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Science is a rollercoaster

The re-emergence of ABP1 as an exciting auxin receptor, after a rather bumpy history, shows once again how scientific ideas can survive sudden losses in popularity.

It is a story that starts exactly fifty years ago[1], at the beginning of the 1970s. While the hippie movement is in decline and the last Apollo missions are under way, researchers in Germany, in an avid search for the elusive auxin hormone receptor, noticed that membrane fractions of corn coleoptiles specifically bind radiolabelled auxin in vitro[2]. A few years later, these binding sites were associated with the endoplasmic reticulum (ER)[3]. The protein itself, which is quite short at just 22 kD in length, was purified in 1985 by immunological methods[4] and was later christened AUXIN-BINDING PROTEIN 1 (ABP1). Cloning and full sequencing of the maize gene was achieved in 1989[5].

Biochemical studies suggested that, while most of the ABP1 protein is indeed localised in the ER, a limited amount of ABP1 is secreted into the apoplast, and its activity takes place at the plasma membrane. ABP1 is a member of the cupin superfamily, which also includes the germin seed storage proteins, is conserved in vascular plants and is present in *Arabidopsis* as a single-copy gene. An embryo-lethal knock-out mutant was described in 2001, which was both bad and good news for the auxin community — applying traditional genetic approaches would be difficult, but the severe phenotype underlined the vital importance of this gene[6]. The structure of the glycoprotein with auxin bound to the protein was described in 2002[7]. A transmembrane kinase-interacting partner named TMK that anchors ABP1 into the plasma membrane, possibly explaining downstream signalling, was discovered in 2014[8]. For decades, ABP1 was at the forefront of auxin research as it was the closest thing to a receptor there was.

While in other fields of plant hormone biology, ethylene signalling being the most prominent example, a flurry of amazing discoveries came in rapid succession and were enabled thanks to modern genetics and molecular biology approaches, progress on ABP1 was slow. After all, this strange ER protein didn't really conform to our expectations for an hormone receptor, and unlike many other ethylene or auxin proteins, its gene never appeared in phenotype-based genetic screens. In the auxin field, the focus and interest shifted to rapid advances being made on a different pathway, culminating in the 2005 discovery of nuclear-located TIR1 and other related F-boxes as the main intracellular auxin receptors. These receptors control practically all transcriptional responses to auxin through degradation of Aux/IAA proteins and activation of AUXIN RESPONSE FACTOR (ARF) transcription factors[9,10]. Then 2015 happened, the *annus horribilis* for ABP1.

New, more precise mutants, made with CRISPR technology, indicated that knocking out *ABP1* didn't affect *Arabidopsis* development[11], which completely contradicts previously published results. The embryo lethality of the older mutant was demonstrated to be due to the deletion of an unrelated gene next to *ABP1*[12,13]. Another TILLING *abp1* mutant contained thousands of random background mutations, including some in *PHYB*[14]. Comprehensive re-examination of multiple auxin-related phenotypes concluded that ABP1 was, in fact, not involved in most of them. Enthusiasm for this protein waned. ABP1 became a pariah, with researchers quickly dropping the term 'ABP1' from manuscript titles and grant applications. During conferences you could only hear hushed whispers about the disgraced protein. We tweeted that these recent articles were the final nails in ABP1's coffin. Nobody in their right mind would consider this protein ever again.

Scientific progress is not linear. It is more akin to the up and down of a rollercoaster. Ideas, genes and fields of research suddenly become fashionable just as quickly as they become unfashionable again. They can be discredited and then rediscovered. Brilliant theories are debunked or falsified. Temporary failures can be resurrected and given a second life. All driven by the arrival of new data. These dramatic changes and discoveries are what make science exciting. This is why you wake up at 6am on a Sunday to check the results of your PCR. We all want to discover something new, and we all have widely accepted hypotheses that we would like to prove wrong. There is a contradiction in the heart of all scientists — they must accept the current consensus, while secretly wanting to break it.

It should, therefore, not have come as too much of a surprise to see the recent rehabilitation of ABP1, which has included a new study published last month in *Nature*[15]. Using clean mutants and modern approaches such as ultrafast phosphoproteomics, the authors demonstrate that auxin induces phosphorylation of a thousand sites after two minutes, but that this response is almost entirely blocked in both *abp1* and *tmk1* mutants. These mutants also show a defect during auxin-mediated regeneration of vasculature after wounding. A publication last year showed that gain-of-function ABP1 plants have a broad range of developmental defects[16]. These results, which indicate plenty of potential downstream events, might be enough to resurrect ABP1's reputation and to reboot enthusiasm for this auxin-responsive pathway, half a century after its discovery.

The large number of people who worked hard for decades to understand the function of ABP1 did not work in vain. There is knowledge to be extracted from every published article, every data set and even from experiments with negative results. The *abp1* mutant episode is a reminder that a causal relationship between a gene and a phenotype must be robustly confirmed, including by genetic rescue. Past results that proved difficult to analyse or to reconcile with existing knowledge now need to be re-examined under the light of recent studies.

Such ups and downs are part of the normal scientific process. There will always be fields, biological processes or genes that attract sudden enthusiasm. Researchers may decide to follow the current trend and study them or, conversely, to consciously avoid them. In the plant signalling field, the recent increase of interest in liquid–liquid phase separation might be an example. We cannot guess if the interest will stay afloat for long or if the bubble will burst soon or never, but the accumulated novel knowledge is already impressive.

These fluctuations in focus on cyclically fashionable topics of research are part of the self-correcting aspect of science. Ideas that are exciting today will be boring tomorrow and vice versa. After decades, stagnant disinterest

and rapid advances compensate for each other. Both participate in the slow building of a universal body of scientific knowledge. As long as science is conducted by human beings, subjectivity and trends will exist. Scientific research may be driven by passion, and passion is volatile. The continuing story of ABP1 should teach us to not worry about our sometimes subjective and irrational focus on one problem to the exclusion of others. In the long term, science will always win.

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