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Review

# The role of tetraspanins in the pathogenesis of infectious diseases

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**Abstract**

Tetraspanin proteins on host cells are involved in the pathogenesis of infectious diseases at different stages. In this review, we will focus on tetraspanins expressed in the immune system and the role they play in the defense to viral, bacterial, parasitic and fungal infections.


*Keywords:* Tetraspanin; Infectious diseases; Immune system; Antigen-presenting cell

## 1. Introduction

The superfamily of tetraspanins is comprised of small (20–50 kDa) transmembrane four proteins that are expressed at the cell surface and in intracellular membranes. Tetraspanins are highly conserved between species and have been identified in eukaryotic organisms as diverse as plants, fungi and mammals. Tetraspanin proteins share key structural features that include the presence of conserved cysteines and a CCG motif in the large extracellular domain, four transmembrane domains and membrane-proximal palmitoylation sites [1] (http://www.ebi.ac.uk/interpro/IPR000301). To date, 33 different tetraspanins have been discovered in humans. Whereas a large subset of tetraspanins (CD9, CD63, CD81, CD82, CD151 among others) have a broad tissue distribution profile, restricted expression is documented for CD37 and CD53 (immune system), Tssc6 and Penumbra (hematopoietic), Uroplakins (bladder epithelium) and Rom-1 and RDS (ocular) (Table 1).

There is now compelling evidence that tetraspanins play an important role in the lateral organization of membrane proteins at the cell surface. Tetraspanins interact with one another as well as with specific receptors and signaling proteins, whereby they form functional complexes in the plasma cell membrane that are called "tetraspanin microdomains" [2–4]. Consequently, tetraspanins are important in several fundamental cellular processes including migration, proliferation, differentiation and in malignant and infectious disease [3–5]. Tetraspanin-partner protein interactions have been classified into three categories based on their strength. Level 1 (primary) interactions represent direct interactions whereas levels 2 and 3 (secondary and tertiary) represent indirect interactions [6,7]. Novel insights have now demonstrated that the composition and localization of tetraspanin microdomains are highly dynamic [8,9]. This may provide the cell with a mechanism to constantly adapt to its environment and explain why many tetraspanin protein interactions are weak or temporary.

It is well established that tetraspanin interactions with partner molecules form functional units. For example, CD151 associates with integrins $\alpha_3\beta_1$ and $\alpha_6\beta_4$, and as such regulates integrin-dependent cell morphology, migration and adhesion strengthening. Patients with a CD151 mutation in the integrin-binding domain suffer from hereditary nephritis and skin-blistering disease [10]. Important progress in our understanding of tetraspanin function has been made with the generation and study of tetraspanin-deficient mice (reviewed in [2,7]). Analyses of tetraspanin-deficient mice have revealed specific non-redundant roles for tetraspanins in the immune system (CD37, CD81, Tssc6, CD151), erythropoiesis (Penumbra), platelets (Tssc6, CD151), cell fusion (CD9, CD81), kidney biology/tissue architecture (CD151, CD63 and

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Table 1
Tetraspanin expression profiles on human tissues with reported involvement in the pathogenesis of infectious diseases. Expression data is derived from cited references and the protein database <www.uniprot.org>. Note that tetraspanin-infection studies include both *in vitro* data and animal models.

| Tetraspanin | Alternative names | Tissue distribution | Involved in infectious disease | Refs |
|---|---|---|---|---|
| CD9 | Tspan 29, BA2, p24, GIG2, MIC3, MRP-1, BTCC-1, DRAP-27 | Broad | Linked with HIV-1, FIV, CDV. Modulates Diphtheria toxin binding. | [13],[21],[25],[29], [30],[32],[37] |
| CD37 | Tspan 26, Gp40–52 | Immune system (B and T cells, monocytes, macrophages, granulocytes, immature DC) | Regulates immune response to *C. albicans*. | [46],[47] |
| CD53 | Tspan 25, MOX44 | Immune system (B,T and NK cells, monocytes, macrophages, granulocytes, DC) | Human CD53 deficiency linked to recurrent infections. Role in HIV-1 egress. | [12],[22],[27],[29] |
| CD63 | Tspan 30, MEL1, ME491, granulophysin, LAMP3, OMA81H, MLA1, NGA, LIMP | Broad | Roles in HIV-1 entry and egress, HTLV-mediated syncytium formation, endocytosis of HPV16. | [20],[22],[23],[25], [6],[27],[36] |
| CD81 | Tspan 28, TAPA-1, S5.7 | Broad | Receptor for HCV. Role in HIV-1, HTLV. Binds to *P. falciparum* and *P. yoelii*. | [14],[15],[16],[17], [19],[21],[24],[25], [27],[30],[42] |
| CD82 | Tspan 27, Kangai1, R2, 4F9, C33, IA4, ST6, GR15, KAI1, SAR2 | Broad | Role in HIV-1 and HTLV assembly. | [22],[27],[33],[34] |
| CD151 | Tspan 24, PETA3, SFA1, gp27 | Broad | Involved in endocytosis of HPV16, role in porcine RRSV. | [35],[36] |
| Uroplakin Ia | Tspan 21, UP1A, UPIA, UPKA, MGC14388 | Bladder epithelium | Binds FimH protein in *E. coli* during urinary tract infection. | [38] |
| Uroplakin Ib | Tspan 20, UPIB, UPK1 | Bladder epithelium | Binds FimH protein in *E. coli* during urinary tract infection. | [38] |

CD37 (Rops and Van Spriel *Unpublished*)) and retina function (Peripherin, Rom-1). These studies demonstrate that tetraspanin absence or dysfunction can result in the development of multiple phenotypic defects. Interestingly, human CD53 deficiency has been linked to recurrent infectious diseases caused by bacteria, fungi and viruses [11]. In the immune system, tetraspanins form functional interactions with prominent leukocyte receptors including MHC molecules, proteins of the B cell receptor complex, CD4, CD8, integrins and C-type lectins. Hence, tetraspanins can modulate immune receptor signaling and regulate leukocyte proliferation, antigen presentation, cytokine production and migration. It is evident that these important cellular processes will control immune responses in general, and thus also immunity to infectious diseases. The function of tetraspanins as general immune modulators has been accurately evaluated previously [4,7,12]. In this review we evaluate novel insights into the role of tetraspanin microdomains as functional platforms that control pathogen binding, entry and subsequent immune responses, or alternatively microbial invasion.

## 2. Viral infections

### 2.1. Hepatitis C virus

Tetraspanin involvement in viral infections has been widely reported (reviewed in [13]). One of the first discoveries was the identification of CD81 as a ligand for Hepatitis C virus (HCV) [14]. HCV is a small enveloped RNA virus that belongs to the *Flaviviridae* family (genus *Hepacivirus*). HCV infection occurs in approximately three percent of the world's population and is a major cause of chronic liver disease. It was found that the major envelope protein of HCV (HCV-E2) interacts with the large extracellular loop of CD81 on various human cells. This interaction was specific for CD81, since other tetraspanins tested (CD9, CD63, CD151) did not bind HCV-E2 protein [15]. HCV exploits CD81 to invade not only hepatocytes, but also to bind B cells, T cells, NK cells and dendritic cells (DC) (reviewed in [13]). HCV infection in leukocytes has multiple effects on the immune system including impaired DC migration and lymphocyte cell disorders. This may explain the impaired anti-viral immune response and the development of the liver inflammation and autoimmunity that accompanies HCV infection. The physiological relevance of HCV-CD81 interaction was recently shown by the ability of CD81-specific antibodies to mediate protection to HCV infection *in vivo* [16]. Recent studies have demonstrated that the molecular interaction between HCV and CD81 is more complex, since certain human liver cell lines are non permissive to infection by HCV despite CD81 expression. Also, CD81 mutations that considerably reduce HCV-E2 binding have been shown to have minimal effects on HCV infection. It has now been demonstrated that cell entry of HCV is mediated through combinations of various receptors including CD81, scavenger receptor class B member 1, claudin-1, occludin, DC-SIGN, L-SIGN, LDLR, heparan sulphate proteoglycans and the asialoglycoprotein receptor. Interestingly, certain HCV-binding receptors on host cells can also inhibit viral entry. The CD81 partner EWI-$2^{wint}$, which is not expressed on hepatocytes, blocks HCV entry [17]. This demonstrates that a pathogen can gain entry into host cells which lack a specific inhibitory factor. In conjunction with viral entry, a role for CD81 in post-binding steps of HCV infection has also been suggested. After virus binding, the virus-receptor complex undergoes endocytosis and pH-dependent membrane fusion. CD81-HCV binding may