more studies now indicating that *H. pylori* infection can have clear beneficial effects on the development of asthma and other chronic allergic and autoimmune diseases (20, 21), the distinction between "good" and "bad" *H. pylori* strains is becoming increasingly important in a clinical setting. The decision of whether to treat a given individual to eradicate their *H. pylori* infection could potentially be guided by a detailed analysis of the CagA phosphorylation status, and, in my opinion, treatment should probably be reserved for symptomatic carriers of strains expressing virulent CagA variants.

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Parkinson's disease: don't mess with calcium

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The hallmark of the movement disorder Parkinson's disease (PD) is progressive degeneration of dopaminergic neurons. Mitochondrial dysfunction, impaired ubiquitin-mediated proteolysis of α-synuclein, and ER stress are each implicated in the complex and poorly understood sequence of events leading to dopaminergic neuron demise. In this issue of the *JCI*, Selvaraj et al. report that in a mouse neurotoxin-based model of PD, reduced Ca^{2+} influx through transient receptor potential C1 (TRPC1) channels in the plasma membrane of dopaminergic neurons triggers a cell death–inducing ER stress response. These new findings suggest that TRPC1 channels normally function in Ca^{2+}-mediated signaling pathways that couple adaptive/neurotrophic responses to metabolic and oxidative stress and suggest that disruption of these pathways may contribute to PD.

Introduction

Approximately one million Americans have Parkinson's disease (PD), a fatal neurodegenerative disorder that involves progressive dysfunction and death of neurons in the brain stem, midbrain, and cerebral cortex. The tremors and rigidity that typify PD result from degeneration of neurons in the substantia nigra that normally produce and release the neurotransmitter dopamine. Despite this long-standing knowledge, the sequence of events leading to dopaminergic neuron demise is complex and poorly understood. PD most commonly manifests late in life and is sporadic, suggesting an important etiologic role for environmental factors. There are, however, rare cases of PD caused by mutations in the genes encoding α-synuclein, leucine-rich repeat kinase 2 (LRRK2), Parkin, PTEN-induced putative kinase 1 (PINK1), or DJ-1 (1). In most cases of PD, α-synuclein aggregates and accumulates inside vulnerable neurons, and this is thought to be a crucial component of disease pathogenesis.

A link between mitochondrial dysfunction and the demise of dopaminergic neurons in PD has been recognized for several decades. Early insight came from an incident in California in which several individuals with drug addiction presented with a PD-like syndrome of rapid onset as a result of unwitting ingestion of the

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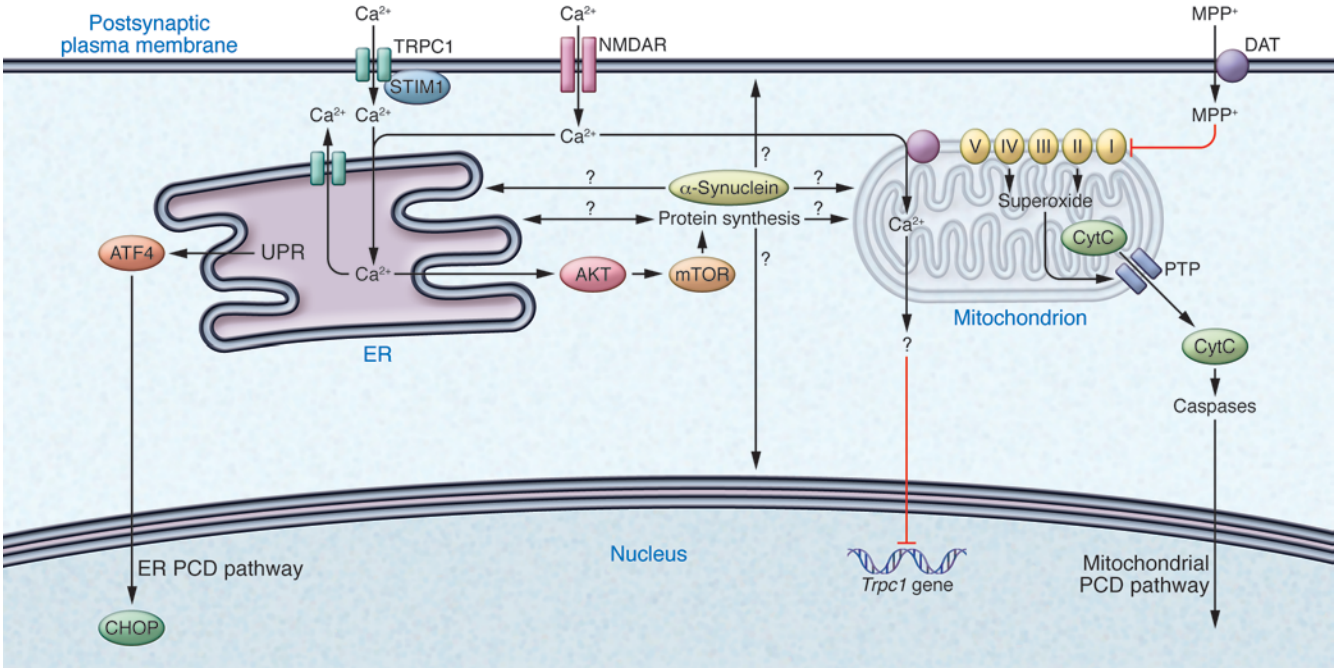

Figure 1
Aberrant Ca^{2+} signaling, interorganellar stress responses, and degeneration of dopaminergic neurons in PD. Dopaminergic neurons receive excitatory input from glutamatergic neurons. Excitation results in Ca^{2+} influx across the plasma membrane through NMDA receptors. Ca^{2+} is transported into the ER and mitochondria. In response to either IP_3 or elevated cytosolic Ca^{2+} levels, Ca^{2+} is released from the ER through IP_3 or ryanodine receptor channels. ER Ca^{2+} stores are replenished by SOCE, a process in which STIM1 interacts with TRPC1 Ca^{2+} channels in the plasma membrane, resulting in Ca^{2+} influx. Much of the Ca^{2+} that enters through TRPC1 channels is transported into the ER, replenishing the ER Ca^{2+} pool. SOCE may also lead to activation of AKT, which, in turn, activates mTOR. In this issue of the *JCI*, Selvaraj et al. (6) reveal a role for impaired SOCE in the degeneration of dopaminergic neurons caused by the mitochondrial toxin MPTP. MPP^+, a metabolite of MPTP, is transported into dopaminergic neurons via the dopamine transporter protein (DAT) and then interacts with and inhibits complex I in the mitochondrial electron transport chain. This results in excessive generation of superoxide and dysregulation of mitochondrial Ca^{2+} regulation. One consequence of these mitochondrial alterations is suppression of expression of the *Trpc1* gene, resulting in impaired SOCE, ER Ca^{2+} store depletion, and activation of the UPR. If strong and sustained, the UPR can trigger a programmed cell death (PCD) pathway involving the proteins activating transcription factor 4 (ATF4) and CHOP. CytC, cytochrome *c*; PTP, permeability transition pore.

chemical intermediate 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) (2, 3). The administration of MPTP to mice and nonhuman primates has subsequently been widely used to model PD. Upon entering the brain, MPTP is converted in astrocytes to 1-methyl-4-phenylpyridinium (MPP^+), which is then selectively transported into presynaptic terminals of dopaminergic neurons via the dopamine transporter. MPP^+ inhibits complex I in the mitochondrial electron transport chain, resulting in a reduction in ATP levels and increased generation of superoxide and other reactive oxygen species, leading to degeneration of the neurons (Figure 1).

Studies of both neurotoxin and genetic models of PD also have implicated perturbed cellular Ca^{2+} homeostasis in the neurodegenerative process (4, 5). The alterations may include excessive Ca^{2+} influx through glutamate receptor channels or voltage-dependent Ca^{2+} channels, Ca^{2+} accumulation in mitochondria, and depletion of ER Ca^{2+} stores. In this issue of the *JCI*, Selvaraj et al. (6) provide evidence for a previously unknown role in PD for the plasma membrane Ca^{2+} channel transient receptor potential C1 (TRPC1). Their findings suggest that a deficit in TRPC1-mediated Ca^{2+} influx compromises the ability of dopaminergic neurons to withstand mitochondrial and ER stress.

Ca^{2+} and dopaminergic neurons: a signal for life and a harbinger of death

Ca^{2+} is justifiably considered the most important signaling entity in neurons. Its levels are tightly controlled throughout these cells, including within major organelles such as mitochondria and the ER. Three classes of proteins regulate Ca^{2+} movement across the ER membrane: a Ca^{2+} ATPase that pumps Ca^{2+} into the ER; inositol trisphosphate (IP_3) receptors, which are ER Ca^{2+} release channels activated following cell surface receptor stimulation; and ryanodine receptors, which are ER Ca^{2+} release channels activated by Ca^{2+} itself (5). The ER membrane is typically closely associated with the plasma membrane, and when Ca^{2+} is released from the ER it can trigger Ca^{2+} influx through plasma membrane TRPC1 channels (Figure 1). This process, which is known as ER Ca^{2+} store-operated Ca^{2+} entry (SOCE), is critical for replenishing Ca^{2+} levels in the ER. When SOCE is impaired, depletion of ER Ca^{2+} can trigger a cellular process within the ER called the unfolded protein response (UPR). Selvaraj et al. (6) describe a pivotal role for TRPC1 in preventing ER Ca^{2+} depletion and neuronal death in the MPTP mouse model of PD.

The new findings of Selvaraj et al. (6) identify a potential reason why dopaminergic neurons fail to cope with mitochondrial and ER stress in PD. They

found that levels of GRP78 and CCAAT/enhancer-binding protein homologous protein (CHOP), two ER proteins involved in the UPR, are elevated in the substantia nigra of PD patients and MPTP-treated mice, and in cultured neural cells exposed to MPP^+, compared with appropriate controls. When challenged with MPP^+, dopaminergic neurons exhibited depletion of ER Ca^{2+} and reduced SOCE, suggesting a possible alteration of one or more of the proteins involved in SOCE. The authors then found that levels of TRPC1 were reduced in cultured neurons within 1 hour of exposure to MPP^+, whereas levels of two other SOCE proteins (stromal interaction molecule 1 [STIM1] and Orai1) were unchanged. Similarly, levels of TRPC1, but not STIM1 or Orai1, were reduced in the substantia nigra of PD patients. Subsequent to the reduction in TRPC1 and SOCE, neurons exposed to MPP^+ exhibited depletion of ER Ca^{2+} stores, activation of the UPR, and apoptosis. When TRPC1 levels were reduced in cultured neural cells using RNA interference technology, the cells were more vulnerable to MPP^+-induced ER stress and cell death; conversely, upregulation of TRPC1 protected the cells from being killed by MPP^+. Consistent with these data, mice lacking TRPC1 exhibited elevated basal levels of UPR proteins and increased vulnerability of dopaminergic neurons to MPTP, whereas viral vector–mediated overexpression of TRPC1 protected dopaminergic neurons in wild-type mice. Collectively, the findings of Selvaraj and colleagues demonstrate that by promoting ER stress and the UPR, reduced Ca^{2+} influx through TRPC1 channels contributes to the degeneration of dopaminergic neurons in the MPTP model of PD (6).

How might the reduced TRPC1-mediated Ca^{2+} influx detected by Selvaraj and colleagues (6) be reconciled with previous findings (4, 5, 7, 8) suggesting that increases in cytosolic Ca^{2+} contribute to the demise of dopaminergic neurons in PD? One possibility is that SOCE could provide a mild conditioning stress that activates adaptive cellular stress responses, resulting in the upregulation of genes encoding neuroprotective proteins such as neurotrophic factors, protein chaperones, and antioxidant enzymes (9). Consistent with this possibility, transient Ca^{2+} influx is known to be required for the neurotrophic effects of glutamate receptor activation, and Ca^{2+} influx through TRPC1 channels is known to mediate the actions of brain-derived neurotrophic factor (BDNF) at some synapses (10). Ca^{2+} may also mediate the cell survival–promoting function of glial cell line–derived neurotrophic factor (GDNF) in substantia nigra dopaminergic neurons (11). The involvement of neurotrophic factor signaling upstream or downstream of TRPC1 channel activation may be part of a previously unknown adaptive neuronal stress response pathway.

Whither α-synuclein?

One perceived weakness of neurotoxin models of PD (e.g., the MPTP model) is that damage to dopaminergic neurons occurs rapidly (in hours to days) and may be independent of α-synuclein, which as noted above (see Introduction) is of fundamental importance in PD. Indeed, mutations in the gene encoding α-synuclein cause some cases of familial PD; other mutations that cause familial PD (i.e., mutations in the Parkin, *LRRK2*, *PINK1*, and *DJ-1* genes) also result in accumulation of α-synuclein within dopaminergic neurons (1). Importantly, an elevated level of normal α-synuclein is sufficient to cause PD, and studies of experimental models suggest that α-synuclein accumulation and aggregation may occur as a result of impaired/insufficient degradation of α-synuclein in the proteasome (1, 12). Intracellular accumulation of α-synuclein can cause ER stress–mediated death of dopaminergic neurons, and this adverse effect of α-synuclein can be prevented by Herp, a membrane-associated protein that stabilizes ER Ca^{2+} homeostasis (8).

Although it was recently reported that α-synuclein–null mice exhibit increased resistance to MPTP (13), Selvaraj et al. (6) did not determine whether and how α-synuclein interacts with SOCE and the ER UPR stress pathway. This raises the question of whether the mechanism they describe in the MPTP model also occurs in α-synuclein models of PD and the human condition. It will be of interest to determine whether α-synuclein accumulation adversely affects TRPC1 channels, or whether activation of SOCE might somehow prevent or antagonize α-synuclein pathology (Figure 1).

No clear verdict on the role of mTOR in PD

mTOR is a kinase that stimulates protein synthesis, resulting in cell growth and/or proliferation. It is active when cellular nutrient supply is plentiful (e.g., insulin and growth factors that signal via the PI3K/AKT pathway can activate mTOR in cancer and muscle cells) and inactive under conditions of energy and amino acid restriction. The functions of mTOR in neurons are poorly understood, as are its potential roles in neurodegenerative disorders. Selvaraj et al. (6) found that the activity of both AKT and mTOR was reduced in the substantia nigra of MPTP-treated mice, and that overexpression of TRPC1 restored AKT and mTOR activity. They concluded, therefore, that AKT and mTOR play important roles in the neuroprotective effects of SOCE via TRPC1 channels.

However, findings from other studies have suggested a detrimental role for mTOR in PD. For example, treatment of mice or rats with the mTOR inhibitor rapamycin increases the resistance of dopaminergic neurons to the neurotoxins MPTP and 6-hydroxydopamine (14, 15). Moreover, a reduction in mTOR activity under conditions of nutrient deprivation or treatment with rapamycin stimulates autophagy and thereby removes damaged organelles and protein aggregates. Consistent with the notion of a neuroprotective role for mTOR inhibition, dietary energy restriction protects dopaminergic neurons and improves functional outcome in a nonhuman primate MPTP model of PD (16). Thus, much more work is required to understand the complex interactions among cellular energy metabolism, Ca^{2+} signaling, and the regulation of protein synthesis in the contexts of aging and PD. In this regard, detailed assessment and manipulations of each of these three cellular systems in genetic models of PD will likely bring clarity to the important issues raised by the findings of Selvaraj et al. (6).

Closing remarks: organellar interdependence and PD

Insidious age-related and disease process–specific alterations in mitochondria and/or the ER are increasingly being implicated in the pathogenesis of PD, as well as Alzheimer's and Huntington's diseases (1, 3). Interorganellar Ca^{2+} signaling is of fundamental importance for the regulation of cellular energy metabolism, protein synthesis, and protein degradation. A take-home message from the findings of Selvaraj et al. (6) is that a major "blow" to the mitochondria (in their case as a result of administration of MPTP) results in the disruption of Ca^{2+} signal-

ing pathways involving the ER and the plasma membrane, thereby triggering the UPR and subsequent programmed cell death (Figure 1). A similar scenario may occur in familial PD caused by Parkin deficiency, because Parkin is thought to function to protect the ER and mitochondria. Indeed, it was recently reported that both mitochondrial and ER stress induce Parkin expression and that Parkin counteracts the stress in both organelles, thereby preventing neuronal death (17). The new evidence generated by Selvaraj et al. (6) indicating involvement of impaired SOCE in a mitochondrial toxin–based model of PD suggests potential new therapeutic approaches aimed at halting the neurodegenerative process in PD. These include activation or upregulation of TRPC1 channels, enhancement of ER Ca^{2+} uptake, and tweaking of the UPR.

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A "so cilia" network: cilia proteins start "social" networking

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Cilia are unique cellular organelles found in nearly all cell types. In recent years, the importance of these organelles has been highlighted by the discovery that mutations in genes encoding proteins related to cilia biogenesis and function cause a class of complex syndromes termed ciliopathies. Emerging evidence suggests interactions among the various ciliopathy-associated proteins, but the precise mechanisms by which these interactions generate functional networks have remained elusive. In this issue of the *JCI*, Rachel and colleagues have now clearly linked two ciliopathy-associated proteins (CEP290 and MKKS). Surprisingly, the effects of a hypomorphic disease-causing *Cep290* allele were rescued by loss of MKKS function, suggesting that it might be possible to treat some ciliopathies by fine-tuning interactions within the expanding ciliary network.

Cilia are microtubule-based organelles surrounded by membranes that protrude from the cells. The functional importance of these organelles has only recently been recognized through the identification of genetic diseases associated with defects in ciliogenesis that are now termed ciliopathies (1). Ciliopathies affect diverse organ systems, with overlapping but distinct phenotypes observed in different syndromes. The complexity of this class of disorders is exemplified by Bardet-Biedl syndrome (BBS), one of the best-characterized ciliopathies, with mutations in at least 14 loci identified as causative (2). Moreover, different mutations in a given gene can lead to different syndromes with differing phenotypes. For example, the centrosomal protein 290 kDa (*CEP290*) gene is mutated in individuals with Senior-Løken syndrome, Joubert syndrome, Meckel-Gruber syndrome, and BBS. Similarly, the McKusick-Kaufman syndrome (*MKKS*, also known as *BBS6*) gene is found mutated in individuals with BBS and in those with MKKS. In this issue of the *JCI*, Rachel et al. report new complexity within the ciliopathies (3). Their data indicate that CEP290 and MKKS

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