pathways initiated by GPCR and RTK activation in PC12 cells, through both CRE-binding protein (CREB) and CREB-binding protein (CBP) (Fig. 1) (*17*, *18*).

Transcription of CRE-dependent genes in PC12 cells that is required for differentiation may also depend on additional cis elements in CREB-responsive genes besides the CRE itself. For example, NGF increases expression of the c-*fos* gene through both a CRE and a serum response element (SRE) (*19*). PACAP also increases expression of neuropeptide genes through separate cAMP and calcium signaling pathways (*20*). Thus, combinatorial specificity is a fundamental element in the signaling equation at all levels of transduction, from receptor-stimulated signal generation to transcriptional responses.

PC12 cells continue to be an important model system by which to study how hormones, neurotransmitters, and neurotrophins initiate multiple signaling pathways that converge on specific cellular targets to execute complex processes, such as neurite extension and competence for neuronal excitability. Understanding this complexity will require a broader view of signal transduction, in which pathway specificity is created by the integration of unique combinations of canonical signaling cassettes within a specific cell. The PC12 Cell Differentiation Pathway (http://stke.sciencemag.org/cgi/cm/CMP_8038) (*21*) in the STKE Connections Maps should facilitate this effort as it applies to neuronal differentiation.

### References

1. L. A. Greene, A. S. Tischler, *Proc. Natl. Acad. Sci. U.S.A.* **73**, 2424 (1976).
2. M. V. Chao, B. L. Hempstead, *Trends Neurosci.* **18**, 321 (1995).
3. G. D'Arcangelo, S. Halegoua, *Mol. Cell. Biol.* **13**, 3146 (1993).
4. P. Lazarovici, Y. Matsuda, D. Kaplan, G. Guroff, in *Toxins and Signal Transduction*, P. Lazarovici, Y. Gutman, Eds. (Harwood Academic, Amsterdam, 1997), pp. 69–94.
5. P. Lazarovici, H. Jiang, D. Fink Jr., *Mol. Pharmacol.* **54**, 547 (1998).
6. J. D. Jordan *et al.*, *Cell* **103**, 193 (2000).
7. D. Vaudry *et al.*, *Ann. N.Y. Acad. Sci.*, in press.
8. M. S. Qui, S. H. Green, *Neuron* **9**, 705 (1992).
9. R. D. York *et al.*, *Mol. Cell. Biol.* **20**, 8069 (2000).
10. S. C. Kao *et al.*, *J. Biol. Chem.* **276**, 18169 (2001).
11. S. Leppa *et al.*, *Mol. Cell. Biol.* **21**, 4369 (2001).
12. P. J. Deutsch, Y. Sun, *J. Biol. Chem.* **267**, 5108 (1992).
13. K. Tanaka, I. Shibuya, T. Nagamoto, H. Yasmashita, T. Kanno, *Endocrinology* **137**, 956 (1996).
14. A. P. Barrie, A. M. Clohessy, C. S. Buensuceso, M. V. Rogers, J. M. Allen, *J. Biol. Chem.* **272**, 19666 (1997).
15. A. Hernandez, B. Kimball, G. Romanchuk, M. W. Mulholland, *Peptides* **16**, 927 (1995).
16. M. R. Vossler *et al.*, *Cell* **89**, 73 (1997).
17. T. Nakajima *et al.*, *Cell* **86**, 465 (1996).
18. Y. Z. Liu, N. S. Thomas, D. S. Latchman, *Neuroreport* **10**, 1239 (1999).
19. A. Bonni, D. D. Ginty, H. Dudek, M. E. Greenberg, *Mol. Cell. Neurosci.* **6**, 168 (1995).
20. C. Hamelink, H.-W. Lee, Y. Chen, M. Grimaldi, L. E. Eiden, *J. Neurosci.*, in press.
21. D. Vaudry, P. Stork, P. Lazarovici, L. Eiden, Differentiation Pathway in PC12 Cells, *Science*'s STKE (Connections Map, as seen May 2002), http://stke.sciencemag.org/cgi/cm/CMP_8038.

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VIEWPOINT

# The Jasmonate Pathway

**Robin Liechti and Edward E. Farmer***

**Plants are faced with many of the same problems as animals—a need for regulation of metabolic processes and reproduction and for defense against enemies. Jasmonates in plants serve key roles in gene and metabolic regulation, defense, responses to trauma, reproduction, and possibly communication. Some remarkable features of plant responses, such as production of repellent volatiles as a defense against herbivorous insects, or the massive transcriptional reprogramming that occurs in response to wounding, are under the control of the jasmonate pathway. Details of the jasmonate signaling pathway are currently at the center of active research that is generating exciting results. The Jasmonate Biochemical Pathway at the STKE Connections Maps is designed to present and keep pace with these developments.**

Jasmonates (*1*, *2*) are potent lipid regulators in plants that mediate responses to both mechanical trauma and pathogenesis (*3*–*5*), and play pivotal roles in reproduction (*6*) and metabolic regulation (*7*).The biological activities of these lipid-derived molecules are reminiscent of some of the roles of well-known mediators in animals, most notably prostaglandins. This parallel between the molecules is strongly reinforced when one considers their structures. Whereas prostaglandins are formed from the 20-carbon eicosanoid precursor arachidonic acid, jasmonates are derived principally from the 18-carbon fatty acid linolenic acid. Jasmonate synthesis, at least in reproductive tissues, begins with phospholipase $A_1$-release of linolenic acid (*8*). Oxygenation of linolenic acid is catalyzed by 13-lipoxygenase. The resultant 13-hydroperoxide is dehydrated by allene oxide synthase to an unstable allene oxide intermediate (*9*) before cyclization, guided by allene oxide cyclase, to the cyclopentenone ring-containing 12-oxo-phytodienoic acid (OPDA) (Fig. 1). OPDA can be further metabolized, by reduction of the ring double bond catalyzed by OPDA reductase 3, yielding a cyclopentanone intermediate. This intermediate is then subjected to three rounds of β-oxidation, which yield the best-known jasmonate family member, the 12-carbon regulator jasmonic acid (JA) (*2*). Both OPDA and JA have several fates within plant tissues; both can be conjugated by esterification to other molecules, galactolipids in the case of OPDA (*10*) and various amino acids or simply a methyl group in the case of JA (*2*).

One of the remarkable features of the jasmonate pathway is that its members have different biological activities. Whereas JA synthesis is required for male fertility in the model plant *Arabidopsis*, its precursor OPDA can play an important regulatory role in defense along with JA (*11*). Another remarkable feature of the jasmonate pathway is that the activity of some of its members is not confined within the plant. Volatile jasmonate family members, such as the JA metabolite *cis*-jasmone (cJ), help regulate the behavior of some insects—for example, repelling herbivorous species and attracting their predators—and may act as an indicator of JA metabolism in damaged leaves, thereby signaling leaf quality to herbivores (*12*). Some evidence suggests that certain volatiles of the jasmonate pathway may enable communication among plants (*12*).

Jasmonate concentrations are tightly regulated in plants; the relative basal amount of each jasmonate family member may differ from tissue to tissue. In the case of mechanical wounding, rapid jasmonate biosynthesis occurs with differential control over the concentration of each compound (*11*). Massive transcriptional reprogramming under the control of jasmonates is a feature of wounding (*11*) and a response to certain pathogens (*13*). Upon wounding, the expression of large numbers of genes is increased or decreased in a jasmonate-dependent manner, and those that are increased include front-line defense-related genes encoding wound-related and pathogenesis-related proteins. It is not yet known which jasmonate-regulated genes are necessary for male fertility in *Arabidopsis*.

With a basic understanding of the biochemistry in place, the task now turns to understanding the proteins and genes that are involved in jasmonate signaling. The jasmonate perception

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pathway is currently being delineated through the use of gain-of-function and loss-of-function mutants. Protein kinases are implicated in early events of jasmonate signaling (*14*). Selective proteolysis may be important in the regulation of jasmonate-dependent gene expression by contributing to the removal of transcriptional regulators from target genes (*15*). Progress in identifying other key regulatory genes is imminent (*16–18*). At least five likely developments, from studies currently under way by several groups, should add considerably to interest in the jasmonate pathway. First, the identification of target genes regulated by different jasmonates will clarify how these molecules exert their multiple remarkable biological effects. Second, a better understanding of jasmonate perception will provide vital knowledge on many aspects of regulation. Third, progress on the cell biology of jasmonates will shed light on how these compounds are transported within and between cells and tissues to reach their sites of action. Fourth, more detailed knowledge about how the jasmonate pathway contributes to the coordination of direct defense responses (that is, regulation of defense genes within the plant) and indirect defense responses (for example, control of the behavior of predatory insects in the plant's environment) will permit an understanding of how plants extend their defense umbrella. Finally, further investigation of gas-phase signaling by volatile methyl jasmonate (MJ) within the plant may contribute to the general knowledge of the biology of volatile regulators of gene expression. Aside from answering these basic science questions, advances in the manipulation of the pathway hold promise for future strategies in agriculture. The Jasmonate Biochemical Pathway (http://stke.sciencemag.org/cgi/cm/CMP_7361) (*19*) of the STKE Connections Maps is designed to keep pace with these and other exciting developments. Additionally, the Jasmonate Biochemical Pathway will have interfaces with the Connections Maps of other signaling pathways in plants.

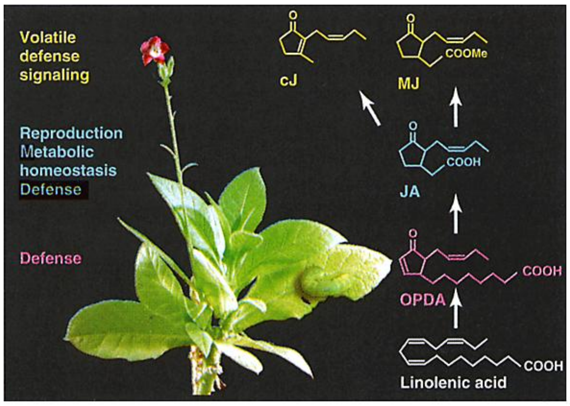

**Fig. 1.** The jasmonate family of regulators is involved in diverse aspects of plant biology. OPDA is an octadecanoid derived from linolenic acid. It is one of the jasmonates, which, together with jasmonic acid (JA), helps control defense responses. JA also plays key roles in reproduction, and its metabolites methyl jasmonate (MJ) and *cis*-jasmone (cJ) are both volatile and may act as signals both within plants and to associated insects.

### References

1. B. A. Vick, D. C. Zimmerman, *Plant Physiol.* **75**, 458 (1984).
→ R. A. Creelman, J. E. Mullet, *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **48**, 355 (1997).
→ E. E. Farmer, C. A. Ryan, *Plant Cell* **4**, 129 (1992).
→ G. S. Howe *et al.*, *Plant Cell* **8**, 2067 (1996).
5. P. Vijayan *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 7209 (1998).
6. B. J. Feys, C. E. Beneditti, C. N. Penfold, J. G. Turner, *Plant Cell* **6**, 751 (1994).
7. L. van der Fits, J. Memelink, *Science* **289**, 295 (2000).
→ S. Ishiguro *et al.*, *Plant Cell* **13**, 2191 (2001).
9. M. Hamberg, P. Fahlstadius, *Arch. Biochem. Biophys.* **276**, 518 (1990).
10. B. A. Stelmach *et al.*, *J. Biol. Chem.* **276**, 12832 (2001).
11. A. Stintzi, H. Weber, P. Reymond, J. Browse, E. E. Farmer, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 12837 (2001).
12. M. A. Birkett *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **97**, 9329 (2000).
13. P. M. Schenk *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **97**, 11655 (2000).
14. M. Petersen *et al.*, *Cell* **103**, 1111 (2000).
15. D. X. Xie *et al.*, *Science* **280**, 1091 (1998).
16. L. Xu *et al.*, *FEBS Lett.* **494**,161 (2001).
→ C. Ellis, J. G. Turner, *Plant Cell* **13**, 1025 (2001).
18. B. Hilpert *et al.*, *Plant J.* **26**, 435 (2001).
19. R. Liechti, E. E. Farmer, Jasmonate Biochemical Pathway, *Science's STKE* (Connections Map, as seen May 2002), http://stke.sciencemag.org/cgi/cm/CMP_7361.

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VIEWPOINT

# Phosphorelay and Transcription Control in Cytokinin Signal Transduction

**Jen Sheen**

**The past decade has seen substantial advances in knowledge of molecular mechanisms and actions of plant hormones, but only in the past few years has research on cytokinins begun to hit its stride. Cytokinins are master regulators of a large number of processes in plant development, which is known to be unusually plastic and adaptive, as well as resilient and perpetual. These characteristics allow plants to respond sensitively and quickly to their environments. Recent studies have demonstrated that cytokinin signaling involves a multistep two-component signaling pathway, resulting in the development of a canonical model of cytokinin signaling that is likely representative in plants. This Viewpoint outlines this general model, focusing on the specific example of *Arabidopsis*, and introduces the STKE Connections Maps for both the canonical module and the specific *Arabidopsis* Cytokinin Signaling Pathway.**

Cytokinins are essential plant hormones that control cell division, shoot meristem initiation, leaf and root differentiation, chloroplast biogenesis, stress tolerance, and senescence. Together with auxin, another plant hormone, cytokinins can reprogram terminally differentiated leaf cells into stem cells and support shoot regeneration indefinitely in plant tissue culture (*1*, *2*). Thus, cytokinins are master regulators of plant growth and development, which are highly plastic and adaptive, as well as remarkably resilient and perpetual. Research interest in the signaling pathways activated by cytokinins has increased recently because of new information arising from studies of *Arabidopsis* and the completion of its genome sequence. However, the importance of this pathway is given additional weight because it represents two-component signaling, a canonical mechanism that mediates diverse biological responses in many taxa. The specific Cytokinin Signaling Pathway (*3*) details the pathway as it has been elucidated in *Arabidopsis*; the canonical Cytokinin Signaling Pathway presents the general view (*4*).

In the *Arabidopsis* cytokinin signal transduction pathway, hybrid histidine protein kinases (AHKs) serve as cytokinin receptors and histidine phosphotransfer proteins (AHPs) transmit the signal from AHKs to nuclear response regulators (ARRs), which can activate or repress transcription (*5–10*). Similar components are also found in maize,

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