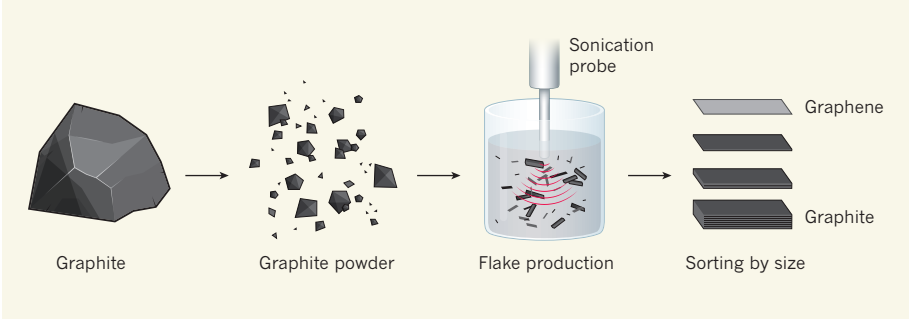

Figure 1 | Liquid-phase exfoliation of graphene. Most commercially available bulk graphene is made by milling graphite into powder, and then subjecting the resulting particles to mechanical forces in a liquid solution to separate the powder into flakes, for example, by using sonication; flakes not shown to scale. The flakes are then sorted according to their size and thickness. Kauling *et al.*[1] analysed commercially available graphene from 60 providers, and found that the majority of the samples contained less than 10% of graphene (flakes that contain fewer than ten layers of carbon atoms[5]). The rest is essentially just graphite powder. (Adapted from ref. 1.)

Moreover, the rigidity of flakes scales with the cube of layer thickness, which means that thin graphene flakes are orders of magnitude more flexible than thicker graphite flakes.

So size really matters: depending on the practical application, graphene and graphite powders can give entirely different results. Without clear standards by which to determine the quality of commercially available graphene, companies and researchers risk wasting time and money doing research on graphite powder disguised as expensive, high-grade graphene. This would stunt the development of graphene technology, harming serious graphene producers and application developers alike.

But are these concerns truly warranted? In a study aimed at answering this question, Kauling *et al.* established a systematic test protocol based on an arsenal of well-established methods for characterizing graphene, and then used the protocol to benchmark 60 graphene products from different producers, a daunting task. The results showed that the statistical distributions of the key material indicators — such as the size, structural integrity and purity of the graphene — varied greatly. Shockingly, the study revealed that less than 10% of the material in most of the products consisted of graphene composed of ten or fewer layers. None of the products tested contained more than 50% of such graphene, and many were heavily contaminated, most likely with chemicals used in the production process.

It seems that the high-profile scientific discoveries, technical breakthroughs and heavy investment in graphene have created a Wild West for business opportunists: the study shows that some producers are labelling black powders that mostly contain cheap graphite as graphene, and selling them for top dollar. The problem is exacerbated because the entry barrier to becoming a graphene provider is exceptionally low — anyone can buy bulk graphite, grind it to powder and make a website to sell it on.

Unless common standards and test protocols are introduced, there is a great risk of dropping the ball at the worst possible time. Dozens of emerging applications for graphene are closely linked to some of society's grand challenges: health, climate, renewable energy and sustainability. Some of these applications might never leave the starting block if the early development is based on 'fake graphene'.

Kauling and colleagues' article is therefore a much-needed wake-up call for graphene producers, buyers and researchers to agree on and to adhere to sound standards: a transparent graphene market would benefit everyone, except perhaps unscrupulous vendors. The first steps towards this have already been taken with the ISO's graphene vocabulary[5] (a document that defines standard terminology for describing graphene) and the UK National Physical Laboratory's helpful Good Practice Guide for graphene characterization[6]. Now it's time to push on.

It should be noted that Kauling and co-workers' study does not cover all the types of bulk graphene on the market[7]. Moreover, although the authors analysed an impressive number of LPE-manufactured products, they could have eliminated any accusations of potential bias by specifying the criteria they used to select the products for analysis. It is also possible that they unintentionally missed high-quality graphene sold by a few excellent producers. And, as the researchers mention, different applications generally make use of different characteristics of graphene — which makes it difficult to come up with a universal metric of quality.

Nevertheless, the work is a timely and ambitious example of the rigorous mindset needed to make rapid progress, not just in graphene research, but in work on any nanomaterial entering the market. To put it bluntly, there can be no quality without quality control. ■

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NEUROSCIENCE

Senescence mediates neurodegeneration

Aggregation of the protein tau is implicated in neurodegenerative diseases in humans. It emerges that eliminating a type of damaged cell that no longer divides can prevent tau-mediated neurodegeneration in mice. SEE LETTER P.578

JAY PENNEY & LI-HUEI TSAI

There is strong interest in understanding how neurodegeneration is affected by a cellular state called senescence, in which cells stop dividing, suppress intrinsic cell-death pathways and release pro-inflammatory molecules that can harm healthy neighbours[1,2]. On page 578, Bussian *et al.*[3] examine the role of senescent cells in a mouse model of a type of neurodegeneration that involves aggregation of the protein tau. They find that neuronal expression of mutant tau triggers senescence in glia, the support cells of the brain. Preventing the build-up of senescent glia can block the cognitive decline and neurodegeneration normally experienced by these mice.

Senescent cells are characterized by various molecular and gene-expression changes, including elevated levels of the cell-cycle inhibitor protein $p16^{INK4A}$. Senescence can be identified by a test that stains cells blue if they

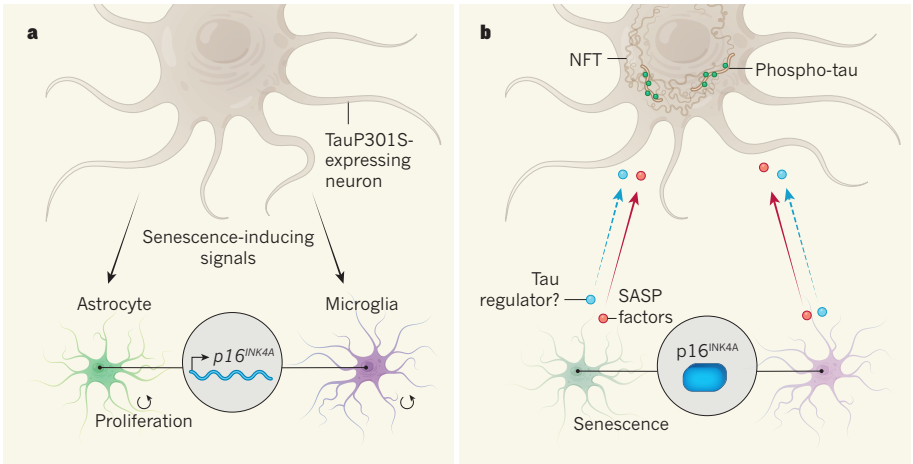

Figure 1 | Cell crosstalk in neurodegeneration. Mice that have been genetically engineered so that their neurons produce a mutant form of the protein tau (tauP301S) model some neurodegenerative diseases of humans. **a**, Bussian *et al.*[3] provide evidence that tauP301S expression leads neurons in these mice to release unknown signals that induce a cellular state called senescence in neighbouring cells. As a result, genes such as *p16*^{INK4A} that are associated with senescence are activated in cells called astrocytes and microglia, which can proliferate. **b**, When senescent, astrocytes and microglia have elevated levels of p16^{INK4A} protein and stop proliferating. They release a group of molecules known as senescence-associated secretory phenotype (SASP) factors that, possibly in combination with other regulators of tau, signal back to neurons. This leads to the phosphorylation of tau and its aggregation into structures called neurofibrillary tangles (NFTs) — two hallmarks of neurodegeneration.

harbour senescence-associated β-galactosidase (SA-β-Gal) — a form of the β-Gal enzyme that is active at pH 6 (in healthy cells, β-Gal is inactive at this pH)[1,4]. The cells also secrete inflammatory signalling molecules, growth factors and protease enzymes that can impair the function, and ultimately the survival, of non-senescent cells in their vicinity[1,4]. This trait is known as the senescence-associated secretory phenotype (SASP).

The gradual build-up of senescent cells contributes to ageing in multicellular organisms[1,2]. Furthermore, senescence can be induced by various cellular insults. Senescent neurons or glia have been described in people with brain injury or neurodegenerative disorders such as Parkinson's and Alzheimer's diseases[1,2,5,6]. Strategies have been developed that selectively target and eliminate senescent cells, counteracting many of the effects of ageing and age-related disorders in animal models[1,7,8]. But despite intense study, the exact effect of senescent cells in different contexts — including in neurodegeneration — remains unclear.

Bussian *et al.* set out to examine the role of senescence in neurodegeneration. They focused on the aggregation-prone neuronal protein tau, which is associated with multiple forms of neurodegeneration. For instance, a mutation in tau that changes amino-acid residue 301 from proline to serine (dubbed tauP301S) causes frontotemporal dementia[9]. And, when phosphorylated at abnormally high levels, tau forms structures called neurofibrillary tangles (NFTs) that are a hallmark of Alzheimer's disease[9].

The authors made use of mice that have been engineered to express human tauP301S in neurons, and so model human tau-mediated neurodegenerative diseases. They found elevated levels of various senescence-associated genes, including *p16*^{INK4A}, in the brains of tauP301S-expressing mice compared with control animals. Using electron microscopy, the researchers examined which types of brain cell stained for SA-β-Gal in tauP301S mice. They observed no staining in neurons, but SA-β-Gal was detected in the two main types of glia — astrocytes and microglia. The group complemented their electron microscopy with an examination of senescence-associated gene expression in isolated brain-cell types. This, too, provided evidence of senescence in astrocytes and microglia, but not in neurons.

Importantly, Bussian and colleagues found that senescence-associated gene expression in tauP301S mice increased with age, but preceded NFT deposition and neurodegeneration. This suggests that the emergence of senescent cells could affect the latter two traits. To examine this possibility, the researchers eliminated senescent cells in the animals as they arose, by using a genetic tool that causes expression of a cell-death-promoting enzyme specifically in cells that produce p16^{INK4A}. Removal of senescent cells prevented brain shrinkage and thinning of a cognition-related brain region called the dentate gyrus — two characteristics of tau-mediated neurodegeneration typically seen in tauP301S animals. Furthermore, cognitive function was maintained in tauP301S mice lacking senescent cells, whereas tauP301S animals in which senescent cells were retained exhibited short-term memory defects.

Perhaps more surprisingly, given that it indicates complex crosstalk between neurons and senescent glia, genetically eliminating senescent astrocytes and microglia reduced neuronal tau phosphorylation and NFT deposition. Moreover, the authors found similar effects when they treated tauP301S mice with a 'senolytic' compound, which triggers pharmacological removal of senescent cells. Together, Bussian and colleagues' data clearly demonstrate that tauP301S expression in neurons can induce senescence in brain astrocytes and microglia. In turn, these senescent glia affect the ability of neurons to regulate tau phosphorylation and aggregation (Fig. 1). Whether by releasing signalling molecules that directly affect tau or through the effects of SASP factors (or both), glial senescence ultimately promotes neuronal degeneration.

Bussian and co-workers' findings point to several avenues for future study. First, the signals from tauP301S-expressing neurons that induce senescence in glia should be defined. Similarly, the mechanisms by which senescent astrocytes and microglia signal back to neurons remain to be determined. It will also be interesting to understand whether the same glia-derived signals affect both tau pathology and neuronal survival, and whether astrocytes and microglia send the same or distinct signals. The answers to these questions are likely to have broader implications for understanding neurodegenerative diseases more generally.

Finally, the current study adds to the growing body of evidence indicating that senolytic treatments could benefit people who have a wide range of conditions[1,2]. Of immediate interest is whether removal of senescent cells can decrease disease severity in other animal models of neurodegeneration. The authors removed senescent cells throughout the lives of their animals, but it will also be valuable to determine whether senolytics can have beneficial effects if treatment is started once a disease has progressed to symptomatic stages — a more likely scenario in humans. Finally, it will be crucial to determine whether the processes uncovered in this paper are evolutionarily conserved in humans. If so, perhaps senolytic treatments can benefit people, as promised by this and other mouse studies[1,2]. ■

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