Table S1: CXADR interactions

Protein/Virus	Function	Reference
Extracellular/Intercellular		
CXADR	Cell adhesion and recognition.	(Cohen et al., 2001a; Honda et al., 2000; Hotta et al., 2003)
Adenovirus (Subgroups A/C/D/E/F)	Viral receptor.	(Leon et al., 1998)
Coxsackie virus (CVB1-CVB6)	Viral receptor.	(Chung et al., 2005; Coyne and Bergelson, 2006; Triantafilou and Triantafilou, 2004)
JAM-L (Amica1)	Cell recognition.	(Guo et al., 2008; Zen et al., 2005)
JAM-C (JAM3)	Spermatid differentiation.	(Mirza et al., 2006)
Laminin-1	Neurite outgrowth.	(Patzke et al., 2010)
Fibronectin	Neurite outgrowth.	(Patzke et al., 2010)
Claudin-3	Tight/Paracellular junction dynamics.	(Mirza et al., 2007)
Occludin	Tight junction integrity.	(Mirza et al., 2007)
N-Cadherin	Cell adhesion.	(Wang et al., 2007)
Tenascin-R	Unknown.	(Matthaus et al., 2017)
Agrin	Unknown.	(Matthaus et al., 2017)
Intracellular		
TJP1/ZO-1	Epithelial tight junction dynamics.	(Cohen et al., 2001a; Cohen et al., 2001b; Lim et al., 2008; Shono et al., 2007; Wang et al., 2007)
MAGI-1	Localization of proteins at the membrane.	(Excoffon et al., 2004; Kolawole et al., 2012)
E-Cadherin	Epithelial junction integrity.	(Hussain et al., 2011; Morton et al., 2013)
PICK1	Localization of proteins at the membrane.	(Excoffon et al., 2004)
PSD-95	Clustering proteins at the membrane.	(Excoffon et al., 2004; Excoffon et al., 2012)
ASIC3	Clustering ion channels at the membrane.	(Excoffon et al., 2012)
LNX/LNX2	Localization of proteins at specific cell sites.	(Mirza et al., 2005; Sollerbrant, 2002)
Cx45	Localization of Cx45 to specific sites of the membrane.	(Lim et al., 2008; Lisewski et al., 2008)
Harmonin	Not determined.	(Excoffon et al., 2006)
MUPP1	Tight junction integrity.	(Coyne et al., 2004)
Actin and dynamin	Regulation of cytoskeleton proteins. Potential endocytosis.	(Huang et al., 2007; Salinas et al., 2014)
Src	Localization of E-cadherin at the membrane.	(Morton et al., 2013)
Cell Signalling		
PI3K and Akt	Cell signalling Co-receptor.	(Verdino and Wilson, 2011; Verdino et al., 2011)
ROCK	Cell adhesion.	(Saito et al., 2013)
β-catenin	Adherens and tight junction dynamics.	(Lim et al., 2008; Walters et al., 2002)
PKCδ	Epithelial homeostasis.	(Morton et al., 2013)
P21 and Rb	Contact initiated growth inhibition.	(Okegawa et al., 2001)
p44/42 MAPK	Localization of proteins at the membrane.	(Farmer et al., 2009)
Raf-MEK-ERK (MAPK/ERK)	Regulation of cell adhesion molecules. Contact initiated growth inhibition.	(Anders et al., 2003; Huang et al., 2005)
Internalisation		
Clathrin/dynamin	CVB3 internalization.	(Chung et al., 2005)

Caveolin-1/DAF	CVB internalization.	(Coyne and Bergelson, 2006)
Lipid rafts and lipid-rich microdomains	Endocytosis.	(Excoffon et al., 2003; Salinas et al., 2014; Triantafilou and Triantafilou, 2004)
Integrin	Adenovirus internalization.	(Farmer et al., 2009; Venkatraman et al., 2005)
Upstream factors		
FSH	Sertoli cell maturation and function.	(Mirza et al., 2007)
Estrogen	Estrogen receptor.	(Vindrieux et al., 2011)
TNF-α and IFN-γ	Cell adhesion molecule.	(Vincent et al., 2004)
Tfap2c	TS regulatory network.	(Kidder and Palmer, 2010)
Eomes	TS regulatory network.	(Kidder and Palmer, 2010)
Epithelial-mesenchymal transition		
Zeb-1	Cell adhesion.	(Lacher et al., 2011)
TGF-β	Cell adhesion.	(Lacher et al., 2006)
SNAIL1-SMAD3/4	Cell adhesion.	(Vincent et al., 2009)

Table S2: CXADR expression

Organ	Expression	Reference
Bladder	Late gestation: Uroepithelium Postnatal: Between uroepithelium basal cells and basal lamina	(Gye et al., 2011)
Blood	Hematopoietic progenitors (10-15%), differentiated erythroid and myeloid cells	(Rebel et al., 2000)
Bone marrow	Mesenchymal stem cells	(Hung et al., 2004)
Cardiac	E9: primitive left ventricle, weak expression seen in right-sided heart structures. E11.5: Ventricle myocardium Postnatal: Intercalated discs of the AV node	(Asher et al., 2005; Chen et al., 2006; Dorner et al., 2005; Lim et al., 2008; Lisewski et al., 2008)
Cochlear	Neonatal (P1-15): Cochlear cell types Postnatal: Restricted to pillar and strial cells	(Excoffon et al., 2006)
Epithelial cells	Postnatal: Colonic mucosa	(Zen et al., 2005)
Endothelial cells	Microvascular endothelial cells Umbilical vein endothelial cells	(Guo et al., 2008; Vincent et al., 2004)
Kidney	Pronephros	(Raschperger et al., 2008)
Liver	Hepatocytes	(Liu et al., 2013)
Lungs	Alveolar epithelial cells	(Sun et al., 2012)
Lymphatics	E14.5 – E16.5: Lymphatic endothelial vessels	(Mirza et al., 2012)
Mesoderm	Mesoderm	(Tashiro et al., 2015)
Nervous system	E8.5 – P7: Neural tube/neuroepithelium E9.5 – E11.5: Cranial motor nerves E13.5 – P7: Optic nerve, motor nerves Postnatal: Few cells at sites of neurogenesis (Hippo/SVZ/RMZ)	(Hauwel et al., 2005; Honda et al., 2000; Hotta et al., 2003)
Olfactory system	Embryonic: Olfactory sensory neurons, olfactory bulb and olfactory epithelium Postnatal: Olfactory epithelium	(Venkatraman et al., 2005)
Oropharynx	Basal layer of oropharyngeal epithelium	(Hutchin et al., 2000)
Pancreas, Thymus and Intestines	Embryonic: Intestinal epithelium; scattered throughout pancreas; thymic epithelium Postnatal: Expression in epithelium of all 3 organs, reticular cells of the thymus	(Kallewaard et al., 2009; Pazirandeh et al., 2011; Tomko et al., 2000)
Pituitary	E11.5: Oral epithelium E13.5 and postnatal: Marginal cell layer and parenchyma	(Chen et al., 2013)
Preimplantation embryo	All cells from mature human oocytes through compaction and blastocyst stages. Trophectoderm and Inner cell mass. Undifferentiated human and mouse ESCs	(Kawabata et al., 2005; Krivega et al., 2014; Kwon et al., 2016; Oh et al., 2016)
Skin	Keratinocytes	(Deng et al., 2013; Witherden et al., 2010)
Testis	Embryonic: Sertoli and germ cells Postnatal: Spermatogonia, preleptotene spermatocyte, spermatids	(Mirza et al., 2007; Sultana et al., 2014; Wang et al., 2007) ((Su et al., 2012)

Table S3: Genotyping primers

Transgene	Forward	Reverse	Amplicon size (bps)
CxadrENU	CTGCAGGCTGGTTGTATGAA	AAGCAAACACACCACACAGG	WT: 562 and 293 (post RE digest), Null: 801
Cxadr Flox	GAGACTGGATTATGAGTTCCAGG CTTTAG	CCTGCTCCAGATTCCCACAATTCC	WT: 741, Flox: 874, Null: 409
Cre	TGCATGATCTCCGGTATTGA	CGTACTGACGGTGGGAGAAT	400
TdTom	AAGGGAGCTGCAGTGGAGTA GGCATTAAAGCAGCGTATCC	CCGAAAATCTGTGGGAAGTC CTGTTCCTGTACGGCATGG	WT: 297, Mutant: 196

Table S4: Mouse lines

Mouse Strain	Reference
*Cxadr*ENU:$210^{Y\text{-}Stop}$	Australian Phenomics Facility Missense Mutation Library
*Cxadr*Flox (B6;129S2-$Cxadr^{tm1.1lcs}$/J)	Pazirandeh et al., 2011
Sox2-Cre (Tg[Sox2-cre]1Amc/J)	Hayashi et al ., 2002; Hayashi et al., 2003
Myh6-Cre (B6.FVB-Tg[*Myh6*-cre]2182Mds/J)	Agah et al., 1997
Tnnt2-Cre (Tg[*Tnnt2*-cre]5Blh/JiaoJ)	Wang et al., 2000; Wang et al., 2001
TdTomato (B6;Cg-*Gt[ROSA]26Sor*$^{tm9(CAG\text{-}tdTomato)Hze}$/J)	Madisen et al., 2009

Table S5: qRT-PCR primers

Gene	Forward	Reverse
Ang1	CAGCTTTGGAATCTCTGTTG	GCTTCTTCTCTTCATCATACG
Ang2	CTCCAGGTACACAAAATTCC	TTTCACCATCATACTTTCGC
Apela	AAGAAAAGATGCGATTCCAG	GGGAAAGTTAACTGGTTTCTG
Apln	GCCTTTCTAAAGCAGGATTG	AATAGATGTGAGGGTTCCAG
Aplnr	TACTTCTTCATTGCCCAAAC	GAAGATGTCAAAGTCACAGG
cMet	CGACAAATACGTTGAAATGC	GATCTACATAGGAGAATGCAC
Ctsq	TTCATTGGCCCAATACCCTA	GAAAGCTCCCAGAATTCACA
Cxadr	CATCATGATATCAGGGAAGAT	AATACCCCTCCATGTTAGAG
Egfl7	GATGTGCTAGAACAGAAACTG	CTCAGTGAATCAATTCGGTC
Fzd5	GATCCTCCGAGAGTTCTG	ACCTGTTGGTTTCTTTTTCTC
Gcm1	ATCTTTTTCCAGTCCAAAGG	CACTTTCTTCATGGCTCTTC
Hgf	CAAATGCAAGGACCTTAGAG	CTTGTTTTGGATAAGTTGCC
Hif1a	CGATGACACAGAAACTGAAG	GAAGGTAAAGGAGACATTGC
Nrp1	TTATCTTTCAGGGAAACACC	TCCAGAGCAAGGATAATCTG
Rhox4b	GTTGAATGGTGGGAAGACA	TTTGTCCCATTCCACTGCT
Rpl13a	CCTATGACAAGAAAAAGCGG	CAGGTAAGCAAACTTTCTGG
R-spondin3	CCAAGTGGATATTACGGAAC	CCATAGTATGATTGTTGGCTTC
Syna	ATGGAGAAACCCCTTACGCT	TAGGGGTCTTTGTGTCCCTG
Tie1	AGAGGTGGAGTTCAACATAG	TTTGGTAGACAAAAGCATGG
Tie2 (Tek)	ATTTCCGTCAAAGTTCTTCC	AAGCTTCTTGGATTTGATGG
Vegfa	TAGAGTACATCTTCAAGCCG	TCTTTCTTTGGTCTGCATTC
Vegfb	GATCCTCATGATCCAGTACC	TTTGGTCTGCATTCACATTG
Vegfc	ACATGCAGTTGTTACAGAAG	GCATAGACAGTGCTAATGTG
Vegfd (Figf)	CTCTTTGAGATATCAGTGCC	GAGGACATTCATCTTCTTCTG
Vegfr1 (Flt1)	TTGTAAACGTGAAACCTCAG	GATTCTTCATTCTCAGTGCAG
Vegfr2 (Flk1, Kdr)	AATGGTACAGAAATGGAAGG	GCATCTCTTTCAGTCACTTC
Wnt2	GTTAATATGAACGTCCCTCTC	TCATGTACCACCATGAAGAG
Wnt6	TAGTAGTGGGCTTAGTTGTC	TTTTACAGTTCATGACGAGC
Wnt5a	AATTCTTGGTGGTCTCTAGG	CAGAGTTTCTTCTGTCCTTG
Wnt11	CCAATAAACTGATGCGTCTAC	ATTTACACTTCGTTTCCAGG

Table S6: In situ hybridisation primers

Gene	Forward (T3)	Reverse (T7)
Aplnr	ACTATGGGGCTGACAACCAG	CAAACTGCCCAGCATGTAGA
cMet	CTACACCCCAGCCCAAACTA	CTCAGGCAGATTCCCAAGAG
Ctsq	AATTAACCCTCACTAAAGGG	TAATACGACTCACTATAGGG
Cxadr	ACCAGGGACCACTGGACA	GGCGCACGTTCAAAGTCT
Gcm1	AATTAACCCTCACTAAAGGG	TAATACGACTCACTATAGGG
Mest	GAGAGAGTGGTGGGTCCAAG	CGATCACTCGATGGAACCTC
Myh6	GAAAAGGAGGCATTGATTTC	CTTCTCCCAGCTGTTCAGTC
Syna	AATTAACCCTCACTAAAGGG	TAATACGACTCACTATAGGG
Vegfa	CGGAAACTTTTCGTCCAACT	GCGAGTCTGTGTTTTTGCAG
Vegfc	CAAGGCTTTTGAAGGCAAAG	CACAGCGGCATACTTCTTCA

Table S7: Antibodies

Primary Antibody	Animal	Tissue processing	Antigen Retrieval	Concentration	Distributor
MCT4 (AB331I4P)	Rabbit	Frozen/Paraffin	EDTA/Citrate	1:200	Millipore
MCT1 (AB1286-I)	Chicken	Frozen/Paraffin	EDTA/Citrate	1:200	Millipore
CXADR (ab100811)	Rabbit	Frozen/Paraffin	Citrate/None/ Methanol/ Acetone	1:500	Abcam
ENDOMUCIN V.SC7 (SC-53941)	Rat	Frozen/Paraffin	EDTA/Citrate	1:100	Santa Cruz
CASP3 Asp175 (#9661)	Rabbit	Frozen/Paraffin	Citrate	1:300	Cell Signalling
CD31 PECAM1 (ab28364)	Rabbit	Frozen/Paraffin	Citrate	1:100	Abcam
Secondary Antibody	**Animal**			**Concentration**	**Distributor**
Anti-Rat 488	Donkey			1:400	Abcam (ab150153)
Anti-Rabbit Cy3	Donkey			1:400	Jackson Immuno Research (711-165-152)
Anti-Rabbit 488	Donkey			1:400	Jackson Immuno Research (711-545-152)
Anti-Chicken 488	Donkey			1:400	Jackson Immuno Research (703-546-155)
Anti-rabbit HRP	Goat			1:500	Invitrogen

Table S8: Genotypes of progeny from *Cxadr*ENU intercrosses

<table>
<tr><th>Stage</th><th>Cxadr$^{+/+}$</th><th>Cxadr$^{+/210}$</th><th colspan="2">Cxadr$^{210/210}$</th><th>Dead (genotype)</th></tr>
<tr><td>E10.5</td><td>23
33.3%</td><td>30
43.5%</td><td colspan="2">14
20.3%</td><td>2 (Cxadr$^{+/+}$)
2.9%</td></tr>
<tr><td>E11.5</td><td>18
31%</td><td>24
41.4%</td><td>11
19%</td><td>4 (↓HR)
6.9%</td><td>1 (Cxadr$^{+/210}$)
1.7%</td></tr>
<tr><td>E12.5</td><td>7
22.6%</td><td>16
51.6%</td><td colspan="2">0
0%</td><td>8 (Cxadr$^{210/210}$)
25.8%</td></tr>
<tr><td>Expected</td><td>25%</td><td>50%</td><td colspan="2">25%</td><td></td></tr>
</table>

↓HR = Erratic heart rate, E = Embryonic day

Table S9: Genotypes of progeny from *Cxadr*$^{+/\Delta}$;Tg$^{Myh6\text{-Cre}}$ crossed to *Cxadr*$^{f/f}$ mice

Stage	*Cxadr*$^{\Delta/\Delta(f)}$;Tg$^{Myh6\text{-Cre}}$	*Cxadr*$^{+/\Delta}$;Tg$^{Myh6\text{-Cre}}$	*Cxadr*$^{+/\Delta}$	*Cxadr*$^{+/f}$
E11.5	8	4	9	2
E12.5	7	7	3	4
E13.5	2	6	2	7
E16.5	4 (1)	9	6	9

(1) = Embryo with severe lymphatic oedema

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