Plant genetics: a decade of integration

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doi:10.1038/ng1108

The last decade provided the plant science community with the complete genome sequence of *Arabidopsis thaliana* and rice, tools to investigate the function of potentially every plant gene, methods to dissect virtually any aspect of the plant life cycle, and a wealth of information on gene expression and protein function. Focusing on *Arabidopsis* as a model system has led to an integration of the plant sciences that triggered the development of new technologies and concepts benefiting plant research in general. These enormous changes led to an unprecedented increase in our understanding of the genetic basis and molecular mechanisms of developmental, physiological and biochemical processes, some of which will be discussed in this article.

Throughout its history, the study of genetics has been intimately intertwined with the plant sciences. From the discovery of the principles underlying heredity[1–4] to the discovery of transposable DNA elements[5] and post-transcriptional gene silencing (PTGS) or RNA interference (RNAi)[6–8], plant systems have had a crucial role in genetic discoveries. But although excellent plant systems such as maize existed for doing classical genetics and cytogenetics, the plant sciences lacked a model organism in which to do rapid and routine genetic analyses—something akin to *Drosophila melanogaster* or *Caenorhabditis elegans*.

Arabidopsis thaliana, the model plant eventually adopted by the plant science community, has a long history of its own. The first assessment of *Arabidopsis* as a cytogenetic model organism was published by Laibach[9] in 1907. Laibach went on to champion *Arabidopsis* as a possible genetic model organism[10], and the next three decades saw *Arabidopsis* attract a small but loyal following among plant geneticists. During this time, the tractability of *Arabidopsis* genetics was amply shown by the identification of numerous mutants affecting both the morphology and biochemistry of the plant[11,12]. In the 1980s, the popularity of *Arabidopsis* grew explosively, partly owing to the rediscovery of its small and simple genome in the context of molecular biology[13,14] and partly owing to many influential reviews promoting its use as a genetic model[15–18].

Focusing on a model plant has led to an integration of the plant sciences that has greatly advanced our understanding of plant biology over the past decade and has changed the scope, style and depth of plant research completely. In each of the areas reviewed here, the use of genetic analysis in *Arabidopsis* has been instrumental in increasing our knowledge. More importantly, perhaps, the focusing of financial and intellectual resources on a single model plant has allowed the creation of tools that have enabled those genetic analyses to proceed at a rate far greater than was possible 10 years ago.

Indeed, the past decade has been remarkable by any standards with advances in technology contributing to an unprecedented quantity of data and tools with which to investigate biological processes. The past few years have provided the plant science community with the complete genetic blueprints of two of their favorite model organisms: *Arabidopsis thaliana*[19] and rice[20,21]. These completed genome sequences not only facilitate the cloning of genes identified by mutation, but also provide a complete picture of the genes available in these model plants, which is a powerful tool for comparisons with animals and fungi. This has revolutionized the study of biological phenomena by facilitating a systematic global approach that has the potential to lead us to a more integrated view of how whole organisms function.

That is not to say that *Arabidopsis* is the only important organism in plant genetics today[22]. Some of the key insights into the genetics of the systems described here have come from *Antirrhinum majus*, maize, petunia and tobacco, as well as other plant species. Rice is increasingly chosen as the model for cereal crop genetics, and both the moss *Physcomitrella patens*[23] and the fern *Ceratopteris richardii*[24] offer genetically tractable systems in which to study evolutionary aspects of plant developmental genetics. Over the next few years, more plant genomes will be sequenced, allowing the tools of comparative genome analysis to be brought to bear more fully in the plant kingdom and facilitating studies on the evolution of diversity in plants.

In this review, we focus on five areas in which plant genetics has made great strides in the past decade. We find these topics to be of particular interest, although other areas of plant research have certainly made comparable advances.

Control of floral organ identity: ABC and beyond

In the late 1980s, studies of floral homeotic mutants of *Arabidopsis* and *Antirrhinum* led to the proposal of the ABC model of flower development, in which the combinatorial activity of homeotic gene products specifies the identities of the four whorls

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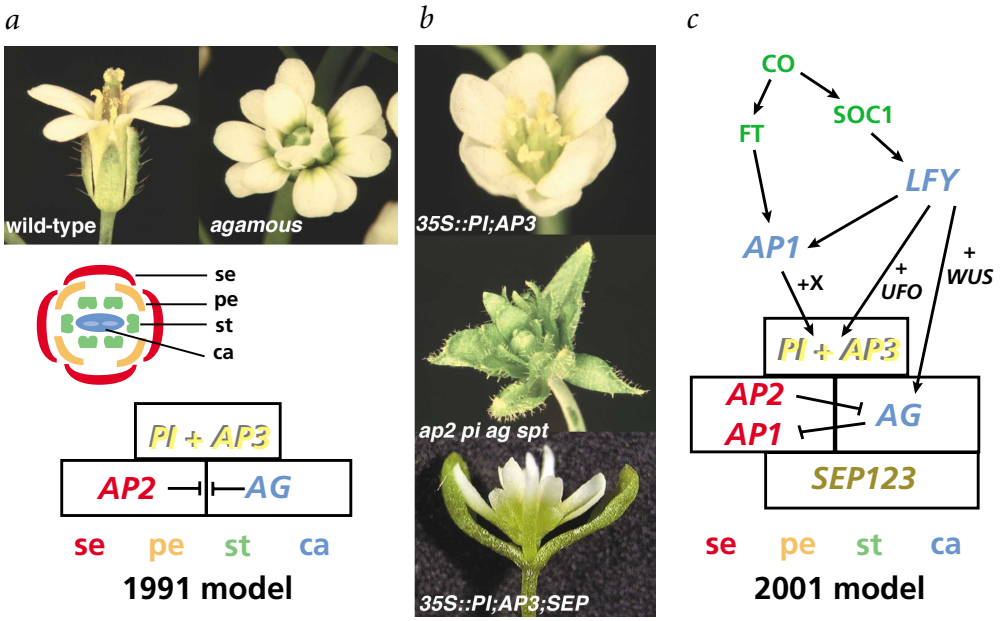

Fig. 1 Progress in our molecular genetic understanding of flower development. ***a***, The ABC model was proposed on the basis of the phenotypes of homeotic floral mutants such as *agamous* (*ag*) and genetic interactions among such mutants[25–27]. In this model, the combinatorial activity of three classes of homeotic gene products specifies floral organ identity: A (*AP2*) = sepals (se); A + B (*AP3* + *PI*) = petals (pe); B + C (*AG*) = stamens (st); and C = carpels (ca). Loss-of-function alleles of these genes result in homeotic alterations; for example, in *ag* mutants, petals develop in the positions normally occupied by stamens, and another flower meristem replaces the carpels. ***b***, The cloning of these genes allowed gain-of-function mutants to be constructed. For example, when both *AP3* and *PI* are constitutively expressed (*35S:PI;AP3*), flowers form that have petals where sepals normally develop, and stamens where carpels normally develop[43]. But leaves are not converted into floral organs unless a *SEP* gene is also expressed ectopically[59,60]. Shown here is *35S:PI;AP3;SEP*, in which all leaves (except the cotyledons) are converted into petals. Loss of all floral homeotic gene activities plus the gene *SPT*, which promotes carpel development, results in flowers consisting totally of leaves (*ap2 pi ag spt*)[212]. Thus, leaves can be converted into floral organs and floral organs into leaves. ***c***, Current understanding of the activation of floral organ identity genes. *LEAFY* (*LFY*) and *APETALA1* (*AP1*) act in conjunction with other spatially restricted factors (X, *UFO* and *WUS*) to activate the B and C class genes directly[47–49,213–215]. The meristem identity genes *LFY* and *AP1* are themselves activated directly or indirectly by factors (such as *CO*, *FT* and *SOC1*) that mediate floral induction, only some of which are shown for simplicity[216,217].

of floral organs[25–27]. In the past decade, the molecular basis of the ABC model has been elucidated along with the preceding step of floral meristem specification (Fig. 1). The first two floral homeotic genes cloned, *DEFICIENS* in *Antirrhinum* and *AGAMOUS* in *Arabidopsis*, both encoded members of the MADS-box family of transcription factors[28,29], thereby suggesting that floral organ identity may be specified by closely related members of a gene family, analogous in some way to segment identity in metazoans[30,31]. This was confirmed when the remaining floral organ identity genes were cloned and found mainly to be members of the MADS box gene family[32–37].

The tenets of the ABC model—that combinatorial gene activity specifies organ identity and that A and C classes are antagonistic—were based on loss-of-function alleles of the respective genes. Molecular analyses of the ABC genes and their ectopic expression in *Arabidopsis* have largely supported the genetic model and have led to numerous refinements and further insights[38–43]. But although the phenotypes of loss- and gain-of-function alleles of B and C class genes are complementary, A class activity remains enigmatic. Most A class genes are also involved in the earlier developmental process of flower meristem specification and, although their constitutive expression does not repress C class activity, it does result in the conversion of inflorescence meristems to flower meristems[44].

Before the floral organ identity genes become active, the cells of the flower meristem need to be specified, and work in both *Antirrhinum* and *Arabidopsis* has identified the principal molecules involved in this process[44–46]. A key breakthrough was the finding that the floral homeotic genes were direct targets of the floral meristem identity genes[47–49]. Parcy *et al.*[47] argued that the floral meristem identity factors combine with regional meristem identity factors to create the concentric whorled pattern of floral homeotic gene expression that specifies organ identity, thereby linking the earliest stages of flower development to the establishment of floral organ identity. In contrast to these upstream events, little is known about the potential targets of the floral homeotic genes and the process of organ morphogenesis itself, and this will be a challenge for the genomic era. Likewise, little is known about the establishment of basic species-specific floral ground plans—in other words, the numbers and positions of the floral organs.

The knowledge gained from model systems is being increasingly applied to evolutionarily related taxa that are morphologically diverse. Functional studies in maize[50] and rice[51] have provided evidence for the evolutionary conservation of B and C class gene activity and notably for a homologous relationship between petals and lodicules, the specialized organs of the grass flower. In addition, functional orthologs of B and C class genes correlate with the development of reproductive structures in gymnosperms, suggesting that at least some of the genetic program that specifies floral organ identity predates the origin of the angiosperms[52–54]. By contrast, the conservation of A class function is debatable, and investigation in this area should lead to a better understanding of the origin of flowers.

Ectopic expression of the ABC genes in the leaves alone is not in itself sufficient to transform them into floral organs. Floral organ specification is also dependent on the *SEPALLATA* MADS box genes, which were identified originally in petunia and tomato[55,56] and subsequently by reverse genetics in *Arabidopsis*[57]. The SEPALLATA proteins function as transcriptional activation cofactors in multimeric complexes with the B and C class proteins[57–60]. Ectopic expression of the ABC genes plus the *SEPALLATA* genes results in the conversion of leaves into floral organs, thus confirming Goethe's hypothesis[61] that floral organs and leaves are homologous structures.

Perception of light and time: a path to gene regulation

Because much of their life is dictated by light, it is perhaps not surprising that plants have numerous receptors that perceive a broad range of light and regulate much of plant development and behavior (Fig. 2). Plants perceive red and far-red light through the phytochromes, and blue and ultraviolet-A light through two classes of receptor, the cryptochromes and the phototropins[62–67]. Although circadian rhythms and light responses in plants have been known for millenia, in the past decade genetic screens have been crucial in identifying the molecular components of light receptors and the circadian clock[68,69].

Two decades ago Koornneef *et al.*[70] screened for mutants, called long hypocotyl or *hy* mutants, that when grown in white light behaved as though they were grown in the dark. One of the *hy* mutants, *hy4*, was particularly insensitive to blue light, and the corresponding gene was shown to encode a blue light receptor, cryptochrome1 (ref. 71). Cryptochromes have been shown subsequently to interact physically with phytochrome and to function genetically in phototropism, illustrating the complexity of the interactions among signaling pathways that originate in different photoreceptors[72–74]. The molecular identification of cryptochrome in *Arabidopsis* has led to advances in other organisms in which cryptochromes are responsible for mediating various responses to blue light[75,76].

Three other *hy* complementation groups were found to represent mutations in phytochrome isoforms or phytochrome cofactors[77–83]. Phytochrome has been known to be a light receptor since early physiological experiments[63]. Loss-of-function mutations in each of the five phytochrome isoforms were derived from screens for *hy* mutants; additional genetic screens in red light and reverse genetics have facilitated an understanding of the various roles of the five different phytochromes present in flowering plants[84].

For many years it has been proposed that light signals perceived by receptors are transduced to the nucleus, resulting ultimately in changes in gene expression. A surprisingly direct example of this is the manner in which phytochromes interact with transcription factors to form a complex that is subsequently imported into the nucleus in a light-dependent manner[85–87]. In addition, further evidence indicates that phytochromes are kinases that are probably derived from two-component system histidine kinases[88,89]. Thus, determining the precise role of phosphorylation in signal transduction will be of great interest[90].

Complementary screens[91,92] for mutants that when grown in the dark behave as though they were grown in the light have identified a universal signaling pathway, the COP signalosome[93,94], that regulates proteolysis during the transduction of light signals. One of the targets for degradation is HY5 (ref. 95), a transcription factor that positively regulates genes that are responsive to light[96,97]. Again, the signal cascade from light to gene expression may be direct because the regulatory unit of the COP signalosome, COP1, interacts directly with both HY5 (ref. 98) and cryptochromes[99]. Because phytochromes also mediate this light responsiveness and also interact with cryptochromes[72], a challenge for the future will be to understand the integration of signals from the numerous light receptors that allow plants to respond to subtle changes in light quantity and quality.

Plants can track the source of light, and this process is mediated by a blue light receptor. Biochemical approaches detected a membrane-associated protein that became phosphorylated when plants were exposed to blue light but were not able to identify it[100]. Genetic screens for non-phototropic mutants[101] allowed, however, the identification of flavin-binding kinases as the phototropism receptors[102,103]. The same receptors are used for both phototropic growth of the whole plant and the avoidance response to high-intensity light, which causes chloroplast movement in individual cells[101,104,105]. It is not yet understood how signals from these receptors can mediate such a spectrum of physiological responses.

The alternation of night and day is a constant periodic environmental change to which all organisms must adapt. Circadian rhythms in the form of leaf movements were noted in the fourth century BC[106], and many processes, including expression of 5–6% of the *Arabidopsis* genome[107,108], have been subsequently identified as regulated by the circadian clock. The circadian clock is intimately connected with light receptors and also with the mechanism by which plants measure day length, which in turn influences many physiological processes including the time at which flowering occurs. The past decade has seen the unification of the mechanisms of these processes, largely through the convergence of many genetic screens that have identified the shared molecular components[109–112]. A light receptor was first linked to

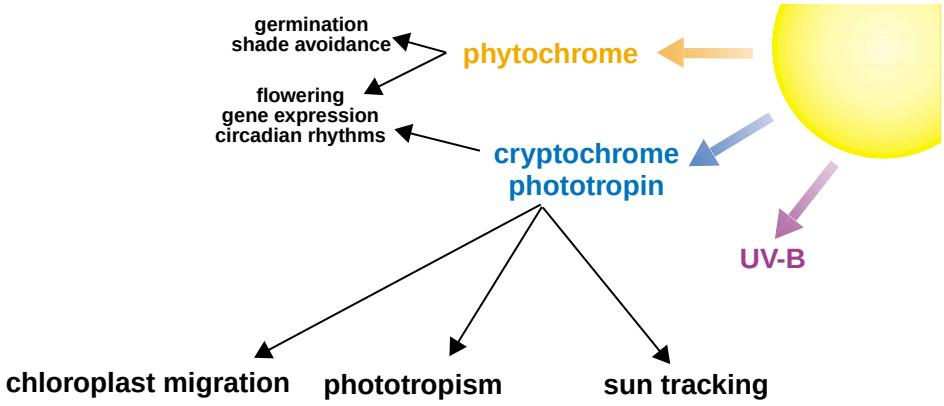

Fig. 2 Plants respond to environmental light conditions through several distinct photoreceptors with sensitivities ranging from far-red/red in phytochromes, to blue/ultraviolet-A in cryptochromes and phototropins, to ultraviolet-B in as yet unidentified receptors (top)[62–67]. The elucidation of their signal transduction pathways has identified much cross-talk among the receptors, and in some cases the receptors interact directly among themselves. It has been known for two centuries that plants grow towards light, and early experiments—by Darwin among others—led to the idea that the shoot tip was the site of light perception and that a diffusible signal, which was subsequently identified as the phytohormone auxin, led to growth changes at a distance from the apex (reviewed in ref. 221). The past decade saw the molecular identification of both the blue-light phototropic receptor phototropin and a downstream component that seems to be involved in auxin perception. The identification of phototropins as flavin mononucleotide–binding light receptor kinases corroborated the idea that an early phosphorylation event regulates phototropic responses. A key feature of phototropin is its ability to mediate a range of processes, from subcellular responses such as chloroplast migration after exposure to damaging, high-intensity light, to whole-organ or even whole-plant responses such as sunflowers tracking the relative motion of the sun during phototropism. Elucidating the downstream signaling pathways involved, and in particular those between phototropin and auxin (in essence a molecular description of the classical phototropism experiments), will be a principal goal in the coming years.

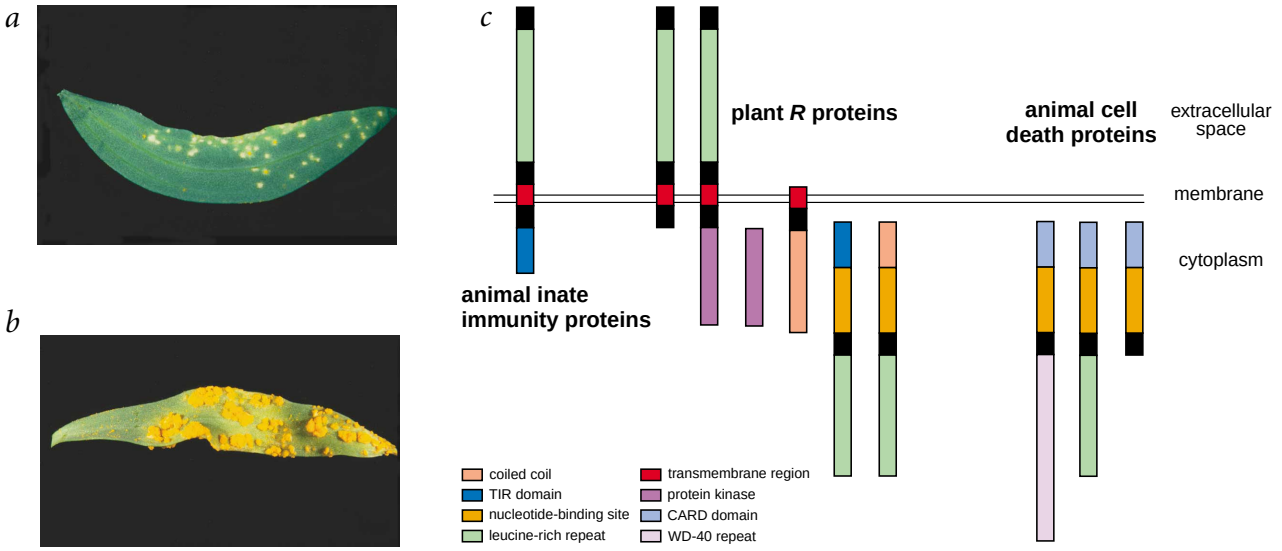

Fig. 3 Plant-pathogen interactions. ***a*** and ***b***, Flax leaves infected with flax rust, the plant-pathogen system that led to the formulation of the "gene for gene" hypothesis[123] ***a***, Incompatible interaction: the flax plant carries a resistance (*R*) gene against this particular race of flax rust which induces *a* hypersensitive response. Local cell death prevents the spread of the pathogen. ***b***, Compatible interaction: the flax plant lacks the *R* gene and is susceptible to the pathogen which grows on the plant. (Photos courtesy of Jeff Ellis.) **c**,The various classes of plant *R* proteins and related proteins in animals. Modified, with permission, from ref. 126. The *R* proteins characterized so far fall into six categories: two classes of NBS-LRR proteins (RPM1, RPP5), membrane-anchored coiled-coil proteins (RPW8), cytoplasmic protein kinases (Pto), LRR receptor kinases (Xa21) and membrane-anchored extracellular LRR proteins (Cf-9). Some *R* proteins have arrangements of structural domains similar to those in Toll-like receptors, which are involved in animal innate immunity (Toll), whereas others seem to be related to various CARD domain–containing proteins involved in animal cell death (Ced4, CARD4, Apaf-1).

the circadian clock when cryptochromes were identified as input sensors to the clock[113]; subsequently, this was also shown in metazoans, where the cryptochromes actually form part of the central oscillator of the clock[75,76].

Mutations in cryptochrome also result in alterations in flowering time[114,115]. These mutations are similar to those in several other genes that result in changes in both flowering time and circadian gene regulation, providing a genetic link between the two processes[116–120]. Indeed, sensitivity to *CONSTANS*, a promoter of flowering in long days, varies with the circadian rhythm[121], providing a mechanistic link between these processes that had been first proposed many decades previously[122].

This is just one example of what has made this a remarkable decade in biology. The wealth of information generated by structural and functional genomics projects combined with classical genetics has allowed molecular insights into biological phenomena that have been known for generations. In addition, this combination of approaches has begun to provide syntheses of the molecular mechanisms of biological processes, a striking example being the genetic networks that integrate environmental signals, such as day length and season, with the transition to flowering, which has brought together research on the circadian clock, flower development and epigenetics.

Plant–pathogen interactions

Genetic analyses in many plant species have been essential to our understanding of the interactions between plants and their pathogens. Although plants lack a system analogous to adaptive immunity in animals, they do possess many defense mechanisms designed to provide resistance to pathogen attack.

One of the most intensely studied systems is known as 'gene-for-gene' resistance—a mechanism that was first defined genetically in flax and flax rust[123] (Fig. 3). In this type of resistance, the plant carries a specific allele of a resistance gene (*R* gene) and the pathogen carries a specific avirulence gene (*avr* gene). When both of these genetic components are present, the plant can detect and respond to the pathogen, resulting in resistance to the disease. If either component is absent, the pathogen is not detected by the plant and disease results. The simplest view of this type of interaction is that the *avr* gene encodes an 'elicitor' and the corresponding *R* gene encodes a receptor for that elicitor. An interesting aspect of this response is that some *R* genes can provide protection against several pathogens, including viruses, bacteria, fungi, nematodes and insects. The tomato *Mi* gene, for example, provides protection against both aphids and nematodes[124].

In the past decade, molecular genetic research in both model and crop plants has led to the cloning of many *R* genes (reviewed in refs. 125, 126). The products of the *R* genes cloned so far define several different classes of protein that contain different domains known to be involved in protein-protein interactions and/or signal transduction (Fig. 3). Notably, these domains (and sometimes their arrangement in the protein) are shared with proteins involved in animal innate immunity and in the coupling of pathogen recognition to cell death, suggesting that there may be an ancient origin of these pathways. Whether these structural similarities translate into true mechanistic similarities remains to be determined.

Molecular cloning has allowed the characterization of several *R* gene products. Although the many classes of *R* protein could be imagined to be the receptors for the pathogen elicitors predicted by the gene-for-gene hypothesis, in many cases direct interactions between *avr* gene products and *R* gene products have not been shown[126]. In addition, there are several examples in which *avr* gene products that lack sequence similarity act through the same *R* gene product. A current model proposes that the *R* gene products 'guard' specific cellular processes that are targeted by *avr* gene products[127]. Association

of the *avr* gene product with its cellular target leads to activation of the corresponding *R* gene product without necessarily requiring a direct interaction between the two. Many recent studies have identified various mechanisms by which this can happen, providing substantial support for the 'guard hypothesis' (refs. 128–131; reviewed in ref. 132).

Genetic screens also have been used to identify other genes that are required for plant *R* gene function. Two genes, *EDS1* and *NDR1*, are each required for the function of distinct sets of *R* genes[133–135]. This implies the existence of at least two distinct pathways downstream of *avr*–*R* recognition events. The presence of additional *R* genes, which require neither *EDS1* nor *NDR1*, indicates that additional distinct pathways remain to be identified.

The availability of the complete *Arabidopsis* genome sequence allows the cataloging of all gene sequences that are related to known *R* genes. There are about 150 genes encoding nucleotide-binding site–leucine-rich repeat (NBS-LRR) proteins spread throughout the genome. Some are present as single genes, whereas others are present as gene clusters. Most notable is the degree of polymorphism that is seen between *Arabidopsis* accessions. Comparison of *R* gene loci in different accessions shows the deletion and duplication of specific *R* genes. Extreme divergence of *R* gene haplotypes is seen even between the common laboratory strains Columbia and Landsberg *erecta*[136,137], which on average show less than 0.1% nucleotide sequence divergence[22]. More complete sequence data from other accessions will be required to produce a detailed picture of *R* gene evolution. It is clear, however, that *R* genes seem to be under selection to increase variability.

Quantitative-trait loci: from concept to genes

The dissection of the genetic pathways that control the developmental and physiological processes described above relied largely on the analysis of qualitative traits; however, most of the observable variation between individuals in populations is quantitative. Such quantitative traits (for example, plant height, yield, dry weight or leaf size) are typically affected by many genes and the environment (Fig. 4*a*). Although first attempts to study quantitative traits predate the twentieth century[138], and powerful statistical tools to analyze quantitative traits were already available in the first half of the past century[139–141], it was not until recently that the individual genes underlying variation in such complex traits could be identified. Because quantitative traits affecting many biological phenomena have been studied, below we have chosen to focus on technical achievements rather than on specific processes.

Much of the early progress in determining the architecture of quantitative traits, such as their number, location and epistatic interactions, was made in *Drosophila* (reviewed in ref. 142). By contrast, recent milestones such as the isolation of genes corresponding to single quantitative-trait loci (QTL) have been achieved in plants—both in crops and model species. The rapid progress in elucidating the nature of QTL was made possible through the development of molecular markers that allowed detection of extensive variation at the DNA level and the combination of interval mapping[143] with molecular marker-based maps as proposed by Lander and Botstein[144]. Powerful algorithms and software for interval mapping and more advanced, related approaches have since been developed (reviewed in ref. 145).

An important step from QTL to the relevant genes is the separation of an individual QTL from other segregating loci to obtain genotypes with monogenic segregation. Such a 'mendelization' of a QTL can be achieved by constructing a near-isogenic line (NIL) and was first done for loci controlling flowering time (Fig. 4*b*-*d*)[146,147]. Like any other mutant, NILs with monogenic segregation can be characterized genetically to determine dominance relationships and to perform complementation tests.

Complementation tests were used in the analysis of QTL controlling the difference in inflorescence morphology between maize and its wild progenitor teosinte, although an atypical QTL with an

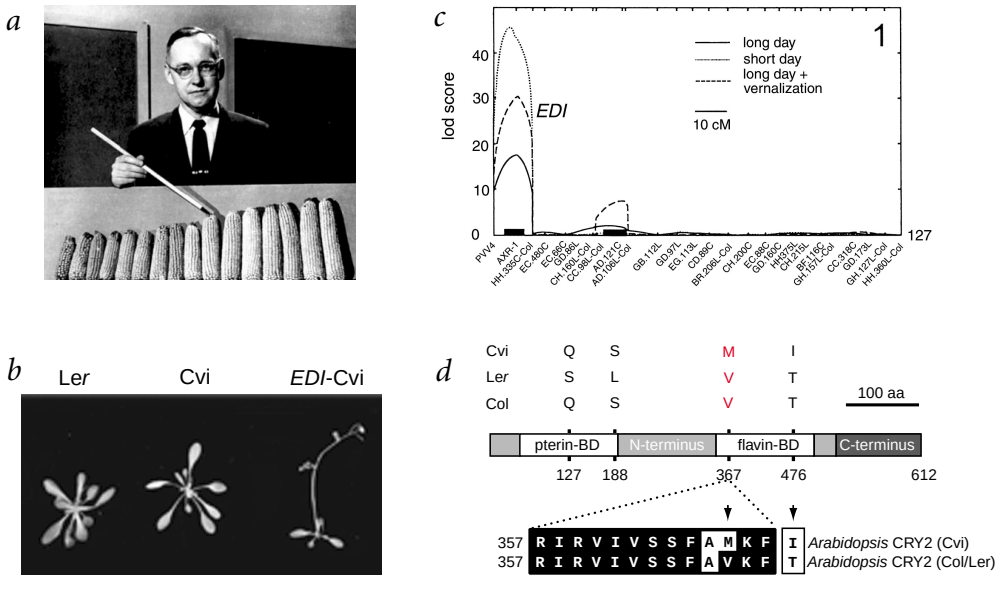

Fig. 4 From QTL to QTN. ***a***, James Crow pointing out natural variation for typical quantitative traits such as cob size and kernel number in *Zea mays*. (Photo courtesy of the Calvin Company.) ***b***, Flowering response under short days in the *Arabidopsis* accessions Landsberg *erecta* (Ler) and Cape Verde Islands (Cvi). The parental accessions show little difference in their flowering response to photoperiod length[218]; however, segregating populations derived from crosses between them show much larger variation in flowering time. Recombinant inbred lines (RILs) were used to map QTL involved in flowering control. A region containing such a QTL, *early day-length insensitive* (*EDI*) was introgressed into the L*er* background. The introgression line *EDI*-Cvi flowered much earlier than either parent. ***c***, QTL likelihood map for total leaf number, which correlates with flowering time. Only chromosome 1, which contains the large effect QTL named *EDI*[218], is shown. Abscissa corresponds to the genetic map in centimorgans (Courtesy of the Genetics Society of America). ***d***, Fine mapping and positional cloning of *EDI*[156] showed that it was an allele of the blue light photoreceptor *CRY2* (ref. 74). *CRY2* was previously shown to promote flowering under long-day conditions[114] and the unique flowering phenotype of *EDI* was shown to be due to a single amino acid change that converts a valine (V) in L*er* to a methionine (M) in Cvi[156]. This amino acid difference reduces the light induced destabilization of the CRY2 protein in short-day grown plants. BD, binding domain.

extremely large effect was studied in this case. One QTL explaining most of the morphological difference mapped to a region including the maize locus *teosinte-branched 1* (*tb1*), and the QTL effect was similar to the mutant phenotype of *tb1* (refs. 148, 149). A NIL containing the teosinte QTL in a maize background did not complement the *tb1* mutated allele, suggesting that the QTL was indeed *tb1* (ref. 150). Although such genetic complementation tests can provide evidence for a genetic interaction, this interaction may be allelic or epistatic in nature. Thus, a failure to complement is not proof that the QTL and the candidate gene are identical. In the above example, further evidence based on gene expression was needed to confirm that *tb1* was the gene underlying the QTL[151].

Another example of how to determine which gene corresponds to a QTL was based on introgression lines between the wild tomato *Lycopersicon pennellii* and the cultivated tomato *Lycopersicon esculentum*, which were used to analyze fruit traits[152]. High-resolution mapping of the *Brix 9-2-5* QTL, which controls fruit sugar content, showed that recombinants in a region of 484 bp in the apoplastic invertase gene *Lin5* co-segregate with the QTL phenotype[153]. Such co-segregation of intragenic recombinant genotypes of a gene with the QTL phenotype constitutes unambiguous genetic proof that the candidate gene corresponds to the QTL.

Alternatively, functional complementation in which a transgene confers the quantitative trait phenotype is another 'gold standard' for gene identification. This was first shown for the *fw.2.2* fruit weight QTL in tomato: transformation of cultivated tomato with the *ORFX* gene from the wild tomato *L. pennellii*, which produces tiny fruits, resulted in a reduction of fruit size in the transformants[154]. So far, *Brix 9-2-5* and *fw.2.2* are the only QTL to be cloned that were not detectable as mendelian factors in F2 populations.

The final step in linking a QTL phenotype to a specific polymorphic site causing the difference in the trait phenotype, the quantitative-trait nucleotide (QTN), has been achieved recently in both *Drosophila*[155] and *Arabidopsis* (Fig. 4*b*,*c*). Polymorphisms causing single amino acid substitutions in the *Arabidopsis* photoreceptors CRY2 and PHYA could be linked directly to QTL for flowering time[156] and natural variation in light sensitivity[157], respectively. The biochemical analysis of these natural variants identified properties of the corresponding proteins that explain their different behavior with respect to flowering time and light sensitivity. These studies show how the plasticity in plant growth and development among different *Arabidopsis* accessions can be used advantageously to dissect plant biology and how it will ultimately lead to a better understanding of natural selection[158,159].

In addition to the progress in going from the QTL to the gene to the QTN illustrated by these examples, QTL analyses have yielded insight into the genetic basis of many traits important for seed production and plant breeding[160]. These include the analysis of such complex and elusive traits as inbreeding depression and hybrid vigor (see, for example, refs. 161–163), hybrid sterility[164] and pollinator preference[165]. For example, such analyses have shown that most QTL contributing to heterosis in rice are overdominant and involve epistatic relationships between multiple QTL. These complex traits play crucial roles in evolution, for example by maintaining genetic variation in populations (heterosis) and during speciation (reproductive barriers). The elucidation of their molecular basis will be a principal challenge for the future and promises to shed light on plant evolution and crop improvement.

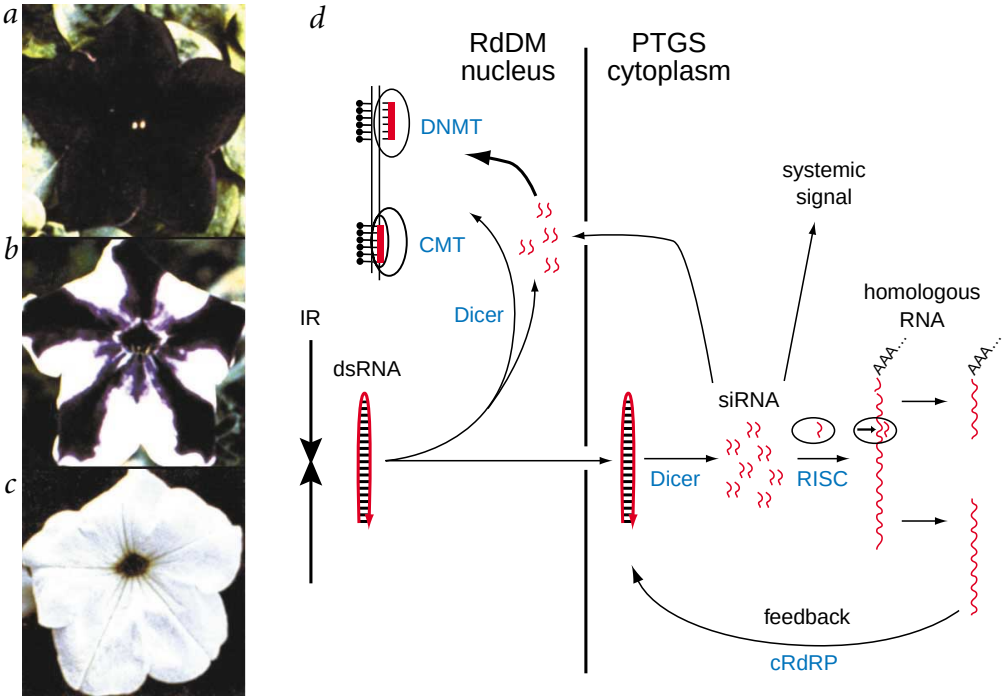

Fig. 5 Epigenetic phenomena and underlying mechanisms. *a*–*c*, One of the first examples of gene silencing resulting from the introduction of a transgene encoding chalcone synthase (CHS) into petunia[6]. ***a***, The parental control plant of the V26 inbred line produces deep violet flowers. ***b***,***c***, Two flowers of transgenic plant 218.38 showing partial (*b*) or complete (*c*) loss of anthocyanin pigmentation owing to silencing (co-suppression) of endogenous and transgenic CHS (copyright the American Society of Plant Biologists, reprinted with permission). ***d***, Current model of RNA-mediated silencing. dsRNA, derived from direct injection (not shown), transcribed from inverted repeats (IR), represented by aberrant RNAs of distinct origin (not shown) or produced by a viral RNA–dependent RNA polymerase (not shown), can trigger RNA-mediated silencing. Gene silencing can be caused by RNA-directed DNA methylation (RdDM), which leads to transcriptional gene silencing (TGS) or to cytoplasmic post-transcriptional gene silencing (PTGS), which is also known as RNAi. The dsRNA is cleaved into siRNAs by RNAse III–type enzymes such as Dicer (named DCL1 in *Arabidopsis*)[202], possibly in both the cytoplasm and the nucleus. In the nucleus, siRNAs may guide changes in chromatin configuration or DNA methylation, possibly dependent on either interactions of the siRNAs with a chromomethylase (CMT) or the formation of a DNA-RNA duplex, which attracts a *de novo* DNA methyltransferase (DNMT). In the cytoplasm, the siRNAs guide the cleavage of homologous RNAs, in combination with the RNA-induced silencing complex (RISC). RISC degrades homologous RNAs and may lead to the production of aberrant RNAs, which in turn act as templates for a cellular RNA–dependent RNA polymerase (cRdRP), which is part of a feedback loop that maintains PTGS. Viral suppressors such as HC-Pro suppress the production of siRNAs[220]. PTGS is systemic, in other words, it can affect the whole plant, starting from a small area where gene silencing is triggered. The nature of the systemic signal is unknown, but it may involve siRNAs or some other kind of dsRNA or aberrant RNAs. Modified, with permission, from ref. 183.

Beyond genetic control: epigenetics

We have concentrated above on the genetic control of developmental and physiological processes by both qualitative and quantitative traits; however, much of gene expression during development is regulated epigenetically—that is, by a mitotically and/or meiotically stable change in gene function that does not involve a change in DNA sequence. Epigenetic phenomena are often identified through their odd behavior and non-mendelian inheritance.

Again, plant research has led to the discovery of many epigenetic phenomena, including the identification of transposable 'controlling' elements by McClintock[5] in the 1940s and 1950s; the characterization of paramutation, whereby the regulation of one allele is altered through its interaction with another[166,167]; gene-specific genomic imprinting, in which gene activity depends on parental origin[168]; and the silencing of endogenous genes by additional transgenic copies[6–8].

Plants and fungi have been pivotal in dissecting the genetic mechanisms that underlie epigenetic phenomena, such as the genetic dissection of epigenetic processes (reviewed in refs. 169, 170) and the role of DNA methylation (reviewed in refs. 171, 172). Elegant genetic screens in *Arabidopsis* have yielded fundamental insight into the role of DNA methylation in gene regulation and silencing[173–178]. Epigenetic phenomena are a hot topic of research and many review issues and books on epigenetics have been published recently[179–182]; we therefore briefly mention only two distinct aspects of epigenetic control that have clear analogies to other systems: RNA silencing and gene regulation mediated by *Polycomb* group proteins.

In 1990, it was reported that petunia plants overexpressing a transgene that should confer flower pigmentation produced white flowers (Fig. 5*a–c*)[6,7]. Since this apparently baffling discovery, molecular studies in petunia and tobacco, combined with genetic studies in *Arabidopsis*, have led to the characterization of both transcriptional and post-transcriptional silencing mechanisms. Recent findings suggest that these two types of gene silencing are interrelated and may involve common components relying on RNA (Fig. 5*d*)[183]. RNA silencing is thought to have evolved as a protection system against viruses and transposons, and it targets nucleic acids in a homology-dependent manner. Similar silencing mechanisms have been described in *Neurospora crassa* (quelling) and in animals (RNAi).

Many studies in different systems have elucidated the involvement of DNA methylation, double-stranded RNA (dsRNA) and small interfering RNAs (siRNA)[184] in gene silencing (reviewed in refs. 183, 185). Complex transgene insertions often produce inverted repeats that are transcribed and hybridize intramolecularly to form dsRNA. Such dsRNA, whether transcribed from a complex insert or by deliberate expression or injection, is processed into siRNAs of 21–25 nucleotides. The siRNAs are incorporated into a protein complex that degrades RNAs that share homology with the siRNAs, thereby leading to the destruction of both transgenic and endogenous RNAs.

siRNAs have also been detected in some cases of transcriptional gene silencing that are associated with DNA methylation. In this situation, the siRNAs may mediate DNA or chromatin modifications (reviewed in ref. 183). Notably, gene silencing is not restricted to the cell in which it was initiated. It is amplified and can spread systemically throughout the plant[186,187]. This systemic spread may have a role in the defense against viruses, but it also raises the possibility of potential roles in developmental control[188].

Just as gene silencing mechanisms have been found to have a fundamental role in plants, animals and fungi, chromatin-based cellular memory mechanisms that were studied extensively in *Drosophila* have now been found to be important in plants. Proteins of the *Polycomb* group are best known for their role in regulating homeotic genes in *Drosophila*, where they ensure the stable inheritance of gene expression states over many cell divisions. *Polycomb* group proteins are thought to suppress gene expression by modulating the higher order structure of chromatin[189–191].

Polycomb group proteins have a similar role in plants (reviewed in ref. 192): the *CURLY LEAF* gene, a homolog of *Enhancer of zeste* from *Drosophila*, is involved in repressing the floral homeotic gene *AG* outside its normal expression domain[193]. In addition, many *Polycomb* group genes in animals are involved in regulating growth and proliferation[194]. This function is also conserved in plants, where the genes of the *FERTILIZATION-INDEPENDENT SEED* (*FIS*) class—*MEDEA*[195], *FERTILIZATION-INDEPENDENT ENDOSPERM*[196] and *FIS2*[197]—regulate cell proliferation during seed development (reviewed in ref. 198).

Another *Polycomb* group protein, *VERNALIZATION2* (*VRN2*), mediates a cellular memory mechanism involved in the flowering response[199]. Many *Arabidopsis* accessions respond to 'vernalization'—exposure to a period of low temperature that accelerates flowering. Because the flowering response occurs several weeks after cold treatment, an epigenetic memory is involved in vernalization and *VRN2* plays a role in maintaining this memory by affecting the chromatin state of one of the key regulators of the flowering response, *FLC*.

In summary, it seems that many epigenetic phenomena share cellular mechanisms that are common to all eukaryotes and must therefore have an early evolutionary origin[200,201].

Challenges and prospects

The past ten years have seen a marked increase both in the amount of information available about plant genes and in our understanding of the roles of specific genes within the lifetime of the plant. One of the biggest challenges for the coming decade will be to convert more of that information into knowledge. We have the complete sequences of two plant genomes—can we convert these sequences into an understanding of what each and every gene actually does?

Work in *Arabidopsis* and other organisms shows that a main problem in determining the function of every gene is genetic redundancy. Deletion analysis of all yeast genes indicates that only about 20% are essential for viability[202,203]. The remaining 80% are non-essential for growth under standard laboratory conditions or their functions are redundant in the genome. A fraction of these genes, although not strictly essential for viability, have subtle or obvious mutant phenotypes under at least some growth conditions[204,205]. A similar situation probably exists in *Arabidopsis*, for which genetic redundancy has been shown previously through classical genetic methods (see, for example, ref. 206). In fact, the problem may be more severe in *Arabidopsis*, owing to the relatively large number of segmental duplications contained in the genome sequence[22].

There are many approaches that can potentially deal with this problem. One is to obtain knockouts, not only of individual genes but also of gene families, and to determine whether knocking out two or more related genes will generate a phenotype. This approach has shown some success and clearly indicates the existence of partially overlapping functions for some sequence-similar genes in *Arabidopsis* (see, for example, ref. 57). It is likely, however, that there are also many instances of functional redundancy among genes that are not related in sequence. Other methods will be required to identify those genes and the most effective approach may be to rely on the unbiased power of classical genetics. Genetic screens, either to discover second-site enhancers or suppressors of known

mutations or performed in a background of a 'phenotypeless' knockout, offer a powerful method for detecting genetic redundancy, whether or not that redundancy is based on sequence similarity (reviewed in ref. 207). Some genes with partially or completely redundant functions can also be identified through the isolation of gain-of-function mutations using either classical mutagens or activation tagging[208].

Another future challenge involves the need to expand our genomic information base to include a greater representation of the diversity that makes up the plant kingdom. At present we have two complete genome sequences representing two families of flowering plants. Although this is a tremendous resource for investigating certain issues in plant biology, there are many others that cannot be readily addressed. When considering the future of plant genomics, two fields of study immediately spring to mind: the evolution of plant development and plant biochemistry.

During the evolution of land plants, developmental patterns and life cycles underwent marked changes. An understanding of these evolutionary changes will facilitate our understanding of the mechanisms underlying developmental processes. The study of the evolution of development in the plant kingdom will benefit greatly if plant genomics is extended to include a broad variety of plant taxonomic groups, rather than focusing exclusively on the flowering plants, which represent just the tip of the iceberg.

The study of plant biochemistry presents a different type of diversity. Collectively, plants have the metabolic capacity to produce thousands of unique compounds, many of which are restricted to a few plant families. These compounds have been used by humans as drugs, dyes, flavorings and polymers, and for a host of other purposes. An understanding of the evolution and function of the biochemical pathways that produce these compounds is not only of great intrinsic interest but also of tremendous potential value in many practical applications.

These are just two examples in which a single model organism (or a few, relatively closely related model organisms) fails to provide the depth of information required to resolve the most interesting issues. Data gathered from genetics and genomics in the model organisms will still be tremendously useful in these fields, but ultimately they will be served best by exploring the breadth of the plant kingdom.

A final challenge concerns the future of plant biotechnology. The ability to modify agriculturally important plants by inserting single genes into their genomes has led to the production of many commercial plant varieties incorporating various traits. One can debate the economic benefits and environmental consequences of these genetically modified organisms, but their rapid adoption by US farmers reflects the fact that these varieties offer strategies for controlling weeds and insect pests (reviewed in ref. 209). Similar technology has been used to modify the nutrient content of rice, and this approach could be used to produce more nutritious crops or crops containing specific pharmaceutical agents[210,211]. Although combining this technology with the recent advances in plant genetics and genomics may hold great promise, the debate of the past few years makes it clear that certain scientific and non-scientific issues must be resolved by society as a whole before the technology will be accepted in the world at large.

Acknowledgments

We apologize to colleagues whose research areas we could not cover. We thank J. Banks, C. Chapple, S. Curtis, R. Dudler, Y. Eshed, S. Goodwin, M. Green, M. Koornneef, C. Lagarias, S. Lolle, S. Scofield, D. Smyth and J.-R. Xu for critically reading the manuscript.

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