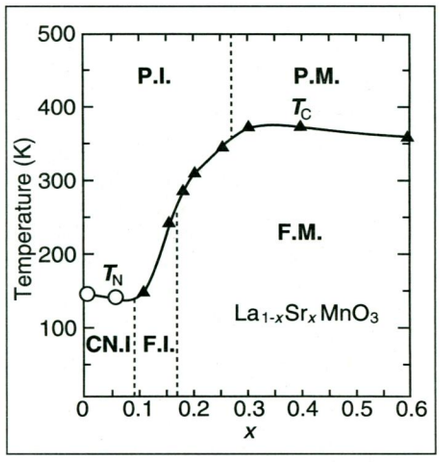

Fig. 2. Electronic phase diagram of $La_{1-x}Sr_xMnO_3$. PI, Paramagnetic insulator; PM, paramagnetic metal; CNI, spin-canted insulator; FI, ferromagnetic insulator; FM, Ferromagnetic metal [from (*6*)].

and increases with the resistivity at this temperature, it seems desirable to examine materials that are magnetic insulators (with reasonable resistivities) at room temperature in order to exploit the property for technological applications. Quaternary oxides, such as $LnMn_{1-y}Cr_yO_3$, would be good candidates for this purpose. Oxide spinels, the $A_2Mn_3O_8$ family of oxides, as well as oxides with the scheelite structure (with appropriate modifications), would be other suitable candidates. Among nonoxide materials, magnetic sulfides, rendered marginally metallic by appropriate substitution, could be examined. There is also need for good measurements on well-characterized samples of the manganates and other oxides exhibiting GMR. For example, structural studies in the presence of a magnetic field would be of considerable interest.

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Green Light for Steroid Hormones

David W. Russell

Since its founding in the 19th century, endocrinology has been constantly innervated by the contributions and methodologies of other fields. These innervations came first from chemists who elucidated the structures of steroid hormones, then from biochemists who purified peptide hormones and their receptors, and eventually from molecular biologists who isolated the genes encoding these molecules. These incursions have forced card-carrying endocrinologists to constantly learn new techniques, new literature, and new approaches, which in turn has allowed them to shed more light on the mechanisms by which tissues and cells communicate across vast distances.

Throughout this history, endocrinologists have assumed that at least one research field could be safely ignored: the field of botany. For although we may have learned as undergraduates that plants have hormones, so-called phytohormones—auxins, abscisic acid, and gibberellin—it was widely held in advanced training that the mechanisms green plants use to send intercellular signals are radically different from those of higher mammals, which have complex circulatory systems and rights of passage such as puberty.

The work described by Li and co-workers in this issue renders these notions antiquated (*1*). They have isolated by positional cloning an *Arabidopsis* gene (*DET2*) that markedly affects light-regulated development (*2*) (Fig. 1), and they determined the molecular basis of seven defects in this gene. Database searches reveal that the protein encoded by *DET2* is almost certainly a plant ortholog of the mammalian steroid 5α-reductases, a group of enzymes involved in male hormone (androgen) biosynthesis (*3*). This sequence identity in turn led the authors to test the hypothesis that plants lacking an active DET2 protein might be defective in the biosynthesis of a phytohormone, specifically one that possessed or was derived from a cyclopentanoperhydrophenanthrene skeleton. Proof of principle was obtained when the plant steroid brassinolide, a bizarre steroid with 28 carbon atoms, successfully reversed the growth defects associated with a genetic deficiency (null allele) in the DET2 protein. Together, the sequence identity and the rescue experiments indicate that the product of the *DET2* gene is involved in the biosynthetic pathway leading to brassinolide (Fig. 2), a member of a large class of ubiquitous plant

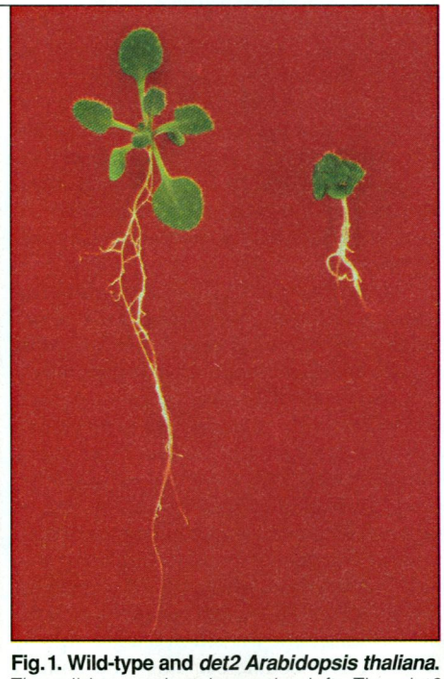

Fig. 1. Wild-type and *det2 Arabidopsis thaliana*. The wild-type plant is on the left. The *det2* plant on the right exhibits dwarfism, infertility, reduced apical dominance, and a darker green color due to delayed leaf and chloroplast senescence. *DET2* encodes a steroid 5α-reductase and its mutation eliminates the biosynthesis of brassinolide, a plant steroid hormone required for development and light-regulated gene expression. [Reprinted from (*7*) with permission]

The author is in the Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, TX 75235–9046, USA. E-mail: russell@utsw.swmed.edu

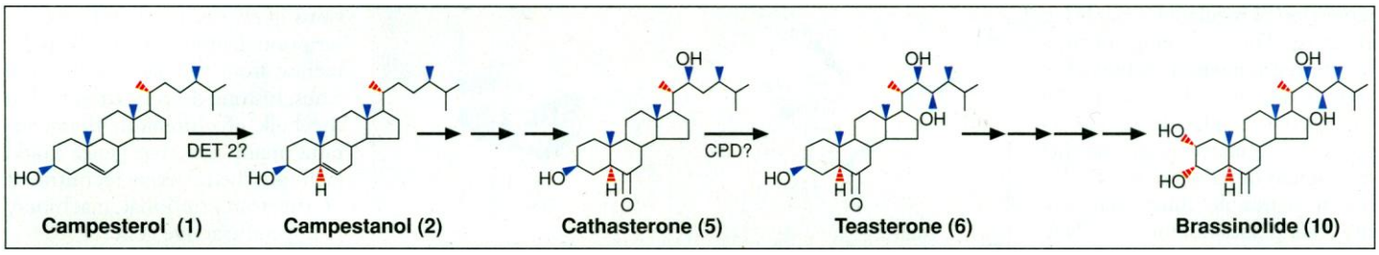

Fig. 2. The biosynthetic pathway of brassinolide. Genetic evidence in *Arabidopsis* suggests that the *DET2* and *CPD* gene products catalyze the indicated reactions in the multistep pathway leading to brassinolide. [Courtesy J. Chory, Salk Institute]

steroids termed brassinosteroids, and that these steroids may play a role in the regulation of gene expression by light.

A conclusive demonstration of this role is provided by Szekeres *et al.* (*4*). These authors show that a pleiotropic phenotype arising from mutation of the *Arabidopsis CPD* gene, which includes disregulation of light-responsive genes, dwarfism, male sterility, and activation of stress-response genes, can also be traced to a defect in brassinolide synthesis. The DNA sequence of the *CPD* gene reveals it to be a member of the cytochrome P450 class of enzymes, with distinct sequence identity to P450s involved in mammalian steroid hormone biosynthesis. Because steroid intermediates in the brassinolide pathway with a 23-hydroxyl group successfully reverse the phenotypes arising from mutation of the *CPD* gene, whereas those that lack this modification do not, it seems likely that the CPD enzyme catalyzes the 23-hydroxylation of cathasterone to form teasterone, which is thereafter converted into brassinolide. Szekeres *et al.* (*4*) go on to show that brassinolide will overcome the pathologies associated with at least five other *Arabidopsis* mutations (*det1*, *cop1*, several *fus* mutations, *dim1*, and *axr2*), each of which lead to disruptions in light-mediated development. These results implicate brassinolide as a major player in the growth and differentiation of *Arabidopsis*.

The studies of Li *et al.* (*1*) and Szekeres *et al.* (*4*) reveal the tip of an iceberg that will affect disciplines ranging from botany to biochemistry to endocrinology. We can look forward to the elucidation of several processes including the mechanism of intracellular signaling through which brassinosteroids work, the role of steroid reductases and P450 monooxygenases in the biosynthesis of this widely distributed class of compounds, and the cross-talk that must occur between light-activated regulatory systems and those that respond to steroid hormones, and perhaps we will also gain insight into nonreceptor-based actions of steroid hormones, as it is rumored that plants lack DNA sequences common to mammalian steroid hormone receptors (*5*). Finally, the development of therapeutic inhibitors of steroid 5α-reductase is a thriving area in the pharmaceutical industry (*3*). At least some of these inhibitors come from plant sources (*6*), and it is conceivable that by acting on DET2-like enzymes, or other enzymes in the pathway, they serve as endogenous regulators of brassinosteroid synthesis. The seeds of the *Arabidopsis* findings will sprout much future research!

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Histone Deacetylase: A Regulator of Transcription

Alan P. Wolffe

Histones, nuclear proteins that interact with DNA to form nucleosomes, are essential for both the regulation of transcription and the packaging of DNA within chromosomes. The stability and positioning of chromatin structures determine whether nucleosomes repress (*1*) or activate transcription (*2*). Mutation of individual histones in vivo alters the general organization of chromatin throughout the eukaryotic nucleus, yet the concomitant changes in gene expression are highly selective (*3*). This selectivity appears to depend on the assembly of specific nucleoprotein architectures. Within these structures, transcriptional regulators make direct contact with specific domains of individual core histones (*4*, *5*). Targeting of these "chromatin organizers" to particular genes, through protein-protein or protein-DNA interactions, can account for the selective impact of histone mutations on gene expression. This conceptual framework only provides a static image of gene regulation. In reality, events are much more dynamic, as highlighted in a report in this week's issue of *Science* (*6*) describing the cloning of one of these organizers, histone deacetylase.

The author is at the Laboratory of Molecular Embryology, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892–2710, USA. E-mail: awlme@helix.nih.gov

A major source of dynamic variation in chromatin structure in vivo is histone acetylation. Acetylated lysine residues in the NH_2-terminal tail domains of nucleosomal histones serve as landmarks for transcriptionally active chromatin within the chromosome (*7*). Hyperacetylation of the histones reduces their ability to constrain the path of DNA within chromatin, resulting in allosteric changes in nucleosomal conformation (see figure, part A) (*8*), destabilization of internucleosomal contacts (*9*), and an increase in the accessibility of nucleosomal DNA to transcription factors (*10*). The elimination of histone acetylation is correlated with transcriptional silencing (*11*). The amount of histone acetylation is determined by an equilibrium between histone acetyltransferases and deacetylases. Thus, chromatin structure could be reversibly modulated to activate or silence transcription by targeting histone acetyltransferases or deacetylases to a particular gene. This model now receives strong support from the recent purification and molecular characterization of a human deacetylase with remarkable identity (~60%) to the *Saccharomyces cerevisiae* transcriptional regulator Rpd3p (*6*).

Rpd3p is a global transcriptional regulator required for target genes to achieve maximal transcriptional efficiency (*12*). Without Rpd3p, both the activation and