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Journal club

PLANT BIOLOGY INFORMS DRUG DISCOVERY

In times of tight budgets, researchers are frequently asked to focus on 'translational science', although paradigm-shifting breakthroughs often emerge from basic research that is conducted without aiming for therapeutically relevant applications. An unconventional marriage between plant biology and embryology provides a striking example.

Auxins are a class of phytohormones that regulate multiple aspects of plant growth, but how auxins are sensed and translated into developmental responses was unclear. Elegant studies by Mark Estelle's laboratory showed that the ubiquitin ligase subunit TRANSPORT INHIBITOR RESPONSE 1 (TIR1) was required for auxin-dependent signalling. Rather than binding to a plasma membrane receptor, auxin diffuses into cells, binds to TIR1 and induces degradation of AUX/IAA (auxin and indole-3-acetic acid) transcriptional repressors (Dharmasiri *et al.*). These results were the first to suggest that a drug-like small molecule could bind to a ubiquitin ligase and have an impact on the stability of its substrates.

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In one of my favourite studies, Ning Zheng's group then revealed the mechanism by which auxin regulates TIR1 (Tan *et al.*). The signature domains of TIR1 are its F-box, which connects it to the core ubiquitin ligase, and a Leu-rich repeat, which associates with AUX/IAA proteins. Auxin binds to a cavity on the Leu-rich repeat and provides the ubiquitin ligase with a patch of 'velcro' to recruit AUX/IAA proteins for ubiquitylation and degradation. Thus, auxin functions as molecular glue that enables substrate recruitment.

Is auxin a one-hit wonder or the poster child for a new paradigm of signal transduction? An argument for the latter emerged from studies of human embryology. In the 1950s, pregnant women were treated for morning sickness with thalidomide, which was taken off the market after children were born with limb malformations. It turned out that thalidomide binds to cereblon, a substrate adaptor of a ubiquitin ligase required for limb development (Ito *et al.*). Today, thalidomide is used in the clinic as a chemotherapeutic to treat leukaemia. Akin to auxin, thalidomide clamps transcription factors to the ubiquitin ligase, triggers their degradation and thereby promotes cancer cell death (Krönke *et al.* and Lu *et al.*). Although a structural picture of these interactions is missing, thalidomide seems to be another example of a molecular glue that triggers a specific degradation event. These studies nicely highlight how gaining insight into a basic question — that is, how plants grow — ultimately helps us to understand the mechanism of action of successful chemotherapeutics.

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The author declares competing interests: see Web version for details.

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