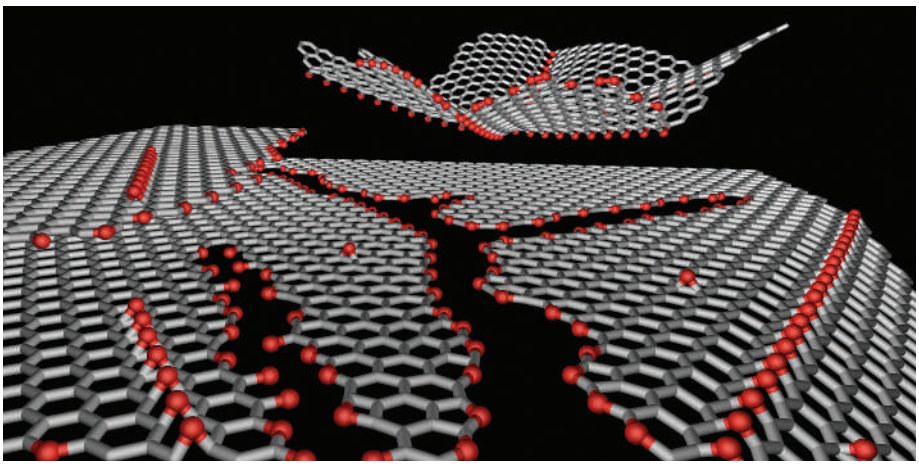

Figure 1 | Oxygen attack on graphite. Li *et al.*[2] show that when oxygen atoms (in red) bind to a graphite surface, they form two-legged epoxy bridges, which line up to lower their energy. This exerts a collective tension, breaking the underlying carbon–carbon bonds. Structural relaxation around the emerging ridges results in crumpling of the initially flat graphite sheets. This eases their separation, giving rise to distorted flakes of graphite, such as the one at the top of the figure. Faults along the oxygen trails lead to further mechanical fractures.

The paper by Li *et al.*[2] provides insight into the atomic-level mechanisms of oxidation in carbon. Graphite and its artefacts, such as carbon nanotubes, are materials with a wide range of uses, from lubrication to electronics. Controlled oxidative scission to extract nanoscale graphitic structures (for example, cut-to-size nanotubes[6] or nanosize graphene sheets[7]) from larger domains of these materials would be an extremely powerful technique for all sorts of applications. Understanding how oxygen breaks up the atomic structure of graphite could lead to a whole new area of nanotechnology based on nanoscale graphite origami[8]. ■

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NEURODEGENERATION

Good riddance to bad rubbish

Daniel J. Klionsky

Autophagy — cellular 'self-eating' — can be induced by stress, but it also acts continuously in a housekeeping role, disposing of unwanted proteins. Can it protect against neurodegenerative diseases?

Alzheimer's, Parkinson's and Huntington's diseases are names we hear with a certain dread. These devastating illnesses, typically associated with ageing, result from the death of neurons. The cause of cell death is not known, but the onset of the disease symptoms is often accompanied by the appearance of large aggregates of particular proteins, such as Aβ in Alzheimer's, α-synuclein in Parkinson's, or huntingtin in Huntington's disease[1]. These are normal proteins — everyone has them — although their function is not always clear. For years, the consensus theory has been that the aggregated proteins lead directly to cell death. But perhaps the cellular housekeeper that should get rid of the proteins is at fault? There have been hints that autophagy may have a role in protecting against neurodegeneration, based on studies with human cell lines or animals with mutations that predispose them to these diseases[1]. In this issue, Komatsu *et al.*[2] (page 880) and Hara *et al.*[3] (page 885) provide the first genetic evidence that the housekeeping role of autophagy is essential for preventing neurodegenerative disease in healthy animals.

Protein aggregates have long been considered the major culprits in neurodegenerative disease because of the linear correlation between the age of disease onset and the time of aggregate appearance. Furthermore, certain mutated forms of the implicated proteins are more prone to aggregation and/or resistant to degradation, and result in earlier onset of neurological symptoms. Accordingly, many scientists in the field of neurodegeneration have focused on these mutated proteins and the accompanying large aggregates or 'inclusions' in cells.

Cells have several mechanisms to dispose of proteins when they misfold, become damaged or are no longer needed. One of the main degradation systems is the proteasome, a multi-subunit enzyme that breaks down proteins that have been tagged with ubiquitin. The proteasome only degrades unfolded, monomeric proteins, however, so it cannot handle protein aggregates. In addition, some of the mutant neuronal proteins are not good substrates for the proteasome.

The other principal degradation system is macroautophagy (which we shall refer to here as autophagy). The hallmark of this process is the formation of double-membrane bubble-like 'vesicles' that sequester portions of the cell's cytoplasm and deliver them to an organelle called the lysosome, where they are broken down (Fig. 1, overleaf). Autophagy can be induced by starvation and various hormonal stimuli[4]. Autophagic vesicles, or autophagosomes, can engulf entire organelles as well as the large aggregates generated by misfolded neuronal proteins. So, there is potential therapeutic value in being able to regulate autophagy to prevent or ameliorate some diseases. Recent data indicate, however, that the large protein aggregates are not the toxic species in these conditions[5,6]. Rather, the soluble or micro-aggregated forms may be the ones that cause cell death. What, then, is the role of autophagy, and its capacity to sequester large structures, in protecting against neurodegeneration?

Komatsu *et al.*[2] and Hara *et al.*[3] have engineered mice that lack the *Atg7* and *Atg5* autophagy genes, respectively. Both groups have used a genetic trick to delete the gene only from neural cells and only during later stages of embryogenesis, in order to bypass developmental defects that would arise from the elimination of the corresponding gene products constitutively (that is, in all cells throughout development). In both cases, mice lacking the autophagy genes develop symptoms of neurodegeneration, including neuronal cell death.

One reason these studies are of such significance is that they examine mice that are not genetically prone to neurodegenerative disease — the genes encoding the various neuronal proteins in these mice do not have the mutations associated with early onset of disease symptoms. These are healthy animals in which autophagy cannot be acting as an induced cytoprotective response to damaged proteins. This implies that the basal, housekeeping

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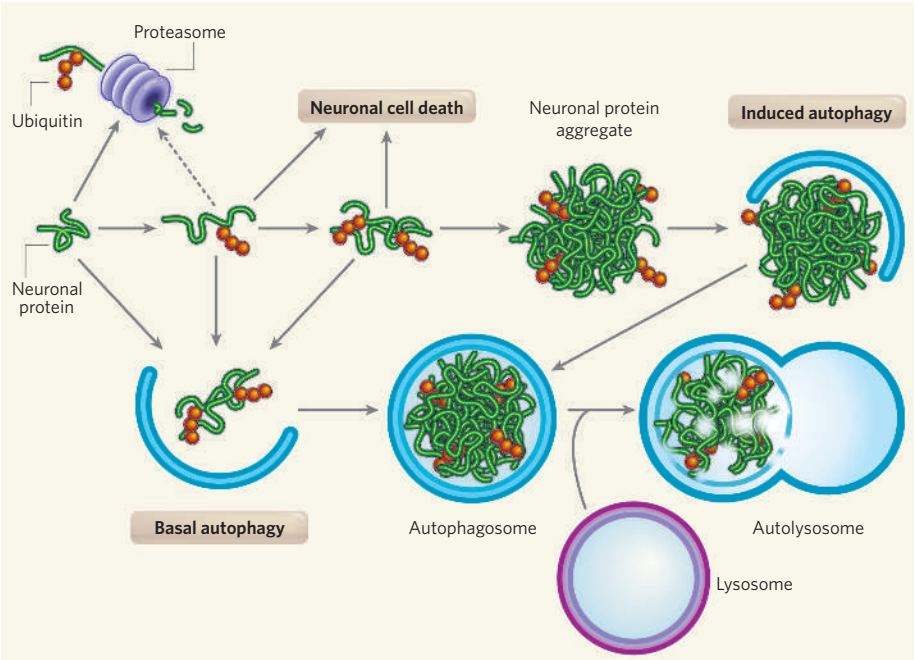

Figure 1 | The role of autophagy in protecting against neuronal cell death. Certain key neuronal proteins may misfold. These misfolded proteins can become ubiquitinated (red circles) and degraded by the proteasome. However, these proteins may be poor substrates for the proteasome, and instead will accumulate in the cytoplasm, making microaggregates and possibly leading to cell death. Basal autophagy can keep the levels of these proteins low enough to prevent toxic effects by sequestering them inside autophagosomes that deliver them to the lysosome for subsequent degradation. The misfolded proteins may also form large aggregates or inclusion bodies that can induce an autophagic response. These large aggregates may be more protective than harmful.

function of autophagy is involved in preventing neurodegeneration.

The previous focus on the role of autophagy in removing large protein aggregates resulted in part from the emphasis on studying patients or animal models with genetic mutations that predisposed the individual to neurodegeneration. In these cases, autophagy might be induced, but its cytoprotective effect could be limited because these large aggregates are not toxic, or are not the initial toxic form. The large aggregates highlighted by studies of mutant proteins may actually be a relatively terminal state of neurodegeneration, rather than the crucial intermediate that leads to disease onset, and where therapeutic intervention may be most effective.

Loss of autophagy in the mice engineered by Komatsu *et al.*[2] and Hara *et al.*[3] also eventually leads to the formation of inclusion bodies analogous to those seen in neurodegeneration. But the initial result of the loss of the *Atg* genes was accumulation of diffuse ubiquitinated proteins in the cytoplasm of the neural cells; the large inclusion bodies were seen later[2]. One implication of this is that everyone, even people without genetic mutations that promote the formation of the large protein aggregates, is potentially susceptible to neurodegenerative disease, and autophagy is a key protective mechanism in otherwise healthy individuals.

As Hara *et al.*[3] put it, "a low level of constitutive autophagy must be important for intracellular clearance under normal conditions." Even though this seems like an uncontroversial statement, there have previously been few data to support it. Basal autophagy may be particularly vital in neurons, as these cells do not grow and cannot eliminate waste such as protein aggregates by cell division. In addition, the brain typically does not experience a shortage of nutrients, so autophagy is generally not induced there as part of a starvation response[7]. The current studies therefore suggest that basal autophagy, the routine clearance of the cytosol, is in fact crucial for maintaining healthy cells. These papers will shift the focus of the field of autophagy and neurodegeneration away from large protein aggregates and induced autophagy.

Finally, Komatsu *et al.*[2] show that the proteasome functions normally in their experimental mice; however, it is obviously not capable of handling all waste disposal for the cell in the absence of autophagy. So why isn't autophagy normally just turned on at higher levels to prevent neurodegeneration prophylactically? Unfortunately, too much autophagy may cause other problems, including autophagic cell death. Routine, but limited, induction of autophagy may have beneficial effects, particularly in individuals who are prone to certain neurodegenerative diseases, but additional studies will be needed to determine whether this is the case. ■

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QUANTUM PHYSICS

United through repulsion

Leonardo Fallani and Massimo Inguscio

Mutually repulsive atoms placed at periodic intervals in a 'crystal of light' can, counterintuitively, be forced into stable couplings. That theoretical prediction has just seen experimental confirmation.

Nature likes to save energy. Whenever independent particles can arrange themselves freely, they choose the configuration that minimizes their total energy. That's why a molecule can be formed from two or more atoms: the bound configuration is stable because the total energy of the atoms is smaller when they are close together than when they are far apart. On page 853 of this issue, Winkler *et al.*[1] report a fundamental extension to this concept of a molecule — atom pairs bound together through repulsive, rather than attractive, forces.

It seems intuitive that, to obtain a bound system of particles, an attractive force between them is required. But it is also easy to see that attraction by itself is not sufficient: to reach an equilibrium configuration, a repulsive force must also be present, or the system would simply collapse. This phenomenon is quite general In astrophysics, for example, certain types of supernovae are the results of implosions that occur when a star's self-gravity is no longer balanced by the pressure generated by thermonuclear reactions in its core. Stable stars, on the other hand, exist when some repulsive force counterbalances the attraction of gravity. In a neutron star, this repulsion is provided by the rules of quantum mechanics, which forbid