Suplementary information 3 (Table) | **Examples of pH-sensitive targets and functional outcomes**

pH-sensitive targets	Effect of pH	Refs
Ion Homeostasis		
Ca^{2+}-ATPases	Plasma membrane and sarco(endo)plasmic reticulum Ca^{2+}-ATPase activities are steeply pH dependent, with decreased activity occurring at alkaline or acidic pH values away from the optimum, and regulate cellular calcium homeostasis	1
Ryanodine receptors	Ryanodine receptors are sarcoplasmic reticulum Ca^{2+} release channels that are inhibited by acid pH (6.9), leading to a two-fold increase in SR Ca^{2+} stores.	2, 3
Kir1.1 K^+ Channels (ROMK)	Intracellular acidification inhibits ROMK, an Inward-rectifier ATP-regulated K^+ channel present at the apical membranes of the distal nephron, and serves as a mechanism for preserving K^+ levels during metabolic acidosis.	4, 5
N-methyl-D-aspartate (NMDA) receptor channels	Transient increases in extracellular H^+ generated by excitatory amino acids inhibits further calcium influx via certain neurotransmitter receptor channels, such as the NMDA receptor, thereby acting as a feedback mechanism to modulate synaptic transmission.	6, 7
Acid-sensing ion channels (ASIC) Channels	ASIC channels are Na^+ channels that are activated by extracellular acidification and play important roles in nociception, mechanosensation, and synaptic plasticity.	8-11
TASK K^+ Channels	H^+-dependent inhibition of TASK channels, a two-pore domain K^+ channel, can depolarize and increase excitability of specific neurons in the brainstem and may contribute to ventilatory and arousal reflexes associated with extracellular acidosis.	12, 13
Voltage-gated cation channels	Voltage-gated Na^+, K^+ and Ca^{2+} channels are differentially sensitive to extracellular or intracellular acidosis and modulate neuronal excitability.	14-16
Signal Transduction / Cell Communication		
H^+-gated G-protein coupled receptors OGR1 and GPR4	Activation of OGR1 and GPR4 by extracellular H^+ causes coupled phospholipase C activation and downstream ER Ca^{2+} channel opening.	17, 18
Soluble-adenylate cyclase	Activated in the presence of HCO^{3-} (bicarbonate sensor), leading to increased cAMP production.	19
Connexins-36 and -43	Gap junctions (neuronal and cardiomyocyte) close outside physiological pH range, limiting intercellular electrical connectivity.	20, 21
Bax inhibitor-1 (BI-1)	Intracellular acidification activates BI-1 which increases Ca^{2+} leakage from the ER, induces Bax recruitment to mitochondria, followed by increased cytochrome c release and apoptosis.	22
Cell Shape, Motility & Contractility		
Cofilin	Increases in intracellular pH activate the actin filament severing activity of cofilin, leading to increased actin free barbed ends required for actin filament remodelling and membrane protrusions at the leading edge of motile cells.	23, 24
Villin	Alkalinization increases villin-dependent bundling of actin filaments	25
Gelsolin	Acidic pH promotes gelsolin actin-severing activity	26, 27
Na^+/H^+ exchanger NHE1	Activation of NHE1 is permissive for cell migration; NHE1 accumulates at leading edge of lamellipodia.	28-30
Cathepsin B and Hyaluronidase-2	Localized secretion of H^+ into extracellular space activates proteases involved in degradation of extracellular matrix tumour cell invasion.	31
Troponin C	Acidic pH reduces the affinity of troponin C for Ca^{2+} and decreases myofilament contractility	32, 33
Metabolism		
Phosphofructokinase	Inhibited by acidic pH; major control point for glycolysis	34, 35
Vesicle Trafficking		
V-ATPase a2-subunit	Association of the guanine nucleotide-exchange factor ARNO with the V-ATPase a2-subunit was dependent on endosomal acidification and subsequent recruitment of coat proteins necessary for vesicle traffic between early and late endosomes.	36

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