

EVOLUTION OF CELLULARITY: ROLE OF THE SODIUM/POTASSIUM HOMEOSTASIS IN THE EMERGENCE OF ION-TIGHT CELL MEMBRANES, MEMBRANE BIOENERGETICS, AND G-PROTEIN COUPLED RECEPTORS

Daria N. Shalaeva^{1,2}, Daria V. Dibrova³, Olesya I. Klimchuk², Michael Y. Galperin⁴, Armen Y. Mulkidjanian^{1,2,3}

¹*School of Physics, Osnabrueck University, 49069, Osnabrueck, Germany (amulkid@uni-osnabrueck.de);* ²*School of Bioengineering and Bioinformatics, and* ³*A.N. Belozersky Institute of Physico-Chemical Biology, Lomonosov Moscow State University, Moscow 117999, Russia,* ⁴*National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, Maryland 20894, USA*

The cytoplasm of all living cells contains more potassium ions than sodium ions, as first noted by Archibald Macallum [1]. In modern prokaryotic cells, the $[K^+]/[Na^+]$ ratio > 1.0 is maintained by ion-tight cellular membranes and an arsenal of ion pumps. It is quite unlikely that the very first organisms could possess modern-type ion-tight membranes, not to mention a plethora of ion-pumping machines [2-5]. It is far more likely that the monovalent ion content of the cytoplasm of the first organisms was in equilibrium with the environment [1,4,5]. Prevalence of K^+ ions over Na^+ ions is crucial for the activity of numerous key enzymes that are found in all free-living organisms, including those components of the translation system that even preceded the Last Universal Cellular Ancestor (LUCA) [4,5]. These observations support the emergence of first organisms in K^+ -rich habitats, as originally suggested by Macallum [1].

Different, albeit complementary, scenarios have been recently proposed for the primordial K^+ -rich environments based on experimental data and theoretical considerations [4,6,7]. Specifically, building on the observation of $[K^+]/[Na^+] > 1$ at vapor-dominated zones of inland geothermal systems, we argued that the first cells could have emerged in the pools and puddles at the periphery of primordial anoxic geothermal fields, where the elementary composition of the condensed vapor would resemble the internal milieu of modern cells [4,7].

To invade marine environments, while maintaining the cytoplasmic $[K^+]/[Na^+] > 1$, primordial organisms needed ion-tight membranes and means to extrude sodium ions. The foray into new, Na^+ -rich habitats was the likely driving force behind the evolution of ion-tight membranes and diverse redox-, light-, chemo- or osmotic sodium export pumps [2,3,5,8].

One of such export pumps was the Na^+ -translocating rotary ATPase, which, under the conditions of high salinity of the primordial ocean, could change the direction of rotation and start to synthesize ATP at the expense of the transmembrane sodium potential, thus launching the sodium-dependent membrane bioenergetics [2,3,5,8].

The transition to proton-dependent bioenergetics may have taken place independently in bacteria and archaea [2,3,8]. Proton-dependent bioenergetics appears to be particularly beneficial under oxidizing conditions [8], so that its spreading should have followed the Great Oxygenation Event.

Because of the current prevalence of proton-dependent bioenergetics, the search for primordial sodium-dependent enzymes remains a challenge. Still, by combining comparative phylogenomic and structural analyses we could identify novel energy-converting, sodium-translocating enzymes [9,10] and could trace the emergence of the G-protein coupled receptors from Na^+ -translocating bacterial rhodopsins [11].

Acknowledgements: This work was supported by the Federal Ministry of Education and Research of Germany (AYM), a fellowship from the German Academic Exchange Service (DNS), the Russian Science Foundation (DVD, grant #14-50-00029), and the NIH Intramural Research Program at the National Library of Medicine (MYG)

References

1. Macallum, A.B. (1926) *Phys. Rev.*, 6:316-357.
2. Mulkidjanian, A.Y., Galperin, M.Y., Makarova, K.S., Wolf, Y.I., Koonin, E.V. (2008) *Biol Direct* 3:13.
3. Mulkidjanian, A.Y., Galperin, M.Y., and Koonin, E.V. (2009) *Trends Biochem. Sci.*, 34:206-215.
4. Mulkidjanian A.Y., Bychkov A.Y., Dibrova D.V., Galperin M.Y., Koonin E.V. (2012) *Proc Natl Acad Sci USA* 109:E821-830.
5. Dibrova, D. V., M. Y. Galperin, E. V. Koonin, A. Y. Mulkidjanian (2015) *Biochemistry (Moscow)* 80:590-611.
6. Maruyama, S. et al., (2013), *Geoscience Frontiers*, 4:141-165.
7. Mulkidjanian, A.Y., Bychkov, A.Y., Dibrova, D.V., Galperin, M.Y., and Koonin, E.V. (2012) *Orig. Life Evol. Biosph.*, 42:507-516.
8. Mulkidjanian, A.Y., Dibrov, P., and Galperin, M.Y. (2008), *Biochim. Biophys. Acta*, 1777:985-992.
9. Dibrova, D.V., Galperin, M.Y., and Mulkidjanian, A.Y. (2010) *Bioinformatics*, 26:1473-1476.
10. Klimchuk O.I., Dibrova D.V., Mulkidjanian A.Y. (2016) *Biochemistry (Moscow)*, 81:481-490.
11. Shalaeva, D. N., Galperin, M.Y., Mulkidjanian, A.Y. (2015) *Biol. Direct* 10:63.