CELL BIOLOGY

Vitamin K_2 Takes Charge

A vitamin carries electrons in the mitochondrial transport chain.

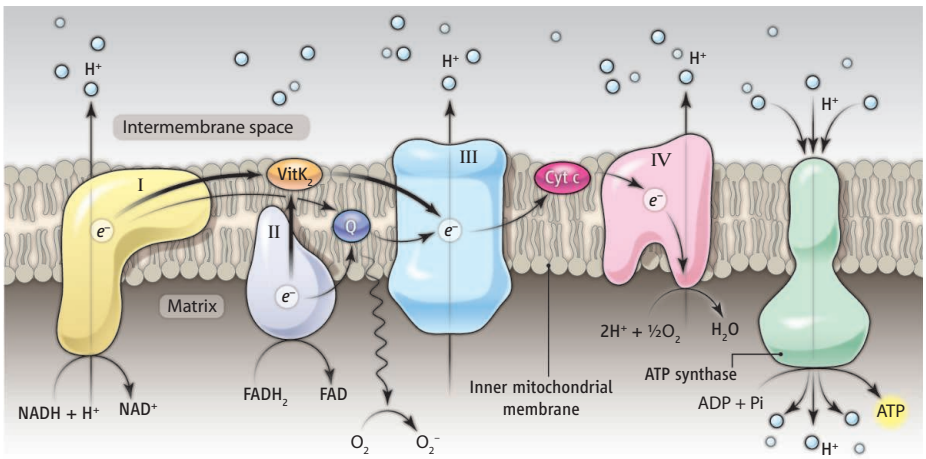
Sheetal Bhalerao and Thomas R. Clandinin

Mitochondria are dynamic organelles that play central roles in eukaryotic cellular energy metabolism. They harbor an electron transport chain (ETC) that couples electron transfer to the movement of protons across the mitochondrial inner membrane, forming an electrochemical gradient that captures chemical energy in the form of adenosine triphosphate (ATP). The biochemical and biophysical properties of the ETC have been studied in detail (*1*). On page 1306 of this issue, Vos *et al*. (*2*) report a new constituent of this chain. The authors show that vitamin K_2 is an electron carrier, suggesting this small organic molecule as a possible treatment for mitochondrial pathologies such as Parkinson's disease and amyotrophic lateral sclerosis.

In the ETC, a series of electron donors pass electrons to more electronegative acceptors until electrons are passed to oxygen, forming water (see the figure). A number of vitamins are involved in this relay. For example, nicotinamide (vitamin B_3) is the precursor of NADH (the reduced form of nicotinamide adenine dinucleotide) and delivers electrons to the first protein complex in the ETC, complex I; riboflavin (vitamin B_2) is the precursor of $FADH_2$ (the reduced form of flavin adenine dinucleotide) and is a cofactor for electron transport.

Mitochondrial dysfunction has been linked to neurodegenerative diseases such as Parkinson's disease and amyotrophic lateral sclerosis (*1*, *3*). In many of these diseases, some electrons react with oxygen prematurely, generating reactive oxygen species that damage cellular components. Causal links between mitochondrial dysfunction and neurodegeneration have been established, but the molecular mechanisms by which perturbing mitochondrial activity leads to synapse loss and neuronal degeneration are unknown.

Although our understanding of the etiology of Parkinson's disease is incomplete, genes associated with rare, familial forms of the disease have been identified. Mouse and fruit fly models of the disease suggest that two genes, *pink1* and *parkin*, function in mitochondrial quality control (*4*–*8*). Pink1 is a protein kinase that detects decreases in mitochondrial membrane potential and recruits cytoplasmic Parkin to damaged mitochondria (*9*). Parkin is an E3 ubiquitin ligase that directs the ubiquitin-proteasome system to degrade specific target proteins (*10*). Together, Pink1 and Parkin sequester damaged mitochondria prior to their clearance through a process called mitophagy (*11*, *12*). However, these proteins likely have other functions that are as yet unknown.



Parallel pathways. Energy obtained through the transfer of electrons (e^-) in the ETC is used by complex I (NADH coenzyme Q reductase), complex III (cytochrome bc_1), and complex IV (cytochrome c oxidase) to pump protons (H^+) from the mitochondrial matrix into the intermembrane space, creating a proton gradient. While electrons are transferred from complexes I and II to complex III by coenzyme Q (ubiquinone; Q), cytochrome c (Cyt c) carries electrons to complex IV, where molecular oxygen (O_2) is reduced to water (H_2O). ATP synthase uses the flow of H^+ back into the matrix to generate ATP from adenosine diphosphate (ADP) and inorganic phosphate (Pi). Reactive oxygen species (O_2^-) are generated by electrons that fail to complete the series. Vitamin K_2 ($VitK_2$) transfers electrons from complexes I and II to complex III.

Vos *et al*. screened a collection of mutant fruit flies with abnormal synaptic function for loci that enhanced or suppressed the flight defects seen in *pink1* mutants. The screen identified *heixuedian* (*heix*), a gene that dominantly influences flight behavior, ATP levels, and mitochondrial activity in *pink1* mutants. *heix* encodes an evolutionarily conserved enzyme involved in the synthesis of the quinone vitamin K_2. Vitamin K_2 has a well-established role in posttranslational modification of proteins involved in blood coagulation (*13*); more intriguingly, it functions as an electron carrier in prokaryotes (*14*). Vos *et al*. show that vitamin K_2 functions as an electron carrier required for ATP production via the ETC in eukaryotic cells. Furthermore, supplementing the diet of *pink1* mutant flies with vitamin K_2 increased ETC efficiency and partially alleviated defects in mitochondrial membrane potential and ATP production.

A striking feature of this study is the uncoupling of defects in mitochondrial morphology from functional deficits. That is, although functional defects in *pink1* and *parkin* mutant flies were alleviated by boosting ETC activity via rescue of *heix* function or by providing exogenous vitamin K_2, these manipulations had a less dramatic effect on the defects in mitochondrial morphology observed in these animals. Also, although rescuing *heix* function or uptake of vitamin K_2 in *pink1* or *parkin* mutant flies provided functional rescue, whether Pink1 directly regulates Heix enzymatic activity is unknown. Defining these interactions will provide insights into both mitochondrial biology and the function of Pink1.

It is tempting to speculate that evolution might have favored the emergence of parallel pathways for electron transport. Although these could simply provide "fail-safe" mechanisms for energy generation, the presence of parallel pathways could also hint at tissue-specific or cell type–specific specializations in the ETC. For neurodegenerative disorders in which there is mitochondrial dysfunction, each disease manifests in characteristic subpopulations of neurons. For example, in

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Parkinson's disease there is relatively selective loss of dopaminergic neurons in the substantia nigra, whereas degeneration of motor neurons in the ventral horn of the spinal cord is prominent in amyotrophic lateral sclerosis (*3*). If ETC function is generic, why do these unique patterns of loss arise? The conventional explanation is that the specific cells affected are particularly metabolically active (and hence most sensitive to mitochondrial dysfunction). However, it is also possible that core mitochondrial functions in different neurons could be differentially dependent on different pathways and genes. As a result, the different genes affected in each disease might all regulate ETC function, but do so in a cell type–specific manner because the ETC itself is different in distinct cells. Future investigations of ETC function in different cell types will be needed to examine this notion.

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CLIMATE CHANGE

Dancing to the Tune of the Glacial Cycles

An oxygen isotopic record from Borneo shows how the tropical water cycle responded to deglaciations and interglacials in the past half-million years.

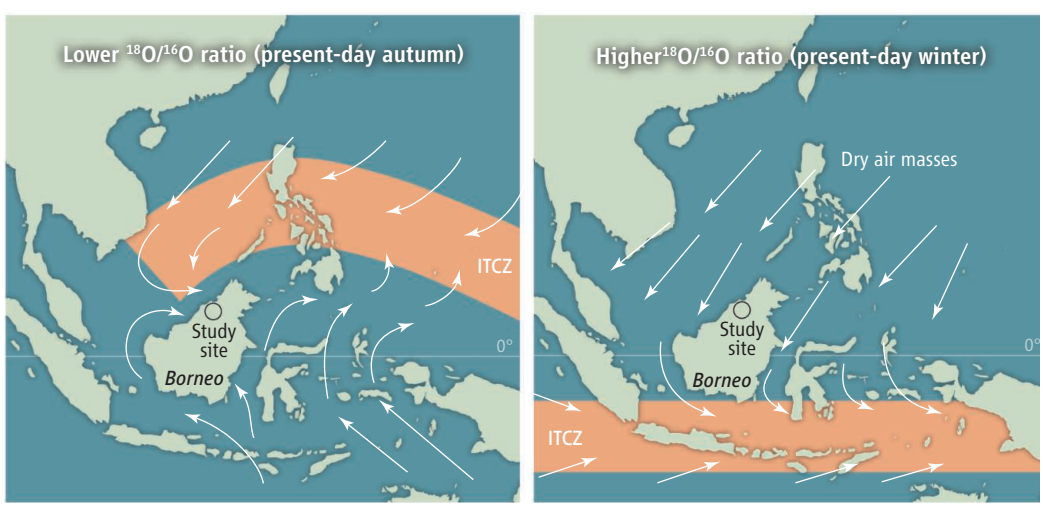
Naoyuki Kurita

Tropical convection acts as a heat engine that drives the world's atmospheric circulation. Any perturbation of this force has a global influence through interaction with other weather phenomena, such as monsoons, the El Nino/Southern Oscillation, and the genesis of tropical cyclones. How will a possibly warmer future climate affect tropical convective activity? On page 1301 of this issue, Meckler *et al.* (*1*) provide insight to this question through their analysis of an oxygen isotope record from a stalagmite in northern Borneo, reflecting tropical Pacific convective activity from 570,000 to 210,000 years ago. The record illustrates how sensitive tropical convection is to variations in global climate.

During the past 1,000,000 years, interglacials occurred every ~100,000 years. However, these interglacials were not all the same: Climate boundary conditions—such as the magnitude of incoming sunlight, the extent of the continental ice sheet, and atmospheric greenhouse gas concentrations—differed from one interglacial to the next (*2*). The Mid-Brunhes Event (MBE), ~430,000 years ago, marks the transition between "cooler" interglacials with lower CO_2 values and "warmer" interglacials with higher CO_2 values, which are similar to present interglacials.

Many paleoclimate records (such as ice cores, marine sediments, and speleothems) from mid and high latitudes show clear changes across the MBE (*3*–*5*). However, Meckler *et al*. find no change in the stalagmite record between pre-MBE and post-MBE interglacials. Moreover, during all interglacials studied by Meckler *et al*., the magnitudes and levels of variation of the oxygen isotope values are similar to those during the Holocene (since 11,700 years ago) (*6*). Thus, the distinct change noted in high- or mid-latitude interglacial climates does not seem to extend to the tropics.

The authors also analyzed the response to deglaciations. Here, a very different picture emerges. The oxygen isotope maxima from deglaciation periods seem to reflect a global climate process. The maximum peak decreases progressively, corresponding to



Isotopic response associated with ITCZ migration. The subsidence/downdraft associated with large-scale convective systems transports moisture with relatively lower $^{18}O/^{16}O$ isotope ratio to the lower atmosphere, resulting in lower $^{18}O/^{16}O$ ratios in surface water downwind from the convectively active area (*10*–*12*). During boreal autumn, moisture drawn from the convectively active region downwind of the ITCZ reaches northern Borneo and dominates local precipitation at Meckler *et al.*'s study site (black dot). This precipitation has lower $^{18}O/^{16}O$ ratios than during any another season. On the other hand, when the ITCZ has moved to south of the equator in boreal winter, surface moisture is transported from the subtropical drying region over the western Pacific and isotopic values are higher than in boreal autumn. High $^{18}O/^{16}O$ ratios during deglaciation periods may thus mean that the ITCZ became locked in the Southern Hemisphere.

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Editor's Summary