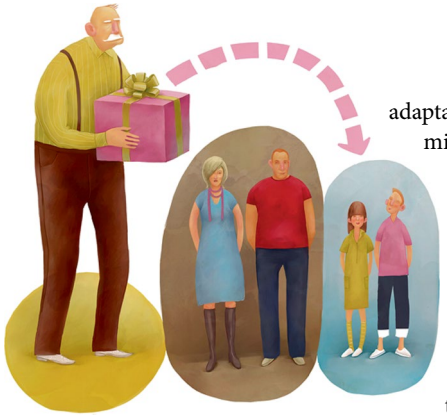

Credit: Oxana Grivina/Alamy Stock Photo

adaptation to a natural mitochondrial stress, a pathogenic *Pseudomonas* strain, was also transgenerationally inherited. Furthermore, the involvement of 6mA in stress tolerance may be conserved in other phyla, as *Drosophila melanogaster* S2 cells and ovaries also showed elevated 6mA levels after antimycin treatment.

In the future, it will be interesting to study the mechanisms involved in 6mA-mediated stress tolerance.

Grant Otto

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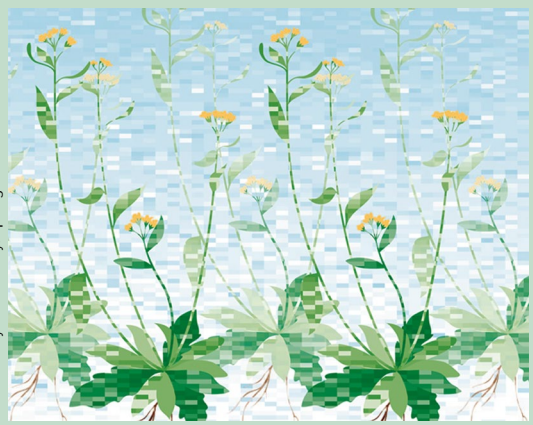

Credit: Vicky Summersby/Springer Nature Limited

counteracts the repressive effect of RdDM-mediated silencing of transposons inserted near genes. This is consistent with these proteins being recruited downstream of the RdDM pathway, which is known to target transposons and to cause mild repression of neighbouring genes.

Eytan Zlotorynski

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Journal club

'FORWARD GENETICS' AND THE CAUSES OF ALS

For over 20 years I have witnessed antagonisms between proponents of hypothesis-driven research and supporters of unbiased screens (so-called big-data experiments), the latter of which are often dismissed as 'fishing expeditions' unworthy of true scientists (and guaranteed to sink grant proposals). Gitler and colleagues combined unbiased genetic screens with intuition testing across three species (yeast, flies and humans) to study the causes underlying the fatal human neurological disease amyotrophic lateral sclerosis (ALS). Vindicating the screening approach, their results are of a beauty and completeness rarely seen in contemporary research.

Affected neurons of virtually all ALS patients display pathological accumulation, in cytoplasmic inclusions, of the DNA-binding protein TDP43. Capitalizing on concepts developed by Susan Lindquist, Gitler suggested that yeast cells could be coerced to model ALS, and his team went on to perform an unbiased genetic screen to identify suppressors or enhancers of TDP43 toxicity. By expressing 5,500 individual yeast genes in a yeast strain expressing human DP43, they identified *PBP1* as an enhancer of TDP43 toxicity. *PBP1* is the orthologue of human *ATXN2* (which encodes ataxin-2), which causes neurodegeneration when carrying very long polyglutamine tract expansions.

> "his team found that suppressing ataxin-2 expression dramatically improved life expectancy in a mouse model of ALS"

I have found that there is often a watershed moment when a discovery is pinned down. Thereafter, details may still need to be ironed out, but the endeavour is essentially de-risked and likely to lead to a successful story. The Gitler team may have experienced such feelings when identifying a genetic connection between TDP43 and ataxin-2 in *Drosophila melanogaster*, by expressing wild-type and mutant versions of human TDP43 in fly neurons and modulating the expression of fly *Atx2*. Again, Atx2 showed synthetic toxicity to TDP43. From then on, straightforward biochemistry established the physical interaction between TDP43 and ataxin-2, and its predicted dependence on RNA (as both proteins are involved in RNA metabolism).

The real game-changer, however, resulted from a brilliant intuition: could ALS patients carry ataxin-2 mutations? Indeed, ATXN2 normally has 22–23 polyglutamine repeats, yet Gitler found that ATXN2 in most ALS patients had more than 27 repeats, suggesting that ataxin-2 is a modifier of ALS — and thus a plausible therapeutic target.

While many studies claim to "empower the development of new therapies for this devastating disease", very few actually do. However, it is now clear that Gitler's discovery is having a real impact on the progress of medicine. In a follow-up study, his team found that suppressing ataxin-2 expression dramatically improved life expectancy in a mouse model of ALS. I have little doubt that the lines of discoveries opened by these studies will lead to the development of drugs that improve the life of patients — an outcome every biomedical scientist aspires to.

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The author declares no competing interests.

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