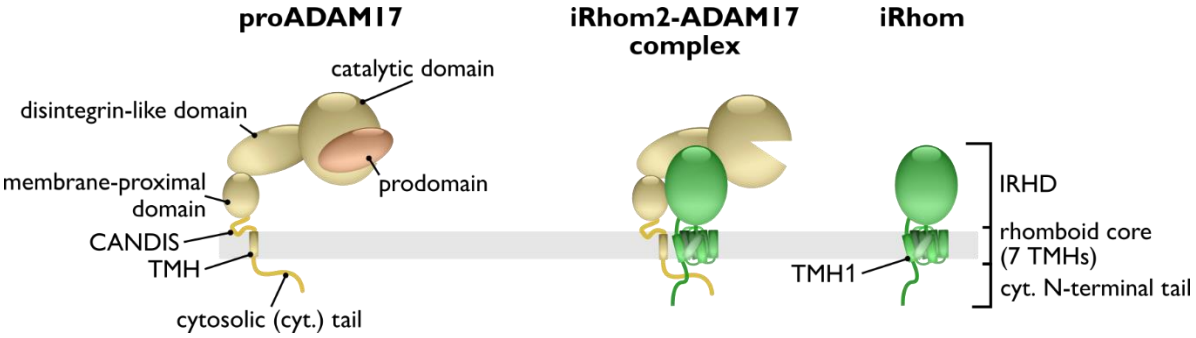
Table S1: Potential interaction sides between murine iRhom2 and murine ADAM17. The relaxed structures (best predicted model/rank 1) of the iRhom2-mature-ADAM17 complex and the iRhom2-proADAM17 complex were used to investigate interaction interfaces and identify putative residues involved. The analysis was performed with ChimeraX and InterProSurf. Residues that have putative intermolecular interactions (hydrogen bonds, van der Waal contacts) with each other are listed with their position in the respective substructure/domain. TMH = transmembrane helix; CANDIS = Conserved ADAM-SeventeeN Dynamic Interaction Sequence.



residues in murine iRhom2		residues in ADAM17	
R373	TMH1	D695	TMH
Y375	TMH1	V691	TMH
		W684	TMH
Y378	TMH1	W684	TMH
W379	TMH1	S680	TMH
		W684	TMH
		L681	TMH
V383	TMH1	L677	TMH
		S680	TMH
		V676	TMH
I387	TMH1	V673	CANDIS
		V676	TMH
L390	TMH1	V676	TMH
T394	TMH1	I672	CANDIS
Y395	TMH1	A669	CANDIS
		V676	TMH
		I672	CANDIS
T408	IRHD	I672	CANDIS
		G121	prodomain
L410	IRHD	R241	catalytic domain
		H118	prodomain

		Y82	prodomain
		V120	prodomain
L412	IRHD	K57	prodomain
R415	IRHD	E253	catalytic domain
	IRHD	R257	catalytic domain
G416	IRHD	K57	prodomain
V417	IRHD	Y250	catalytic domain
		N249	catalytic domain
		E253	catalytic domain
		Y82	prodomain
		T84	prodomain
		H65	prodomain
Y418	IRHD	R241	catalytic domain
	IRHD	Y250	catalytic domain
Y418	IRHD	Y82	prodomain
		H118	prodomain
		K57	prodomain
E419	IRHD	T396	catalytic domain
S420	IRHD	T396	catalytic domain
		P123	prodomain
K422	IRHD	D443	catalytic domain
		D124	prodomain
		P123	prodomain
H440	IRHD	D670	CANDIS
L441	IRHD	D670	CANDIS
		I672	CANDIS
N475	IRHD	N480	catalytic domain
		S481	disintegrin-like domain
		R482	disintegrin-like domain
D476	IRHD	S481	disintegrin-like domain
		S62	prodomain
		A63	prodomain
		T64	prodomain
R477	IRHD	P520	disintegrin-like domain
S489	IRHD	D256	catalytic domain

		E253	catalytic domain
		E88	prodomain
E490	IRHD	R473	catalytic domain
		N475	catalytic domain
		R482	disintegrin-like domain
T491	IRHD	N480	catalytic domain
		D256	catalytic domain
		I252	catalytic domain
		E88	prodomain
		N475	catalytic domain
L492	IRHD	I252	catalytic domain
		T64	prodomain
		S86	prodomain
R525	IRHD	A540	disintegrin-like domain
		T541	disintegrin-like domain
		L568	disintegrin-like domain
T526	IRHD	I538	disintegrin-like domain
		A540	disintegrin-like domain
E528	IRHD	R625	MPD
		L568	disintegrin-like domain
E529	IRHD	R625	MPD
		K626	MPD
P530	IRHD	G627	MPD
		K628	MPD
		K626	MPD
A531	IRHD	L568	disintegrin-like domain
		K628	MPD
		D569	disintegrin-like domain
S533	IRHD	D569	disintegrin-like domain
A535	IRHD	C591	MPD
		A592	MPD
H536	IRHD	K628	MPD
		P629	MPD
		L624	MPD
E550	IRHD	R625	MPD

S554	IRHD	E536	disintegrin-like domain
H556	IRHD	E536	disintegrin-like domain
		C534	disintegrin-like domain
		Q535	disintegrin-like domain
T557	IRHD	Q535	disintegrin-like domain
		I538	disintegrin-like domain
K565	IRHD	D59	prodomain
L613	IRHD	D670	CANDIS
		N671	CANDIS
L614	IRHD	R651	CANDIS
		F667	CANDIS
P615	IRHD	R651	CANDIS
L617	IRHD	Q646	CANDIS
		V645	MPD
		V648	CANDIS
		R651	CANDIS
N618	IRHD	V645	MPD
P619	IRHD	R644	MPD
L630	IRHD	R473	catalytic domain
		V673	CANDIS
F633	IRHD	V673	CANDIS
		L677	TMH