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The Impact of *Arabidopsis* on Human Health: Diversifying Our Portfolio

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Studies of the model plant *Arabidopsis thaliana* may seem to have little impact on advances in medical research, yet a survey of the scientific literature shows that this is a misconception. Many discoveries with direct relevance to human health and disease have been elaborated using *Arabidopsis*, and several processes important to human biology are more easily studied in this versatile model plant.

Arabidopsis thaliana, the reference species for plant biology and a key model system for all of biology, has had a greater impact on human health research than may seem evident at first glance. In this Essay, we highlight examples where research using *Arabidopsis* has informed the identification of a prototype protein or domain involved in a human disease, human development, or other important aspects of human biology. These examples do not include the enormous impact that *Arabidopsis* research has had on plant biology, improving food security, and alleviating malnutrition, which is a major threat to human health and is the basis of 50% of human disease worldwide. We make the case that well-chosen, deep investment into research using plant genetic models will help to elucidate basic life processes and to illuminate the evolutionary plasticity of cellular pathways and networks.

The *Arabidopsis thaliana* genome sequence was completed in 2000. Three years later, with the reporting of the annotated human genome sequence, it became evident that a majority of human genes that were suspected or known to play a role in disease had orthologs in *Arabidopsis* (http://mips.gsf.de/proj/thal/db/tables/disease.html). This marked degree of similarity in "disease genes" is comparable to that observed in other model organisms. For example, among cancer genes, 70% of genes implicated in cancer have *Arabidopsis* orthologs with E-value cutoffs of less than E^10, whereas the percentage of orthologs in the fruit fly *Drosophila melanogaster* is 67%, in the worm *Caenorhabditis elegans* is 72%, and in the budding yeast *Saccharomyces cerevisiae* is 41%. In one sense, this high percentage of shared genes is not surprising given that development and disease follow the normal and abnormal activities, respectively, of proteins that serve basic cellular functions. But with 1.6 billion years for *Arabidopsis* and humans to have diverged, is it too much to expect that the original functions of these gene products survived intact? Are the distinct body plans and life strategies of humans and plants so different that the respective human and plant orthologs were not similarly constrained in their evolution and could not conceivably function in a similar way? We answer "no" to both questions by highlighting several examples where *Arabidopsis* research led the way in the discovery or analysis of genes and processes of importance in human health. Many model systems greatly impacted human health, and we argue that *Arabidopsis* is a part of this diversified portfolio of tools needed to understand basic cellular processes.

Innate Immunity and Intracellular Receptors

Plant NB-LRR proteins (nucleotide-binding site - leucine-rich repeats) are the primary intracellular receptors of the plant immune system and are encoded by what are historically termed disease resistance genes (Jones and Dangl, 2006). The first plant *NB-LRR* genes were reported in 1994 and 1995. There are ~150 of these genes in *Arabidopsis*, and their definition enabled annotation of candidate disease resistance genes in many flowering plants. Equivalent human orthologous and paralogous genes in the animal innate immune system are variously called *NOD/CARD/CATERPILLAR* (Ting et al., 2006).

These proteins are involved in a variety of inflammatory responses. Most importantly, genetic variation in NOD2, cryopyrin, and CIITA (MHC class II transactivator) in humans and Naip5 (neuronal apoptosis inhibitory protein 5) in mice is

associated with inflammatory disease or increased susceptibility to bacterial infections as well as cold-induced autoinflammatory syndrome and Mediterranean fever. Mammalian NOD proteins may be cytosolic sensors for the induction of apoptosis, as well as for innate recognition of microorganisms and for regulation of inflammatory responses. The first human *NOD* gene, *CIITA*, was isolated in 2000 (Ting et al., 2006), and the connection was made to the *NB-LRR* plant disease resistance genes. *NOD2* was the first candidate gene cloned for Crohn's disease, a severe inflammatory disorder of the small intestine (Hugot et al., 2001). This candidate gene was identified by virtue of its homology with the plant NB-LRR proteins.

The plant NB-LRR proteins are associated with molecular chaperones that may be required to "hold and mold" them in a signal-competent manner. The involvement of the cytosolic HSP90 and SGT1 chaperone proteins in the immune response was first defined in plants, along with the plant-specific RAR1 protein, which is structurally related to animal p24 (Jones and Dangl, 2006). Animal orthologs of cytosolic HSP90 and SGT1 were subsequently shown to control NOD/CATERPILLAR function in animal innate immunity (da Silva Correia et al., 2007; Mayor et al., 2007). The NB-LRR and the NOD/CARD/CATERPILLAR proteins exist in a complex functional relationship with the Toll-like receptors (TLRs), which are pattern recognition receptors involved in detection of microbial pathogens. A distinct set of extracellular pattern recognition receptors operates in the plant innate immune system. These carry extracellular leucine-rich repeats but use cytosolic serine-threonine kinase signaling domains instead of Toll/interleukin-1 receptor (TIR) domains. Several of these act like animal TLRs to recognize pathogen-associated molecular patterns (Zipfel et al., 2006).

Light Signaling, Protein Degradation, and Cancer

Plants exhibit considerable phenotypic plasticity as most plant organs do not arise until after the seed germinates, allowing organ size, shape, and physiology to be optimized to the local environment throughout their development. Because they are sessile and photosynthetic, plants are especially attuned to their light environment. Light influences every developmental transition from seed germination to flowering, with particularly dramatic effects on the morphogenesis of seedlings. Light signals do not act autonomously but are integrated with seasonal and diurnal changes in temperature, as well as with intrinsic developmental programs to specify correct spatial and temporal regulation of gene expression, organelle development, and cellular differentiation. The diverse responses that plants have to light provide a unique model system for understanding phenotypic plasticity. As a result, the study of light signaling in plants has not only provided insight into plant growth and development but also has led to the discovery of conserved proteins that regulate transcription, tumorigenesis, and lipid metabolism in metazoans (Yi and Deng, 2005).

Almost 20 years ago, mutant screens for dark-grown seedlings that resemble light-grown plants led to the discovery of a handful of genes, called *DET*, *COP*, and *FUS*, which based on genetic experiments encode regulatory proteins that act downstream of multiple photoreceptors (Chory et al., 1989). Many of these genes were cloned by the early 1990s, and biochemical studies revealed that most of these proteins played a role in targeted protein turnover. These proteins were found to be either part of an evolutionarily conserved protein complex of eight subunits (CSN1-8), called the COP9 signalosome after its prototype subunit COP9, or part of an E3 ligase called the CDD complex (COP10, DET1, DDB1) characterized in both plants and animals (Wei and Deng, 2003; Yi and Deng, 2005). The CDD complex is now the most recently characterized E3 ligase and functions in the light-regulated development of plants. The best characterized activity of the CSN is its ability to cleave and remove the ubiquitin-like protein, Nedd8, from cullin ubiquitin ligase subunits (a process called denedyllation). Neddylation is another process that was elucidated first in *Arabidopsis* (see below).

The discovery of light signaling pathway components in plants, such as the COP1 E3 ligase, the COP9 signalosome, and DET1, boosted our understanding of the effects on gene expression of the mammalian p53 tumor suppressor (Dornan et al., 2004) and the transcription factors CREB (Qi et al., 2006) and c-JUN (Wertz et al., 2004). Understanding of these plant molecules also shed light on T cell homeostasis (Menon et al., 2007) and on fatty-acid synthetic enzymes in lipid metabolism in animals (Qi et al., 2006). Detailed biochemical studies of the plant proteins revealed how turnover of the mammalian factors is regulated. Considerable work in plants elucidated the function of the COP9 signalosome and COP1, which facilitated research on these proteins in animal cells. Thus, studying light signaling in plants enabled new avenues of inquiry relevant to mammalian tumorigenesis, DNA damage, and lipid metabolism.

Cryptochromes and the Circadian Clock

After years searching for a blue-light photoreceptor in plants, Ahmad and Cashmore (1993) identified a gene that, upon careful scrutiny, encoded a protein that fit the bill. The name cryptochrome (CRY1) was given because many of the blue-light responses that were used historically as diagnostics were found in cryptogams, an old term describing nonflowering plants like ferns, mosses, and algae. Cryptochromes modulate developmental processes, such as flowering, that are under control of the photoperiod. Many other blue-light responses in plants are regulated by another family of blue-light photoreceptors called phytotropins. *Arabidopsis* has two cryptochromes, CRY1 and CRY2, prototypes among members of the larger class found in eukaryotes, which evolved from DNA photolyases. Most plant cryptochromes contain an amino-terminal photolyase-like domain and a carboxy-terminal domain, which are important for trafficking of molecules between the nucleus and cytosol. The carboxy-terminal domain also forms protein-protein interfaces with other photoreceptors and with the protein degradation machinery (including COP1) to target specific transcription factors (Li and Yang, 2007).

Among the many developmental phenomena that involve plant cryptochromes is circadian rhythm. Mammalian CRY homologs were cloned in 1998

by Aziz Sancar's group (Thresher et al., 1998). Loss of either the mouse *CRY1* or *CRY2* gene confers altered (and opposite) free-running circadian periods. Loss of CRY2 attenuates the light induction of the *Per* gene, which encodes a component of the circadian clock (Thresher et al., 1998). CRY1 and CRY2 along with the proteins PER1 and PER2 form the core of the mammalian clock. CRY is targeted for degradation by an F box protein of an E3 ubiquitin ligase and mutations in this F box protein extend the circadian period in mice (Virshup and Forger, 2007). These contributions and other work using the *Drosophila CRY* and *Per* gene homologs led to the conclusion that cryptochromes entrain the circadian clock by interacting with some of the clock components.

It may not be surprising then that a number of diseases that depend on a functioning circadian clock are suspected to be caused by defects in the cryptochrome pathway. For example, altered circadian rhythm is associated with some cancers, although the jury is still out on whether the circadian defects are causative.

AXR1, The Ubiquitin Cycle, and Alzheimer's Disease

Auxins are low molecular weight plant hormones that regulate virtually all aspects of plant development through effects on cell division, elongation, and differentiation. Genetic and biochemical studies in *Arabidopsis* showed that auxin regulates gene expression by promoting the ubiquitin-dependent degradation of transcriptional repressors called Aux/IAA proteins (Parry and Estelle, 2006). Because the ubiquitin pathway is highly conserved among eukaryotes, several discoveries in auxin research had important implications for cellular regulation in animals. The first *Arabidopsis* protein shown to be required for an auxin response was AXR1 (Parry and Estelle, 2006). Working simultaneously in both *Arabidopsis* and yeast, researchers in the Estelle lab demonstrated that AXR1 is required for conjugation of a ubiquitin-related protein called RUB1 onto CUL1, a subunit of a ubiquitin protein ligase (E3 type) called SCF (Parry and Estelle, 2006). Genetic studies in *Arabidopsis* indicate that RUB1 modification of CUL1 is essential for SCF activity. One such E3 ligase, SCF^{TIR1}, targets the Aux/IAAs for degradation (Kepinski, 2007). Subsequent studies in animal systems demonstrated that the animal ortholog of RUB1, Nedd8, is also required for SCF function and that the RUB1/Nedd8 conjugation pathway is conserved between plants and animals (Petroski and Deshaies, 2005). SCFs are involved in many aspects of cell growth in animals and are implicated in human diseases including cancer (Petroski and Deshaies, 2005). In addition, altered cullin neddylation is associated with Alzheimer's disease. For example, the human protein APP-AB1 binds to amyloid precursor protein (APP), the source of β-amyloid plaques that accumulate in the brains of patients with Alzheimer's disease (Chow et al., 1996). The significance of this interaction is not completely clear, but recent evidence in *Drosophila* suggests that APP binding to APP-AB1 reduces cullin neddylation, thus potentially altering the activity of many different SCFs (Chow et al., 1996; Kim et al., 2007a).

Given that activity of the ubiquitin pathway, and SCFs in particular, has such an important role in human disease, there has been extensive research on regulation of SCF-substrate interactions. For many SCFs, phosphorylation of the substrate is required for binding (Petroski and Deshaies, 2005). However, in the case of SCF^{TIR1}, substrate recognition is governed by binding of auxin directly to the F box protein subunit of the SCF (Kepinski, 2007). In a sense, auxin may act like "molecular glue," stabilizing an interaction between these two proteins. Thus, work in *Arabidopsis* introduced an entirely new way of regulating protein-protein interactions. At this point it is not known if animals use this type of regulation, but given the conservation of fundamental biochemical processes, it certainly seems likely.

Argonautes and RNA Silencing

A variety of small regulatory RNAs including small-interfering RNAs (siRNAs), microRNAs (miRNAs), transacting siRNAs (tasiRNAs), and Piwi-interacting RNAs (piRNAs) are major regulators of myriad processes in eukaryotic cells through silencing different classes of genes (Chapman and Carrington, 2007). For example, more than a third of human protein-coding RNAs appear to be targets of different microRNAs. The Argonaute proteins, which serve as catalytic components of the RNA-induced silencing complex, are key regulators of these various RNA-silencing processes and interact directly with the relevant small RNA to help guide it to its target mRNA. Plant research has made a major impact on the field of RNA silencing. Some of the first descriptions of homology-dependent gene silencing phenomena, such as cosuppression and RNA-directed DNA methylation, and the discovery of siRNAs and of the enzyme Dicer were made in plants (Matzke et al., 2001). In addition, the first *Argonaute* gene was cloned from *Arabidopsis*.

The implications for Argonaute proteins and RNA silencing in human health and disease are immense. First and foremost, RNA interference (RNAi) may hold promise for treating a diverse array of human diseases including age-related macular degeneration, Alzheimer's disease, and arthritis (Kim and Rossi, 2007). RNAi is under development for downregulating viruses such as the hepatitis B virus, HIV, and respiratory syncytial virus, as well as oncogenes important in tumorigenesis. RNAi has proved invaluable for studying the loss of gene function in mammalian systems, speeding along basic research and allowing the rapid development of animal models in which disease genes are silenced by RNAi (Kim and Rossi, 2007). Finally, misregulation of microRNAs is associated with a variety of clinically important diseases and cancers, and Argonaute proteins themselves have been linked to disorders such as fragile X syndrome and some forms of autoimmune disease.

DNA Methylation

Cytosine DNA methylation is an epigenetic mark for gene silencing that is important in many gene regulatory systems including genomic imprinting, X chromosome inactivation, and the silencing of transposons and other DNA sequences containing either direct or inverted repeats. Despite the importance of DNA methylation and decades of phenomenological descriptions of epigenetic regulatory systems (Chan et al., 2005; Goll and Bestor, 2005), genetic studies of the mechanisms regulating

DNA methylation are still underdeveloped. In part, this reflects the fact that although methylation is present in most eukaryotes, it was curiously lost in several well-studied model organisms such as baker's yeast and *C. elegans*. *Arabidopsis* is arguably one of the best organisms for genetic studies of DNA methylation because it has much in common with mammalian systems, having orthologs of the two major human DNA methyltransferases, Dnmt1 and Dnmt3. Furthermore, unlike the mouse where DNA methylation mutants are not viable, *Arabidopsis* tolerates mutations that virtually eliminate methylation, thus allowing detailed genetic analyses (Chan et al., 2005).

Several discoveries concerning DNA methylation were made first in *Arabidopsis* and were later translated to mammalian systems. For instance, the chromatin remodeling factor *DECREASE IN DNA METHYLATION 1* (*DDM1*) was first discovered in screens for *Arabidopsis* mutants with loss of centromeric methylation (Chan et al., 2005; Goll and Bestor, 2005). Only later was the mammalian ortholog LSH shown to have the same effect. A second example is the relationship between histone methylation and DNA methylation, which was initially described in fungi and *Arabidopsis* and only subsequently in mammalian systems (Chan et al., 2005; Goll and Bestor, 2005). A third example is the function of an accessory factor for Dnmt1, UHRF1. Its ortholog, VIM1/ORTH2 was first shown in plant systems to be required for the maintenance of CG DNA methylation. A key domain in this protein, the SRA domain, binds directly to methylated DNA, giving clues to its mechanism of action. These early findings paved the way for functional studies of mouse and human UHRF1 showing it to be a critical cofactor that binds to hemimethylated DNA and directly recruits the maintenance DNA methyltransferase Dnmt1 (Ooi and Bestor, 2008).

Evidence for a role of DNA methylation in human health and disease is overwhelming. Mutations in the human DNA methyltransferase gene *Dnmt3b* are the cause of ICF syndrome (immunodeficiency, centromeric instability, and facial anomalies), and mutations affecting the methyl DNA-binding domain protein MeCP2 cause Rett syndrome, a childhood neurodevelopmental disorder (Goll and Bestor, 2005). Furthermore, it is increasingly clear that epigenetic mutations, in the form of heritable hypermethylation or hypomethylation of particular tumor suppressor genes or oncogenes, are a major contributor to cancer (Jones and Baylin, 2007).

Leucine-Rich Receptor Kinases, Ion Transport, and G Protein Signaling

Studies of *Arabidopsis* also changed the direction of mammalian research in other ways, even when the prototype gene for a particular function or process may have been observed first in another model system. For example, the finding of Shaker-like potassium channels in *Arabidopsis* (Rodriguez-Navarro and Rubio, 2006) advanced research into potassium fluxes in renal (Wang, 2004) and heart (Schwartz, 2005) disease. The discovery of nitrate transporters in *Arabidopsis* (Tsay et al., 1993) led to the identification of peptide transporters in yeast and mammals. Leucine-rich serine/threonine kinase receptors were first discovered in *Arabidopsis* (Chang et al., 1992). One member of the leucine-rich receptor kinase subfamily identified in humans, LRRK2, is genetically associated with Parkinson's disease (Mata et al., 2006).

Considering the maturity of the field of heterotrimeric G protein signaling, it is hard to imagine how another model system could make an impact, but breakthroughs in G protein research in *Arabidopsis* have done just that. No other multicellular model system has a G protein repertoire as simple as that of *Arabidopsis* (Temple and Jones, 2007). Plants and animals diverged from an ancestral cell 1.6 billion years ago, suggesting that much can be learned from studying the similarities and differences in their molecular properties (Johnston et al., 2007). Indeed, comparative genomic and proteomic studies have opened up new research avenues. An excellent example is the comparison of the proteomic profiles of *Arabidopsis* (which does not have centrioles) and the single-celled alga *Chlamydomonas* (which does), yielding several new basal body proteins in humans (Li et al., 2004).

Natural Genetic Variation

The main focus of human genetics is currently the role that heritable differences play in disease susceptibility and the response to drugs. For natural genetic variation, *Arabidopsis* is arguably the best model organism available. The species grows naturally under a wide range of environmental conditions throughout much of the Northern hemisphere. Because it is self-fertile, locally adapted lines collected from the wild are naturally inbred. This in turn enables repeated phenotyping of the same genotypes under diverse controlled conditions, making *Arabidopsis* extremely well suited for studying genotype-environment interactions, a problem of direct importance to the human genetics community.

Natural alleles that affect performance in the wild have been identified for many traits, a prominent example being the *FRIGIDA* gene controlling flowering (Johanson et al., 2000). An important question, which was central for designing human association mapping studies, is whether common genetic syndromes are caused by just a few high-frequency alleles or by many rare alleles. *Arabidopsis* provides examples of both—indeed, the *FRIGIDA* work nicely showed that common and rare alleles with the same phenotypic effect can be found at the same locus.

The self-fertilizing habit of *Arabidopsis* makes genome-wide association studies extremely cost effective. Unlike human case-control studies, it is possible to genotype once and then phenotype many times under a huge variety of conditions. *Arabidopsis* now has a larger genomic polymorphism database than any other nonhuman organism. For example, a 250,000 SNP-chip for genome-wide association studies is currently being used to genotype over 1,000 wild strains (Kim et al., 2007b) (http://walnut.usc.edu/2010). Given that the extent of linkage disequilibrium is comparable to that in humans, coverage of the genome is likely better for *Arabidopsis* because of its smaller genome. Similarly, filling in between the HapMap tag-SNPs will be much more straightforward, and efforts to accomplish this are under way. The genetic variation resource can be easily complemented by whole-genome epigenomic

information. *Arabidopsis* is thus likely to lead the way in the endeavor to productively combine the most important current trends in medical research: genetic diversity and systems biology.

Diversifying Our Portfolio

In addition to the discoveries described here, it is worth mentioning some of the earlier examples of fundamental findings made first in plants that have turned out to be critical for our understanding of human biology: cells, nuclei, genes, molecular chaperones, viruses, transposable elements, programmed cell death, and gaseous hormones. As the predominant plant model system, *Arabidopsis* has followed in this tradition. It has proven to be the reference plant for translational work on agricultural improvements, and even as a relative newcomer on the "genetic model" block, it has shown its mettle in eukaryotic research, with clear examples of how *Arabidopsis* research has impacted human health. The trend will continue, and we expect that soon *Arabidopsis* will be universally recognized and appreciated as part of the diverse portfolio used in human health research.

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