual biological system.

Regulation of Concentration

Mechanisms by which the expression of CD151 is regulated are not completely understood, but an interaction with the E3 ubiquitin ligase GRAIL (gene related to anergy in lymphocytes) was recently identified. This interaction targets CD151 for proteasomal-mediated degradation (Lineberry *et al*. 2008). Recently it has been suggested that hypoxia is able to regulate CD151 expression and potentially alter CD151-mediated adhesion of tumor cells. The ability of hypoxia to downregulate CD151 expression is due to the activation of a hypoxia response element (HRE) located in the CD151 promoter region (Chien *et al*. 2008). Transcriptional regulation of CD151 is also achieved by Sp1, which is responsible for the basal activation of CD151 and chromatin accessibility of the CD151 promoter (Wang *et al*. 2010). Within individual cells the CD151 concentration is controlled by subcellular distribution. Within tissues CD151 is nearly ubiquitously expressed, but present at elevated levels in endothelial cells, platelets, and epithelial cells that contact basement membranes. CD151 expression is frequently altered in tumor cells, although the mechanism is unknown.

Subcellular Localization

In normal tissues and confluent endothelial or epithelial cell cultures CD151 is predominantly localized to the basolateral surface and to areas of cell–cell contact (Chattopadhyay *et al*. 2003; Huang *et al*. 2005; Shigeta *et al*. 2003; Sincock *et al*. 1999; Yáñez-Mó *et al*. 1998). In individually cultured cells without cell–cell contact or non-

adherent cells, CD151 is frequently internalized into endosomal and lysosomal compartments (Liu *et al*. 2007; Sincock *et al*. 1999) as a component of the endocytic pathway. In contrast, tumor cells frequently exhibit general cell surface distribution and localization in cytoplasmic vesicles. In epithelial cells, CD151 is also seen in hemidesmosome-like structures, where it associates with α6β4 (Sterk *et al*. 2000; Wright *et al*. 2004). More recently, CD151, along with other tetraspanins, has been shown to be enriched in exosomes (Hemler 2003; Zöller 2009).

Major Sites of Expression

Although CD151 was originally identified as a platelet cell surface antigen (Ashman *et al*. 1991; Fitter *et al*. 1995), it is expressed in nearly all tissues. It is abundantly expressed in many cells of the vascular system, including endothelial cells, megakaryocytes and platelets. In normal breast CD151 is expressed in myoepithelial cells, while high levels of expression are seen in ductal epithelial cells of the colon and prostate. CD151 is also highly expressed in the glomeruli and tubules of the kidney, the basal epithelia of the skin, cardiomyocytes, and Schwann cells of the peripheral nervous system (Sincock *et al*. 1997; Yang *et al*. 2008). CD151 is also expressed in most solid tumors and upregulated in many aggressive neoplasia. In contrast, it is distinctly absent from lymphoma.

Expression patterns for CD151 can be reviewed effectively at Proteinatlas.

Phenotypes

In humans, genetic mutations in CD151 result in hereditary nephrotic syndrome, which ultimately leads to end-stage renal failure. These patients also suffer from sensorineural deafness, skin blistering, and thalassemia, a blood disorder characterized by abnormal hemoglobin production (Wright *et al*. 2004; Karamatic Crew *et al*. 2004; Sachs *et al*. 2006). Several CD151 knockout mice have been generated to further investigate the biological function of this Tspan (Baleato *et al*. 2008b; Sachs *et al*. 2006; Wright *et al*. 2004). CD151 null mice on a B6 background were generated using the Cre recombinase system. Due to the known associations of CD151 with integrin family members, it was anticipated that the loss of CD151 would lead to a loss or alteration in cell surface integrin expression in various isolated cells and tissues, but integrin expression was unchanged in the absence of CD151. It was also anticipated that the formation of hemidesmosomes would be altered in CD151 null mice due to the strong associations of CD151 with α6 β4, but the expression of the integrin and the formation of these structures was unchanged (Wright *et al*. 2004). Initial phenotypic characterization of the mice showed that they are healthy, viable, and fertile. Although the phenotype of the CD151 null mice is relatively mild, they do have a minor bleeding deficiency characterized by a decrease in bleeding time endpoint coupled with an increased tendency to re-bleed when compared with CD151 wild-type mice. Although these data suggest that the CD151 null mice are relatively healthy, in addition to minor defects in hemostasis they exhibit alterations in skin wound healing both *in vitro* and *in vivo* (Orlowski *et al*. 2009; Wright *et al*. 2004; Cowin *et al*. 2006). Interestingly, T cell activation is also diminished in CD151 null mice due to defects in dendritic cell co-stimulation (Sheng *et al*. 2009). In contrast with the B6 background, CD151 knockout mice on a mixed background

(FVB/Nx129 and the FVB/B6) develop severe kidney disease with pronounced proteinuria and glomerulosclerosis (Sachs *et al*. 2006). These mice have served as suitable models to investigate the role of CD151 in the kidney and the pathologies associated with the development of glomerulosclerosis due to the loss of CD151. A strain-dependent penetrance phenotype has subsequently been described (Baleato *et al*. 2008a) and may be indicative of compensatory mechanisms in CD151-deficient mouse models.

Splice Variants

While no splice variants have been found in the human CD151 sequence, alternative splicing of murine CD151 generates three transcripts with different 5′ untranslated regions (Fitter *et al*. 1998).

Antibodies

A majority of the information currently known about CD151 has been generated using specific monoclonal antibodies generated against the protein. Although all of these antibodies bind CD151, they do not recognize it when it is contained in certain protein complexes (Serru *et al*. 1999; Geary *et al*. 2001; Yamada *et al*. 2008), and furthermore tissue staining patterns can differ between antibodies (Geary *et al*. 2001). Below is a list of the commonly used and referenced antibodies.

mAbs against human CD151 include:

1A5 (Testa *et al*. 1999; Zijlstra *et al*. 2008)

8C3 (Nishiuchi *et al*. 2005)

SFA1.2B4 (Charrin *et al*. 2001)

TS151 (Serru *et al*. 1999)

TS151r (Serru *et al*. 1999)

LIA1/1 (Yáñez-Mó *et al*. 1998)

VJ1/16 (Yáñez-Mó *et al*. 1998)

11B1 (Geary *et al*. 2001)

14B1 (Hasegawa *et al*. 1996)

5C11 (Yauch *et al*. 2000)

14A2.H1 (Ashman *et al*. 1991)

The epitope binding and staining patterns of many of these antibodies have been documented by the laboratories of Ashman and Sekiguchi (Yamada *et al*. 2008b; Geary *et al*. 2001).

11G5 is the most commonly available commercial antibody.

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