3.10: Mitochondrial Calcium Ion Transport

Influx

Mitochondria isolated from various types of animal cells—but, interestingly, not those from plant cells—can rapidly accumulate exogenous Ca^{2+}.[59] The transporter is located in the inner membrane and the driving force behind the Ca^{2+} transport appears to be merely the high potential difference across this membrane ($\Delta\Psi \approx 150$ to 180 mV, negative in the inner matrix). This potential difference is fairly closely maintained by the pumping out of H^+ from the matrix by cell respiration. For the transport of 1 mol Ca^{2+} from the "outside" (= cytoplasm) to the "inside" (= inner mitchondrial matrix), we may deduce from Equation (3.4) that the free-energy change ΔG may be written ($\Delta n_{Ca^{2+}} = -1$)

$$\Delta G = -RT \cdot ln \frac{[Ca^{2+}]_o}{[Ca^{2+}]_i} - 2F\Delta\Psi. \tag{3.11}$$

From this analysis it may be inferred that the limiting Ca^{2+} concentration (or activity) ratio that can be achieved by this **electrogenic** pump (i.e., $\Delta G = 0$) is

$$\frac{[Ca^{2+}]_o}{[Ca^{2+}]_i} = e^{\frac{-2F\Delta\Psi}{RT}} \tag{3.12}$$

With $\Delta\Psi$ = 150 mV, this ratio is calculated to be 8.4 x 10^{-6} at 25 °C. It is evident that, as long as the Ca^{2+} influx would not lower the membrane potential difference, the Ca^{2+} **uniporter** has a very high pumping potential. Measured values of the pumping rate, V_{max}, are indeed high (>10 nmol/mg protein[59]) and probably limited only by the rate of electron transport and H^+ extrusion in the mitochondria.

Mitochondria may accumulate large quantities of Ca^{2+}, probably to maintain electroneutrality. To prevent the buildup of high concentrations of free Ca^{2+} (and of osmotic pressure), phosphate ions are also transported into the inner matrix, where an amorphous calcium phosphate—or possibly a phosphocitrate[60]—is formed. The equilibrium concentration of free Ca^{2+} in the mitochondrial matrix may as a result be comparatively low, on the order of 1 μM.

The molecular nature of the mitochondrial Ca^{2+} uniporter continues to be elusive, and needs to be studied further.

Efflux

Mitochondria, as well as SR, release Ca^{2+} ions by mechanisms other than "back leakage" through the pumps. In mitochondria from excitable cells, the efflux occurs mainly through an antiport, where 2 Na^+ ions are transported inward for every Ca^{2+} ion departing for the cytosolic compartment.[61] In other cells there is evidence for the dominance of a $2H^+$-Ca^{2+} antiport.[59] In all likelihood the Ca^{2+} efflux is regulated, possibly by the redox state of pyridine nucleotides in the mitochondria. As with the Ca^{2+} uniporter, few details on the molecular nature of the antiporters are presently available.

Ca^{2+} Efflux from Non-mitrochondrial Stores

Release of Ca^{2+} from ER and SR presently appears to be the prime effect of the new intracellular messenger 1,4,5-triphosphoinositol (1,4,5-IP_3) released into the cytoplasm as a result of an external hormonal stimulus (see Section IV.C). It seems that receptors for 1,4,5-IP_3 have been established on ER, and that the binding of 1,4,5-IP_3 causes a release of Ca^{2+} stored in this organelle.[62,63,170,171] In addition to the receptor-controlled Ca^{2+} efflux, there may be other pathways for Ca^{2+} release, and Ca^{2+} mobilization may be regulated by other intracellular entities, the Ca^{2+} ions themselves included.

Other Voltage-gated or Receptor-activated Ca^{2+} Channels

In addition to the transport pathways already discussed, some cells seem to have Ca^{2+} channels in the plasma membrane that can be opened by the action of an agonist on a receptor or that are gated in response to changes in membrane potential.[64] For example, Ca^{2+} channels can be opened by nicotinic cholinergic agonists[65] or by the excitatory amino acid N-methyl-D-aspartate (NMDA).[66] Endochrine cells and also some muscle and neuronal cells have voltage-sensitive Ca^{2+} channels.[67,68] We will not discuss these further, but merely point to their existence. We finally note that during the last few years knowledge about the mechanisms of Ca^{2+} entry and release to and from extracellular and intracellular pools has increased dramatically, and we refer the reader to recent reviews of the field.[175,176]