

### Supplementary Materials:

**Reagents:** PbTx-1 and tetrodotoxin (TTX) were purchased from Latoxan (Valence, France). A total of two concentrations of TTX were used: 100  $\mu\text{M}$ , which antagonizes both TTX-resistant (TTX-r) and TTX-sensitive (TTX-s)  $\text{Na}_v$  channels, and 300 nM, which inhibits only TTX-s  $\text{Na}_v$  channels [25,61,77]. The difference in the inhibitory effects between 100  $\mu\text{M}$  and 300 nM represents the contributory part of TTX-r  $\text{Na}_v$ -dependent mechanisms. Pure P-CTX-2 was isolated from moray eel (*Gymnothorax javanicus*) livers as previously described [65] and provided by Richard J. Lewis (Institute of Molecular Biosciences, Brisbane, Australia). Stock solution of 1.15 mM of PbTx-1 was prepared in pure methanol (MeOH), aliquoted and dried, and then resolubilized in the medium before use. P-CTX-2 was dissolved in MeOH: water (1:1) to prepare a 10 mM stock solution. Culture media were supplemented with 100 mg/mL Normocin® (InvivoGen, Toulouse, France) obtained from Life Technologies (Saint Aubin, France). Keratinocyte-Serum Free Medium (KSFM) was supplemented with L-glutamine, epidermal growth factor (EGF), and bovine pituitary extract (BPE) (Life Technologies, Saint Aubin, France) to obtain a so-called complete KSFM. GB83 was purchased from Axon Medchem (Groningen, Netherlands) and Z-FL-COCHO was purchased from Merck-Milipore (Burlington, USA). Antagonists such as bisindolylmaleimide X hydrochloride (BimX), H89, and HC-067047 were provided by Sigma-Aldrich (Saint Quentin Fallavier, France). Xestospongin C (XestC) was purchased from Abcam (Cambridge, UK) and the human recombinant Cat-S was obtained from R&D systems (Minneapolis, USA). All antagonists and final concentrations used are summarized in Table S1.

**Table S1.** Antagonists—their respective targets and the referenced concentrations.

<b>Antagonists</b>	<b>Target</b>	<b>Concentration</b>	<b>References</b>
TTX	All Nav channels	100 $\mu$ M	[77]
	TTX-sensitive Nav channels (TTX-s)	300 nM	
GB83	PAR2	5 $\mu$ M	[62]
HC-067047	TRPV4	10 $\mu$ M	[63]
Z-FL-COCHO	Cat-S	10 nM	[81]
BimX	PKC	10 $\mu$ M	[63]
H89	PKA	3 $\mu$ M	[48]
XestC	IP3R	5 $\mu$ M	[44,103]