possibilities using simple statistical models at the global level have been inconclusive.

There are good reasons for thinking that some effects of climate change might be cumulative. For instance, climate and weather will affect the level, and potentially the growth rate and efficiency, of capital and labour. Furthermore, climate might induce technological change through both adaptation and mitigation measures. Pinning down these macroeconomic processes to resolve just how large the effects of climate will be on the long-term growth of GDP needs to be a high priority for future work. ■

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NEURODEGENERATION

Sabotage by the brain's supporting cells

Several neurodegenerative disorders are linked to the build-up of abnormal α-synuclein protein in distinct cell types. It emerges that differing intracellular factors dictate the properties of this protein in each cell type. SEE LETTER P.558

LARY C. WALKER

One of the many mysteries surrounding neurodegenerative diseases is how they can manifest in such a variety of ways. Disorders such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (also known as motor neuron disease) are each defined by a core set of nervous-system abnormalities, but every affected person's brain responds slightly differently. Moreover, although each of these disorders is associated with the abnormal accumulation of a different protein in or around cells, some protein aggregates can give rise to more than one neurodegenerative disease. How can this happen? On page 558, Peng *et al.*[1] present persuasive evidence that different types of cell accumulate structurally distinct forms of one protein, α-synuclein. By shaping the 3D architecture of the corrupted protein, the cell type helps to determine the nature of the resulting disease.

Most normal proteins fold into characteristic conformations that are strongly governed by the protein's amino-acid sequence. But in age-related neurodegenerative conditions, certain proteins misfold, and induce other proteins of the same type also to misfold and to stick to one another. In this way, the abnormal molecular structure propagates by means of a crystallization-like process called seeded protein aggregation[2].

One such protein is α-synuclein. Under normal circumstances, α-synuclein is located mainly in nerve terminals. But in some cases, the protein forms intraneuronal aggregates called Lewy bodies and Lewy neurites — for instance in Parkinson's disease and a condition known as dementia with Lewy bodies, which are collectively referred to as Lewy body diseases (LBDs). In a more-aggressive brain disorder called multiple system atrophy (MSA), misfolded α-synuclein accumulates mostly in neuron-supporting cells called oligodendrocytes[3], in clumps known as glial cytoplasmic inclusions.

Why α-synuclein aggregates are mainly found in different cell types in MSA and LBDs has been uncertain. It cannot be attributed to differences in amino-acid sequence, because α-synuclein is not typically mutated in the common form of either condition[4,5]. However, previous work[6] has shown that aberrant α-synuclein in LBDs is structurally and functionally different from that in MSA. These variant molecular states are known as protein strains[7]. When injected into the brains of susceptible mice, the MSA strain causes a fatal disease similar to human MSA. By contrast, injecting the LBD strain fails to induce major signs of disease in this model[8].

Peng *et al.* set out to investigate the causes behind this difference in α-synuclein potency. The authors first confirmed that protein aggregates in the oligodendrocytes of people with MSA are conformationally distinct from those in neurons from people who have LBDs. In MSA, a few neurons do harbour α-synuclein aggregates, but the researchers found that these aggregates display the LBD conformation — thus, the two strains can occupy the same brain, albeit in different cell types. Next, the team exposed cultured cells to each strain, and found that MSA-derived α-synuclein is approximately 1,000 times more potent at inducing aggregation than is the LBD-derived protein.

The authors then injected the two types of aggregated α-synuclein (called seeds) into the brains of wild-type mice. This *in vivo* experiment confirmed that MSA-derived seeds are much more effective than seeds derived from LBDs at seeding aggregation. However, the seeds instigated aggregation only in neurons, not in oligodendrocytes.

Why might this be the case? Oligodendrocytes normally produce little, if any, α-synuclein[9]. The authors therefore genetically engineered mice to express α-synuclein only in oligodendrocytes. They found that α-synuclein aggregation could be induced in oligodendrocytes in these mice using seeds from either the MSA or the LBD strain — but again, the MSA strain was much the more potent. Importantly, the aggregates that emerged were always the MSA strain, regardless of the type of seed injected. Finally, when Peng *et al.* exposed synthetic, unaggregated

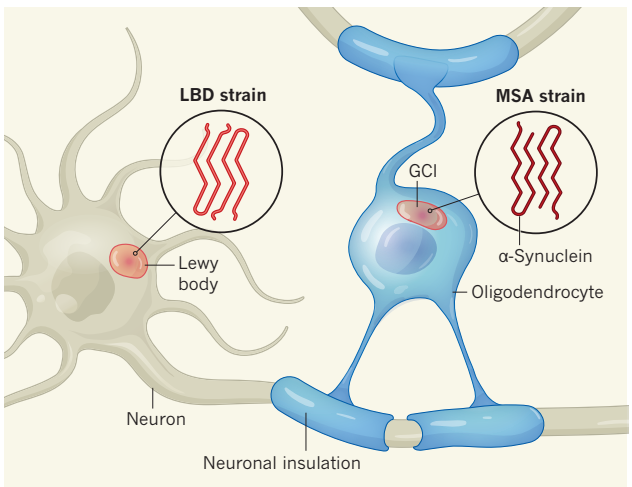

Figure 1 | Distinct strains of α-synuclein protein. In Parkinson's disease and dementia with Lewy bodies (collectively referred to as Lewy body diseases; LBDs), a misfolded form of α-synuclein called the LBD strain aggregates mainly in neurons to form anomalous structures called Lewy bodies and Lewy neurites (not shown). But in a disease known as multiple system atrophy (MSA), a different strain of misfolded α-synuclein forms aggregates called glial cytoplasmic inclusions (GCIs) in oligodendrocytes — non-neuronal cells that normally produce the fatty insulation for neuronal projections. Peng *et al.*[1] show that differences in the intracellular environments of the two cell types are responsible for the formation of the two strains.

α-synuclein to cellular material that had been isolated from ruptured oligodendrocytes or neurons, the oligodendrocytic homogenate caused the protein to aggregate into a strain of greater seeding potency than did the neuronal homogenate. Some as yet unidentified factors in oligodendrocytes, then, seem to drive the formation of the MSA strain.

Collectively, the authors' experiments show that oligodendrocytes produce a structural variant of α-synuclein that robustly seeds aggregation in both oligodendrocytes and neurons. However, the cell type strongly influences the molecular strain of the aggregates that forms: oligodendrocytes specifically generate the MSA strain, whereas neurons preferentially produce the LBD strain (Fig. 1). The authors conclude that cell-type-specific factors regulate the molecular architecture and distinctive harmful properties of aberrant α-synuclein aggregates. They further suggest that the robust seeding capacity of the MSA strain contributes to the aggressive clinical progression of MSA.

The recognition that different cells generate different disease-causing protein strains raises a wealth of questions. An especially perplexing problem is how such large amounts of α-synuclein end up in oligodendrocytes in MSA, given that these cells do not produce much of the protein[9]. Possible mechanisms include augmented oligodendrocytic expression of α-synuclein in the disease state, or the uptake of α-synuclein that has been released from neurons[10].

MSA can affect different brain systems in people with the condition[3]. Peng and colleagues' findings demonstrate the possible role of cell composition in these differences, but what other factors might be involved? Perhaps the metabolism of α-synuclein in neurons and oligodendrocytes varies between brain regions. Or maybe the regional vulnerability to α-synuclein deposition is dictated mainly by where seeding first occurs. Two other types of neuron-supporting cell, astrocytes and microglia, are also involved in MSA, but their roles in the disease remain to be defined[11]. Finally, the role of small, toxic α-synuclein assemblages called oligomers[12], which might act in different brain regions from the larger aggregates, needs further exploration. Clarification of these issues could improve our understanding not just of α-synuclein diseases, but also of other neurodegenerative disorders that involve protein aggregation.

In sum, the authors' work highlights the interplay between a cell's composition and proteins that can cause disease. Identification of the cell-specific factors that impel α-synuclein to aggregate into the MSA strain could reveal ways to treat this debilitating and ultimately fatal brain disorder. Peng and colleagues' findings are also a salutary reminder of the salient part played by non-neuronal cells in both the health and failure of the nervous system. ■

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CANCER

Subtype switch foils pancreatic tumours

Mutations in the gene *KDM6A* drive an aggressive subtype of pancreatic cancer by causing repositioning of an enzyme complex that modifies histone proteins associated with DNA, leading to altered gene expression.

FIEKE FROELING & DAVID TUVESON

Pancreatic ductal adenocarcinoma (PDAC) is one of the most deadly cancers in Western society[1] because it tends to be diagnosed late and responds poorly to therapy. PDAC tumours fall into two main groups[2–4]: a 'classical' subtype, and a more aggressive 'squamous' subtype in which pancreatic cells fail to undergo proper differentiation. The squamous subtype often involves mutations in members of the COMPASS-like complex — a group of methyltransferase and demethylase enzymes that, respectively, add or remove methyl groups from lysine amino-acid residues on histone proteins, around which DNA is packaged. Such histone modification can lead to changes in the expression of histone-associated genes involved in pancreatic-cell differentiation. Writing in *Cancer Cell*, Andricovich *et al.*[5] demonstrate the role of mutations in one member of this complex, KDM6A, in driving the squamous PDAC subtype.

The *KDM6A* gene is found on the X chromosome, and, in males, the presence of a *KDM6A* mutation can co-occur with mutation of a related gene on the Y chromosome, *UTY*. Andricovich *et al.* found that *KDM6A* and *UTY* mutations were associated with the squamous subtype of PDAC, and with shortened length of patient survival. They then used mouse models to confirm that functional KDM6A acts to suppress the development of PDAC. Mice harbouring *Kdm6a* gene mutations developed aggressive, poorly differentiated squamous tumours that showed protein- and gene-expression patterns characteristic of human tumours of the squamous subtype[2]. These defects were more pronounced in females than in males, consistent with the fact that females carry two copies of *Kdm6a* in their cells and males have one copy of *Kdm6a* on the X chromosome and *Uty* on the Y.

KDM6A is a demethylase that removes a methyl modification dubbed H3K27me3 from lysine residue 27 on histone H3 proteins. But Andricovich and colleagues found that only a small percentage of H3K27me3 marks were altered in cells from *Kdm6a*-mutant mice, compared with controls. This observation led the authors to posit that altered KDM6A demethylase activity was not the driver of *Kdm6a*-mutant PDAC. Instead, they found that loss of *Kdm6a* resulted in changes in other histone modifications, specifically at groups of gene-regulatory DNA sequences called super-enhancers, whose activation promotes the expression of certain genes that are highly expressed in PDAC.

In particular, the researchers observed changes in the distribution across super-enhancers of a different methyl modification (dubbed H3K4me1) and a modification involving acetyl groups at lysine 27 of histone H3 (H3K27ac). Such changes were associated with a repositioning of the COMPASS-like complex to these regions. The authors found that the altered histone modifications led to activation of some super-enhancers, and, in some cases, to an increased reach — an ability to regulate distant genes that the super-enhancer cannot normally influence. These findings indicate that KDM6A exerts its tumour-suppressive role not only through its demethylase activity, but also by altering