

Supporting Table S3. List of 71 extracellular and intracellular direct/indirect syndecan-4 interaction partners previously reported in different species, tissues and cells^{a)}. 29 out of 71 literature partners were also identified to interact with syndecan-4 in LV lysate (this study) (second rightmost column: IP-SDC4 versus IP-IgG in LV, $p < 0.01$, $n = 1-3$). We also identified 9 literature partners to have an altered interaction with syndecan-4 during development of heart failure (rightmost column: IP-SDC4 in ABHF versus SHAM, $p < 0.05$, $n = 3$, t-test p values are given in Table S1).

Gene	Protein (Uniprot)	Binding	Evidence for interaction	Biological function	Reference	IP-SDC4 ^{b)} (LV) ($p < 0.01$)	IP-SDC4 ^{c)} (SHAM vs. ABHF) ($p < 0.05$)
<i>ACTN2</i> *	α -actinin	V-region Direct	Co-localization, Co-IP, Pull down, peptide competition assay	Link to actin cytoskeleton	(1)	n=1	n=3
<i>ADAM17</i>	Disintegrin and metalloproteinase domain-containing protein 17 (TACE)	Ectodomain Direct	Cleavage analysis	Shedding	(2)	n=0	n=0
<i>ADAMTS1</i>	A disintegrin and metalloproteinase with thrombospondin motifs 1	Ectodomain Direct	Cleavage assay	Shedding Cell adhesion	(3)	n=0	ns
<i>ADAMTS6</i>	A disintegrin and metalloproteinase with thrombospondin motifs 6	Ectodomain + HS chains Direct	Biacore KDs of 125 ± 47 nM	Regulation of cell adhesion	(4)	n=0	n=0
<i>ADAMTS10</i>	A disintegrin and metalloproteinase with thrombospondin motifs 10	Ectodomain + HS chains Direct	Biacore KDs of $14. \pm 1.1$ nM	Cleavage	(4)	n=0	n=0
<i>AKT1</i>	RAC-alpha serine/threonine-protein kinase	Indirect	Functional interaction: Akt phosphorylation decreased in SDC4KO	SDC4 recruits Akt1 to cell surface through PKC α and PAK	(5)	n=0	ns

<i>ARF6*</i>	ADP-ribosylation factor 6	Indirect	Functional interaction: -Arf6 regulates SDC4 mediated integrin recycling to the surface. -SDC4 engagement trigger Arf6 activation -Arf6 binds to syntenin and β 1-integrin	Intracellular trafficking	(6)	ns (n=1, p<0.05)	n=3
<i>ARHGAP35</i>	Rho GTPase-activating protein 35	Indirect	Functional interaction: - SDC4 focal adhesion formation depends on ARHGAP35 expression - SDC4 recruits ARHGAP35 to the cell surface - Co-localization	Adhesion	(7)	n=0	n=0
<i>ARHGDI A</i>	Rho GDP-dissociation inhibitor 1 (RhoGDI1)/RhoGDI- α	Indirect	Pull down in cell lysates	Regulation of cell migration	(8)	ns	ns
<i>APP</i>	A β ₄₂ fibrils/ Amyloid-beta A4 protein	Ectodomain Direct	Surface plasmon resonance imaging (Biacore Flexchip)	ND	(9)	n=1	ns
<i>CALM1</i>	Calmodulin 1	Cytoplasmic tail Indirect	Co-IP	Co-activator of calcineurin A	(10)	n=1	ns
<i>CAMK2A</i>	Calcium/calmodulin-dependent protein kinase type II subunit alpha	Indirect	Co-IP	Non-canonical wnt signaling	(11)	n=3	ns
<i>CASK</i>	CASK	C2 (motif: EFYA) Direct	Peptide binding assays, Y2H and co-localization	Membrane scaffold	(12,13)	n=0	n=0
<i>CDH11</i>	Cadherin-11	Indirect	Co-IP	Focal adhesion formation	(14)	n=0	n=0
<i>CLTC</i>	Clathrin	Indirect	Functional interaction: Rspo3 binds SDC4 and is then endocytosed in a	Endocytosis	(15)	n=1	ns

			clathrin dependent way				
<i>COL1A1</i> *	Collagen 1	Ectodomain, Direct	Cross-linking assay	Collagen crosslinking	(16)	n=3	n=3
<i>CTNNB</i>	Catenin β 1	Indirect	Co-IP	Cell adhesion	(14)	n=3	ns
<i>CTTN</i>	Cortactin	C1 (Motif: RMKKKDE GSY) Indirect	Affinity chromatography	Engagement of SDC4 might activate cortactin (neurite outgrowth)	(17)	ns (n=1, p<0.05)	ns
<i>CYLD</i>	Ubiquitin carboxyl-terminal hydrolase CYLD	Cytoplasmic domain Indirect	Co-IP, co-localization.	Antiviral signalling	(18)	n=0	n=0
<i>CXCR4</i>	C-X-C chemokine receptor type 4	Indirect	Co-IP	Growth factor signaling	(19)	n=0	n=0
<i>DDX58</i>	Retinoic acid-inducible gene I / Probable ATP-dependent RNA helicase DDX58	Cytoplasmic tail Direct	Y2H, co-IP, mutagenesis	Anti-viral signaling	(18)	n=0	n=0
<i>DVL2</i>	Dishevelled	Cytoplasmic domain Indirect	Co-IP	Wnt signalling	(20)	n=0	ns
<i>DNM2</i>	Dynamin-2	C1 Indirect	Co-IP, Y2H, pull down	Focal adhesion and stress-fiber formation	(21)	n=2	ns
<i>EGFR</i>	Epidermal growth factor receptor	Ectodomain (Amino acids 87-131) Direct	Co-IP	EGFR-dependent chemotaxis	(22,23)	n=0	n=0
<i>EZR</i>	Ezrin	C1 (motif: DEGSYD) Direct	Pull-down	Link to actin cytoskeleton	(24)	ns	ns

<i>F2</i>	Thrombin	Ectodomain Direct	Cleavage analysis	Cleavage of SDC4	(25)	ns	ns
<i>FAK</i>	Focal adhesion kinase	Cytoplasmic tail, Indirect	Functional interaction: Lower phosphorylation in absence of SDC4	Adhesion	(26)	n=0	n=0
<i>FYN</i>	Fyn	Cytoplasmic tail, Indirect	Co-IP	In a signal complex in brain	(17)	ns (n=2, p<0.05)	n=0
<i>FZD7</i>	Frizzled-7	Indirect	Co-IP, Proximity ligation assay	Wnt signalling	(20,27)	n=0	n=0
<i>GIPC1</i>	Synectin / PDZ domain-containing protein GIPC	C2 (motif: EFYA) Indirect	Y2H, Co-IP	Migration	(28)	n=0	n=0
<i>GPNMB</i>	Transmembrane glycoprotein NMB / DC-HIL	Ectodomain + HS Indirect	Co-IP, Blocking antibodies	Inhibitory function of T cell activation	(29)	n=0	n=0
<i>IGFIR</i>	Insulin-like growth factor 1 receptor	Indirect	Co-IP	Trafficking	(30)	n=0	n=0
<i>ITGA2^{d)}</i>	Integrin $\alpha2\beta1$	Indirect	Cooperative interaction: Both integrin $\alpha2\beta1$ and SDC4 bind laminin	Cooperation of SDC4 and integrin $\alpha2\beta1$ to laminin adhesion	(31)	n=1	n=0
<i>ITGA3^{d)}</i>	Integrin $\alpha3\beta1$	Indirect	Pull down	In complex with SDC4-EGFR. Motility	(23)	n=0	n=0
<i>ITGA5^{d)}</i>	Integrin $\alpha5\beta1$	Indirect	Cooperative interaction: Both integrin $\alpha5\beta1$ and SDC4 bind FN	Cooperation of SDC4 and RGD binding integrin $\alpha5\beta1$ to FN adhesion	(32-34)	ns (n=2, p<0.05)	n=0
<i>ITGB1</i>	Integrin $\beta1$	Ectodomain (NXIP motif) Indirect	Co-IP, Cell adhesion assay	Adhesion	(34-36)	n=2	ns

<i>ITGB3</i>	Integrin β_3	Indirect	Co-IP, co-localization	The shed SDC4 fragment may regulate integrin β_3 signaling	(37)	n=0	n=0
<i>ITGB4</i>	Integrin- β_4	C2 + V Direct	Y2H, co-IP, pull down	Cell spreading	(22,38)	n=0	n=0
<i>LAMA3</i>	Laminin subunit alpha-3	Ectodomain + HS chains Direct	Surface plasmon resonance, ELISA	Cell Attachment	(39)	n=0	n=0
<i>LOXL2</i>	Lysyl oxidase homolog 2	Ectodomain Direct	Cross-linking assay	Crosslinking of collagen	(16)	n=0	n=0
<i>MMP2</i>	Matrix metalloproteinase-2	Ectodomain Direct	Cleavage analysis	Cleavage	(40)	n=3	ns
<i>MMP3</i>	Matrix metalloproteinase-3	Ectodomain Direct	Cleavage analysis	Cleavage	(40)	n=0	n=0
<i>MMP7</i>	Matrix metalloproteinase-7	Ectodomain Direct	Cleavage analysis	Cleavage	(40)	n=0	n=0
<i>MMP9</i>	Matrix metalloproteinase-9	Ectodomain + HS chains Direct	Cleavage analysis	Cleavage	(40,41)	ns (n=1, p<0.05)	ns
<i>MMP14</i>	Matrix metalloproteinase-14	Ectodomain Direct	Cleavage analysis	Cleavage	(40)	n=0	n=0
<i>MTOR</i>	Serine/threonine-protein kinase mTOR	Indirect	Functional interaction: mTORC2 activity is increased in SDC4 ^{-/-} endothelial cells and tissues	Signaling via SDC4-PKC α -richter recruits mTORC2 components to lipid rafts	(42)	n=1	ns
<i>NF1</i> *	Neurofibromin	Cytoplasmic domain Indirect	Y2H, pull down, co-localization	Recruitment to membrane	(43)	ns (n=2, p<0.05)	n=3
<i>NOX1</i>	NADPH oxidase 1	Cytoplasmic domain Direct	Pull down, co-IP, co-localization	Hypoxia signaling Bridging partner to Rac1	(44)	n=0	n=0

<i>PDCD6IP</i>	ALIX (programmed cell death 6-interacting protein)	Indirect	Biacore	Forms complex with syntenin Involved in exosomes	(45)	n=1	ns
<i>PLG</i>	Plasminogen	Direct	Cleavage analysis	Cleavage	(25)	n=3	ns
<i>PPP3CA</i>	Calcineurin A	V-region Direct	Pull down, co-IP	Dephosphorylates NFATc4 in response to pressure overload	(10)	ns (n=2, p<0.05)	ns
	PI(4,5)P2 (A lipid)	V-region, Direct	Crystal structure	Form complex, activation of PKC α , dimerization of SDC4	(46)	-	-
<i>PRKCA</i> **	PKC α	V-region, Direct	Phosphorylation assay	Phosphorylation, adhesion, trafficking, and signalling	(46,47)	n=0	n=3
<i>PRKCD</i> **	PKC δ	Direct	Phosphorylation assay	Phosphorylation	(48)	n=0	n=3
<i>PTPRJ</i>	Receptor-type tyrosine-protein phosphatase eta	Indirect, through syntenin	Co-IP	Regulation of T cell activation	(49)	n=0	n=0
<i>PTP4A1</i>	Protein tyrosine phosphatase type IVA 1	Indirect	2YH	ND	(50)	n=0	n=0
<i>PTP4A3</i>	Protein tyrosine phosphatase type IVA 3	Indirect	2YH	ND	(50)	n=0	n=0
<i>PDGFRB</i>	Platelet-derived growth factor receptor beta	Indirect	Co-IP	Form complex with SDC4 and integrin β 1 upon stimulation with tenascin	(36)	n=0	n=0
<i>PXN</i>	Paxillin	Indirect	Co-IP	In complex with SDC4 and	(1)	n=1	ns

				syndesmos			
<i>RAC1</i>	Ras-related C3 botulinum toxin substrate 1	Indirect	Co-IP, pull down	Growth factor response through SDC4 Migration	(44,51)	n=1	ns
<i>RHOA*</i>	Transforming protein RhoA	Indirect	Functional Interaction: - SDC4 cyt tail is able to activate RhoA	Stress fiber formation (and muscle differentiation (52))	(52,53)	n=1	n=3
<i>RHOG*</i>	Rho-related GTP-binding protein RhoG	Indirect	Functional interaction: - SDC4 can regulate activity of RhoG through synectin - SDC4 controls spatial distribution of RhoG.		(6) (8)	n=2	n=3
<i>SDC2</i>	Syndecan-2	Transmembrane domain Direct	NMR, co-IP, pull down	Heterodimerization Regulation of syndecan signaling mechanisms	(54,55)	n=0	n=0
<i>SDC4</i>	Syndecan-4	GXXXG Direct	Mutagenesis	Dimerization	(47,56)	n=0	n=0
<i>SDCBP*</i>	Syntenin-1	C2 (EFYA) Direct	Y2H, surface plasmon resonance (Biacore), pull down	Membrane adaptor and trafficking	(57,58)	n=3	n=3
<i>SDOS</i>	Syndesmos/ NUDT16L1	C1 + V Direct	Y2H, co-IP, pull down, crystal structure	Membrane scaffold	(59,60)	n=0	n=0

<i>SRC</i>	Proto-oncogene tyrosine-protein kinase Src	Direct	Phosphorylation assay	Phosphorylation of Tyr-180 (Y180). Regulate integrin trafficking	(61,62)	ns (n=2, p<0.05)	n=0
<i>TIAM1</i>	Tiam1	C2 (EFYA) Direct	Co-IP, fluorescence- and NMR-based binding assays	Cell migration	(63,64)	n=0	n=0
<i>TRAPPC4</i>	Trafficking protein particle complex subunit 4 / Synbindin	C2 (EFYA) Direct	Co-IP, pull-down, ligand overlay, Y2H and co-localization	Vesicle trafficking (Spine maturation)	(65)	ns	ns
<i>TRPC4</i>	Short transient receptor potential channel 4	Indirect	Co-IP	Calcium homeostasis in epithelial cells	(66)	n=0	n=0
<i>TRPC6</i>	Short transient receptor potential channel 6	Indirect	Co-IP		(67)	n=0	n=0
<i>TRPC7</i>	Short transient receptor potential channel 7	Indirect	Co-localization, co-IP,	Calcium homeostasis and adhesion	(66)	n=0	n=0

^{a)} Indirect interaction partners which have not been shown to be in complex with SDC4 or binds through heparan sulfate (HS) glycosaminoglycans (GAGs) chains are excluded

^{b)} IP- SDC4 versus IP-IgG in left ventricle (LV) lysate (each n is performed in triplicates) (p<0.01)

^{c)} IP- SDC4 in ABHF (heart failure) vs SHAM (control) lysate (p<0.05)

^{d)} Interaction probably through integrin β 1

SDC4=syndecan-4; Ectodomain = extracellular part of protein; ns=not significant

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