of key genes (Figure 1). Sorting out the detailed molecular and developmental mechanisms presents many challenges.

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Calcium Signalling: Fishing Out Molecules of Mitochondrial Calcium Transport

Cellular energy metabolism, survival and death are controlled by mitochondrial calcium signals originating in the cytoplasm. Now, RNAi studies link three proteins — MICU1, NCLX and LETM1 — to the previously unknown molecular mechanism of mitochondrial calcium transport.

György Hajnóczky* and György Csordás

Twenty years ago, mitochondria were viewed as cellular power plants, regulated solely by substrates. Nowadays, mitochondria are also considered as nodes of signalling pathways that engage a variety of effector mechanisms to control the cell's life. A key factor in this advance was the discovery of the participation of mitochondria in calcium signalling.

Early studies with isolated mitochondria showed the requirement for supraphysiological [Ca^{2+}] elevations to stimulate Ca^{2+} uptake. Thus, it was a major surprise when the studies of Rizzuto and Pozzan and colleagues [1] revealed propagation of hormone-induced cytoplasmic [Ca^{2+}] ([Ca^{2+}]$_c$) calcium signals to the mitochondrial matrix in cells [1]. They proposed that mitochondria sensed the high local [Ca^{2+}]$_c$ in the vicinity of the open inositol 1,4,5-trisphosphate receptors (IP_3Rs) and ryanodine receptors (RyRs) rather than the substantially lower global [Ca^{2+}]$_c$. Very recently, this idea has been directly validated by targeting Ca^{2+}-sensitive fluorescent proteins to the mitochondrial surface. These measurements provided evidence that mitochondria see a 10-fold higher [Ca^{2+}]$_c$ than the global [Ca^{2+}]$_c$ signal [2,3]. Another line of studies revealed that positioning of mitochondria close to the endoplasmic/sarcoplasmic reticulum (ER/SR) is supported by interorganellar tethers (Figure 1) [4]. One proposed tether between the ER and the outer mitochondrial membrane includes the IP_3R and the voltage-dependent anion-selective channel (VDAC), which would provide a shortcut for the released Ca^{2+} to access and cross the outer mitochondrial membrane [5]. Strategic positioning of mitochondria is also facilitated dynamically by Ca^{2+}-induced inhibition of mitochondrial movements close to the open IP_3Rs/RyRs [6]. These results illustrate that cells have developed a collection of sophisticated means to ensure that mitochondria recognize Ca^{2+} mobilization from the ER/SR.

It has been known for almost 50 years that Ca^{2+} uptake across the inner mitochondrial membrane is mediated by the mitochondrial Ca^{2+} uniporter (MCU). A patch clamp study of mitoplasts — i.e. mitochondria lacking the outer mitochondrial membrane — has provided evidence

that the MCU is a highly Ca^{2+}-selective ion channel (I_{MiCa}) [7]. Mitochondrial Ca^{2+} efflux has been attributed to exchangers that directly couple Ca^{2+} release to Na^+ or H^+ uptake [8]. However, the identity of the proteins mediating Ca^{2+} influx and efflux remained elusive. Among the early candidates for the MCU were mitochondria-localized RyR1 [9] and the uncoupling proteins UCP2/3 [10], but such a role for these proteins has yet to be confirmed by other groups and these proteins do not seem to be expressed in some tissues displaying robust MCU activity.

Over the past year, three novel candidate proteins have now been proposed to mediate Ca^{2+} transport across the inner mitochondrial membrane. Jiang *et al.* [11] reported the identification of LETM1 as a protein that regulates mitochondrial Ca^{2+} and H^+ concentrations in a genome-wide *Drosophila* RNA interference (RNAi) screen. LETM1, previously described as a K^+/H^+ exchanger [12,13], was suggested to support electrogenic import of Ca^{2+} (one Ca^{2+} in for one H^+ out) when the mitochondrial matrix $[Ca^{2+}]$ ($[Ca^{2+}]_m$) is low, but, when $[Ca^{2+}]_m$ is high or the cytoplasmic pH is low, LETM1 would mediate Ca^{2+} export [11]. Notably, silencing of LETM1 was found to suppress the majority of the IP_3R-linked $[Ca^{2+}]_m$ signal in HeLa cells without attenuating the mitochondrial membrane potential, the major component of the driving force for the Ca^{2+} uptake [11]. LETM1 activity was inhibited by both ruthenium red/Ru360 and CGP37157, inhibitors of the MCU and of the exchangers that mediate mitochondrial Ca^{2+} efflux, respectively [11]. These results remain a subject of intense discussion because they diverge in several regards from previous studies that have reported the following: the LETM1 had been linked to K^+ homeostasis; the mitochondrial H^+/Ca^{2+} exchanger had appeared to be non-electrogenic (one Ca^{2+} for two H^+); the loss of LETM1 had been shown to result in loss of the mitochondrial membrane potential; CGP37157 had not been seen to suppress the IP_3R-linked $[Ca^{2+}]_m$ signal; and the exchanger was not thought to be sensitive to ruthenium red.

NCLX/NCKX6 was first identified as a member of the Na^+/Ca^{2+} exchanger family in 2004. It was originally proposed to localize to the ER or to the plasma membrane [14]. However, NCLX was found to catalyze Na^+- or Li^+-dependent Ca^{2+} transport at similar rates, a distinguishing feature of the mitochondrial exchange. In a recent study, Palty *et al.* [15] reevaluated the subcellular distribution of NCLX and found that the endogenous protein localized to the inner mitochondrial membrane in several tissues and that overexpression of NCLX in cell lines resulted in the same localization. Mitochondrial Na^+-dependent Ca^{2+} efflux was enhanced upon overexpression of NCLX and reduced by silencing of NCLX expression by RNAi, which could be rescued by the expression of heterologous NCLX [15]. Mitochondria-localized NCLX was inhibited by CGP37157 and showed Li^+/Ca^{2+} exchange, further supporting NCLX as a mediator of mitochondrial Na^+/Ca^{2+} exchange [15]. Since electron microscopy showed that the NCLX immunoreactivity is spread along the cristae [15], Ca^{2+} efflux might occur across the entire surface of the inner mitochondrial membrane, in contrast to Ca^{2+} uptake, which is concentrated in foci [1–3].

In the most recent work, MICU1 has been identified as an essential element of mitochondrial Ca^{2+} uptake [16]. Perocchi *et al.* [16] first selected from the mouse and human genes encoding inner mitochondrial membrane proteins the 18 genes that were found in the majority of mammalian organs and also conserved in kinetoplastids but not in *Saccharomyces cerevisiae*. Then, they performed an RNAi screen of the top 13 candidates in HeLa cells expressing a $[Ca^{2+}]_m$ reporter. RNAi against only one candidate, MICU1, caused significant suppression of the $[Ca^{2+}]_m$ signal evoked by an IP_3-linked agonist. MICU1 is a single-pass, transmembrane protein of the inner mitochondrial membrane, which does not seem to participate in channel pore formation. However, MICU1 has a pair of Ca^{2+}-binding EF-hand domains, the mutation of which eliminates the mitochondrial Ca^{2+} uptake. Thus, MICU1 is likely to serve as a Ca^{2+}-sensing regulatory subunit of the MCU (Figure 1).

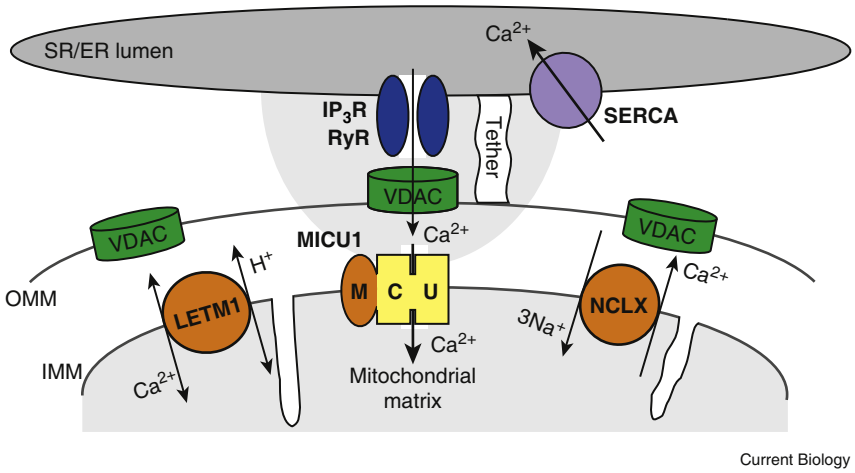

Figure 1. Molecular aspects of mitochondrial Ca^{2+} transport.

The scheme depicts the new molecules (MICU1, LETM1 and NCLX, in orange) mediating Ca^{2+} influx and efflux across the inner mitochondrial membrane (IMM) at an area of endoplasmic reticulum (ER)–mitochondrial association. The shades of gray represent the $[Ca^{2+}]$: dark gray, 100–500 μM; white, 100 nM. SR, sarcoplasmic reticulum; SERCA, sarcoplasmic ER Ca2 + ATPase; OMM, outer mitochondrial membrane; VDAC, voltage-dependent anion-selective channel; IP_3R, inositol 1,4,5-trisphosphate receptor; RyR, ryanodine receptor.

These results indicate that the MCU comprises distinct pore-forming and regulatory proteins. Combined with the observation that I_{MiCa} is highly selective for Ca^{2+}, functional relatives of the MCU seem to be the Ca^{2+} channels that mediate store-operated Ca^{2+} entry (SOCE) and the voltage-dependent Ca^{2+} channels (VDCCs). Consideration of the structure and function of these channels might offer some clues to the organization of the MCU (Table 1). SOCE involves the pore-forming ORAI subunits in the plasma membrane, which are activated upon binding to the ER membrane protein, STIM, which senses changes in ER luminal $[Ca^{2+}]$ by its EF hand. During ER Ca^{2+} release, dissociation of Ca^{2+} from STIM induces oligomerization, translocation to ER

Table 1. Location and structure of the MCU compared with STIM–ORAI and VDCC L-type channels.

	MCU (I_{MiCa})	STIM–ORAI	VDCC (L type)
Subcellular location	IMM	ORAI, PM; STIM, ER	PM
Subunit structure			
Pore:	?	ORAI tetramer (4 TM each)	α1 (four domains each with 6 TM) involves the voltage sensor and gating apparatus
Regulator:	MICU1 (1 TM)? Ca^{2+}-dependent gating	STIM (1 TM) Ca^{2+} unbinding in ER induces oligomerization, traffic to PM and gating of ORAI	α2+ β + δ (1 TM) + γ (4 TM) shift the kinetics and voltage dependence of activation and inactivation, surface expression
Inhibitor	Ru360 (IC_{50} 2 nM) RuRed (IC_{50} 9 nM)	La^{3+}, Gd^{3+}, SKF96365 or 2-APB (high μM range)	Phenylalkylamines (verapamil) Dihydropyridines (nifedipine) Benzothiazepines (diltiazem)

The transient receptor potential (TRP) V5 and V6 channels are not shown in the table because they lack a discrete regulatory subunit. However, these channels are also highly Ca^{2+} selective and display several functional similarities to the I_{MiCa}. IMM, inner mitochondrial membrane; PM, plasma membrane; ER, endoplasmic reticulum; TM, transmembrane domain.

domains close to the plasma membrane and interaction with ORAI [17]. Thus, one might speculate about a model where Ca^{2+} binding to MICU1 leads to a conformational change that allows the interaction with the pore subunit of the MCU. Notably, high Ca^{2+} exposure leads to activation of the MCU in milliseconds, indicating that the Ca^{2+} effect on MICU1 is efficiently relayed to the pore. For the VDCC, a $[Ca^{2+}]_c$ change does not trigger channel opening and the α1 subunit acts as both Ca^{2+} sensor and pore (Table 1) [18].

The Ca^{2+} selectivity is high for all three channels, but the order of divalents is different for I_{MiCa} ($Ca^{2+} \approx Sr^{2+} >> Mn^{2+} \approx Ba^{2+}$) compared with STIM–ORAI and the VDCC ($Ba^{2+} > Sr^{2+} > Ca^{2+}$). The blocking affinity of Ca^{2+} for monovalents is three to four orders higher for I_{MiCa} (2 nM) than for STIM–ORAI and VDCC (20 μM and 1 μM), which may be relevant because the $[Ca^{2+}]_c$ surrounding the MCU is lower than the millimolar extracellular $[Ca^{2+}]$ to which ORAI and VDCC are exposed. The unitary conductance of the MCU is similar to that of the VDCC (pS) and much higher than the fS conductance of ORAI. A distinctive feature of the I_{MiCa} is the lack of Ca^{2+}-induced inactivation ([7], but see [19]). The Ca^{2+}-induced inhibition and facilitation are mediated through calmodulin at least in part for both STIM–ORAI and VDCC. A calmodulin-binding domain has not been identified on MICU1 but evidence for Ca^{2+}–calmodulin-mediated facilitation has been presented for the MCU [19,20]. The I_{MiCa} is voltage dependent like the VDCC. Interestingly, it is activated by hyperpolarization, like the hyperpolarization-activated cyclic nucleotide-gated ion channels (HCN). Finally, the MCU, STIM–ORAI and VDCC display different pharmacological profiles (Table 1). Thus, striking similarities exist between the MCU and STIM–ORAI or VDCC structure and function, but the MCU has its unique fingerprint.

In MICU1-deficient cells, lower resting $[Ca^{2+}]_m$ was observed [16]. This result indicates that some mitochondrial Ca^{2+} uptake was active at $\approx$100 nM $[Ca^{2+}]_c$. Indeed, ruthenium red-sensitive and low $[Ca^{2+}]_c$-activated mitochondrial Ca^{2+} uptake mechanisms have been described earlier (e.g. rapid uptake mode) [8]. Thus, MICU1 might confer Ca^{2+} sensitivity to multiple pores at distinct $[Ca^{2+}]_c$ concentrations or to a single pore at multiple $[Ca^{2+}]_c$ concentrations, depending on the regulatory inputs (e.g. post-translational modification). In any case, analysis of the proteins that partner MICU1 will provide insight into the remaining mystery of the MCU.

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Chemosensory Ecology: Deceiving *Drosophila*

The Solomon's lily arum mimics the odours of yeast to attract drosophilid flies as unrewarded pollinators.

Richard Benton

Dawn, just outside Haifa, Israel. On the warm breeze, a drosophilid fly catches the appealing scent of rotting fruit. Lured to the source, it finds itself not upon an overripe pomelit or loquat — where it would feed and breed — but trapped within a mesh of spines. The fly has been caught in the cavernous flower of the Solomon's lily, *Arum palaestinum* (Figure 1). But it is not doomed: a day later, the fly can push past the wilting prison bars, becoming dusted with pollen as it does so, and escape. A new odour plume attracts its attention, but is the unavoidable temptation this time from a fruit, or another lily to which the unwitting carrier will transfer its pollen cargo?

Plants have evolved numerous elaborate strategies to manipulate animal behaviour to their own benefit, especially for reproductive purposes such as pollination and seed dispersal. In some cases, plants offer the animal reward for its service, such as a sweet, juicy fruit. In others, no compensation is provided. To take advantage of animals, in particular insects, many plants have devised sophisticated mimicry mechanisms, in which their flowers produce visual or chemical stimuli that advertise rewards that do not exist [1]. Classic examples have been described among members of the *Ophrys* genus of orchids, whose flowers are irresistible to one of a variety of male insects (including flies and bees) by virtue of their physical and olfactory resemblance to females of the corresponding species [2]. In the course of ultimately unsatisfying copulation with a flower, males are coated with pollen, which they may subsequently transmit to another orchid.

The *Arum* genus, distinguished by its morphologically striking influorescence (Figure 1), has also provided fascinating examples of olfactory mimicry [3]. Living up to its common name, the flower of the dead-horse arum (*Helicodiceros muscivorus*) produces foul-smelling oligosulphides characteristic of animal carcasses, thereby attracting visits by blowflies fooled into thinking it to be a suitable oviposition site [4]. In a beautiful study reported in this issue of *Current Biology*, Johannes Stökl and Antonia Strutz, in Marcus Stensmyr's group, have now deciphered the mechanism of deceptive pollination by a rather more pleasant smelling arum, the Solomon's lily [5]. Importantly, because this species attracts drosophilid flies, the authors are able to exploit the genetic and genomic power of the laboratory model *Drosophila melanogaster* to reveal how the lily odour bouquet so effectively tricks this insect's olfactory system.

The authors began by studying wild lily populations in the northern Israeli countryside and found that individual plants can trap several hundred insects. This is an impressive haul, considering that the lily flowers for just a few hours once a year, in synchrony with other plants in a population. Strikingly, more than 99% of the caught insects were drosophilid flies, principally *D. simulans* (which is abundant in this rural location) but also *D. melanogaster*.

What makes the lily so attractive to these species? Stökl *et al.* [5] first collected volatiles emitted from the flowers in the wild. Back in the laboratory, they then used gas chromatography-electroantennographic detection and mass spectrometry to identify the odorous components that activate olfactory sensory neurons (OSNs) in the drosophilid nose, the antenna. This analysis revealed six principal stimulatory compounds: 3-hydroxybutan-2-yl acetate, 3-oxobutan-2-yl acetate, ethyl hexanoate, hexyl acetate, 2-phenylethyl alcohol and 2-phenethyl acetate. By name alone, these are not particularly recognisable, but when chemically synthesised and mixed — in a similar ratio to that measured in the lily odours — they reproduce, to the human nose, a reasonable impression of a fruity wine. More importantly, for drosophilids, this mix recapitulated the behavioural attraction of the lily, confirming the significance of this chemical bouquet as the potent olfactory temptation.

Intriguingly, Stensmyr and colleagues [5] noted that these six compounds — as well as several minor lily volatiles — are all characteristic of fermentative yeast, and several are present in well-known domestic drosophilid attractants such as red wine and balsamic vinegar, as well as a commercial *Drosophila* bait, Vector960®. A principle component analysis of the chemical constituents of these and other natural food sources confirmed that the lily odor mix clusters in 'olfactory space' more closely with fermentation products (wine and vinegar) than extracts from several different ripe (but not overripe) fruits. Thus, the lily appears to have evolved an unusual, generic mimicry of yeast-fermented vegetal substrates that form the favoured diet and breeding site of many drosophilid species [6].

This study then comes into its own by identifying the specific OSNs and