compaction and progress through many cell divisions. To treat cancer, might it be possible to target the chromosome-condensation machinery to completely stall mitosis and so stop tumour-cell division? The new findings[3–5] give us reason to explore this possibility. ■

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NEURODEGENERATION

An expansion in ALS genetics

Clotilde Lagier-Tourenne and Don W. Cleveland

Aggregates and mutations of the proteins ataxin-2 and TDP-43 have been implicated in distinct neurodegenerative disorders. An interplay between these proteins is now reported for amyotrophic lateral sclerosis.

Amyotrophic lateral sclerosis (ALS) is a fatal, adult-onset motor-neuron disease. Although the cause of this neuromuscular disorder is not well understood, genetic factors have been implicated in roughly 10% of cases. Elden *et al.*[1] present evidence on page 1069 of this issue that short expansions of glutamine (Q) amino-acid residues — a polyglutamine, or polyQ tract — in the ataxin-2 protein are associated with increased risk of ALS. This unexpected finding comes 15 years after the discovery[2–4] that long polyQ expansions in ataxin-2 cause spinocerebellar ataxia type 2, a neurodegenerative disorder involving abnormalities of gait. The neurotoxic effects of ataxin-2 seem to be RNA dependent and involve another protein, TDP-43.

That TDP-43, an RNA/DNA-binding protein, is central to the development of neurodegeneration is well documented. Normally found in the nucleus, TDP-43 mislocalizes to the cytoplasm of neurons and glial cells to form protein aggregates in most cases of sporadic ALS[5,6], and such mislocalization has been found in a growing number of other neurological disorders, for example frontotemporal lobar dementia (FTLD), Alzheimer's disease and parkinsonism (reviewed in ref. 7). In addition, TDP-43 mutations have been reported in cases of sporadic and familial ALS[8–10] and in patients with FTLD. How TDP-43 forms aggregates and how this then leads to neuronal death have been largely unknown, although for a few patients mutation in another gene (such as that encoding granulin in FTLD) is one component leading to TDP-43 aggregates.

Elden *et al.*[1] report that the cytoplasmic protein ataxin-2 may also enhance TDP-43-dependent toxicity to drive the death of motor neurons in ALS. The initial evidence for the role of ataxin-2 as a modulator of TDP-43 damage came from a genetic screen in yeast. The authors then powerfully extended this lesson in yeast to the fruitfly, establishing that TDP-43 toxicity is respectively enhanced or alleviated by increased or reduced levels of the fly ataxin-2.

Elden and colleagues further show that, when wild-type and mutant ataxin-2 or TDP-43 are expressed in yeast and in human cells in culture, these proteins interact physically. Intriguingly, treatment with RNase enzymes, which degrade RNA, or expression of a TDP-43 mutant that cannot bind to RNA abolishes this interaction, indicating that the ataxin-2–TDP-43 association is RNA dependent. Notably, the authors could not detect interaction between the native proteins, which suggests that the interaction does not normally occur and may require an initiating stress, including any that may lead to an age-dependent accumulation of either protein.

Does ataxin-2 also modulate TDP-43 toxicity in humans, and does it have a role in neurodegeneration? Apparently, on both counts it does. Ataxin-2 contains a polyQ tract, which can be of variable length — most commonly 22 or 23 residues. An expansion of this tract to 34 or more repeats causes, in most instances, spinocerebellar ataxia type 2 (SCA2)[2–4] and, in some instances, parkinsonism. Elden *et al.*[1] demonstrate that the length of the ataxin-2 polyQ tract in humans influences TDP-43 toxicity in motor neurons, thereby also contributing to ALS (Fig. 1).

The authors report that intermediate-length polyQ-tract expansions are a risk factor for ALS. Expansions ranging from 27 to 33 repeats occurred in 4.7% of around 900 patients with ALS, but in only 1.4% of healthy individuals. Association of ataxin-2 intermediate-length polyQ expansions with ALS was also accompanied by a significantly earlier age of disease onset.

A common feature of SCA2 and ALS is the presence of cytoplasmic aggregates of TDP-43 and ataxin-2 in the affected cells. Indeed, Elden *et al.*[1] find TDP-43 cytoplasmic inclusions in the cerebellum and brainstem of patients with SCA2, adding this disorder to the list of conditions involving abnormalities in TDP-43. The

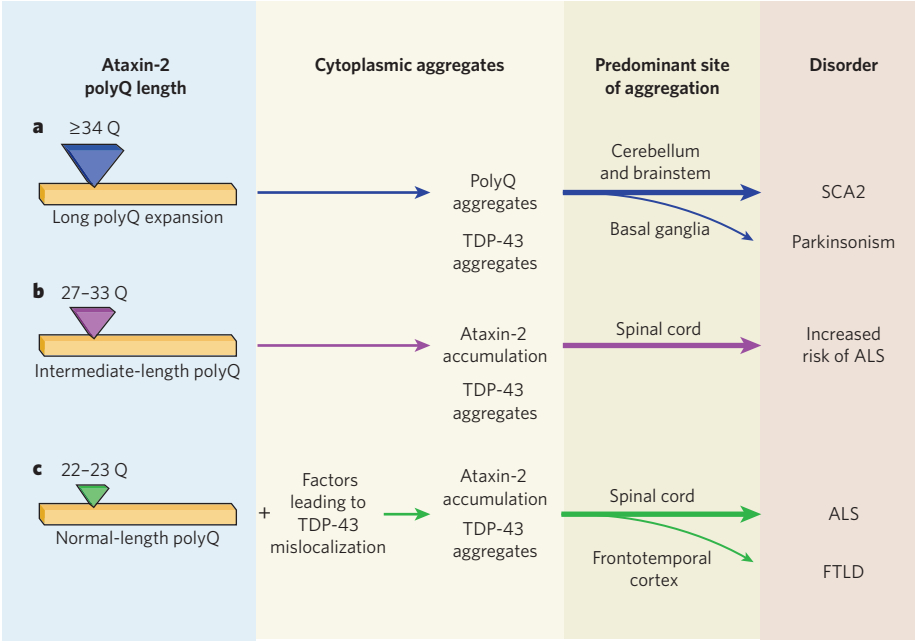

Figure 1 | PolyQ-tract size matters. a, Previous studies have shown that long polyQ-tract expansion (≥34 glutamines (Q)) in ataxin-2 leads to neurodegeneration, which — depending on the brain site predominantly affected — causes spinocerebellar ataxia type 2 (SCA2) or parkinsonism. **b,** Elden *et al.*[1] show that polyQ-tract expansions of intermediate length (27–33 Q) in this protein drive TDP-43 aggregation in motor neurons in the spinal cord, increasing the risk of ALS. **c,** Abnormal accumulation of ataxin-2 containing the normal number (22–23 Q) of glutamines, presumably mediated by other factors, has been observed in sporadic ALS and frontotemporal lobar dementia (FTLD). In at least three cases (SCA2, ALS and FTLD), TDP-43 aggregation in the affected neurons accompanies ataxin-2 accumulation. The thickness of the arrows on the right reflects the apparent frequency with which ataxin-2 accumulation is observed in associated disorders.

authors also describe the presence of distinct cytoplasmic accumulations of ataxin-2 in motor neurons of patients with sporadic ALS as well as those of patients with FTLD. The authors therefore propose that "Ataxin-2 serves as a bridge, either directly or via RNA, to bring TDP-43 to sites of a toxic function".

Notably, accumulations of ataxin-2 and TDP-43 were distinct in patients with ALS, whereas in patients with FTLD some co-localization could be seen. Whether, in SCA2, the interaction between these proteins is transient or TDP-43 is sequestered into polyQ aggregates remains unknown. The latter seems more likely, because a recent study[11] found that expression of long polyQ tracts in cultured cells results in recruitment of TDP-43 into polyQ aggregates, accompanied by reduced nuclear function of this protein.

Elden and co-workers' study[1] underscores how an interplay between TDP-43 and ataxin-2 — each of which was previously implicated in divergent neurodegenerative diseases — may be central to the development of an increasingly broad spectrum of disorders. Ataxin-2 polyQ expansion classically leads to the development of ataxia and, in a few cases, to Parkinson's disease (reviewed in ref. 12). Intriguingly, roughly 30% of patients with SCA2 also have dementia, and in a few instances motor-neuron degeneration precedes or follows the onset of cerebellar ataxia. Considering the presence of TDP-43 aggregates in Parkinson's disease and in different forms of dementia, including FTLD and 30% of Alzheimer's disease cases, it is crucial to determine the role of ataxin-2 polyQ-tract length in different forms of dementia, and whether mislocalization of ataxin-2 also occurs in Parkinson's disease, FTLD and Alzheimer's disease.

Identification of an association between ataxin-2 and ALS also provides additional evidence that altered RNA processing may be central to this disorder. Indeed, ataxin-2 itself contains a structural motif for RNA binding and has been proposed to influence RNA translation and the formation of stress granules — cytoplasmic foci of proteins and RNA formed under conditions of stress. Similar roles have been proposed for TDP-43 and another RNA/DNA-binding protein, FUS/TLS, mutation in either of which can cause ALS or FTLD (reviewed in ref. 7).

Interaction between ataxin-2 and TDP-43 also seems to require RNA, with a complete abolition of toxicity in yeast when wild-type TDP-43 is substituted with a mutant that does not bind RNA; despite forming aggregates, this TDP-43 mutant is not toxic. It is not known whether TDP-43 and ataxin-2 interact by binding to the same RNA or whether the two proteins interact directly after TDP-43 binds to RNA. To assess which RNAs might be misprocessed by loss of TDP-43 from the nucleus, and whether RNAs are sequestered in the cytoplasm as part of TDP-43 toxic aggregates, it will now be crucial to determine how ataxin-2–TDP-43 interaction and the associated nuclear exclusion of TDP-43 perturb RNA processing. ■

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QUANTUM MECHANICS

The usefulness of uselessness

Andreas Winter

A game for three or more players called 'guess your neighbour's input' reveals common ground between classical and quantum physics — at the expense of more exotic, super-quantum, theories of nature.

Why play games that quantum dice don't help you win? Writing in *Physical Review Letters*[1], Almeida *et al.* provide a surprising twist on the foundations of quantum mechanics and tell us why we should be at least interested in this question. When John Bell came up with the first of his eponymous inequalities[2], it was to show that quantum mechanics is not just incompatible with classical physics but that it violates its deep conceptual tenets. Now, Almeida *et al.*[1] show that there are 'useless' Bell inequalities that quantum mechanics cannot violate. Instead, these inequalities can provide insights into what distinguishes quantum mechanics from even stranger theories of nature.

Encounters with quantum mechanics often produce a reaction of wonder, coupled with bemusement. To understand nature, is it really necessary to believe in complementarity (such as wave–particle duality), fundamental indeterminism and uncertainty relations? Is it necessary to adopt the view that perfectly sound physical quantities don't have a value unless they're measured? It was Bell's great insight[2] (which developed from the ideas of Einstein, Podolsky and Rosen[3]) that — under the assumption of locality, which states that a particle is affected directly only by its immediate environments — one can answer these controversial questions experimentally[4,5].

To begin, it is absolutely consistent to think that the quantum indeterminism of a single particle is not 'real' in the sense that there might be 'true' values of all observables (even complementary ones), which are governed by an appropriate probability distribution. If these variables remain somehow eternally hidden from direct access, quantum mechanics can be reproduced perfectly.

This is no longer the case, however, for systems of many particles, as can be understood within the framework of 'non-local games' between distant players. In these games, each player gets an input ('setting'), x, y, …, from a referee and has to respond with an answer ('outcome'), a, b, …. The players reply without consulting the other players but potentially using a pre-agreed strategy and pre-shared randomness, a quantum state or something even more exotic. This leads to a correlation of the outcomes with each other depending on the settings, this correlation being encoded in conditional probabilities $P(ab\ldots|xy\ldots)$.

Players of such games win or lose depending on whether their collective inputs and outputs satisfy a certain relation, $W(ab\ldots, xy\ldots)$. The players' goal is to maximize the probability of winning, P_{win}. Figure 1 (overleaf) illustrates this idea for the Clauser–Horne–Shimony–Holt (CHSH) game[4]. Classical playing strategies are based on local realistic correlations: the players may share some information (independent of x, y, …) but otherwise have to rely on local instruction sets (a depending only on x, b only on y, and so on). A Bell inequality is an upper bound on P_{win} under arbitrary, local realistic correlations. If the players adopt a strategy based on quantum 'entanglement', then they can violate Bell inequalities by measuring local observables.

It is a curious property of both classical and quantum correlations that they are 'no-signalling': the choice of input at one site cannot have an observable effect at another site. This property allows classical probability and quantum theory to coexist peacefully alongside Einstein's relativity, and it may be expected that any contender theory of nature will have to share this property. But when it was realized[6,7] that there are no-signalling correlations beyond those accessible in quantum mechanics, this created a mystery of enduring appeal. What are the underlying principles, in addition to