temperature. These studies could be further enriched by introducing dipole–dipole interactions between the spins, or by transforming the electron spin states into nuclear spin states.

Moreover, if the spin coherence time in the maser were longer than the photon storage time of the cavity, a photon–spin mixture could be realized in which the quantum coherence is associated mainly with the spins. The result would be a superradiant maser[13] that, unlike the authors' maser, has an emission frequency that is insensitive to the temperature fluctuations caused by laser heating. Thanks to Breeze and colleagues, a diamond age of masers can now be envisaged. ■

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NEURODEGENERATION

Protein aggregates caught stalling

Low-complexity protein aggregates are a hallmark of neurodegeneration. High-resolution snapshots of the structure of one such aggregate offer an unprecedented view of how these proteins disrupt crucial cellular functions.

LAURA PONTANO VAITES & J. WADE HARPER

Neurodegenerative diseases are often associated with genetic mutations that cause repetition of short sequences of nucleotides. In the disorders amyotrophic lateral sclerosis (ALS, also known as motor neuron disease) and frontotemporal dementia, such an expansion in a non-protein-coding region of the *C9orf72* gene[1,2], leads to aberrant translation products that contain repetitive stretches of glycine and alanine amino-acid residues. These 'poly(GA)' products form aggregates in neurons, and have been implicated in the disruption of a key cellular process in which complexes called proteasomes degrade proteins[3,4]. However, the biochemical basis for this disruption, and how it might promote disease, is poorly understood. Writing in *Cell*, Guo *et al.*[5] precisely map the organizational and structural features of poly(GA) aggregates and associated macromolecular complexes in neurons using a technique called 3D cryo-electron tomography (cryo-ET), to provide direct visualization of how proteasomes are disrupted by poly(GA) proteins.

Cryo-ET in 3D uses electron microscopy to view very thin, frozen but hydrated sections of a cell from various angles. The resulting images are combined to produce a 3D image called a tomogram. Guo *et al.* used 3D cryo-ET to visualize neurons that had been genetically engineered to express a poly(GA) tract that contained either 175 or 73 repeats. The tracts were fused with a green fluorescent protein that enabled their precise position to be determined using correlative light microscopy. The engineered protein mimics poly(GA) tracts that are produced from *C9orf72* expansion, which take a long time to form *in vivo*. The authors found that poly(GA) proteins form highly clustered and often bifurcated twisted ribbon structures that are of relatively uniform thickness, but of variable length and width, similar to poly(GA) structures previously observed by conventional electron microscopy *in vitro*[6].

The value of the authors' work lies not only in their observation of the structure of poly(GA) aggregates in detail in cells, but in their comparison of poly(GA) with aggregates formed through a different genetic expansion — a glutamine repeat (poly(Q)) tract, which causes the neurodegenerative disorder Huntington's disease, and which the same group analysed by 3D cryo-ET last year[7]. This comparison revealed structural differences that could explain dissimilarities in pathogenic mechanisms between the conditions.

First, the aggregates formed in each case are themselves structurally distinct. Poly(Q) proteins form fibril structures that show little

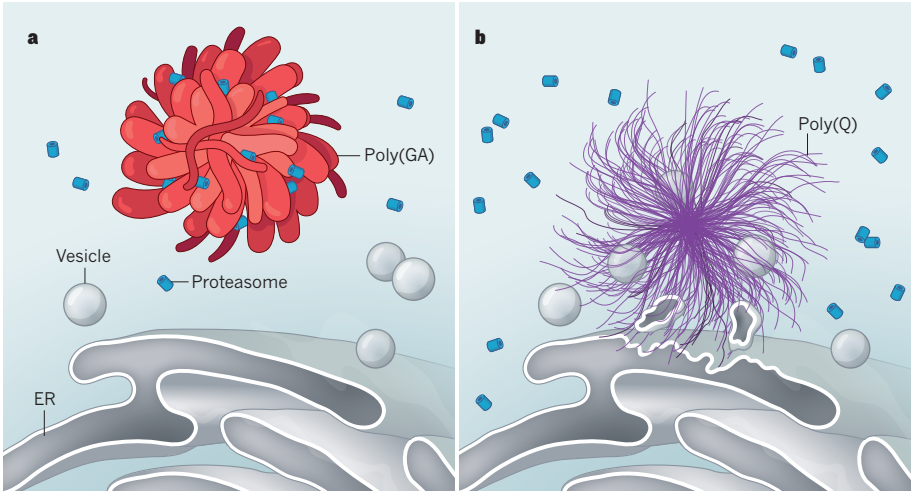

Figure 1 | Contrasting mechanisms of aggregate toxicity. a, In some cases of the neurodegenerative disorder amyotrophic lateral sclerosis, long chains of glycine and alanine amino-acid residues (dubbed poly(GA) tracts) aggregate in neurons. Guo *et al.*[5] show, through high-resolution structures in cells, that poly(GA) tracts form ribbon-like aggregates that capture protein complexes called proteasomes, which normally process other proteins for degradation. Such capture causes proteasome stalling, providing an explanation for the toxicity of this aggregate. Poly(GA) aggregates do not bind membrane-bound organelles such as vesicles and the endoplasmic reticulum (ER). **b**, By contrast, repetitive tracts of the amino acid glutamine (poly(Q) tracts), which are associated with Huntington's disease, form fibril-like aggregates[7]. These aggregates deform the membranes of vesicles and the ER, suggesting that different aggregates cause neurodegeneration through different mechanisms.

50 Years Ago

The British Home Office seems to be modifying slightly its attitude to the tests by which motorists in Britain can now be convicted of driving under the influence of alcohol. A recent paper … by Professor J. B. Payne … suggests that the methods used … are far from accurate … So far the Home Office has not been forced to act, because no motorist accused of driving under the influence of drink has quoted Professor Payne's work in his defence … Originally … police surgeons were advised to take small samples of capillary blood for use in the test, although it was also open to them to take venous blood if they preferred. The work at the Royal College of Surgeons suggests that the latter is likely to give more accurate results … The Home Office has now sent a circular to police authorities pointing out that it is within their discretion to take venous rather than capillary blood … The circular also points out that the motorist has the right to keep a sample of his own blood for independent analysis.
From *Nature* 23 March 1968

100 Years Ago

Now that our rations of food, particularly of meat and wheaten bread, have been so appreciably reduced the necessity of arranging our diet so as to ensure a sufficient supply of those elusive substances, the so-called "vitamines", is more important than ever. It is known that these substances exist in certain foods, and that an adequate supply of them is necessary to health, but they have not yet been isolated in a pure condition, although several workers claim to have done so successfully. As a result of some recent work, McCollum and Davis concluded that two distinct types of vitamine exist, the "fat-soluble A" and the "water-soluble B".
From *Nature* 21 March 1918

branching and are less densely packed than poly(GA) ribbons[7].

Second, when the authors used powerful computational approaches to search for known macromolecular complexes in each aggregate, they found many proteasomes incorporated in poly(GA) aggregates (Fig. 1). Indeed, biochemical data suggested that as many as 50% of the proteasome complexes in the neuron become highly entangled within poly(GA) ribbons. Removal of proteasomes from their normal location in cells through this sequestration mechanism might explain the reduced proteasomal activity in cells harbouring these aggregates[4,8]. Complexes called ribosomes, which mediate protein production and are comparable in size to proteasomes, were largely excluded from poly(GA) ribbons, suggesting that poly(GA) aggregates are actively recruited or retained by proteasomes. By contrast, poly(Q) fibrils did not contain proteasomes, but formed close contacts with membranes from multiple types of organelle. This interaction leads to deformation of the membranes around organelles, such as the endoplasmic reticulum. Such deformation might alter pathways involved in protein translation, trafficking and degradation[7].

The proteasome consists of a barrel-shaped core particle in which substrate cleavage takes place, and one or two regulatory particles that cap the ends of the barrel, restricting access to the core so that only proteins tagged with the pro-degradation molecule ubiquitin can enter. Regulatory particles have been observed in multiple conformations[9,10], indicating that proteasomes progress through a reaction cycle that involves ground, committed and substrate-engaged states. Guo *et al.* used computational particle averaging to quantify the proteasomal states (technique reviewed in ref. 11), and found both ground and substrate-engaged states within poly(GA) aggregates. They also found a large increase in the proportion of doubly capped proteasomes (indicating engagement with substrate) compared with control neurons that did not contain poly(GA) products. Almost one-quarter of the proteasomes within aggregates adopted a conformation recently described[9] as substrate-engaged yet stalled, in which the substrate becomes trapped in the barrel. And that proportion rose to 36% for those proteasomes closest to poly(GA) ribbons.

Why might this stalling occur? The authors' tomographic reconstructions revealed numerous regions of electron density located between a poly(GA) ribbon and the site where the protein RAD23 binds to the proteasome. RAD23 is involved in recruiting ubiquitin-tagged proteins to the proteasome and is known to be enriched in poly(GA) aggregates[8]. Thus, this electron density could indicate RAD23-associated ubiquitin that is attached to proteins within the aggregate. Which protein or proteins the proteasome is choking on is currently unclear, although possibilities include the poly(GA) peptides themselves, which probably inhibit proteasome activity directly. Regardless of the mechanism, it seems likely that depletion of proteasomal activity in the cell proper would be detrimental to protein-degradation pathways, thereby contributing to cellular toxicity.

These results raise several important questions. First, pathogenesis in cases of ALS driven by *C9orf72* expansion has been linked both to changes mediated by poly(GA) formation and to changes caused by reduced production of C9orf72 protein — but what are the relative contributions of each mechanism? C9orf72 is part of a complex involved in autophagy[12], a process by which cellular material, including proteins, is degraded and recycled. It is therefore possible that reduced C9orf72 levels conspire with poly(GA)-dependent proteasome inhibition to increase neuronal toxicity. Second, is toxicity promoted by the capture of other proteins within poly(GA) aggregates? One candidate is the autophagy cargo receptor p62, which is known to accumulate in poly(GA) aggregates[8]. Third, several molecular machines involved in disassembling aggregates do not accumulate in poly(GA) structures, but the reasons for this are unclear.

Finally, although poly(GA) is the most abundant repetitive protein produced by *C9orf72* expansion, it is not the only one — mutation can also produce tracts of glycine–arginine (poly(GR)) and proline–arginine (poly(PR)). How do the structures of these other aggregates compare to that of poly(GA) proteins? Most data on poly(GR) and poly(PR) aggregates indicate that they do not accumulate proteasomes, suggesting alternative toxicity mechanisms[13,14]. Further analysis by 3D cryo-ET, and analysis of natural products of *C9orf72* expansion rather than the engineered product used in the current study, might clarify the similarities and differences between the aggregates that occur in patients and the model aggregate structures studied by Guo and colleagues.

In sum, the current work highlights the unprecedented resolution of 3D cryo-ET for visualizing fundamental processes within cells[11]. Moreover, it sets the stage for a more comprehensive mechanistic understanding of aggregate-associated neurodegenerative diseases. ■

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SOLAR SYSTEM

Calcium signals in planetary embryos

The calcium–isotope composition of planetary bodies in the inner Solar System correlates with the masses of such objects. This finding could have implications for our understanding of how the Solar System formed. SEE LETTER P.507

ALESSANDRO MORBIDELLI

For decades, researchers have debated how planetary bodies in the Solar System with diameters of more than a few hundred kilometres were formed. Current models[1] suggest that such bodies accumulated (accreted) small particles known as pebbles that were drifting towards the Sun in a cloud of gas and dust called the protoplanetary disk. However, these models have difficulty in explaining the diverse composition of objects in the Solar System: if all such bodies grew by accretion from the same flow of pebbles, then why do they have different compositions? On page 507, Schiller *et al.*[2] provide a possible answer to this question, on the basis of their observation that the composition of calcium isotopes in planetary bodies correlates with the masses of these bodies.

The authors measured the calcium-isotope content of samples from the parent bodies of types of meteorite known as angrites and ureilites, as well as from Earth, Mars and the asteroid Vesta. They present their data in terms of the value μ^{48}Ca, which expresses the ratio of two calcium isotopes (^{48}Ca and ^{44}Ca) in a sample relative to that in a terrestrial reference standard, and is given as parts per million (p.p.m.). The authors identified a positive correlation between μ^{48}Ca and planetary-body mass for Earth, Mars and Vesta, which have known masses, and for the parent bodies of angrites and ureilites, the masses of which were inferred from thermal models[3,4].

Schiller *et al.* account for this correlation by assuming that the pebble-accretion scenario is correct, but by rejecting the conventional idea that bodies of different masses grew at different rates throughout the lifetime of the protoplanetary disk. Instead, the authors suggest that all bodies grew at the same rate, but stopped growing at different times: smaller bodies ceased accretion earlier than did larger ones.

This unorthodox view of growth is, in fact, supported by numerical simulations[5], which show that growing bodies perturb each other's orbits around the Sun. Bodies that acquire eccentric or inclined orbits stop accumulating pebbles, whereas those that remain on circular trajectories in the mid-plane region of the disk continue to grow. The correlation of μ^{48}Ca values with planetary-body masses therefore also becomes a correlation with the timescale of the growth of such bodies. The authors confirm this using growth timescales for angrites, ureilites, Vesta and Mars that were inferred by nuclear chronometry (a dating technique that uses the decay of radioactive isotopes) and thermal models.

Schiller and colleagues propose that material in the inner part of the disk initially had low μ^{48}Ca values (about −150 p.p.m.). Planetary bodies grew from this matter until they reached the size of the ureilite parent body (about 200 km in diameter). The inner disk then started to be fed with pebbles that drifted

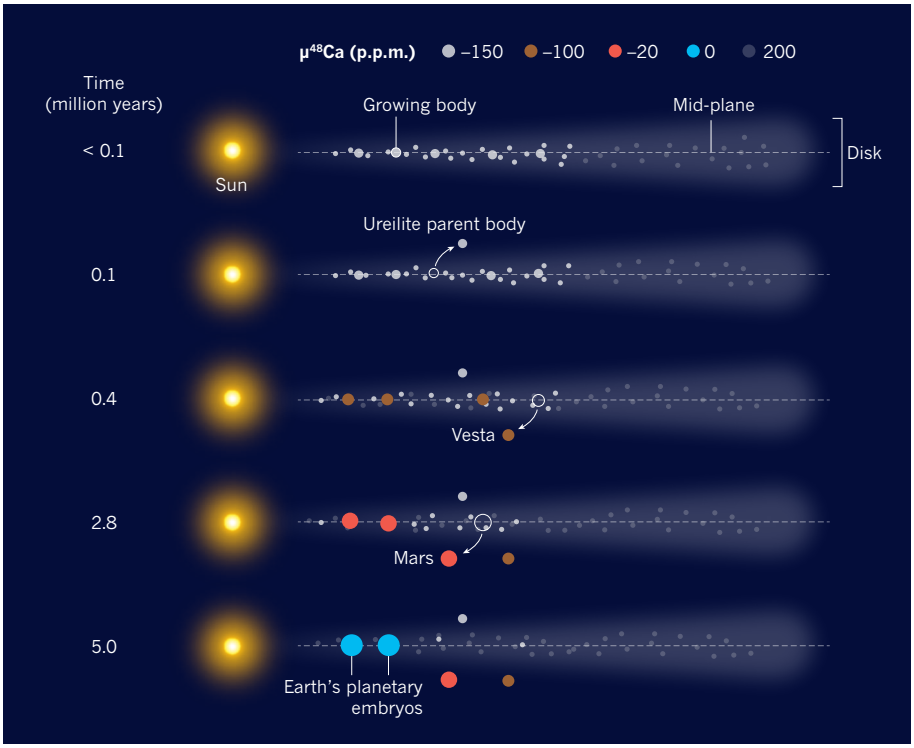

Figure 1 | A model of planetary accretion. Schiller *et al.*[2] report a correlation between the calcium-isotope contents and the masses of planetary bodies in the inner Solar System, and propose a model to explain this observation. They present their data in terms of the value μ^{48}Ca, which expresses the ratio of two calcium isotopes (^{48}Ca and ^{44}Ca) in a body relative to that in a terrestrial reference standard, and is given as parts per million (p.p.m.). In the authors' model, the disk of gas and dust that surrounded the newly formed Sun initially contained inner-disk material with low μ^{48}Ca values (−150 p.p.m.) and outer-disk particles with high μ^{48}Ca values (200 p.p.m.). The planetary bodies grew by accumulating (accreting) matter from the inner disk. Over time, the inner-disk material was replaced by particles that flowed in from the outer disk, which progressively increased the mean μ^{48}Ca value of the inner disk. Bodies continued to grow until they were displaced (curved arrows) from the mid-plane of the disk by perturbations from other bodies. The times indicate stages in the disk's lifetime; in particular, the stages at which various bodies were formed — the parent bodies of a type of meteorite known as ureilites, the asteroid Vesta, Mars and the planetary embryos that eventually produced Earth.