Supporting Information for

Crosstalk between regulatory elements in the disordered TRPV4 N-terminus modulates lipid-dependent channel activity

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Table S1 – SAXS data reporting table for native TRPV4 NTD, ARD and IDR as well as PIP₂-binding site mutants.

| SASEDB Accession Codes Non- Non | Sample details SAMPLE | NTD | NTDAAWAA | ARD | IDR | IDR ^{AAWAA} | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| 20 mM Tris pH 7.0, 10 mM DTT300 mM10.0 mg/ml10.1 mg/ml | | 2-382 | 2-382 | | 2-134 | 2-134 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| NaCl concentration300 mM100 mMSample injection volume40 µl40 µl <td< td=""><td>(0,</td><td>2-302</td><td></td><td></td><td></td><td>2-134</td></td<> | (0, | 2-302 | | | | 2-134 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| $\begin{array}{c c c c c c c c c c c c c c c c c c c $ | | . , | . , | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| Porod volume (nm³)5978415837Shape classificationflexibleflexiblecompactrandom chainrandom chainrandom chainMolecular Weight analysis:MW, calculated from amino acid sequence, kDa42.542.228.014.514.2MW, calculated from amino acid sequence, kDa38.4248-5626-2924-2922-25Ab initio modelling:P1WethodDAMMINSymmetryP1#models used for averaging90.58Discrepancy, NSD0.58Resolution estimate, nm24Quality-of-fit, CorMap P / χ^2 0.45/1.06Rigd body/Normal modeSREFLEXmodelling:P1MethodSREFLEXSymmetryP1TemplatePDB ID: 3W9GInitial template fit, CorMap P / χ^2 4.05e-07/1.21Ensemble modelling:FOMMethodEOMSymmetryP1P1P1P1P1P1P1P1P1P1P1TemplatePDB ID: 3W9GNethodEOMSymmetryP1P1P1P1P1P1P1P1P1P1P1P1P1TemplatePDB ID: 3W9GSymmetryP1P1P1P1P1P1P1P1P1P1P1P1< | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| • | 42.5 | 42.2 | 28.0 | 14.5 | 14.2 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| Discrepancy, NSD Resolution estimate, nm Quality-of-fit, CorMap P / χ^2 Quality-of-fit, CorMap P / χ^2 Rigid body/Normal mode modelling: Method SREFLEX Symmetry P1 Template Initial template fit, CorMap P / χ^2 Final model fit, CorMap P / χ^2 Ensemble modelling: Method EOM EOM EOM EOM EOM EOM EOM EOM | 00 | | | 9 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Discrepancy, NSD 24 Resolution estimate, nm 0.45/1.06 Rigid body/Normal mode 0.45/1.06 modelling: V Method SREFLEX Symmetry P1 Template PDB ID: 3W9G Initial template fit, CorMap P / χ² 1.44e-43/3.33 / χ² 1.44e-43/3.33 Final model fit, CorMap P / χ² 4.05e-07/1.21 Ensemble modelling: EOM Method EOM Symmetry P1 P1 P1 P1 P1 Ensemble modelling: P1 Method EOM EOM Symmetry P1 P1 P1 P1 P1 Final model fit; CorMap P / χ² P1 P1 Final model fity P1 P1 P1 P1 P1 P1 P1 Final model fity PDB ID: 3W9G - - | | | | 0.58 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| TemplatePDB ID: $3W9G$ Initial template fit, CorMap P $1.44e-43/3.33$ / χ^2 $1.44e-43/3.33$ Final model fit, CorMap P / χ^2 $4.05e-07/1.21$ Ensemble modelling:MethodEOMEOMSymmetryP1P1PDB ID: $3W9G$ PDB ID: $3W9G$ - | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Initial template fit, CorMap P / χ^2 Final model fit, CorMap P / χ^2 Ensemble modelling: Method EOM EOM EOM EOM EOM EOM Symmetry P1 P1 P1 P1 P1 Template PDB ID: 3W9G PDB ID: 3W9G | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| / χ² I.44e-43/3.33 Final model fit, CorMap P / χ² 4.05e-07/1.21 Ensemble modelling: EOM EOM EOM Method EOM EOM P1 Symmetry P1 P1 P1 Template PDB ID: 3W9G PDB ID: 3W9G - | - | | | PDB ID: 3W9G | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| / χ² 4.05e-07/1.21 Ensemble modelling: 4.05e-07/1.21 Method EOM EOM Symmetry P1 P1 PDB ID: 3W9G PDB ID: 3W9G - | | | | 1.44e-43/3.33 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ensemble modelling: EOM | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Method EOM EOM< | | | | 4.05e-07/1.21 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Symmetry P1 < | Ensemble modelling: | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Template PDB ID: 3W9G PDB ID: 3W9G | Method | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Symmetry | | | | P1 | P1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Final model fit, CorMap P / χ ² 0.72/0.99 0.52/0.99 0.97/0.98 0.19/1.3 | Template | | | | - | - | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Final model fit, CorMap P / χ^2 | 0.72/0.99 | 0.52/0.99 | | 0.97/0.98 | 0.19/1.3 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

Table S2 – SAXS data reporting table for TRPV4 NTD deletion constructs.

| SAMPLE | NTD ^{∆N120} | NTD ^{∆N104} | NTD ^{∆N97} | NTD ^{∆N54} | | | |
|--|--------------------------------|--------------------------------|-------------------------------|---------------------------|--|--|--|
| SASBDB Accession Codes | | | | | | | |
| Organism | | Gallus | gallus | | | | |
| NCBI protein accession ID | 395427 | | | | | | |
| (amino acid range) | 121-382 | 105-382 | 98-382 | 55-134 | | | |
| SEC-SAXS buffer | 121 302 | | 7.0, 10 mM DTT | 55 151 | | | |
| NaCl concentration | | | mM | | | | |
| Sample injection volume | 40 µl | 40 μl | 40 µl | 40 µl | | | |
| Sample injection conc. | 7.4 mg/ml | 9.5 mg/ml | 6.5 mg/ml | 3.7 mg/ml | | | |
| SEC column | 0. | ease 5/150 | 010 1118/111 | 017 118/111 | | | |
| SEC flow rate | 5200 mere | • | ıl/min | | | | |
| SEC temperature | | | °C | | | | |
| Instrument details | | 20 | | | | | |
| Instrument | | EMBL P12 hinSAXS hea | m line, DESY, Hamburg | | | | |
| Exposure time/# frames | | | s (540) | | | | |
| X-ray wavelength/energy | | | | | | | |
| Sample-to-detector distance | 0.124 nm (9996.5 eV) 3 m | | | | | | |
| Scattering intensity scale | | | | | | | |
| SEC-SAXS primary data | Arbitrary unit, a.u. | | | | | | |
| processing | | CHROMIXS (| ATSAS 3.0.1) | | | | |
| # frames used for averaging | 33 | 28 | 33 | 30 | | | |
| Working s-range (nm ⁻¹) | 0.15-3.7 | 0.20-2.88 | 0.18-3.17 | 0.08-2.7 | | | |
| Guinier analysis: | 0.15-5.7 | 0.20-2.88 | 0.18-3.17 | 0.08-2.7 | | | |
| Primary data analysis | | | | | | | |
| software | | PRIMUS (A | TSAS 3.0.1) | | | | |
| Guinier I(0) (σ) | 2046(4) | E264(7) | 1020/21 | 671(2) | | | |
| | . , | 5364(7) | 1828(3) | 671(2) | | | |
| R _g (Guinier, nm) (σ) | 2.67(0.01) 0.42-1.15 | 2.68(0.01) 0.67-1.24 | 2.52(0.01) 0.44-1.33 | 2.63(0.01) 0.21-1.30 | | | |
| sR _g range | 0.42-1.15 | 0.07-1.24 | 0.44-1.55 | 0.21-1.30 | | | |
| p(r) analysis: Method | | CNIC | DM 5 | | | | |
| | 2074/51 | | | (72/2) | | | |
| $I(0), POR(\sigma)$ | 2074(5) | 5574(9) | 1868(5) | 673(2) | | | |
| R_g (POR, nm) (σ) | 2.86(0-02) | 3.01(0.01) | 2.76(0.02) | 2.68(0.02) | | | |
| $D_{max}(nm)$ | 12.5 | 13.0 | 11.9 | 9.5 | | | |
| Quality of fit, CorMap P / χ^2 | 0.71/1.09 | 0.06/1.12 | 0.29/1.05 | 0.36/1.00 | | | |
| Porod volume (nm ³) | 43 | 46 | 42 | 64 flat | | | |
| Shape classification | extended | extended | compact | flat | | | |
| Molecular Weight analysis: | | | | | | | |
| MW, calculated from amino | 29.4 | 31.4 | 32.3 | 37.0 | | | |
| acid sequence, kDa | | | | | | | |
| MW from SAXS data, kDa | 37-40 | 25-29 | 31-35 | 29-31 | | | |
| Ensemble modeling | | | | | | | |
| Method | EOM | EOM | EOM | EOM | | | |
| Symmetry | P1 | P1 | P1 | P1 | | | |
| Template Final model fit, CorMap P / χ^2 | PDB ID: 3W9G 1.13e-64/39.45 | PDB ID: 3W9G 3.01e-66/14.67 | PDB ID: 3W9G 7.16e-04/1.14 | PDB ID: 3W9G 0.01/1.02 | | | |
| | | | | | | | |

Table S3 – Lipid composition used in the coarse-grained molecular dynamics simulations to mimic the plasma membrane inner leaflet.

| Lipid type | MARTINI model | Charge | Abundance [%] |
|--|---------------|--------|------------------|
| Cholesterol | CHOL | 0 | 20.03 |
| 1-palmitoyl-2-oleoyl-glycero-3-phosphocholine | POPC | 0 | 69.14 |
| 1,2-dioleoyl-glycero-3-phosphoserine | DOPS | -1 | 9.94 |
| 1-palmitoyl-2-linoleoyl- <i>sn</i> -glycero-3- phosphoinositol-4,5-bisphosphate | POP2 | -5 | 0.89 |

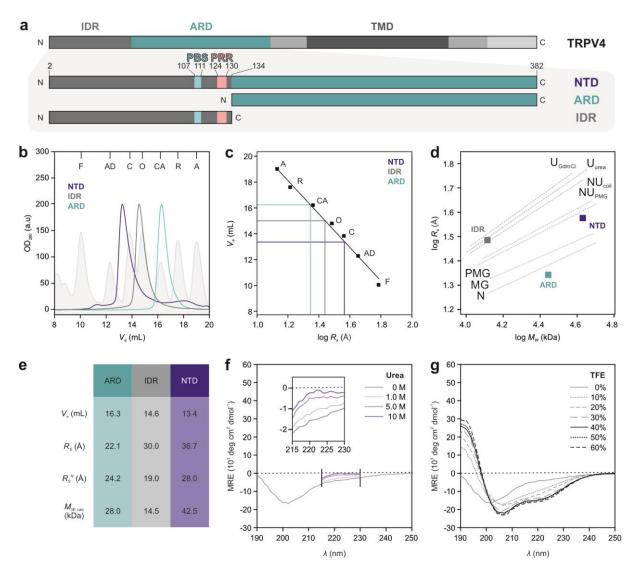


Fig. S1: Structural characterization of heterologously expressed TRPV4 N-terminal constructs.

a Construct design for *G. gallus* TRPV4 NTD, ARD and IDR. Important regulatory sites (PBS: PIP₂-binding site; PRR: proline rich region) are highlighted in light blue and light pink, respectively.

b Analytical size-exclusion chromatography (SEC) of TRPV4 NTD, IDR and ARD. SEC profiles of standard proteins for Stokes radius (*R*_s) determination are shown as filled curves (light grey): F: ferritin; AD: alcohol

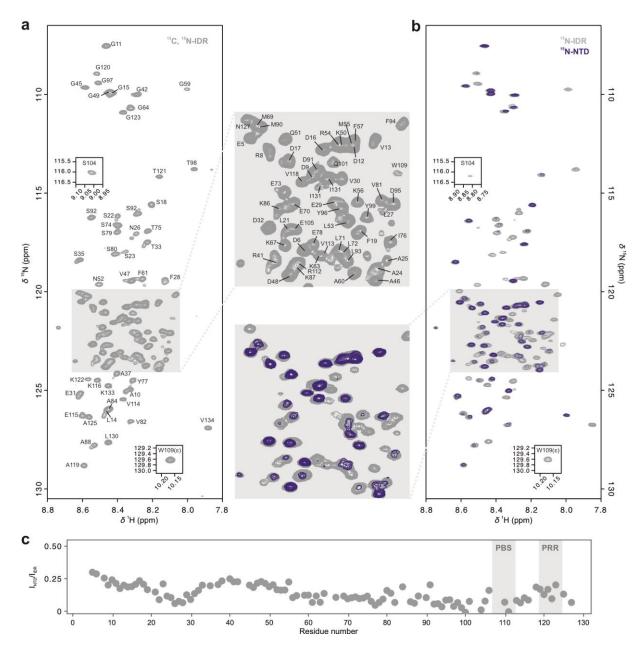
dehydrogenase; C: conalbumin; O: ovalbumin; CA: carbonic anhydrase; R: ribonuclease A; A: aprotinin. SEC profiles of NTD, IDR and ARD were normalized to an OD₂₈₀ of 200 a.u.

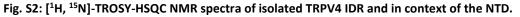
c Calibration curve (black) generated with elution volumes of protein standards shown in (b).

d Structural analysis of TRPV4 N-terminal constructs based on M_w and newly determined R_s . The ARD can be classified as a native, globular protein, the IDR as a native coil-like protein and the NTD as a pre-molten globule-like protein, i.e. a mixture of unfolded and globular states. (N: native; MG: molten globule; PMG: pre-molten globule; NU_{PMG}: native pre-molten globule like; NU_{coil}: native coil-like; U_{urea}: urea unfolded; U_{GdHCI}: guanidinium hydrochloride unfolded (for details on classification, see paper by Uversky et al.¹)).

e Stokes radii (R_s) calculated from the SEC elution volumes (V_e) in the calibration curve shown in (d). Theoretical R_s values (R_s^N) assuming globular, monomeric proteins under native conditions were determined using described procedures¹ based on the calculated molecular weights (M_{Wcalc}) of the three constructs.

f, **g** Far-UV circular dichroism (CD) spectra of purified IDR with increasing amounts of trifluoroethanol (TFE) and urea demonstrates that secondary structure can only be induced at high amounts of TFE and no secondary structure content is lost by urea addition, thereby classifying the IDR as truly intrinsically disordered. Due to high detector voltages in the presence of high urea concentrations, only wavelengths above 215 nm were recorded. The relevant region for changes in secondary structure content is shown in the box.





a Backbone amide resonance assignments of native *G. gallus* TRPV4 IDR comprising residues 2-134².

b Overlay of [¹H, ¹⁵N]-TROSY-HSQC spectra of ¹⁵N-labeled IDR (grey) and NTD (blue). The resonances of the ARD are not visible, presumably due to unfavorable dynamics (see main text for details).

c Relative peak intensity of residues within the IDR in isolation or in the context of the NTD, i.e. in the presence of the ARD. Reduced signal intensity, i.e. a low I_{NTD}/I_{IDR} ratio, suggests intradomain contact sites along the IDR sequence. Previously described functionally important sites in the C-terminal IDR are highlighted by grey boxes (PBS: PIP₂-binding site; PRR: proline rich region).

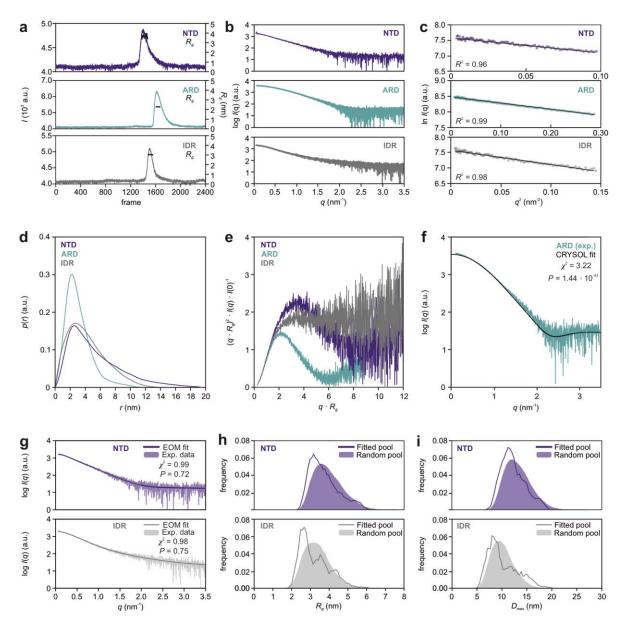


Fig. S3: SEC-SAXS and Ensemble optimization method (EOM) analysis of TRPV4 N-terminal constructs.

a SEC-SAXS profiles of NTD (blue), ARD (cyan), and IDR (grey). Plotted are the partially integrated scattering intensities, *I*, from sequentially recorded 1D-scattering data frames measured throughout the SEC-elution of each sample. After background/buffer subtraction, the respective radii of gyration (R_g) correlation through the elution peaks of each sample were calculated using the Guinier approximation and are indicated in black (with the magnitude on the right axis).

b X-ray scattering profiles of N-terminal constructs plotted as the logarithm of the scattering intensity log(l(q)) (arbitrary units) versus the momentum transfer, q.

c Guinier-plots ($\ln l(q)$ vs q^2 , plotted to low-angle: $qR_g < 1.3$) of N-terminal constructs.

d Real-space pair-distance distribution functions, or p(r) profiles calculated N-terminal constructs. p(r) functions were scaled to an area under the curve value of 1.

e Dimensionless Kratky plots of N-terminal constructs. The scattering from ARD is consistent with a compact/globular particle, while the IDR is highly flexible. The NTD scattering shares features of both.

f CRYSOL fit³ of isolated ARD shows unsatisfactory match between experimental and predicted scattering curves based on ARD X-ray structure (PDB: 3W9G) as demonstrated by a χ^2 value of 3.22 and a CorMap *P* value of 1.44 \cdot 10⁻⁴³.⁴

g Fit of EOM refined IDR and NTD volume-fraction weighted model ensembles (solid line) to the experimental SAXS data of NTD (dark blue) and IDR (grey).

h, i R_g and D_{max} distributions of the random pool of generated IDR and NTD structures (filled curves) compared to the R_g and D_{max} distributions of the EOM refined ensembles (solid lines).

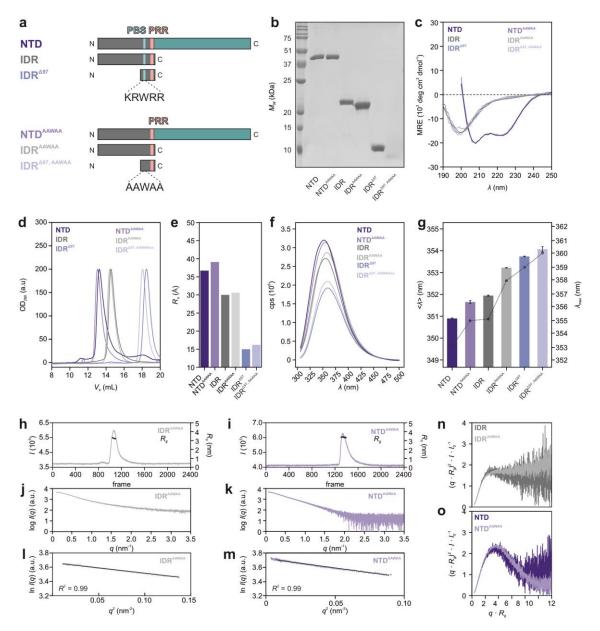


Fig. S4: PIP₂-binding site mutation does not affect the structural integrity of TRPV4 N-terminal constructs. **a** Topology of native and PIP₂-binding site mutant constructs, NTD, IDR, IDR^{ΔN97}. In the AAWAA mutants, the PIP₂-binding site ¹⁰⁷KRWRR¹¹¹ (PBS, yellow) is exchanged to ¹⁰⁷AAWAA¹¹¹ (dark grey). ARD, cyan; IDR, light grey; proline rich region (PRR), light pink.

b Coomassie-stained SDS-PAGE of purified native and AAWAA mutant constructs.

c, d Far-UV CD spectra (c) and SEC profiles (d) of purified constructs.

e Stokes radii (R_s) of native and AAWAA mutant constructs estimated from the elution volumes observed in (d). **f**, **g** Tryptophan fluorescence spectroscopy of native and corresponding AAWAA mutant constructs. Bars show intensity-weighted average wavelength $<\lambda>$ from 320 to 380 nm (left axis). Error bars represent the SD of the mean of n=3. Fluorescence emission maxima λ_{max} are shown as black circles connected by dotted lines (right axis).

h, **i** SEC-SAXS profiles of IDR^{AAWAA} (h) and NTD^{AAWAA} (i). Plotted are the partially integrated scattering intensities, *I*, from sequentially recorded 1D-scattering data frames measured throughout the SEC-elution of each sample. After background/buffer subtraction, the respective radii of gyration (R_g) correlation through the elution peaks of each sample were calculated using the Guinier approximation and are indicated in black (with the magnitude on the right axis).

j, **k** X-ray scattering profiles of IDR^{AAWAA} (j) and NTD^{AAWAA} (k) plotted as the logarithm of the scattering intensity $\log(I(q))$ (arbitrary units) versus the momentum transfer, q.

I, **m** Guinier-plots ($\ln I(q)$ vs q^2 , plotted to low-angle: $qR_g < 1.3$) of IDR^{AAWAA} (I) and NTD^{AAWAA} (m).

n, **o** Dimensionless Kratky plots of IDR and IDR^{AAWAA} (n) as well as NTD and NTD^{AAWAA} (o).

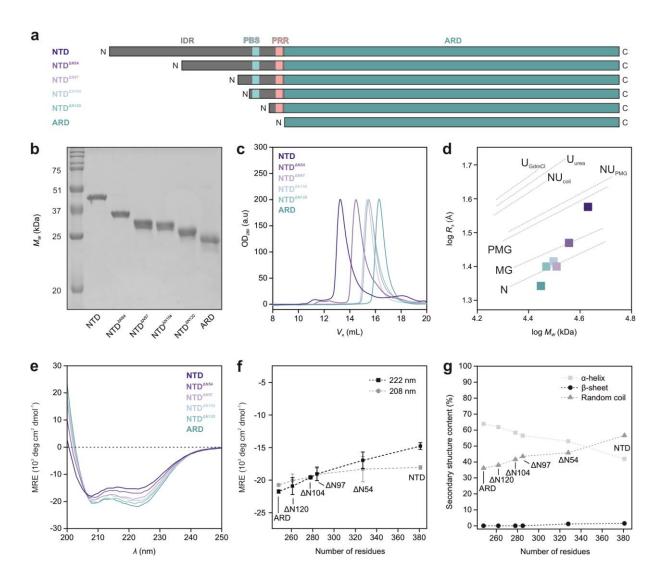


Fig. S5: Structural characterization of N-terminal TRPV4 NTD deletion mutants.

a N-terminally truncated TRPV4 NTD constructs used in this study.

b, **c** Coomassie-stained SDS-PAGE and SEC profiles of NTD deletion constructs.

d R_s - M_W analysis of NTD deletion constructs. NTD: $V_e = 13.4 \text{ mL}$, $R_s = 36.7 \text{ Å}$, $M_W = 42.5 \text{ kDa}$; NTD^{ΔN54}: $V_e = 14.6 \text{ mL}$, $R_s = 29.6 \text{ Å}$, $M_W = 37.0 \text{ kDa}$; NTD^{ΔN97}: $V_e = 15.4 \text{ mL}$, $R_s = 25.4 \text{ Å}$, $M_W = 32.3 \text{ kDa}$; NTD^{ΔN104}: $V_e = 15.4 \text{ mL}$, $R_s = 26.0 \text{ Å}$, $M_W = 31.4 \text{ kDa}$; NTD^{ΔN120}: $V_e = 15.5 \text{ mL}$, $R_s = 25.5 \text{ Å}$, $M_W = 29.4 \text{ kDa}$; ARD: $V_e = 16.3 \text{ mL}$, $R_s = 22.1 \text{ Å}$, $M_W = 28.0 \text{ kDa}$.

e, **f** Far-UV CD spectra of NTD deletion constructs and mean residue ellipticity (MRE) at 208 nm and 222 nm. Error bars correspond to SD of mean from n=3.

g BeStSel⁵ based secondary structure analysis plotted versus the number of amino acids in the NTD constructs shows that overall secondary structure content of the ARD is not affected by consecutive N-terminal deletions of the intrinsically disordered IDR.

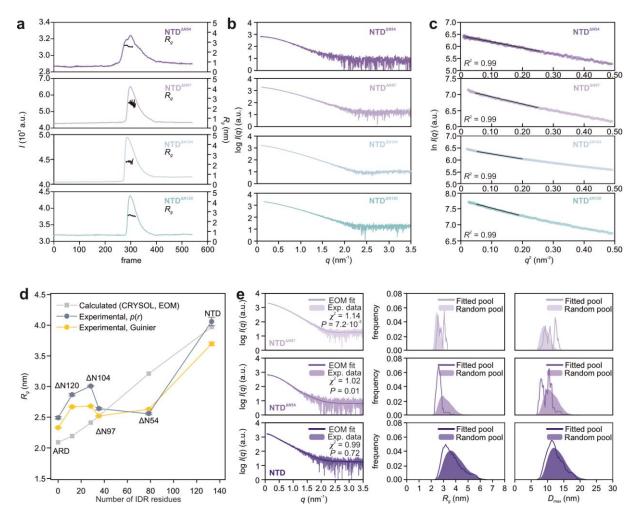


Fig. S6: SAXS analysis of N-terminal deletion mutants of TRPV4 NTD.

a SEC-SAXS profiles of NTD^{Δ N54}, NTD^{Δ N97}, NTD^{Δ N104} and NTD^{Δ N120}. Plotted are the partially integrated scattering intensities, *I*, from sequentially recorded 1D-scattering data frames measured throughout the SEC elution of each sample. After background/buffer subtraction, the respective radius of gyration (*R*_g) correlations with the elution peaks of each sample were calculated using the Guinier approximation (indicated in black, right axis).

b Background subtracted SAXS profiles of the NTD deletion mutations extracted from the SEC traces shown in (a).

c Corresponding Guinier-plot of scattering data shown in (b).

d Experimental and calculated radius of gyration (R_g) plotted versus the number of IDR residues included in the respective NTD constructs. The R_g of the isolated ARD was calculated with CRYSOL³ (grey). The R_g of the NTD and the deletion mutants represent the average R_g value of a random pool of conformations calculated via EOM analysis⁶ assuming a random chain behavior of the IDR. R_g values were experimentally obtained from the Guinier analysis (yellow) or the pair-distance distribution (blue-grey).

e EOM analysis of NTD^{Δ N97}, NTD^{Δ N54}, and wildtype NTD. Shown is the EOM fit (solid line) to the respective experimental data (left). On the right, the EOM derived R_g and D_{max} distributions of a random pool of generated conformations (filled curves) were compared to the EOM-selected ensemble fit to the experimental data. The experimental SAXS profiles of the NTD^{Δ N104} and NTD^{Δ N120} mutants could not be reliably fitted to a random pool of conformations using the EOM algorithm (not shown).

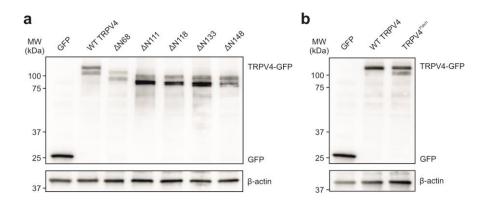


Fig. S7: Expression of human TRPV4 N-terminal constructs in MN-1 cells.
a Western Blot of consecutive human TRPV4 N-terminal deletion constructs.
b Western Blot of human TRPV4^{Patch} mutant.

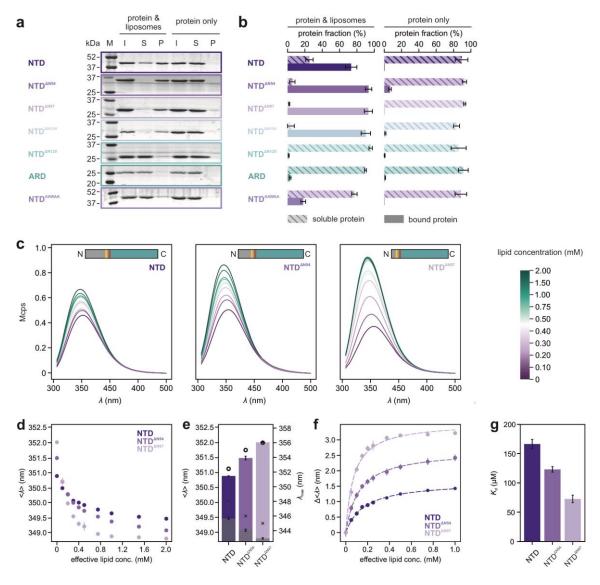


Fig. S8: Effect of N-terminal truncations on the lipid interaction of the TRPV4 NTD.

a Representative SDS-PAGEs for liposome sedimentation assay. I: input; S: supernatant; P: pellet. Control experiments were carried out in the absence of liposomes ('protein only'). A lipid mixture of 50% (w/w) POPG and 50% (w/w) POPC was used to prepare liposomes with 100 nm diameter.

b Protein distribution between pellet and supernatant after centrifugation. The protein fraction in the pellet and supernatant was quantified via densitometry of SDS-PAGE protein bands using imageJ⁷. Representative gels are shown, error bars represent SD of mean from n=3.

c Tryptophan fluorescence spectra of TRPV4 NTD and N-terminal deletion mutants in the presence of 0/0.1/0.2/0.3/0.4/0.5/0.75/1.0/1.5/2.0 mM lipids (100 nm liposomes, POPG:POPC in a 1:1 ratio).

d Intensity-weighted average wavelength $<\lambda$ > plotted against the lipid concentration.

e Intensity-weighted average wavelength $\langle \lambda \rangle$ of TRPV4 NTD constructs without (colored bars) and in the presence of 2 mM lipid (grey bars) ($\langle \lambda \rangle$ on left axis). Tryptophan fluorescence emission maximum wavelengths λ_{max} without lipids and in the presence of liposomes (2 mM lipid) are shown as black circles and black crosses respectively (values for λ_{max} on right axis).

f Intensity-weighted average wavelength shift $\Delta < \lambda >$ plotted against the effective lipid concentration (half of total lipid concentration). The data were fitted with a Hill equation with a Hill coefficient of 1 to obtain K_d values.

g Comparison of determined K_d values in (d) for NTD (165.1 ± 7.9 μ M), NTD^{ΔN54} (122.1 ± 4.6 μ M) and NTD^{ΔN97} (72.1 ± 6.4 μ M).

The error bars in (b, c, d) represent the SD of mean from n=3. The error bars in (e) are the fit errors from (d).

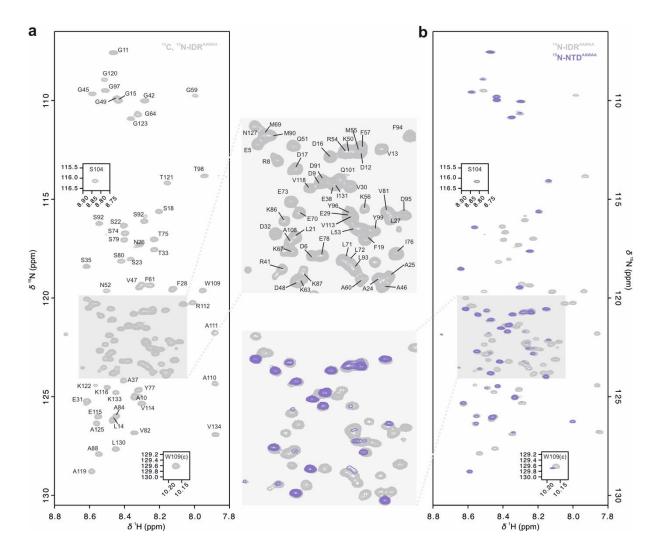


Fig. S9: NMR backbone assignments of TRPV4 IDR^{AAWAA}.

a [¹H, ¹⁵N]-TROSY-HSQC NMR spectrum of ¹³C, ¹⁵N-labeled IDR^{AAWAA}. The basic residues in the PIP₂-binding site (¹⁰⁷KRWRR¹¹¹) have been mutated to alanine.

b Overlay of the spectra of ¹⁵N-labeled IDR^{AAWAA} and NTD^{AAWAA}.

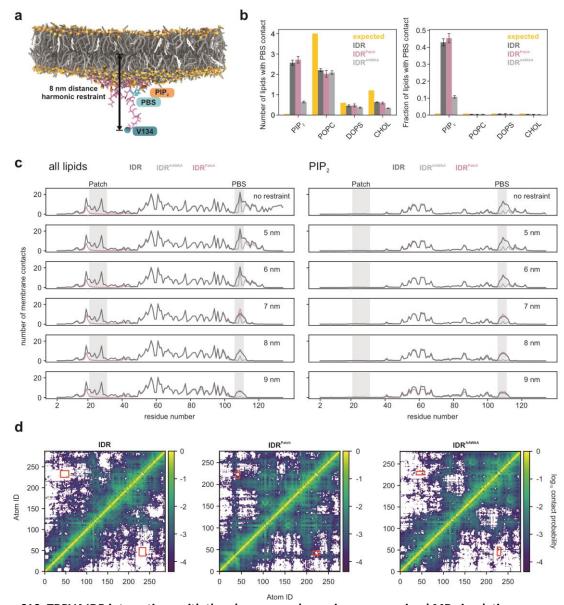


Figure S10: TRPV4 IDR interactions with the plasma membrane in coarse-grained MD simulations. a Snapshot of the bent membrane from a simulation of the native IDR (pink) restrained at 8 nm (distance to membrane midplane) after 15.5 µs of simulation on a lipid bilayer membrane consisting of PIP₂ (1%, dark orange), POPC (69%, dark grey), DOPS (10%, light gray) and cholesterol (20%, white) (see Table S3). Headgroup phosphates are shown as orange spheres. The PIP₂-binding site of the TRPV4 IDR is highlighted in cyan, the C-terminal residue V134 as a blue sphere.

b Absolute (left) and relative (right) number of contacts between the PIP₂-binding site (PBS) and each lipid type in simulations of the native IDR (dark grey), IDR^{AAWAA} (light grey) and IDR^{Patch} (mauve). Values are based on simulations carried out without a height restraint. Yellow bars indicate the number of expected contacts for the PIP₂-binding site based on the respective mol-fractions of lipid types and the observed total number of contacts. Error bars depict the standard error of the mean (SEM) of the individual replicate simulations.

c Average number of membrane contacts for each IDR residue for all lipids (left) or PIP₂ (right). The distance between residue V134 in the IDR C-terminus and the membrane midplane was either not restrained (top panels) or restrained at a specific height (5-9 nm, bottom panels) to emulate the role of the ARD on IDR positioning.

For all conditions shown in (a-c), four replicate simulations per IDR sequence were carried out for \sim 38 µs and contact averages were calculated from the last \sim 28 µs of each simulation.

d Heat map showing the probability of two coarse-grained atoms of the IDR being in contact with each other in simulations of the native IDR (left), the IDR^{Patch} (center) and the IDR^{AAWAA} (right). Contact maps were calculated after pooling the last ~28 μ s of all four replicate simulations without height restraints. A contact was counted when two coarse-grained atoms came closer than 0.6 nm. Red boxes indicate the area of N-terminal patch interaction with the PBS.

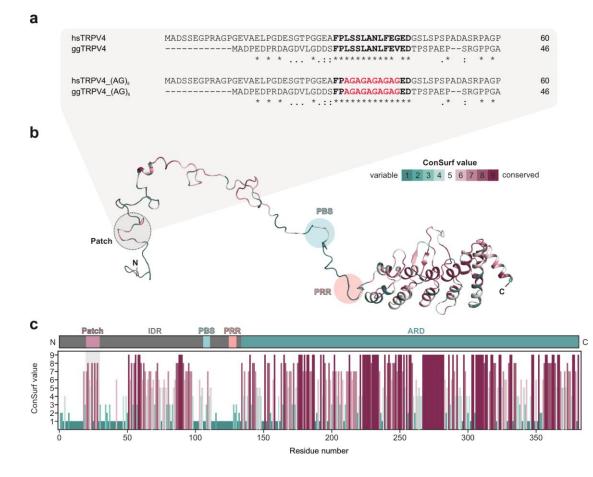


Fig. S11: sequence alignment and conservation of *H. sapiens* and *G. gallus* TRPV4 IDR.

a Sequence alignment of N-terminal IDR of human and chicken TRPV4. The conserved regulatory patch is shown in bold. The corresponding (AG)₅ mutants of the conserved patch are shown below and highlighted in red. Alignments were carried out with ClustalOmega⁸.

b Conservation of residues in TRPV4 NTD shown mapped onto a *G. gallus* TRPV4 NTD conformer obtained from our EOM analysis (Fig. 1). Analysis was carried out with the ConSurf server⁹ (PBS: PIP₂-binding site; PRR: proline rich region).

c TRPV4 NTD topology and sequence conservation of TRPV4 NTD residues based on the ConSurf analysis⁹.

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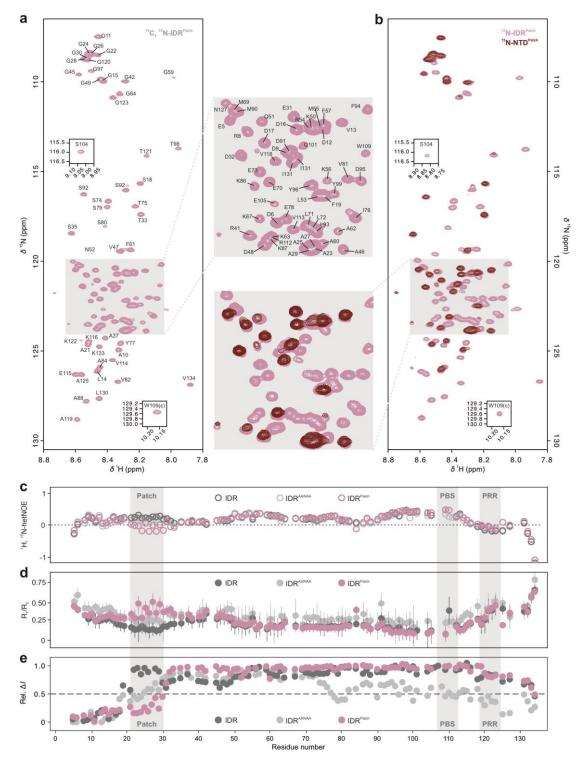


Fig. S12: Backbone NMR assignment of TRPV4 IDR^{Patch}, relaxation measurements of IDR mutants and liposome titrations.

a [¹H, ¹⁵N]-TROSY-HSQC NMR spectrum of ¹³C, ¹⁵N-labeled IDR^{Patch}. Here, residues ¹⁹FPLSSLANLFEVE³¹ were exchanged to glycine and alanine yielding ¹⁹FP(AG)₅E³¹ (see Fig. S11).

b Overlay of the HSQC spectra of ¹⁵N-labeled IDR^{Patch} and NTD^{Patch}.

c, **d** ${}^{1}H{}^{15}N$ -hetNOE and T_{1}/T_{2} relaxation data of of ${}^{15}N$ -labeled IDR (dark grey), IDR^{AAWAA} (light grey), IDR^{Patch} (mauve).

e NMR signal intensity differences for ¹⁵N-labeled IDR (dark grey), IDR^{AAWAA} (light grey) and IDR^{Patch} (mauve) in the absence and presence of POPC-POPG containing liposomes. For better comparison, the data from Fig. 6d, e for native IDR and IDR^{AAWAA} were added here.

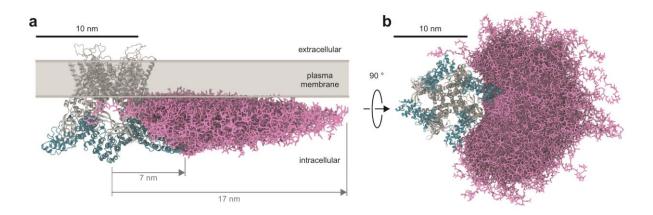


Figure S13: Structural model of the conformational space sampled by the IDR of a single TRPV4 subunit in the presence of the plasma membrane.

a, **b** Superimposed IDR conformations (pink licorice) from coarse-grained MD simulations shown for one subunit in the TRPV4 tetramer from the side (a) and top (b). The structured transmembrane core (grey) including the ARDs (cyan) of *G. gallus* TRPV4 has been predicted by AlphaFold multimer¹⁰.

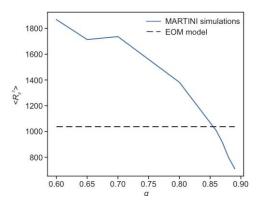


Fig. S14: Optimizing the scaling factor in MD simulations to best describe the measured R_g distribution of the native IDR.

Averaged squared R_g (R_g^2) in simulations with different rescaling constants of the protein/protein interactions (α). All simulations were performed without a membrane. The dotted black line shows the averaged squared R_g of the EOM refined model (Fig. 1, Fig. S. 3)

Supporting Information References

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