Divergent Cl; -; and H; +; pathways underlie transport coupling and gating in CLC exchangers and channels

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Author(s) Leisle, Lilia; Xu, Yanyan; Fortea, Eva; Lee, Sangyun; Galpin, Jason D.; Vien, Malvin; Ahern, Christopher A.; Accardi, Alessio; Bernèche, Simon
Author(s) at UniBasel Bernèche, Simon ; Xu, Yanyan ;
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The CLC family comprises H; +; -coupled exchangers and Cl; -; channels, and mutations causing their dysfunction lead to genetic disorders. The CLC exchangers, unlike canonical 'ping-pong' antiporters, simultaneously bind and translocate substrates through partially congruent pathways. How ions of opposite charge bypass each other while moving through a shared pathway remains unknown. Here, we use MD simulations, biochemical and electrophysiological measurements to identify two conserved phenylalanine residues that form an aromatic pathway whose dynamic rearrangements enable H; +; movement outside the Cl; -; pore. These residues are important for H; +; transport and voltage-dependent gating in the CLC exchangers. The aromatic pathway residues are evolutionarily conserved in CLC channels where their electrostatic properties and conformational flexibility determine gating. We propose that Cl; -; and H; +; move through physically distinct and evolutionarily conserved routes through the CLC channels and transporters and suggest a unifying mechanism that describes the gating mechanism of both CLC subtypes.
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