

# **The remembrance of the things past: Conserved ionic signalling pathways link prokaryotes and protozoa to mammalian nervous system**

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Ion gradients and the maintenance of ion homeostasis within the cytoplasm is a ubiquitous property of all life forms on planet Earth. What was the ionic composition of the cytosol of the first cellular ancestor, to what extent it reflected the ion concentrations of the primeval ocean, what was the role of Donnan forces and which mechanisms (if any) this primary cell employed to maintain cytosolic ion concentrations are all questions which remain unanswered. Environmental stresses (for example an increase in osmotic pressure due to evaporation or its decrease due to rain) alter the concentrations of extracellular ions and therefore trigger changes in intracellular ions. In this way, ions became messengers coupling environmental challenges with cellular responses required for survival. Thus, ionic signalling was born and it remains omnipresent in all cellular systems to this day. Cellular physiology has always balanced the need for cytosolic ionic homeostasis (which, when compromised, leads to rapid death) and the need to produce relevant intracellular ion changes that trigger signalling cascades responsible for specific responses. Evolution has therefore selected both for systems maintaining transmembrane ionic gradients and mechanisms for fast transmembrane ion transport (which shape ionic signals), with the former enabling and regulating the latter. Molecular cascades of ionic homeostasis and signalling (pumps, channels SLC transporters, binding proteins and molecular sensors) emerged in prokaryotes and further developed at the unicellular stage of eukaryote evolution. With progressive evolution, mechanisms of signalling became diversified reflecting multiplication and specialisation of ion-regulated cellular activities.