Electronic Supplementary Material (ESI) for Molecular BioSystems.

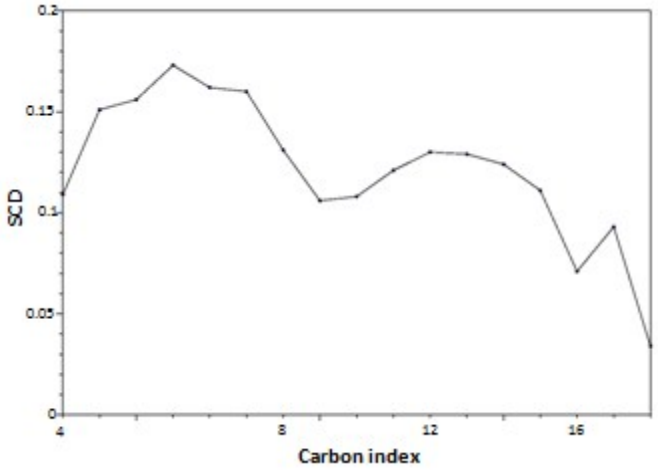

Figure S1. The segmental order parameter SCD calculated for the membrane during the MD simulation.

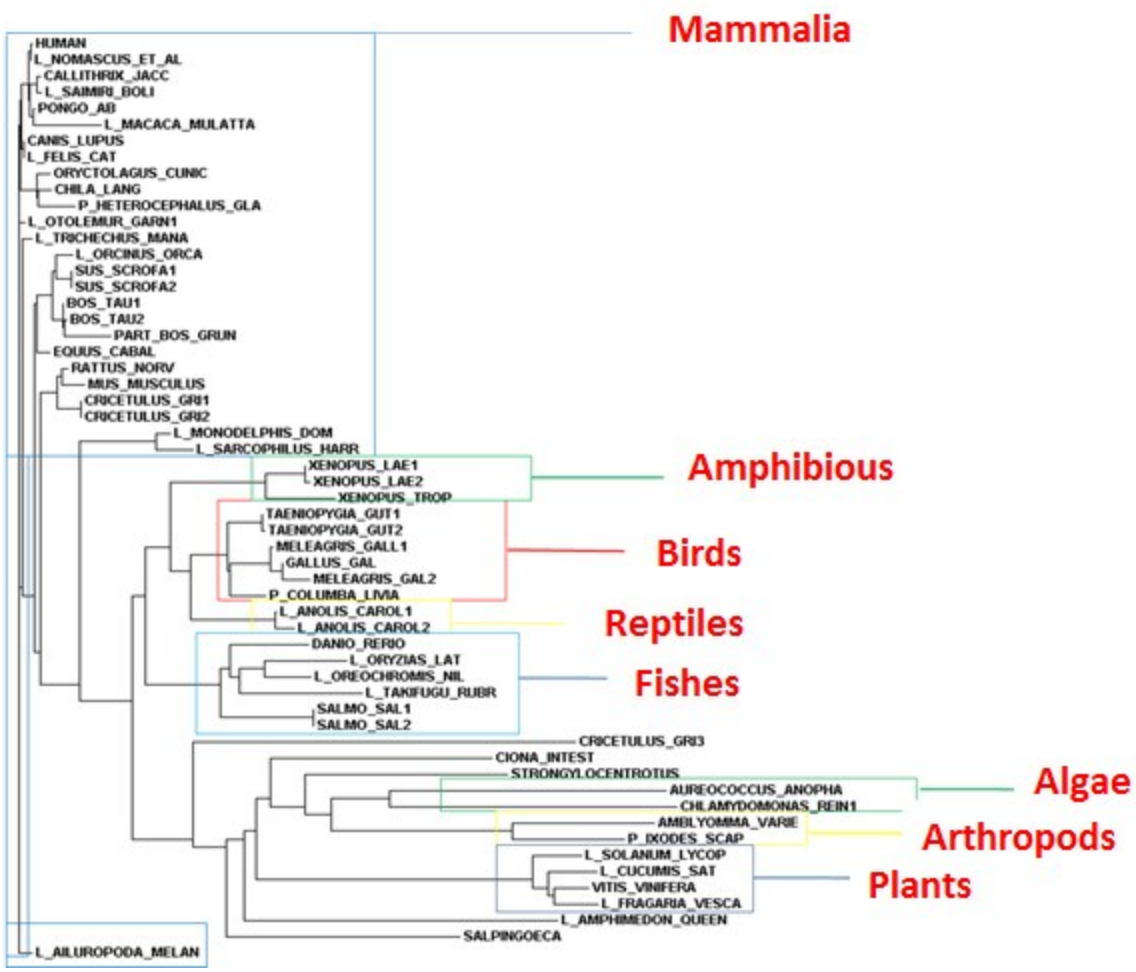

Figure S2. Phylogenetic analysis on SELK sequences from different organisms.

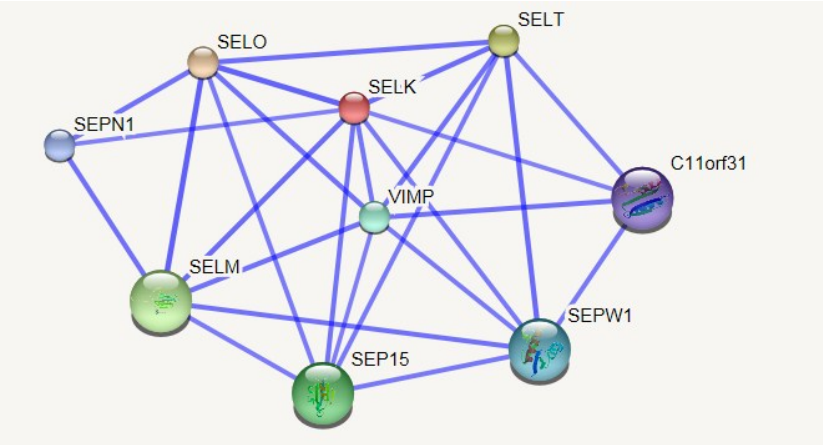

Figure S3. Network analysis on SELK performed by STRING (http://string-db.org/)

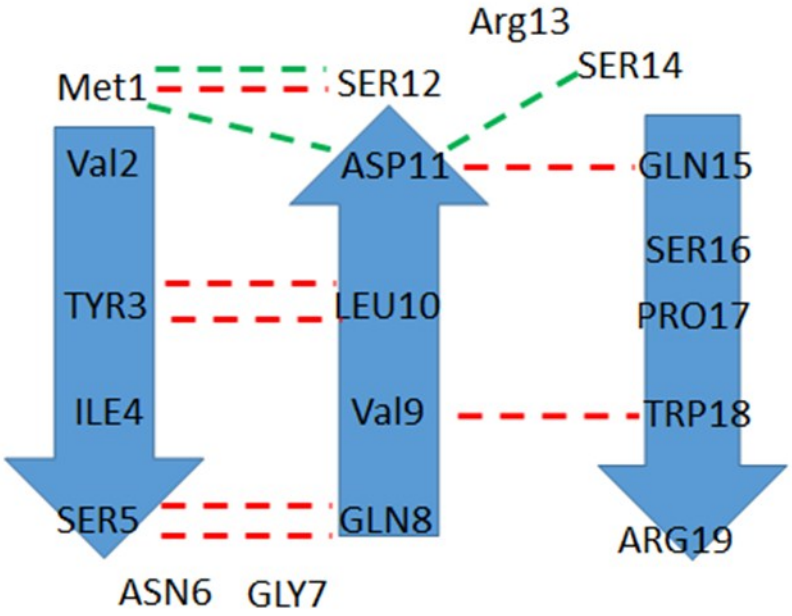

Figure S4. Picture of the most compact representation of the N-terminal sheet as suggested by the H-bonds determined during the dynamics. In red the MM-MM H-bonds and in green the H-bonds interacting through the side chains.

Table S1.H-bonds and occupancy between the residues present in the N-terminal domain.

donor	acceptor	occupancy
MET1-Main	SER12-Side	11.16%
TYR3-Main	LEU10-Main	8.09%
GLN15-Main	ASP11-Main	2.70%
SER14-Main	ASP11-Side	0.67%
SER16-Side	SER14-Main	0.31%
LEU10-Main	TYR3-Main	5.76%
GLN8-Main	SER5-Main	1.10%
SER12-Main	MET1-Main	1.23%
TRP18-Main	VAL9-Main	7.88%
SER5-Main	GLN8-Main	1.44%
ARG13-Side	SER14-Side	0.03%
SER14-Side	ASP11-Side	5.18%
ASP11-Main	SER16-Main	0.34%
SER16-Main	ASP11-Main	0.06%
TRP18-Side	ASP11-Side	0.12%
MET1-Main	ASP11-Side	19.37%
ARG13-Main	ASP11-Side	0.06%
TRP18-Side	SER14-Side	0.09%
SER5-Side	ASN6-Side	0.40%
SER16-Side	PRO17-Main	0.06%
ARG13-Side	ASP11-Side	93.39%
GLN8-Side	SER5-Main	0.03%
MET1-Main	TYR3-Side	0.03%
GLN8-Side	ASN6-Main	0.03%

SER14-Main	ASP11-Main	0.06%
GLN8-Side	GLY7-Main	0.18%
SER14-Side	SER16-Main	0.03%

Table S2.H-bonds and occupancy between the residues of the N-terminal domain and the lipids.

donor	acceptor	occupancy
ARG19-Side	POPC4-Side	69.27%
ARG19-Side	POPC11-Side	69.33%
ARG19-Side	POPC9-Side	86.07%
GLN8-Side	POPC11-Side	0.25%
SER16-Side	POPC3-Side	0.25%
ARG19-Main	POPC3-Side	0.06%
POPC17-Side	GLY7-Main	0.03%
SER14-Side	POPC26-Side	0.78%
ARG13-Side	POPC27-Side	0.41%
SER14-Side	POPC27-Side	4.17%
ARG13-Side	POPC20-Side	15.57%

Table S3.H-bonds and occupancy between the N-terminal domain and the water molecules.

donor	acceptor	occupancy
water-O	TRP18-Main	14.82%
water-O	GLY7-Main	8.95%
water-O	GLN15-Side	11.46%
water-O	GLN15-Main	7.60%
TYR3-Side	water-O	4.77%
water-O	ARG19-Main	4.09%
SER14-Side	water-O	3.63%
water-O	ASP11-Side	28.26%
water-O	SER14-Main	6.76%
water-O	ASN6-Main	8.90%
water-O	SER5-Main	3.51%
water-O	ARG13-Main	6.65%
water-O	ILE4-Main	7.11%
water-O	SER14-Side	2.61%
ASN6-Side	water-O	0.34%
ARG19-Side	water-O	2.54%
water-O	SER5-Side	3.07%
ARG13-Side	water-O	6.15%
water-O	PRO17-Main	7.91%
SER12-Side	water-O	5.04%
MET1-Main	water-O	9.62%
water-O	GLN8-Side	9.73%
SER16-Side	water-O	4.46%
water-O	VAL2-Main	7.60%

water-O	TYR3-Side	2.08%
water-O	SER12-Main	5.93%
ARG19-Main	water-O	0.81%
VAL2-Main	water-O	0.57%
water-O	SER16-Main	2.51%
water-O	ASN6-Side	10.70%
water-O	SER16-Side	3.11%
VAL9-Main	water-O	0.95%
SER5-Side	water-O	3.72%
water-O	LEU20-Main	7.82%
LEU20-Main	water-O	0.29%
water-O	GLN8-Main	1.35%
ILE4-Main	water-O	0.34%
GLN15-Side	water-O	0.52%
GLY7-Main	water-O	0.75%
water-O	ASP11-Main	0.08%
water-O	VAL9-Main	0.48%
water-O	TYR3-Main	0.57%
ASN6-Main	water-O	0.70%
GLN8-Side	water-O	0.43%
water-O	SER12-Side	1.75%
TRP18-Side	water-O	0.21%
water-O	MET1-Main	0.31%
water-O	LEU10-Main	0.02%
ASP11-Main	water-O	0.41%
water-O	TRP18-Side	0.03%

Table S4.H-bonds and occupancy between the residues present in the TM-helix.

donor	acceptor	occupancy
PHE26-Main	LEU22-Main	9.23%
THR40-Side	LEU36-Main	40.77%
TRP28-Main	THR24-Main	1.29%
PHE27-Main	ILE23-Main	5.18%
PHE38-Main	VAL34-Main	4.35%
THR40-Main	LEU36-Main	2.39%
PHE37-Main	PHE33-Main	12.78%
VAL34-Main	ILE30-Main	11.86%
GLU32-Main	TRP28-Main	3.16%
GLY29-Main	ASP25-Main	2.42%
ALA31-Main	PHE27-Main	0.92%
LEU41-Main	PHE37-Main	0.86%
ILE30-Main	PHE26-Main	4.48%
PHE33-Main	GLY29-Main	1.38%
LYS39-Main	VAL35-Main	2.27%
LEU36-Main	GLU32-Main	0.09%
VAL35-Main	ALA31-Main	0.43%
SER21-Side	ASP25-Side	2.45%
THR40-Side	PHE37-Main	0.06%

Table S5.H-bonds and occupancy between the residues of the trans-membrane helix and the lipids.

LYS39-Side	POPC1-Side	35.23%
THR40-Side	POPC6-Side	0.02%

Table S6.H-bonds and occupancy between the residues of the trans-membrane helix and thewater molecules.

donor	acceptor	occupancy
LYS39-Side	water-O	4.17%
water-O	ASP25-Main	2.93%
water-O	THR40-Main	5.12%
water-O	SER21-Side	1.20%
water-O	LEU42-Main	4.03%
SER21-Side	water-O	3.77%
THR24-Side	water-O	2.01%
water-O	THR40-Side	0.18%
LEU22-Main	water-O	0.72%
water-O	SER21-Main	4.86%
water-O	LYS39-Main	0.98%
water-O	PHE38-Main	2.36%
water-O	LEU41-Main	2.48%
water-O	THR24-Side	0.93%
water-O	ILE23-Main	0.08%
SER21-Main	water-O	0.15%
ILE23-Main	water-O	0.12%
ASP25-Main	water-O	0.02%
THR24-Main	water-O	0.03%
water-O	THR24-Main	0.02%

Table S7.H-bonds and occupancy between the residues of theC-terminal region. In details, having used the "all" option, the frequency of interaction may be greater than 100%, because a given residue pair may contain more than one H-bond, each of which is counted separately.

donor	acceptor	occupancy
ARG59-Side	ASP61-Side	120.52%
ARG94-Side	ARG94-Side	9.99%
ARG59-Side	ARG59-Main	0.12%
ASN69-Side	SER84-Side	0.15%
GLY65-Main	SER51-Main	0.55%
ASN54-Side	LYS48-Main	0.03%
TYR60-Side	SER56-Main	0.52%
ARG49-Main	GLN44-Main	1.23%
ARG64-Side	ASP62-Side	0.31%
ARG64-Side	ARG50-Main	2.51%
ASN69-Side	PRO85-Main	0.12%
GLY53-Main	SER51-Side	0.06%
TYR52-Side	ASP62-Side	0.03%
LYS47-Main	GLN43-Main	1.81%
ARG50-Side	ASP45-Side	1.59%
LYS48-Main	GLN44-Main	5.03%
LYS48-Side	GLN44-Side	0.34%
SER55-Side	CYS92-Main	2.64%
ARG50-Main	ASP45-Main	1.04%
MET88-Main	SER55-Side	2.91%
GLY90-Main	ASP57-Side	0.55%
GLN43-Side	ASP45-Side	0.15%
GLY63-Main	ASP62-Side	0.09%

ARG49-Side	ASP57-Main	0.06%
ASN54-Side	GLY53-Main	0.03%
HSD79-Side	ASN78-Side	2.05%
TYR60-Side	ARG49-Main	3.86%
ARG50-Side	ASP45-Main	0.12%
ARG73-Side	ASP62-Side	3.37%
ALA89-Main	SER56-Main	0.67%
ARG76-Main	MET88-Main	2.15%
ARG81-Side	HSD79-Main	0.03%
SER51-Side	ASN54-Side	11.68%
ASN69-Side	SER84-Main	0.12%
SER84-Side	GLY93-Main	0.12%
ARG73-Side	ASP61-Main	6.31%
ARG72-Side	PRO71-Main	17.41%
ASN69-Side	PRO66-Main	0.25%
GLY65-Main	TYR52-Main	4.90%
ARG64-Side	ARG49-Main	9.13%
ARG50-Main	VAL46-Main	0.74%
TYR60-Main	ARG73-Main	0.18%
ASN78-Side	ARG76-Main	0.21%
SER51-Main	LYS47-Main	1.23%
TYR60-Side	ASP57-Main	0.28%
SER56-Side	GLN44-Main	0.09%
LYS48-Side	GLN44-Main	0.18%
SER56-Side	ASP45-Main	0.09%
ARG73-Side	ASP61-Side	3.89%

SER58-Main	ASP57-Side	0.06%
SER84-Side	GLY68-Main	0.03%
SER55-Main	CYS92-Main	0.77%
ARG49-Main	ASP45-Main	0.77%
ARG72-Side	ASN78-Side	1.87%
ARG59-Side	ARG73-Main	0.06%
SER55-Side	GLY91-Main	2.33%
SER84-Side	PRO83-Main	0.09%
ARG72-Side	HSD79-Side	0.03%
SER56-Side	ASP57-Side	0.12%
GLY90-Main	SER56-Main	0.46%
ARG64-Side	GLY63-Main	0.03%
SER55-Side	ARG64-Main	0.09%
ASN78-Side	ASN78-Main	0.03%
ALA89-Main	SER58-Main	0.06%
ARG64-Side	SER51-Main	1.66%
ARG72-Side	ARG76-Main	0.74%
SER84-Side	ASN69-Side	3.28%
LYS48-Side	ASP45-Side	0.61%
ASN69-Side	PRO67-Main	0.21%
SER84-Side	PRO85-Main	0.03%
ARG73-Side	TYR60-Main	0.61%
ARG72-Side	PRO70-Main	0.18%
GLY75-Main	ARG72-Main	0.03%
LYS48-Side	GLY91-Main	0.18%
ARG49-Side	ASP45-Side	27.43%

ASN54-Side	CYS92-Main	0.37%
ARG72-Main	ARG64-Main	4.05%
LYS48-Side	ASP57-Side	0.46%
ARG49-Side	ASP57-Side	0.09%
ASN78-Side	ILE77-Main	0.03%
SER56-Side	SER58-Side	0.06%
ARG76-Side	GLY75-Main	0.06%
ALA89-Main	ASP57-Side	0.06%

Table S8. H-bonds and occupancy between the residues of theC-terminal regionand thelipid molecules.

donor	acceptor	occupancy
LYS47-Side	POPC4-Side	28.74%
GLN44-Side	POPC18-Side	0.75%
TYR52-Main	POPC4-Side	0.18%
LYS48-Side	POPC18-Side	0.02%
ARG50-Side	POPC4-Side	28.23%
GLY68-Main	POPC14-Side	0.26%
SER51-Side	POPC4-Side	0.40%

Table S9. H-bonds and occupancy between the residues of theC-terminal regionand thewater molecules.

donor	acceptor	occupancy
ARG73-Side	water-O	12.98%
SER51-Side	water-O	0.77%
water-O	ASP61-Side	63.86%
water-O	ARG76-Main	9.33%
water-O	MET74-Main	8.32%
water-O	HSD79-Main	7.82%
water-O	ASP62-Side	85.95%
water-O	MET88-Main	11.08%
water-O	ASP45-Side	69.09%
water-O	GLY68-Main	3.19%
water-O	LEU80-Main	10.42%
water-O	GLY90-Main	7.17%
water-O	GLY65-Main	3.65%
water-O	GLY91-Main	7.65%
water-O	ARG94-Side	56.38%
water-O	ASN54-Side	3.25%
ARG76-Side	water-O	13.30%
ARG64-Side	water-O	12.83%
ARG94-Side	water-O	22.42%
water-O	ASP61-Main	8.08%
water-O	SER84-Main	8.60%
water-O	SER56-Side	3.22%
water-O	SER55-Main	1.27%
ARG49-Side	water-O	10.88%
water-O	ARG50-Main	7.89%
water-O	GLY93-Main	5.30%
water-O	PRO83-Main	7.88%
water-O	ASP57-Side	89.09%
water-O	ASN69-Side	9.21%
water-O	GLN44-Side	12.18%
water-O	ARG81-Main	6.90%
LYS48-Side	water-O	8.03%
water-O	PRO87-Main	10.28%
ARG81-Side	water-O	12.67%
water-O	ARG64-Main	4.51%
ARG72-Side	water-O	10.41%
water-O	ILE77-Main	10.48%
water-O	ASN78-Side	8.66%
ARG50-Side	water-O	9.29%
water-O	PRO66-Main	9.24%
SER56-Side	water-O	7.22%
water-O	GLN43-Side	11.40%
water-O	GLY82-Main	10.84%
water-O	PRO67-Main	6.56%
water-O	SER58-Side	3.39%
water-O	LYS47-Main	1.43%
SER58-Side	water-O	6.41%
ARG59-Side	water-O	7.34%
TYR52-Side	water-O	5.24%
ARG72-Main	water-O	0.05%
water-O	ASN69-Main	10.21%
water-O	GLY53-Main	4.09%

water-O	PRO71-Main	5.62%
LYS47-Side	water-O	6.04%
water-O	ASN78-Main	9.82%
water-O	GLY63-Main	7.85%
water-O	TYR52-Side	1.69%
water-O	TYR52-Main	1.55%
ASP61-Main	water-O	0.49%
water-O	SER58-Main	6.11%
water-O	CYS92-Main	0.80%
GLY68-Main	water-O	1.26%
GLN43-Main	water-O	0.61%
water-O	PRO70-Main	7.91%
GLN44-Main	water-O	0.11%
ILE77-Main	water-O	0.35%
water-O	ARG72-Main	5.55%
HSD79-Main	water-O	0.90%
GLY82-Main	water-O	0.06%
ASP57-Main	water-O	0.08%
water-O	GLY75-Main	9.09%
water-O	TYR60-Main	7.92%
water-O	VAL46-Main	0.97%
ASN54-Side	water-O	0.21%
ARG73-Main	water-O	1.66%
water-O	ARG59-Main	7.14%
water-O	HSD79-Side	2.64%
water-O	ARG73-Main	5.21%
water-O	ASP57-Main	7.30%
GLY63-Main	water-O	0.92%
water-O	LYS48-Main	0.09%
water-O	ALA89-Main	8.26%
SER84-Side	water-O	4.81%
GLY75-Main	water-O	0.20%
ASN69-Side	water-O	0.28%
water-O	SER84-Side	3.40%
ASN69-Main	water-O	0.09%
ASP45-Main	water-O	0.32%
water-O	SER56-Main	4.72%
GLN43-Side	water-O	0.43%
water-O	ASP62-Main	7.26%
MET74-Main	water-O	0.60%
water-O	PRO85-Main	6.47%
water-O	GLN43-Main	0.06%
water-O	ASP45-Main	1.61%
SER58-Main	water-O	0.48%
ASN78-Side	water-O	0.46%
water-O	PRO86-Main	11.56%
ASN78-Main	water-O	0.28%
TYR52-Main	water-O	0.81%
GLY65-Main	water-O	0.23%
GLN44-Side	water-O	0.43%
water-O	SER51-Side	0.81%
ARG81-Main	water-O	0.40%
GLY91-Main	water-O	0.32%
GLY93-Main	water-O	0.72%
CYS92-Main	water-O	1.75%
water-O	GLN44-Main	0.06%
GLY90-Main	water-O	0.38%

water-O	SER51-Main	0.92%
LEU80-Main	water-O	0.02%
HSD79-Side	water-O	0.08%
water-O	ARG49-Main	2.93%
water-O	ASN54-Main	0.02%
ARG64-Main	water-O	0.08%
ASP62-Main	water-O	0.18%
water-O	TYR60-Side	1.58%
TYR60-Side	water-O	3.49%
ARG76-Main	water-O	0.06%
SER84-Main	water-O	0.02%
ALA89-Main	water-O	0.28%
SER55-Side	water-O	4.18%
TYR60-Main	water-O	0.23%
SER56-Main	water-O	0.46%
ARG94-Main	water-O	0.03%
ARG59-Main	water-O	0.12%
MET88-Main	water-O	0.15%
water-O	SER55-Side	0.05%
VAL46-Main	water-O	0.02%
SER55-Main	water-O	0.03%

Table S10. RMSD values (expressed in Angstroms) obtained superimposing the five clusters related to three regions of SELK, N-terminal domain (A), trans-membrane helix (B) and C-terminal domain (C).

A

	Cluster1	Cluster2	Cluster3	Cluster4	Cluster5
Cluster1		0.479	1.473	1.453	2.754
Cluster2			1.264	1.687	2.561
Cluster3				1.297	1.977
Cluster4					1.908
Cluster5					

B

	Cluster1	Cluster2	Cluster3	Cluster4	Cluster5
Cluster1		0.436	0.711	0.79	1.248
Cluster2			0.463	0.624	1.16
Cluster3				0.569	1.04
Cluster4					1.071
Cluster5					

C

	Cluster1	Cluster2	Cluster3	Cluster4	Cluster5
Cluster1		1.228	1.015	2.537	3.833
Cluster2			0.822	2.273	3.616
Cluster3				1.941	3.452
Cluster4					2.676
Cluster5					

Table S11. Solvent accessibility (ASA) values evaluated for the prolines and the sequence region reported in the literature as involved in the binding with p97(VCP) [12] and DHHC6 [6].

	Cluster1	Cluster2	Cluster3	Cluster4	Cluster5
Pro83	0.83	0.97	0.78	0.82	0.85
Pro85	0.58	0.48	0.42	0.51	0.55
Pro86	0.07	0.08	0.11	0.13	0.44
Pro87	0.06	0.03	0.06	0.08	0.14
Total ASA	1.54	1.56	1.37	1.54	1.97
Arg64	0.38	0.28	0.23	0.34	0.17
Gly65	0.06	0.17	0.14	0.17	0.18
Pro66	0.23	0.27	0.24	0.25	0.46
Pro67	0.92	0.93	0.95	0.86	0.86
Gly68	0.89	0.90	0.85	0.79	1.00
Asn69	0.25	0.33	0.40	0.50	0.33
Pro70	0.47	0.51	0.59	0.69	0.42
Total ASA	3.19	3.38	3.40	3.58	3.42

Table S12. DSSPof the N-terminal during the dynamics in membrane at 0, 3, 6, 9, 12, 15 and 20 ns. Labels: E is for extended strand, participates in β ladder; Tfor hydrogen bonded turn; B for residue in isolated β-bridge and S for bend. No assigned secondary structure are depicted as " - " .

RES 1M	RES 2	RES 3Y	RES 4	RES 5S	RES 6	RES 7G	RES 8	RES 9V	RES 10L	RES 11	RES 12	RES 13	RES 14	RES 15	RES 16	RES 17P	RES 18W	RES 19	RES 20
-	E	E	E	E	T	T	E	E	E	E	T	T	T	-	-	-	B	-	-
-	E	E	E	E	T	T	E	E	E	E	T	T	T	T	E	E	-	-	-
-	E	E	E	E	T	T	E	E	E	E	T	T	T	T	E	E	-	-	-
-	E	E	E	E	T	T	E	E	E	E	T	T	T	-	-	-	-	-	-
-	E	E	E	E	T	T	E	E	E	E	T	T	T	-	S	-	-	-	-
-	E	E	E	E	T	T	E	E	E	E	T	T	T	-	-	-	-	-	-
-	E	E	E	E	T	T	E	E	E	E	T	T	T	T	E	E	-	-	-

Table S13 Average distance in Å between alpha carbons of residues found involved in the formation of the sheet as reported in table 12 S.

Residue	Counterpart in the sheet	Average Distance Ca - Ca
Met 1	**Asp 11**	**6.93**
Met 1	**Ser 12**	**6.65**
Tyr 3	**Leu 10**	**5.15**
Ser 5	**Gln 8**	**4.90**
Val 9	**Trp 18**	**4.94**
Asp 11	**Gln 15**	**5.35**
Asp 11	**Arg 13**	**5.30**
Asp 11	**Ser 14**	**5.25**

Table S14. We report the result of the analysis by ProFunc server that identifies the most likely biochemical function of a protein from its three-dimensional structure on the basis of fold matching, residue conservation, surface cleft analysis, and functional 3D templates. In details, we show **A)** the name of proteins found by ProFunc, the PDB code related to its three dimensional structure and the RMSD value obtained by superimposing its structure with that of N-terminal region in SELK and **B)** the alignment between the N-terminal region of SELK with the two selected PDB proteins, codes 2ho2 and 2dyf, where the localization of b-strands and the coil regions are reported by yellow arrows and violet lines, respectively.

A

ProteinName	**PDB code**	**RMSD (Å)**
human fe65-ww domain	2ho2	1.42Å
ww domain of fbp11	2dyf	1.79Å

B