Generally Physiological

Of pumps, protons, chloride gradients, and microvesicles at the immunological synapse

This month’s installment of Generally Physiological concerns the identification of the Na⁺/K⁺ pump as a hybrid transporter, investigation of the mechanisms whereby the neuronal chloride gradient is set, and the discovery that T cells send messages to antigen-presenting cells (APCs) via microvesicles.

A proton pathway through the sodium pump

Transport proteins are usually identified by their substrates and co- or counter-transported species. But a small, though growing, number of them are turning out to perform two different jobs, involving distinct substrates. In this issue, Vedovato and Gadsby identify one of the most well-known transporters, the Na⁺/K⁺ ATPase—familiarly known as the Na⁺ pump—as a hybrid transporter that also allows proton entry under physiological conditions. The Na⁺/K⁺ ATPase exports three Na⁺ and imports two K⁺ with every cycle, thereby generating an outward current that is abolished by the Na⁺/K⁺ ATPase inhibitor ouabain. A pH- and membrane potential–dependent ouabain-sensitive inward proton current mediated by the Na⁺/K⁺ ATPase in the absence of extracellular Na⁺ and K⁺ has been viewed as an artifact of these highly unphysiological conditions. Vedovato and Gadsby (2014) now show that this proton import is present at physiological concentrations of Na⁺ and K⁺ and resting potentials, identifying the Na⁺/K⁺ ATPase as a hybrid transporter (see Hilgemann in this issue for a thoughtful and entertaining discussion). The proton current, which is energetically downhill and depends on the reversibility of conformational changes associated with release of extracellular Na⁺, flows through a route distinct from the pathway whereby Na⁺ and K⁺ are transported and is not required for the transport of Na⁺ and K⁺. The authors speculate that it may, however, have physiological or pathophysiological consequences under conditions in which extracellular pH is low, such as in skeletal muscle during vigorous exercise or during ischemia in the heart or brain.

Maintaining your equilibrium

Although the neurotransmitter GABA, which activates a ligand-gated channel permeable to chloride (the GABA_A receptor), has long been viewed as inhibitory, modest changes in intracellular chloride concentration ([Cl⁻]ₗ) can shift the transmembrane chloride concentration gradient so that the GABA_A receptor reversal potential is above threshold for action potential generation. Questioning the prevailing view that neuronal [Cl⁻],
Identifying the Na⁺/K⁺ pump as a hybrid transporter, investigating the neuronal chloride gradient, and discovering that T cells send messages to APCs via microvesicles

Packing up the TCR for special delivery
Adaptive cellular immunity depends on interactions between T cells and APCs, such as B cells, macrophages, and dendritic cells. T cell receptor (TCR) recognition of peptide-bearing major histocompatibility complex molecules (pMHC) on the APC stimulates formation of the immunological synapse. Curiously, the central region of the immunological synapse, where TCRs accumulate, shows little TCR signaling; moreover, TCR-pMHC complexes in this central region show a lack of mobility relative to the periphery of this highly organized structure. Choudhuri et al. (2014) used a combination of total internal reflection fluorescence microscopy, transmission electron microscopy, and electron tomography to investigate formation of the T cell immunological synapse in a model system in which CD4⁺ T cells engage with pMHC and the adhesion ligand ICAM-1 in a supported lipid bilayer. Remarkably, they found that, after movement of TCR-pMHC complexes to the center of the immunological synapse, the center of the contact interface reorganized into an extracellular cavity containing numerous microvesicles. T cells transferred TCRs to B cells bearing cognate pMHC, a process inhibited by knockdown of TSG101, a protein required for TCR sorting into microvesicles. Moreover, isolated TCR-enriched microvesicles were capable of initiating signals in B cells. Thus, T cells appear to use microvesicles to transfer signals to APCs across the immunological synapse.

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REFERENCES