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# Epigenetics of the epigenome

## Editorial overview

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Jeff is the Doris and Normal Giles Professor of Molecular Biology and Functional Genomics in the Department of Genetics at the University of Georgia. He is also a Georgia Research Alliance Eminent Scholar and department head in Genetics. His research has focused on plant genome structure and evolution for more than 30 years, particularly the involvement of transposable elements in the growth and rearrangement of nuclear genomes in the grasses. Jeff's team is now studying the mechanisms responsible for macro-rearrangements and micro-rearrangements, their impact upon gene and genome function, and the use/manipulation of this variation for the improvement of orphan cereal crops and candidate biofuel feedstocks.

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Jian-Kang Zhu's research interests are in the molecular mechanisms of abiotic stress resistance and epigenetic regulation of gene expression. In epigenetics, his group focuses on active DNA demethylation and RNA-directed DNA methylation pathways.

Not all heritable information is encoded in the sequence of DNA. Some heritable information is also controlled by an epigenetic network consisting of patterns of DNA methylation, histone modifications and histone variants, and the three-dimensional structure of chromosomes. This issue of *Current Opinion in Plant Biology* focuses on the mechanisms and functions of epigenetic regulation in plants. Plants provided the first genetic dissection of epigenetic phenomena, with the discovery of both paramutation and imprinting in the 1950s and 1960s, respectively, through study of interesting pigmentation patterns in maize. Plants have continued to provide the first entry into many basic epigenetic phenomena, such as the discovery of sense suppression in the early 1980s. Although most of these epigenetic phenomena are shared across a great range of eukaryotes, epigenetic processes may have been more easily uncovered in plants because of their very deep involvement across the whole symphony of gene regulation, chromosome function, and adaptation. Certain epigenetic features once thought to be unique to plants are now recognized to have counterparts in mammals, albeit with some differences. Whereas DNA methylation in mammals occurs primarily in the CpG sequence context, DNA methylation in plants occurs in CpG, CpHG (H is C, T, or A), and CpHH sequence contexts. Recent DNA methylome sequencing, however, has revealed considerable non-CG methylation in the embryonic stem cells of mammals. The phenomenon of RNA-directed DNA methylation has been studied since 1994 and was considered a plant-specific epigenetic pathway until a few years ago, when researchers discovered that a class of small RNAs, piRNAs, can direct DNA methylation in mammalian germ cells. Genetic and biochemical studies have established a base-excision repair pathway for active DNA demethylation in plants. Although active DNA demethylation in mammals remains a controversial topic, evidence increasingly supports DNA base-excision repair as at least one DNA demethylation mechanism in mammals. The pioneering advances in epigenetics referred to above were possible because of the lead taken by plant geneticists, and the power of the research systems that they pursue. Other recent landmark discoveries in epigenetics where plant research has led the way include the discovery of the connection of paramutation with RNA-directed DNA methylation and the discovery of small interfering RNAs (siRNAs).

Research on plant epigenetics continues to rapidly expand. This is partly the result of technological advances in profiling non-coding RNAs, genome-wide DNA methylation, and histone modification patterns. The rapid advances in plant epigenetics is also partly due to increased awareness of the important roles that epigenetic regulation may play in genome integrity and in many developmental processes, stress responses, natural variation, and even transgenerational memory of environmental challenges. Given the importance of epigenetic regulation and recent advances in understanding

its mechanisms of action, this issue of *Current Opinion in Plant Biology* is quite timely.

Histone variants and modifications can explain chromatin-based control of developmental and environmental response genes. The key roles of histone variant H2A.Z and histone H3K4 and H3K27 methylation in developmental processes, including vegetative to reproductive transition and in biotic and abiotic stresses, are reviewed by Deal and Henikoff. H3K27 trimethylation is also reviewed by Zheng and Chen, who discuss questions regarding the deposition, recognition, and removal of this mark. In addition, they examine recent evidence for the existence of a PRC1-like complex in Arabidopsis.

Comprehensive understanding of the contributions of epigenetics to eukaryotic biology will eventually require a complete (including real-time) description of all of the chromatin and DNA modifications associated with epigenetic function. The review by Schmitz and Zhang describes the powerful technologies that are now uncovering epigenetic status at the full genome scale. There is every reason to believe that this great arc of technology development will continue on its path to further empower epigenetic research.

Compared to histone variants and modifications, DNA methylation is a more stable epigenetic mark. Nevertheless, DNA demethylation can occur passively when maintenance DNA methyltransferases are absent during DNA replication, or can occur actively through the actions of a subfamily of 5-methylcytosine DNA glycosylases. The dynamic regulation of DNA methylation and demethylation is reviewed by Furner and Matzke. Locus-specific *de novo* DNA methylation in plants is largely controlled by siRNAs through the RNA-directed DNA methylation (RdDM) pathway. Zhang and Zhu examine different steps and components in RdDM, including the subnuclear locations of the various steps and the role of nascent long non-coding RNAs as scaffolds in the assembly of the RdDM effector complex. The biogenesis and chromatin function of small RNAs are further considered by Simon and Meyers. They also review recent work showing how production and mobilization of small RNAs reinforce transposon silencing in gametogenesis.

Most researchers now acknowledge the likelihood that epigenetic regulation evolved from a still very active process for the silencing of 'non-self' nucleic acids, primarily transposable elements (TEs) and viruses. Lisch and Bennetzen briefly review the current understanding of how TEs are downregulated by epigenetic processes, but mainly concentrate on how TEs are contributing to the evolution of new epigenetic regulation acting on standard nuclear genes. These authors coin the term 'zombie transposons' to cover quiescent TEs with structures that lead to the epigenetic silencing of other TEs in the same

family. Activation of these zombies by stress or as a standard process during gametogenesis and/or seed development is thus proposed to lead to the death by silencing of any potentially active members in the genome. The ability of TEs to pick up and rearrange gene fragments has also led these authors to propose that this process is the ultimate origin of miRNAs, and that the generation of candidate miRNAs by this mechanism is an ongoing process.

The tremendous level of imprinting in the endosperm of seed plants, with apparently vital impact on the development of the adjacent embryo, is discussed in the review by Bauer and Fischer. Results from studies of Arabidopsis lines with mutations in the *DEMETER* DNA demethylase gene have been particularly informative, especially in uncovering the relationships between TE defense, gene regulation, and chromatin composition.

Long non-coding RNAs are widespread in eukaryotic genomes. In addition to their role in RdDM, they can also direct histone modifications in cis and in trans. Using the *FLC* gene as an example, De Lucia and Dean describe how long non-coding RNAs may be involved in regulating histone modifications in plant development. Mayfield and colleagues also describe the study of flowering time control as a model for the investigation of epigenetic regulation, with particular emphasis on how the gene amplification associated with polyploidy provides the opportunity for the evolution of more complex (and, thus, more subtle) flowering time regulation.

Recent advances in deep sequencing and other high throughput technologies have made it possible to develop high resolution maps of epigenetic marks in many organisms. In their review, Feng and Jacobsen compare patterns of epigenetic marks in different organisms and discuss the conservation and divergence of the pathways that mediate DNA methylation and several key histone modifications marks. The heritability of epigenetic marks through mitosis or meiosis depends on the faithful maintenance or copying of the marks during DNA replication. Liu and Gong describe how the copying of epigenetic marks is coupled with DNA replication and the roles of DNA replication-related proteins in epigenetic silencing.

If environmentally induced epigenetic marks are not reset during reproduction, transgenerational epigenetic inheritance occurs. Paszkowski and Grossniklaus discuss the challenges facing this exciting and controversial topic. They point out our lack of understanding of the mechanisms distinguishing epigenetic marks that are inherited from those that are reset, and that mechanistic studies must be carried out if one wants to demonstrate transgenerational epigenetic inheritance. In his review, Richards points to the rapidly accumulating evidence for selection acting on natural epigenetic variation, thereby providing

one explanation for its mechanistic persistence across evolutionary time.

The maize research of Brink and colleagues in the 1950s on paramutation was the seminal discovery of the phenomena now termed epigenetics. Studies on paramutation continue to provide insights into epigenetic gene regulation, as discussed by Erhard and Hollick. The involvement of the siRNA biogenesis pathway in paramutation is firmly established, but these authors conclude that other required components of this process remain to be discovered.

Because of its intimate and comprehensive involvement in gene regulation, it is possible to forget that epigenetic phenomena are central to other aspects of genome structure and function. Heterochromatin, and its effects on such key genomic activities as DNA replication, and chromosome folding, are an outcome of epigenetic determination of chromatin structure. The review by Birchler

and co-authors covers the observations behind the recent synthesis that centromeres are largely epigenetic beasts that can be turned on or off by genome context.

The tremendous advances in epigenetic understanding of the past few years have made it a challenge to cover all of the significant contributions even in the most recent timeframe. The discoveries of new small RNA molecules continue to expand exponentially, and it becomes more and more likely that few if any genes will be exempt from direct or indirect epigenetic control. The potential complexity and subtlety of this regulation, and its possible sensitivity to environmental history, require integration into our understanding of plant development, evolution and adaptation. The reviews in this issue of *Current Opinion in Plant Biology* provide insights into the most important current results and issues in plant epigenetics, but there is every reason to believe that the next few years will yield an even more productive period of growth in epigenetic discovery and understanding.