ionic-wind propulsion systems, as opposed to propellers, is that they can be interfaced directly with batteries — the energy-storage devices of future planes — without affecting the rate of energy conversion. In the decades to come, drones or aircraft that use ionic wind might include secondary ionic-wind propulsion systems dedicated to energy saving and potentially coupled with solar panels.

These technological developments should provide a better understanding of the coupled physics of charged-molecule production and the resulting ionic wind that is central to such propulsion systems. The force generated by ionic wind is directly proportional to the electric current that flows in the system[2,10]. Because this current is strongly dependent on the configuration of emitters and collectors, research into the conception and optimization of ionic-wind propulsion can now begin, thanks to the breakthrough by Xu and colleagues. ■

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NEURODEGENERATION

Disease protein muscles out of the nucleus

Protein aggregation is a characteristic of several neurodegenerative diseases. But disease-associated aggregates of the protein TDP-43 have now been shown to have a beneficial role in healthy muscle. SEE ARTICLE P.508

LINDSAY A. BECKER & AARON D. GITLER

Most neurodegenerative disorders are characterized by the build-up of clumps of proteins in the brain[1]. A prevailing view in the field is that these large protein assemblies are inherently abnormal and are toxic to cells. Vogler *et al.*[2] challenge this canon by reporting on page 508 that muscle cells can contain physiological, reversible protein aggregates that have features similar to the aggregates seen in neurodegenerative disease, but that actually seem to be beneficial.

The protein TDP-43 forms aggregates in nerve cells in nearly all cases of the neurodegenerative disorder amyotrophic lateral sclerosis (ALS, also known as motor neuron disease)[3]. TDP-43 aggregation is also seen in other diseases, including frontotemporal dementia (FTD)[4] and inclusion body myopathy (IBM)[5], in which neurons and muscle cells, respectively, degenerate. FTD and IBM share genetic risk factors with ALS, indicating that the three have common disease mechanisms. In each disease, aggregates of TDP-43 are specifically found in the cytoplasm of dying cells. TDP-43 also has a normal job in the nucleus of healthy cells, where it acts as an RNA-binding protein[4].

Vogler *et al.* set out to investigate the behaviour of TDP-43 in healthy muscle. In doing so, they made a surprising observation. As expected, TDP-43 was located in the nucleus of muscle stem cells. But when the authors coaxed these cells to differentiate into young muscle fibres called myotubes, or if they used a chemical to injure a mouse's leg muscle to stimulate muscle regeneration, TDP-43 accumulated in the cytoplasm. There, it formed transient granular structures, which the researchers dubbed myo-granules, before moving back to the nucleus a few days later, as the myotubes became mature muscle fibres (Fig. 1). These data suggest that cytoplasmic TDP-43 myo-granules could have a role in muscle formation and regeneration.

Do myo-granules resemble the TDP-43 aggregates associated with neurodegenerative diseases? Disease aggregates are typically held together by strong bonds that are resistant to even heavy-duty detergents. Likewise, Vogler and colleagues found that TDP-43 myo-granules were resistant to such detergents. Another key feature of many neurodegenerative-disease proteins (although not all disease-associated TDP-43 aggregates) is that they can adopt a specific conformation, known as amyloid. Amyloids are long fibres made up of building blocks of the misfolded disease proteins arranged in a highly organized manner[6]. Using an array of analytical methods — including an antibody to specifically detect amyloid-like material, and high-resolution microscopy and X-ray diffraction techniques to enable examination of the myo-granule's structure — the authors demonstrated that TDP-43 myo-granules have amyloid-like properties.

Next, Vogler *et al.* investigated differences between TDP-43 in cytoplasmic myo-granules and in the nucleus, by examining the RNAs to which the protein binds in the two settings. They found that the types of messenger RNA that bind to TDP-43 changed markedly as muscle precursors differentiated into muscles. The mRNAs found associated with aggregated TDP-43 included those that encode proteins associated with the sarcomere — a unit of muscle structure that causes muscle contraction. These data suggest that TDP-43 myo-granules might control the development of sarcomeres.

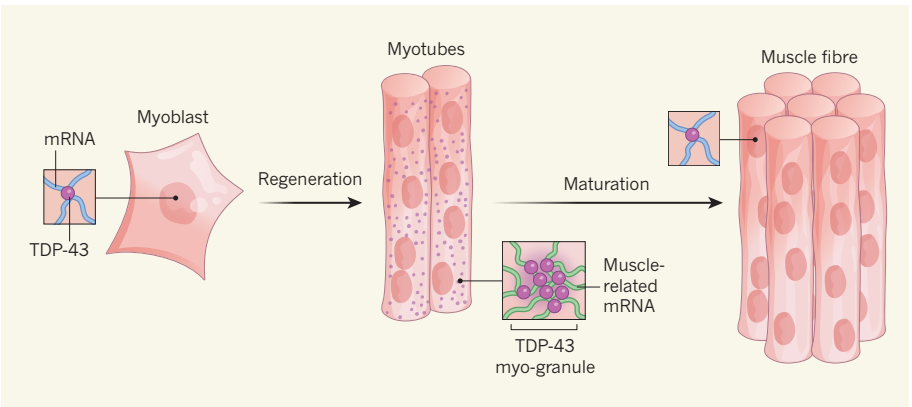

Figure 1 | A functional aggregate forms during muscle regeneration. In muscle precursor cells called myoblasts, the protein TDP-43, which binds messenger RNA, is located in the nucleus. Following muscle injury, myoblasts fuse into multi-nucleated fibres called myotubes that mature into muscle. Vogler *et al.*[2] show that TDP-43 transiently leaves the nucleus and assembles into large aggregate structures dubbed myo-granules, in which the protein binds to, and so might regulate, a distinct set of mRNA molecules involved in muscle formation. After recovery from injury, as the muscle matures, the myo-granules disassemble and TDP-43 returns to the nucleus.

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To confirm a role for TDP-43 in muscle formation, the authors generated mice whose muscle stem cells lacked one of two copies of the gene that encodes the protein. Lowering the level of TDP-43 in this way led to a decrease in the diameter of the muscle fibres generated in response to injury, indicating that TDP-43 is important for full muscle regeneration — probably because it somehow regulates the expression of muscle mRNAs. However, this experiment does not prove that myo-granule formation is necessary for TDP-43 function in muscle regeneration; reducing TDP-43 levels causes cellular dysfunction in many cell types, but Vogler *et al.* report myo-granules only in myotubes.

Regardless of the physiological function of TDP-43 myo-granules, the authors' data beg the question of whether these structures can eventually turn into disease aggregates. To investigate this possibility, the group turned to mice carrying a mutated form of the gene *VCP* that can cause ALS, FTD and IBM in humans[7]. The mutant mice, in which muscle, brain and bone tissue degenerates[5], had many more myotubes harbouring TDP-43 myo-granules than did wild-type mice. This suggests that *VCP* mutations might increase the risk of tissue degeneration by increasing the prevalence of myo-granules. In this scenario, perhaps small seeds of TDP-43 from myo-granules could be transported to the nerves that innervate muscle, where they might initiate a cascade of TDP-43 aggregation. Indeed, the earliest signs of neurodegeneration in ALS seem to originate at the nerve terminals adjacent to muscle, resulting in a 'dying-back' phenomenon that eventually reaches the main body of the neuron, which houses the nucleus[8].

The differences between TDP-43 disease aggregates and myo-granules are as interesting as the similarities. Unlike myo-granules, most TDP-43 disease aggregates seem to have an amorphous structure, although some do have amyloid-like characteristics[9]. Moreover, the disease aggregates seem to be irreversible, whereas myo-granules disassemble as muscle cells mature. Because of this, myo-granules could provide an opportunity to investigate how strongly bound aggregate structures are disassembled. Factors that promote the disassembly of myo-granules might also be effective at clearing disease-associated aggregates.

Vogler and colleagues' findings raise an intriguing question. Strenuous exercise and weight training stimulate repeated rounds of muscle growth and repair — could this activity increase the production of TDP-43 myo-granules, increasing the propensity of TDP-43 to aggregate and so leading to diseases such as ALS? Indeed, there is some evidence for increased prevalence of ALS in elite athletes[10,11]. However, much more evidence for the role of myo-granules and more human data will be needed before such a link can be assumed.

This paper sets the stage for future work characterizing the physiological function and regulation of TDP-43 myo-granules, and for investigating how these complexes might contribute to disease. There are other examples of amyloid-like protein complexes that form in healthy cells[12,13], but Vogler *et al.* describe the first that are made up of a protein that can also aggregate in disease. The race is on to search for more of these kinds of functional granule in other cell types. The idea that amyloid-like structures might have beneficial roles, rather than simply being associated with disease, represents a change in our understanding of these protein aggregates. Myo-granules provide a unique opportunity to unravel the differences between a safe and a dangerous aggregate. ■

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THERAPEUTIC RESISTANCE

A new road to cancer-drug resistance

The discovery of a mechanism that leads to cancer-therapy resistance highlights the many ways that tumour cells can adapt to survive — and reveals the limitations of categorizing patients by their gene mutations. SEE ARTICLE P.522

KATHARINA SCHLACHER

The development of resistance to cancer therapy is a major predictor of patient mortality. Therefore, understanding resistance mechanisms is key to improving therapeutic outcomes. On page 522, He *et al.*[1] report their discovery of a resistance mechanism in ovarian-cancer cells that contain a mutant version of the *BRCA1* gene.

Mutations in *BRCA1* and *BRCA2* genes can cause breast and ovarian cancer by inactivating either of two major biological pathways that ensure genome stability. One of the pathways repairs DNA double-strand breaks through a process called homologous recombination[2] (HR). The other process is called fork protection[3,4], and safeguards newly synthesized DNA at structures called stalled forks that arise during DNA replication.

In HR repair, an essential bottleneck step is the processing (resection) of double-strand breaks by nuclease enzymes to produce single-stranded (ss) DNA. BRCA1 acts as a key regulator protein that coordinates the recruitment of the nucleases, which include the MRE11–RAD50–NBS1 protein complex. BRCA1 also has a second role in HR repair: it recruits BRCA2, which in turn loads the RAD51 protein onto the ssDNA. RAD51 then assists in the binding of the ssDNA to a complementary strand that serves as a template for error-free repair.

Cancer cells that have certain *BRCA1* or *BRCA2* mutations cannot repair double-strand breaks caused by anticancer drugs currently used in the clinic, and so die when treated. Such drugs include cisplatin and PARP inhibitors (PARPi, drugs that specifically target BRCA-mutant tumours by taking advantage of their break-repair defects[5]). However, cancer cells can acquire strategies to circumvent the drugs' actions, causing resistance and limiting the use of these initially effective drugs.

In their rigorous study, He *et al.* used a gene-editing screening method[6] to identify resistance mechanisms in *BRCA1*-mutant ovarian-cancer cells. A known resistance pathway in both *BRCA1*-mutant and *BRCA2*-mutant cells is the restoration of BRCA function by re-mutating the original *BRCA* mutation (see ref. 7, for example; Fig. 1a). A second mechanism is drug avoidance, in which a membrane protein pumps the drug out of the cell or reduces its uptake[8]. He and colleagues' screen correctly identified a membrane protein implicated in the uptake of cisplatin by tumour cells as a contributor to resistance, verifying

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