

# Evolutionary Study on Cell Signalling Pathway

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## Short Communication

Signalling pathways is so important to plants and other organisms. All organisms face a common challenge: how to adapt successfully to changing environmental conditions [1]. For single-celled organisms, the environment is the medium that supports their growth and the challenge is, for example, how to optimise nutrient acquisition if the nutrient is distributed non-uniformly. In practical terms this involves detecting a concentration gradient and moving up it. Multicellular organisms also adapt and respond to changes in their environment. This operates across different levels of scale; at the level of the single cell the environment represents the cell's immediate surroundings, whereas at the level of the whole plant or animal it encompasses air temperature, light conditions and other variables. In the case of plants, adapting to shading or reduced water availability usually involves making co-ordinated alterations to growth and development so as to ensure the optimum capture and use of available resources. Animals also are faced with the task of coordinating the cellular response of a whole organism to environmental buffeting, although animals, unlike sessile plants, at least have the option of packing up and moving to a more hospitable climate. Given that the ability to respond appropriately to changes in the environment is essential to all organisms, from the most primitive to the most advanced [2,3], it seems timely to ask whether there are common themes and solutions to this problem that have been adopted during the course of evolution. Multicellular life forms also face another challenge beyond reacting to their environment, and that is to develop from an egg or a seed into a mature organism. The intricate cell-cell signalling and signal integration that occurs during this process makes environmental-response signalling seem almost simple by comparison. It is believed that plants and animals diverged from their last common ancestor before either became multicellular. Thus, each kingdom has independently invented signalling mechanisms to regulate growth and to pattern tissues [4]. Typically this involves amplification and dissemination of the signal through information relay systems, ultimately terminating in changes to target gene expression. Collectively, the systems responsible for sensing and coupling stimuli to their characteristic intracellular responses are known as signal transduction pathways. A good place to start an investigation of the evolution of signalling pathways is in bacteria. It is focused on the two-component system [5], describing its operation in bacteria and its recruitment into plants and fungi (but apparently not animals) through lateral gene transfer. The canonical two-component

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system consists of a sensor histidine protein kinase and a response regulator. Information relay between the two is through phosphor transfer. There is much to be learned from a study of the evolution and diversification of this enormously successful system [6]. In bacterial two-component systems we encounter information relay through protein-protein interactions (with potential conformational changes) and protein phosphorylation - themes we shall meet again in evolutionarily more complex organisms. In study, of these, cytokinin signalling is closest to the canonical prokaryotic two-component system in that a histidine kinase (the cytokinin receptor), a phosphor relay protein and a response regulator are all employed. Ethylene signalling is also very interesting. There are two subfamilies of ethylene receptor in higher plants; one of these exhibits histidine kinase activity, while the second appears to have evolved serine/threonine kinase activity. This clearly shows the two-component system has diverged after incorporation into higher plants. A striking feature of many of the other signalling pathways described in the articles in this special issue is that they seem to have originated with the colonization of the terrestrial environment. For instance, in the case of abscisic acid (ABA) signalling. In the study there is evidence that ABA is present in the algae (and indeed certain animals), the PYR/RCAR ABA receptors are first encountered in terrestrial plants [7]. ABA is a hydrophobic hormone that binds to intracellular receptors, as is seen in animal steroid hormone signalling. There is an eerie structural similarity between many animal and plant hormones, despite the absence of receptor homology. ABA signalling involves the participation of many other elements familiar in mammalian cell signalling pathways, including phosphor protein phosphatases, protein kinases, reactive oxygen species and calcium ions (acting as intracellular second messengers). An interesting feature to emerge from the investigations of the ABA signalling pathway is that the activated

ABA receptor interacts with and inhibits a protein phosphatase. This results in the activation of a protein kinase that phosphorylates downstream signalling components that include basic region leucine zipper (bZIP) transcription factors and ion channels. Control through negative regulation is a feature that we shall encounter in other plant signalling pathways. In fact we encounter this feature in two other hormonal signalling pathways: the gibberellin (GA) and auxin signal transduction pathways. These pathways also feature a rather common theme—control through targeted protein degradation. When the GA receptor, the GID1 protein, is activated by binding GA it triggers the degradation, through targeted proteolysis, of DELLA proteins. This family of proteins are nuclear transcriptional regulators and are described as 'master growth repressors'. So this is another example of where inhibition or removal of a negative regulator activates downstream signalling responses. In this case GA-activated GID1 binds to DELLA proteins; this complex is then recognized by the F-box protein SLY1, a component of the SCF ubiquitin E3 ligase. This interaction promotes polyubiquitination of DELLA proteins and their subsequent degradation by the 26S proteasome. Interestingly this process has direct parallels in auxin signalling [8]. One of the auxin receptors, TIR1, is an F-box protein. The auxin–TIR1 complex binds to a group of transcriptional repressors known as Aux/IAA proteins, and this results in their ubiquitination by the SCF ubiquitin E3 ligase complex and subsequent degradation by the proteasome. The net result is activation (through de-repression) of genes whose products are involved in auxin-mediated responses. Similar targeted protein degradation pathways involving F-box proteins are also central to plant jasmonate signalling. In mammals, a canonical example of a signalling pathway in which regulated proteolysis plays a primary role is the NFκB pathway involved in inflammation and immunity. Here, signal-regulated phosphorylation of IκB proteins targets them for degradation, liberating NFκB transcription factors from inhibition. Plants, just like animals, make use of peptides and proteins as signals. It has been described that peptide signals that play important roles in the control of development. Peptide signals belonging to the family of epidermal patterning factors (EPFs) inhibit stomatal development and operate through ERECTA family members, which are leucine-rich repeat (LRR) receptor-like kinases. Although there is still much work to be done in identifying the precise sequence of events that results in the repression of stomatal development, the involvement of a receptor kinase is, at least superficially, similar to the situation in mammalian growth factor signalling. What is striking is that the Arabidopsis genome contains over 600 genes encoding receptor-like kinases of these, many have extracellular LRRs. Receptors with extracellular LRRs are also found in animals, where they function both in developmental signalling and as pattern receptors for the innate immune response. Plants use LRRs for innate immunity, but have also found ways to use them in the recognition of smaller, unpatterned ligands such as the peptides described above, as well as non-peptidyl hormones such as brassinosteroids. Plants, just like animals, use the vascular system as a conduit for long-range signalling. A second example of a protein acting as a signal, this time over a relatively long distance, is the product of the Flowering Locus T gene, which is responsible for the promotion of flowering. The FT gene is expressed in leaves

and the FT protein travels through the plant vasculature until it reaches the shoot apex where it binds to the bZIP transcription factor Flowering D (FD) and participates in the control of events which culminate in the transition to flowering. FT signalling is interesting in that it is an example of a signalling pathway with no obvious parallels in animal signalling. Although we have sought to reduce the challenges of signal transduction to understanding the events associated with coupling the perception of a particular stimulus to its characteristic response, this is of course a dangerous over-simplification that ignores the complexities encountered in plant. The reality of the situation is that guard cells are continuously bombarded with an array of constantly changing signals, some of which will tend to promote stomata opening, while others will induce reductions in guard cell turgor. Hence, an additional role for this signalling system is to integrate multiple signals so that gas exchange is optimised to suit the prevailing environmental conditions. Understanding how signal integration is achieved is right at the cutting edge of signalling research, and through the issue of cross-talk [9]. The intracellular wiring of signalling systems is being revealed as increasingly complex and, to reflect this, in some cases it is best represented as a network rather than a simple linear pathway. What is becoming clear from a combination of molecular genetic and mathematical modelling/systems-biology approaches is that the control of these pathways is exerted at different levels and frequently involves interacting feedback loops. It is tempting to assume that the apparent complexity, including the frequently observed gene redundancy, is present to ensure that the pathways are capable of being finely tuned and are robust in the sense that they can tolerate error. Similarly, it is also tempting to assume that there must be inherent advantages to adopting systems in which activation of the response is achieved through the removal of a negative regulator. However, both these assumptions require much further investigation and are examples of instances in which collaborations between biologists, mathematicians and engineers may continue to pay off. Signalling strategies that have little molecular overlap may have more in common when viewed as a network in which the molecules are black boxes functioning to transform input into output, connected by fuzzy logic gates and feedback loops. The forests may be more similar than the trees. So far we have highlighted common elements present in plant and animal signalling systems (and microbial systems in the case of two-component systems), and some of these commonalities reflect the ancient origins of these signalling systems. However, there are also some surprises. So, in the case of intracellular second messengers, the calcium ion is ubiquitous in plants and animals, whereas, although plants possess cAMP, there is no good evidence (unlike the case in animals) that it has been adopted as a common second messenger. The same holds true for heterotrimeric G proteins—all pervasive in animals, while in plants they are present, but with a greatly reduced diversity [10]. As another example, leucine-rich-repeat receptors are found in plants and animals, but are absent in fungi. Then of course there are the two component systems present in microbes, fungi and plants but apparently not represented in advanced animals. These examples can be contrasted with the widespread recruitment of protein kinases to new signalling tasks in both plants and animals.

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