GENETIC SCREEN

Random peptides

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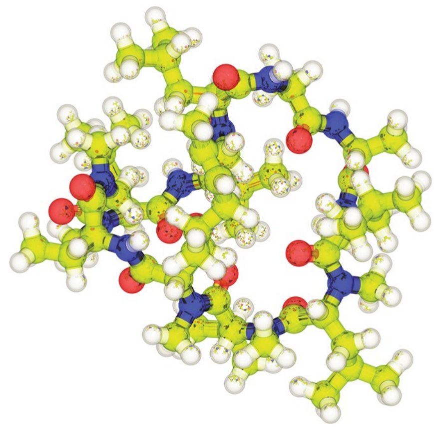
There are many approaches to unravelling complex biological processes. Despite its iconic status as the gold standard of gene discovery, perhaps because many pioneers of plant biology were geneticists, the forward genetics approach is not without problems. Random gain-of-function genetic modifications can bypass some of these limitations. Once a genome has been fully sequenced, targeted reverse genetics can also be used to obtain phenotypes by manipulating known genes. Alternatively chemical genetics can be used, screening the phenotypes induced by altering gene function with exogenously applied chemical compounds.

In a recent study, Kevin Folta and colleagues combined the two approaches by doing a risky but interesting chemical screen using genetically encoded random peptides in *Arabidopsis*. By doing so they accessed new regions of the practically infinite topological space of all possible biological alterations. The authors chose to produce short peptides with a core of 6 or 12 random residues flanked by two invariant cysteines to produce cyclical peptides through a disulphide bond. This class of ring-shaped peptides, found in mushroom toxins or animal venoms, is particularly



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stable, and includes active drugs such as the immunosuppressant cyclosporin and the antibiotic vancomycin. Although the idea is decades old and has been used for drug discovery using phage display, it may be the first time it has been applied in plants.

After designing overexpression vectors containing fragments of random DNA, the authors transformed *Arabidopsis* and screened around 2,000 individual plants for visual phenotypes. The proportion of peptides that had an effect was surprisingly high, given the vast size of the peptide sequence space. Folta and colleagues observed a wide phenotypic spectrum, including dwarfism, larger rosettes, early flowering, insensitivity to red light, reduced fertility and drought tolerance, flower developmental phenotypes, sucrose-dependent growth arrest and so on. A few of the most interesting phenotypes were validated by re-transformation into wild-type *Arabidopsis* or petunia.

Although this study was designed as a proof of concept, and is already making a novel resource accessible to the community, it is easy to speculate that the next stage may be the most difficult to achieve. The bottleneck of this chemical genetics approach is to find out which proteins or processes are targeted by the peptides. Nevertheless, this method could be useful for fundamental and applied plant biology as it offers new probes to analyse biological pathways, and new active chemicals for agriculture.

Guillaume Tena

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