that depend on the two model parameters, such as the choice of metal, precursor concentrations and the temperature of crystallization. Some networks turn out to have relatively direct pathways through which a molecule or ion could move, whereas other networks' pathways are more tortuous. By selecting PBAs that have direct pathways facilitating mass transport, these materials can be optimized for use as battery electrodes, catalysts or ion-exchange materials.

Simonov and colleagues' work addresses a long-standing lack of detailed knowledge about the structural vacancies that determine the physical properties of Prussian blue and its analogues. But numerous challenges remain before the predictive potential of their results can be fully realized. Although remarkably effective, the modelling analysis does not consider further possible complexities, such as the effects of ionic species that dwell in the PBA pores. Extrapolation of the findings from these single-crystal studies to powder samples, which are more technologically relevant, will require further challenging experiments and enhanced modelling that considers the surface structure and chemistry of microparticles. Great care will also be needed to work out how each of the variables in a PBA synthesis correlate with the resulting vacancy ordering and material properties.

Although these challenges necessitate substantial further work, they also represent an opportunity to exert even greater control over the properties of PBAs, guided by a deeper understanding of structure–property relationships. Refinement of more-complex models will dictate how to take advantage of the many variables of a PBA synthesis. Not only has this work resulted in new-found control over the optimization of PBAs for applications in energy storage, ion capture and catalysis, but it also represents a platform on which to build a similar understanding of other framework materials, such as zeolites[11] and metal–organic frameworks[12], which have their own sets of challenges and promising applications.

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Neurodegeneration

A protein's structure used to diagnose disease

Juan Atilio Gerez & Roland Riek

Parkinson's disease and multiple system atrophy involve the protein α-synuclein. Proof that aggregated α-synuclein adopts a different structure in each case suggests that its conformation underlies the distinct disorders. **See p.273**

A snowflake begins life as a tiny crystal that acts as a seed on which water molecules aggregate, increasing the size of the snowflake as it descends to earth. Proteins can also act as seeds – for instance, in a class of age-related disorders called amyloid diseases, in which thousands of copies of a type of protein known as an amyloid adopt an abnormal structure and aggregate in harmful clumps. In Parkinson's disease, aggregates of the amyloid protein α-synuclein accumulate in neurons. A rarer neurodegenerative disease, multiple system atrophy (MSA), involves α-synuclein aggregates in neuron-supporting cells called glia. It can be difficult to distinguish between the two disorders, given their overlapping symptoms, but they require different treatments. Shahnawaz *et al.*[1] provide an explanation for this difference on page 273: like two dissimilar snowflakes composed of identical water molecules, α-synuclein aggregates form distinct 3D architectures in each disease.

In vitro and animal experiments have previously indicated that different aggregate structures of α-synuclein, called strains, yield different effects[2]. The various α-synuclein strains not only can have distinct cell-killing abilities and different seeding and propagation properties, but also can target different cell types and areas of the mammalian brain[3,4].

Shahnawaz *et al.* built on these previous findings using a technique called protein misfolding cyclic amplification (PMCA), which amplifies small amounts of α-synuclein aggregate, allowing thorough examination of minuscule samples. An amyloid-specific fluorescent dye is incorporated into the newly formed aggregates, enabling their analysis.

Impressively, the authors amplified and analysed samples from the cerebrospinal fluid of more than 200 people who had either Parkinson's disease or MSA, or who were healthy (Fig. 1). They found that samples taken from people with Parkinson's disease displayed more fluorescence than those from people with MSA. Thus, PMCA could be used to discriminate between Parkinson's disease and MSA.

The different levels of fluorescence suggested that the amyloid dye interacted with each α-synuclein aggregate differently, and that distinct α-synuclein strains are involved in the two diseases. The authors confirmed this result by showing that the two strains could also be distinguished by using proteinase K digestion (an enzymatic treatment that breaks down strains that have different structures in different ways), and through other biophysical characterizations, including a microscopy approach called cryo-electron tomography.

Shahnawaz and colleagues' work has two major implications. First, it demonstrates that PMCA can be used as a diagnostic tool to discriminate between diseases involving α-synuclein. However, it should be noted that the samples analysed in this study were obtained from people who had already been diagnosed, and it remains unclear whether the approach could be used as a predictive tool to detect disease at earlier stages. Moreover, it is possible that PMCA is affected by the medication given to the participants who had Parkinson's disease. These people typically receive the hormone dopamine (L-dopa), which has been shown to affect α-synuclein aggregation *in vitro*[5].

Second, the study adds to a growing body of evidence supporting the 'one polymorph, one disease' hypothesis[6–8], which states that different structural forms (polymorphs) of the same aggregated protein can cause distinct pathologies and symptoms. What might lead a protein to adopt different structures? *In vitro*, distinct fold structures can result

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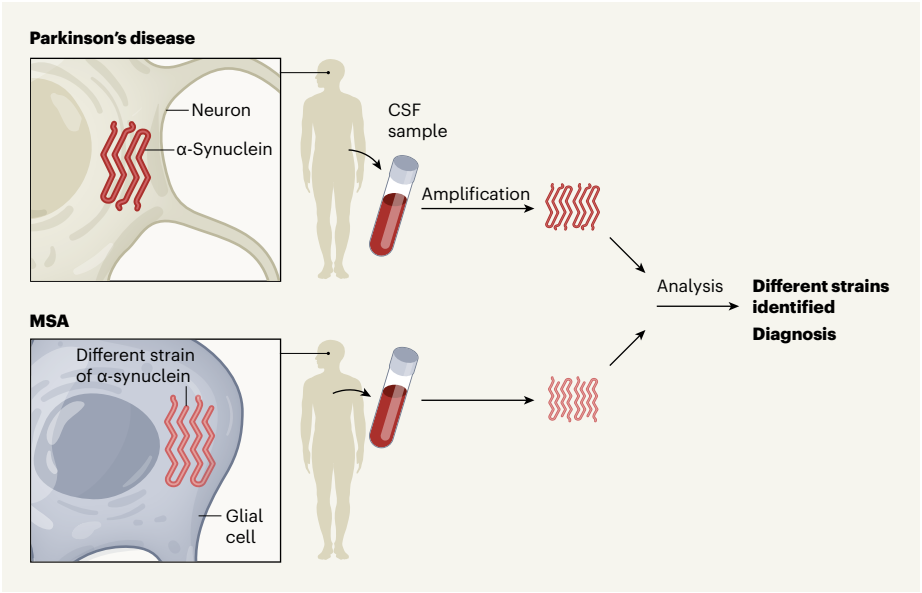

Figure 1 | Different structures for the α-synuclein protein. Two neurodegenerative disorders, Parkinson's disease and multiple system atrophy (MSA), involve aggregates of α-synuclein, which are found in neurons and neuron-supporting glial cells, respectively. Shahnawaz *et al.*[1] have demonstrated that α-synuclein adopts different structures in each disease, indicating that the structure of the protein might contribute to the distinct nature of each disorder. The group extracted tiny amounts of α-synuclein from cerebrospinal fluid (CSF) samples. Protein amplification and analyses revealed different structures for the two samples. These analyses were sufficient to discriminate between the diseases in around 95% of the 200 people studied.

from distinct environmental conditions. For example, different α-synuclein polymorphs arise depending on whether the protein is kept in a phosphate-containing or phosphate-free buffer[9]. *In vivo*, α-synuclein is exposed to several environments. Indeed, the neurons that degenerate in Parkinson's disease and the glia affected in MSA belong to different cell lineages, and have markedly different intracellular environments. In addition, α-synuclein can move between cells, exposing it to both intra- and extracellular environments[2].

The idea of different polymorphs in disease dates back to studies of prion proteins[6] in the 1990s. Much like amyloids, prions aggregate in harmful infectious clumps to cause neurodegenerative conditions such as Creutzfeldt–Jakob disease in humans and scrapie in sheep. Several strains of prion, each adopting a different polymorph, typically coexist in a given sample or organism[7]. The strains have different fitnesses in different environments, which governs their ability to replicate[7] – a phenomenon known as the prion cloud[10].

A corollary of this idea is that if environmental conditions change, the relative abundance of each polymorph might change. This principle also governs the PMCA assay. Under given conditions, the fittest polymorphs should be amplified from a possible mix of pre-existing strains. Indeed, in Shahnawaz and colleagues' experiments, a single distinct polymorph was amplified from Parkinson's disease samples and another from MSA samples.

By contrast, in another recent study that used PMCA, Strohäker and colleagues[11] reported no significant differences between structures of α-synuclein derived from the brains of people who had Parkinson's disease and those with from people with MSA. A possible explanation for this apparent discrepancy is that the two groups used different PMCA protocols. In addition, Strohäker *et al.* used a much smaller group of patients than did Shahnawaz and colleagues. In fact, analysis using nuclear magnetic resonance spectroscopy did indicate distinct structural features in a subset of Strohäker and colleagues' samples.

High-resolution cryo-electron microscopy has been used to demonstrate the existence of distinct disease-specific polymorphs of another neurodegeneration-associated protein, tau, at atomic resolution[8]. A similar approach using samples extracted under mild conditions might give us a clearer picture of the reality for α-synuclein. Taken together with similar observations for Alzheimer's disease[12], our understanding of the structural landscape of amyloid diseases is broadening.

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Medical research

Smoke signals in the DNA of normal lung cells

Gerd P. Pfeifer

Healthy cells in smokers' lungs have a high burden of mutations, similar to the mutational profile of lung cancer. Surprisingly, ex-smokers' lungs have a large fraction of healthy cells with nearly normal profiles. **See p.266**

According to the World Health Organization, there are 1.1 billion smokers worldwide and an estimated 1.8 million deaths from lung cancer annually. Lung cancer caused by smoking can take decades to arise, and smokers have up to a 30-fold higher risk of developing the disease than do non-smokers[1]. Carcinogenic components of tobacco smoke promote lung cancer by causing DNA damage that can lead to mutations through known mechanisms, but what the initial consequences of smoking are for healthy lung cells is poorly understood. On page 266, Yoshida *et al.*[2] report the mutational profiles of 632 healthy lung cells obtained from whole-genome sequencing of biopsied tissue from 16 individuals: children, adults, non-smokers, current smokers and ex-smokers. The authors analysed the frequency and properties of the mutations present, how they differed according to age

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