electron phonon coupling, which is expected from their good metallic conductivity. Heavy metals with sp conduction bands, such as Pb, Tl, and Hg, have strong electron phonon coupling constants but low Debye temperatures. In contrast, the superconductivity in transition metal alloys, such as Nb alloys, oscillates as a function of the number of electrons in the relatively narrow d bands. Their behavior can be understood in terms of the oscillating behavior of the density of states.

In spite of all the success, there was as of 1986 no theoretical reason why superconductivity should be limited to temperatures below the then seemingly impenetrable experimental limit of 23 K found in $Nb_3Ge$. Then, in 1986, Bednortz and Muller reported record high $T_c$'s in copper oxide–based superconductors. The discovery sent shock waves through the physics community. Superconductors with $T_c$'s above the liquid nitrogen temperature were soon discovered and could be prepared very simply.

The characteristics of this new family cannot be explained within the range of the usual BCS parameters. It is believed that the pairing is due to some novel mechanism(s). There are plenty of candidate mechanisms but no consensus as yet as to which is correct. A record $T_c$ above 150 K (*3*) for $HgBa_2Ca_2Cu_3O_{8-x}$ under pressure has been reached, but no further increases have been reported in the past 8 years.

Still, the quest for room temperature superconductors remains alive. Recently, two new superconductors have been discovered whose $T_c$'s far exceed all known noncuprate superconductors. $C_{60}$ doped with electrons by charge transfer from intercalated alkali metals or by field-effect charge transfer has a $T_c$ of up to 40 K and 52 K, respectively (*4*, *5*), and $MgB_2$ reaches 39 K (*6*)—well above the previous record of 23 K. Both systems are composed of light, low-*Z*, main group elements. Their high $T_c$'s are most likely associated with a large preexponential factor in Eq. 1 due to modes associated with vibrations of these light atoms, which couple effectively to the conduction electrons. Less likely, but not yet excluded, is a second pairing mechanism that can supplement the phonon-mediated mechanism and enhance the superconductivity.

The fact that the $T_c$ of $MgB_2$ is well above the $T_c$'s of the other light elements—in fact, well above all known superconductors before 1986 (see the figure)—raises the question of whether there is some novel physics special to the pairing in $MgB_2$. When Akimitsu, the principal author of (*6*), was asked to explain what led to the discovery of the high $T_c$, he replied "It's a long story." It is not clear whether the long story involves simply testing a compound that easily could have been tested a generation ago (*7*), whether the discovery followed from an inspirational recognition of the structural relationship of the graphite-like boron layers intercalated with Mg to that of isoelectronic graphite intercalated with alkali metals (*8*), or whether it involved some as yet undisclosed insight.

$MgB_2$ raises the interesting question of how elemental boron itself will behave, provided that it can be collapsed into a metallic phase. Eremets *et al.* have answered this question in a beautiful set of experiments, which enabled them to carry out electrical measurements on a flake of boron under high pressures. At atmospheric pressure, boron is a semiconductor with an open structure composed of tightly bonded $B_{12}$ icosahedra, which are linked into three-dimensional open structures. Eremets *et al.* find that boron becomes metallic at about 160 GPa at room temperature. The metallic phase becomes superconducting at 6 K. Further increases in pressure up to 250 GPa raise the $T_c$ to 11.2 K.

The structure of the dense metallic boron phase is as yet unknown, but there is no indication of unusual pairing mechanisms as might arise if bonding remained molecular in the metallic phase (as is the case in metallic molecular hydrogen) (*9*). The order-of-magnitude increase in $T_c$ of boron over aluminium is within the range of behavior expected from Eq. 1 and may be attributed to the higher vibrational frequencies in boron without invoking any novel mechanism. The only unusual behavior of superconducting boron is the sign and size of the pressure coefficient of $T_c$.

The Holy Grail of the low-*Z*, high-pressure approach to superconductivity remains metallic hydrogen. Model estimates (*10*) suggest that hydrogen may become a molecular metal at 400 GPa with a $T_c$ as high as room temperature. In the model, the pairing interaction is mediated by high-frequency phonons in combination with molecular excitations. Although Eremets *et al.* have not found enhanced unusual superconductivity in the new metallic phase of boron, they have succeeded in preparing the metallic phase for the first time and have added to the long story on the road to room temperature superconductivity. Perhaps the gap they have filled will inspire someone to write the concluding chapter.

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PERSPECTIVES: NEUROSCIENCE

# Parkin and Its Substrates

**Christian Haass and Philipp J. Kahle**

Parkinson's disease (PD) has long been considered a textbook example of a sporadic neurodegenerative disorder. Patients with PD have characteristic motor deficits caused by loss of dopaminergic neurons in the brain's nigrostriatal pathway. Postmortem brain tissue from PD patients reveals the presence of inclusions called Lewy bodies in dopaminergic neurons, although whether these inclusions are a cause or a result of the disease is still unclear (see the figure). The discovery several years ago of gene mutations causing rare familial forms of PD provided the first molecular glimpse of a reason for the selective dopaminergic neuronal loss in this disorder. Missense mutations in the gene encoding the α-synuclein protein were found in families with an inherited autosomal-dominant form of PD (*1*, *2*). Various mutations in the *PARKIN* gene were discovered in families with a rare autosomal-recessive juvenile form of parkinsonism (AR-JP) (*3*, *4*). It is generally believed that the two familial forms of PD are not connected, and so research on α-synuclein and parkin has proceeded separately. This arrangement, however, is set to change with the article by Shimura and colleagues (*5*) on page 263 of this issue. Knowing that parkin is an E3 ubiquitin ligase and speculating that parkin and α-synuclein might interact, these investigators now provide provocative evidence that parkin regulates the degradation of an unusual form of α-synuclein through the attachment of ubiquitin. The covalent attachment of ubiquitin to a protein by an E3 ubiquitin ligase (ubiquitination) targets that protein for destruction in the cell's garbage dump, the proteasome (*6*). The fact that α-synuclein

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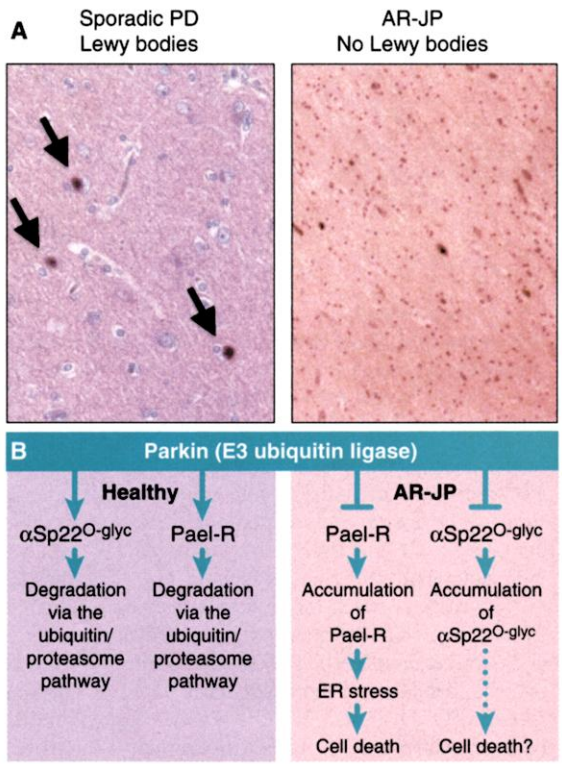
is a substrate for parkin is reminiscent of the relationship between β-amyloid precursor protein (substrate) and presenilin (enzyme), mutant forms of which have been implicated in Alzheimer's disease (*7*).

A small phosphoprotein found in neurons, α-synuclein is thought to be involved in synaptic vesicle transport (*8*). Both ubiquitin and α-synuclein are principal components of Lewy bodies, the brain inclusions characteristic of PD and other diseases associated with α-synuclein defects (*9*). Normal α-synuclein has a tendency to form fibrils that aggregate into sticky clumps. Neurons could get rid of these potentially toxic aggregates by labeling them with ubiquitin and targeting them for degradation. Evidently, this system fails in patients with PD and AR-JP. Intriguingly, protein aggregates associated with other diseases are able to inhibit the ubiquitin-proteasome system (*10*). Consistent with the notion that a defect in protein ubiquitination and degradation could be a cause of PD, mutations in the E3 ubiquitin ligase parkin and in UCH-L1, a ubiquitin carboxyl-terminal hydrolase, are associated with parkinsonism (*11, 12*).

In contrast to brains from patients with sporadic PD, the brains of AR-JP patients do not contain Lewy bodies (see the figure) (*13*). Shimura *et al.* surmised that parkin might be required to catalyze the ubiquitination of α-synuclein and that the absence or impairment of parkin would lead to the accumulation of non-ubiquitinated α-synuclein in the brains of AR-JP patients. These researchers were able to coimmunoprecipitate α-synuclein and parkin from healthy human brain tissue, suggesting that these two proteins normally interact in neurons. Unexpectedly, the authors found that the α-synuclein species interacting with parkin was O-glycosylated (had carbohydrate moieties attached to some of its hydroxyl groups) and therefore had a larger molecular weight (22 kD) than unglycosylated α-synuclein (16 kD). In fact, O-glycosylation seems to be a prerequisite for α-synuclein ubiquitination because only the 22-kD form is ubiquitinated. Patients with AR-JP lack parkin activity—deletion mutations result in premature chain termination during protein synthesis, and point mutations affect the binding of parkin to its substrates or its ability to ubiquitinate them. The failure of mutant parkin to ubiquitinate glycosylated α-synuclein means that neurons cannot degrade this form, which consequently accumulates in the brain (see the figure). It is tempting to conclude from these findings that accumulation of glycosylated α-synuclein is directly associated with the loss of dopaminergic neurons in AR-JP patients. Indeed, these results could be extrapolated to explain sporadic PD where the accumulation of α-synuclein and parkin in Lewy bodies suggests that there is a defect in the parkin-mediated α-synuclein degradation pathway.




**Parkin ubiquitinates α-synuclein. (Left) (A)** A brain section from a patient with Lewy body dementia, stained with antibody to α-synuclein to show Lewy bodies (arrows) containing α-synuclein. **(Right)** (A) Lewy bodies are not found in the brains of AR-JP patients. **(B)** In AR-JP, parkin (an E3 ubiquitin ligase) is defective, leading to accumulation of its substrates: O-glycosylated α-synuclein ($\alpha Sp22^{O\text{-}glyc}$) and the putative G protein–coupled receptor Pael-R. Accumulation of both substrates may result in the selective death of nigrostriatal dopaminergic neurons in the brains of AR-JP patients and the motor deficits associated with this rare juvenile form of PD.

The Shimura *et al.* results imply that an inability to degrade glycosylated α-synuclein results in AR-JP and possibly sporadic PD. This may well turn out to be the case, but detecting the accumulation of nonubiquitinated glycosylated α-synuclein in AR-JP brains only provides indirect evidence for such a scenario. Furthermore, as all known AR-JP–associated mutations apparently result in the inactivation of parkin, one would predict that other parkin substrates should accumulate in the brains of these patients as well. In a complementary paper in *Cell*, Imai *et al.* (*14*) report that another parkin substrate Pael-R (parkin-associated endothelin receptor-like receptor), indeed accumulates in the brains of AR-JP patients. A putative G protein–coupled receptor, Pael-R belongs to the "difficult-to-fold" class of transmembrane proteins. Misfolded Pael-R is normally efficiently ubiquitinated by parkin and degraded by the proteasome (see the figure). If parkin is defective, misfolded Pael-R is not ubiquitinated or degraded and accumulates in the endoplasmic reticulum (ER) of the neuron, leading to ER stress and cell death. Intriguingly, dopaminergic neurons in the brain produce large amounts of Pael-R, which may account for the selective loss of dopaminergic neurons in AR-JP patients. Besides Pael-R and glycosylated α-synuclein, the synaptic vesicle-associated CD-Crel-1 protein (*15*) and an uncharacterized 30-kD protein (*12*) are also ubiquitinated by parkin and would be predicted to accumulate in the brains of AR-JP patients.

The next challenge is to determine the relative contributions of these parkin substrates to dopaminergic cell loss in AR-JP and, more importantly, in sporadic PD. Given that α-synuclein accumulates in large amounts inside Lewy bodies, this protein is likely to be a major contributor to dopaminergic cell death. But it is still not clear how buildup of glycosylated α-synuclein could cause the death of nigrostriatal dopaminergic neurons. Pael-R, on the other hand, has not been identified in Lewy bodies, but is known to be neurotoxic when it accumulates in its misfolded state in the ER. It is possible that the *PAEL-R* gene could be mutated in some cases of sporadic PD. The combined neurotoxic effects of several parkin substrates that accumulate in neurons because they cannot be ubiquitinated or degraded may cause the selective dopaminergic loss in AR-JP and perhaps also in sporadic PD.

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