Supplementary Table

Table-1. Overview of tetraspanin superfamily

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| --- | --- | --- |
| TSPANs | Aliases in the GenBank | Phenotypes of KO mice |
| TSPAN 1 | NET1, TM4C, TM4SF | / |
| TSPAN 2 | NET3, TSN2 | / |
| TSPAN 3 | TM4A, TM4SF8 | TSPAN3-/- mice were born without overt defects, but, TSPAN3 deletion impaired leukemia stem cell self-renewal and disease propagation and markedly improved survival in acute myelogenous leukemia mouse model (Kwon et al., 2015; Seipold et al., 2017). |
| TSPAN 4 | NAG2, TETRASPAN, TM4SF7 | / |
| TSPAN 5 | NET4, TM4SF9 | / |
| TSPAN 6 | T245, TM4SF6 | TSPAN6 deficiency enhanced basal synaptic transmission, impaired long term potentiation (Salas et al., 2017), and altered the amyloid precursor protein processing in neurons (Guix et al., 2017). |
| TSPAN 7 | A15, CCG-B7, CD231, DXS1692E, MRX58, MXS1, TALLA-1, TM4SF2, TM4SF2b | / |
| TSPAN 8 | CO-029, TM4SF3 | Body weight, bone mineral density and phosphorus levels were reduced in male TSPAN8-/- mice (Champy et al., 2011).  The leukocyte migration, wound repair and angiogenesis were defected, and metastasis was impaired in TSPAN8-/-, and TSPAN8/CD151 double KO mice (Zhao et al., 2018a). Moreover, the impaired angiogenesis in KO mice can be rescued by wild type-serum exosome (Zhao et al., 2018b). |
| TSPAN 9 | NET5, PP1057 | TSPAN9-/- mice had normal body weights and the normal numbers of blood cells, however, platelets from TSPAN9-/- mice had a mild but specific defect in GPVI-induced platelet aggregation and secretion (Haining et al., 2017). |
| TSPAN 10 | OCSP | / |
| TSPAN 11 | VSSW1971 | / |
| TSPAN 12 | EVR5, NET2, TM4SF12 | TSPAN12-/- mice displayed that the centrifugal outgrowth of the [nerve fiber](https://www.sciencedirect.com/topics/neuroscience/nerve-fiber) layer vasculature was moderately delayed in retinas between postnatal day 5 (P5) and P12 (Junge et al., 2009); at P11, vertical sprouts and outer plexiform layer capillaries were completely absent in TSPAN12*-/-* mice, while both were appeared in TSPAN12+/+ mice, and the outer plexiform layer remains avascular in adult TSPAN12*-/-* mice (Junge et al., 2009); the [thickness](https://www.sciencedirect.com/topics/immunology-and-microbiology/thickness) of the outer nuclear layer in TSPAN12*-/-* retinas was consistently reduced in adult but not neonatal mice (Junge et al., 2009). Moreover, formation of microaneurisms, aberrant fenestration, and delayed hyaloid vessel regression are displayed in TSPAN12*-/-* mice (Junge et al., 2009). |
| TSPAN 13 | NET6, TM4SF13 | / |
| TSPAN 14 | DC-TM4F2, TM4SF14 | / |
| TSPAN 15 | 2700063A19Rik, NET7, TM4SF15 | / |
| TSPAN 16 | TM-8, TM4-B, TM4SF16 | / |
| TSPAN 17 | FBX23, FBXO23, TM4SF17 | / |
| TSPAN 18 | TSPAN | TSPAN18-/- mice had normal body weights and whole blood cell counts (Noy et al., 2019), and had defective hemostasis due to a defect in non-hematopoietic cells, while deep vein thrombosis and myocardial ischemia/reperfusion injury were improved in these mice (Noy et al., 2019). |
| TSPAN 19 |  | / |
| TSPAN 20 | UPK1B, UPIB, UPK1 | TSPAN20-/- mice exhibited progressive hydronephrosis beginning in adulthood, and possessed unilateral duplex kidneys (Carpenter et al., 2016). |
| TSPAN 21 | UPK1A, UP1A, UPIA, UPKA | / |
| TSPAN 22 | [PRPH2](https://www.ncbi.nlm.nih.gov/gene/5961), AOFMD, AVMD, CACD2, DS, MDBS1, PRPH, RDS, RP7, rd2 | TSPAN22-/- mice failed to form rod outer segments (OSs), and the OSs of TSPAN22+/- mice were short and disorganized (Sanyal et al., 1980; Hawkins et al., 1985; Lee et al., 2006); TSPAN22-/- mice displayed photoreceptor death in animal model of digenic and dominant retinitis pigmentosa (Kedzierski et al., 2001). |
| TSPAN 23 | ROM1, ROM, ROSP1, RP7 | TSPAN23-/- mice formed OSs in which TSPAN22 homotetramers are localized to the disk rims, suggesting that TSPAN22 alone was sufficient for both disk and OS morphogenesis (Clarke et al., 2000). The maximal photoresponse of TSPAN23-/- rod photoreceptors was lower than that of controls (Clarke et al., 2000). |
| TSPAN 24 | CD151, GP27, MER2, PETA-3, RAPH, SFA1 | CD151-/- mice displayed longer average bleeding times, greater average blood loss, and an increased incidence of rebleeding occurrences (Wright et al., 2004); the platelets of CD151-/- mice had impaired outside-in integrin αIIbβ3 signaling (Lau et al., 2004).  CD151-/- mice showed no vascular defects during normal development or during neonatal oxygen-induced retinopathy, while deletion of CD151 resulted in decreased pathologic angiogenesis in other *in vivo* assays and in the *ex vivo* aortic ring assay (Takeda et al., 2007); reduced thrombus growth in FeCl3-induced carotid or mesenteric arterioles injury model, laser-induced cremaster muscle arterioles injury model (Orlowski et al., 2009).  Kidney failure in CD151-/- mice, CD151 deficiency resulted in a strain-dependent glomerular disease due to severe alterations of the glomerular basement membrane (Sachs et al., 2006; Baleato et al., 2008; Sachs et al., 2012).  CD151-/- mice were refractory to airway hyperreactivity in response to allergen challenge (Qiao et al., 2017), and these mice spontaneously exhibited age-related pulmonary fibrosis as a result of epithelial disintegrity (Tsujino et al., 2012), however, CD151-/- mice showed markedly diminished lung metastasis (Takeda et al., 2011) and reduced skin tumor formation (Li et al., 2013; Sachs et al., 2014), impaired mammary tumor onset, decreased tumor cell survival, and decreased spontaneous metastasis in ErbB2-transgenic mice (Deng et al., 2012). Similarly, deletion of CD151 reduced mammary tumorigenesis in the mice model of breast cancer induced by the polyoma middle T antigen (PyMT) driven by the murine mammary tumor virus promoter (MMTV) (Roselli et al., 2014).  CD151-/- mice were defective in wound healing (Cowin et al., 2006), and showed exacerbated the IgE-mediated late phase inflammation in a murine model of passive cutaneous anaphylaxis (Abdala-Valencia et al., 2015). |
| TSPAN 25 | CD53, MOX44 | PKC substrate phosphorylation and the recruitment of PKCβ to the plasma membrane were impaired in primaryB cells from CD53-/- mice (Zuidscherwoude et al., 2017). |
| TSPAN 26 | CD37, GP52-40 | CD37-/- mice had reduced numbers of IgG-secreting plasma cells in lymphoid organs *via* impairing α(4)β(1) integrin-dependent Akt signaling (van Spriel et al., 2012).  The proliferation of T cells from CD37-/- mice were enhanced, however, antigen-specific T-cell development, T-cell-dependent antibody responses, antitumor immunity were impaired in CD37-/- mice (Knobeloch et al., 2000; van Spriel et al., 2004; Gartlan et al., 2013).  Similar to CD151-/- DCs, DCs from CD37-/- mice were hyper-stimulatory to CD4+ and CD8+ T cells, although they had different mechanisms (Sheng et al., 2009). However, CD37 deficiency impaired DCs migration, by contrast, DCs from CD82-/- mice displayed a striking hypermigratory phenotype (Gartlan et al., 2013; Jones et al., 2016).  Neutrophil recruitment in a peritonitis model was impaired in CD37-/- mice (Wee et al., 2015).  CD37-/- mice were protected against *Candida albicans* infection, which was accompanied by increased IL-6 levels and IgA antibodies (van Spriel et al., 2009), however, the increased IL-6 levels contributed to glomerular IgA deposition, and the development of renal failure following LPS treatment in CD37-/- mice (Rops et al., 2018). Through constitutive activation of the IL-6 signaling pathway, CD37-/- mice developed germinal center-derived B cell lymphoma in lymph nodes and spleens with a higher incidence than Bcl2 transgenic mice (de Winde et al., 2016). |
| TSPAN 27 | CD82, 4F9, C33, GR15, IA4, KAI1, R2, SAR2, ST6 | CD82-/- mice selectively lose long-term repopulating hematopoietic stem cells (Hur et al., 2016). Similar to CD37-/- mice, T cells from CD82-/- mice were hyperproliferative *in vitro*, however, the Ag-specific CD8+ responses in CD82-/- mice were decreased due to the dysfunction of DCs (Jones et al., 2016). CD82-/- mice displayed diminished fungicidal activity, increased *Candida albicans* viability within macrophages, and decreased the production of TNF-α, IL-1β in macrophages (Tam et al., 2019); however, another reports indicated that CD82-/- mice showed an increased survival rate, reduced bacillary loads in the lungs and enhanced inflammation in sera in response to *Mycobacterium tuberculosis* (Koh et al., 2018).  [Global deletion of CD82](https://www.ncbi.nlm.nih.gov/pubmed/29782939) attenuated bone growth, enhanced bone marrow adipogenesis and pathological vascular morphogenesis (Wei et al., 2014; Bergsma et al., 2018). |
| TSPAN 28 | CD81, CVID6, S5.7, TAPA1 | Reduced fertility of female mice lacking CD81 (Rubinstein et al., 2006).  CD81-/- mice fail to develop T helper type 2 immune responses, and diminished allergen-induced airway hyper-reactivity (Maecker et al., 1998; Deng et al., 2000; Deng et al., 2002). *P. yoelii* sporozoites failed to infect CD81-deficient mouse hepatocytes *in vivo* (Silvie et al., 2003).  Increased brain size and glial cell number, but diminished sensitivity to cocaine-induced place preference and increased accumbens dopamine in CD81-/- mice (Michna et al., 2001; Geisert et al., 2002). |
| TSPAN 29 | CD9, BTCC-1, DRAP-27, MIC3, MRP-1 | Deletion of CD9 reduced the number and size of *Propionibacterium acnes*-induced hepatic granulomas (Yamane et al., 2005), diminished inflammation-induced and tumor-induced lymphangiogenesis (Iwasaki et al., 2013), while increased the numbers of multinucleated giant cells in *Propionibacterium acnes*-induced lung inflammation model (Takeda et al., 2003), and enhanced macrophage infiltration and TNFα production in the lung after intranasal administration of LPS (Suzuki et al., 2009).  Similar to that in CD81-/- female mice, female fertility was severely reduced in CD9-/- mice because sperm did not fuse with the oocytes from CD9-/- females (Kaji et al., 2000; Le Naour et al., 2000; Miyado et al., 2000). The fertility of CD9-/- mice is severely but not completely impaired, while CD9 and CD81 double-null mice were completely infertile indicating that CD9 and CD81 play complementary roles in sperm-egg fusion (Rubinstein et al., 2006), moreover, these mice spontaneously developed pulmonary emphysema, developed multinucleated giant cells in the lung, impaired lymphangiogenesis under physiological conditions, and showed enhanced osteoclastogenesis in the bone (Takeda et al., 2003; Takeda et al., 2008; Iwasaki et al., 2013). |
| TSPAN 30 | CD63, LAMP-3, ME491, MLA1, OMA81H | The absence of TSPAN30 resulted in a significant decrease of mast cells degranulation, which translated into a reduction of acute allergic reactions *in vivo* (Kraft et al., 2013). TSPAN30-/- mice showed a significant reduction in both leukocyte rolling and recruitment and a failure of leukocyte extravasation in a peritonitis model (Doyle et al., 2011).  TSPAN30-/- mice displayed an increased urinary flow, water intake and renal Na+ excretion; reduced urine osmolality, and higher fecal water content (Schroder et al., 2009; Schulze et al., 2017).  Deficiency of TSPAN30 impaired amyloidogenesis and consequent melanosome maturation *in vivo* (van Niel et al., 2011). TSPAN30-/- mice were less susceptible to hepatic homing and outgrowth of pancreatic ductal adenocarcinoma metastases in the presence of high TIMP1 levels (Grunwald et al., 2016). |
| TSPAN 31 | SAS | / |
| TSPAN 32 | ART1, PHEMX, PHMX, TSSC6 | Similar to CD37-/- mice, TSSC6-/- mice displayed a hyper-proliferative T cell phenotype due to early upregulation of the proliferation-inducing cytokine IL-2 (Tarrant et al., 2002; Gartlan et al., 2010).  TSSC6-/- mice showed features of unstable hemostasis in a tail-bleeding assay, and secondary instability in platelet thrombus formation upon FeCl3-induced vascular injury *in vivo* (Goschnick et al., 2006), and clopidogrel-treated TSSC6-/- mice displayed a synergistic defect in unstable haemostasis in this model (Makkawi et al., 2018). Moreover, clopidogrel-treated TSSC6-/- mice showed further synergy with smaller thrombi on collagen under arterial flow (Makkawi et al., 2018). |
| TSPAN 33 | PEN, PEN. | TSPAN33-/- mice developed massive splenomegaly, basophilic macrocytic red blood cells, and anemia as they age (Heikens et al., 2007). |

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