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EDITORIAL

From genotype to phenotype. What do epigenetics and epigenomics tell us?

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High-throughput sequencing is becoming quicker and increasingly affordable, and as a result there has been a dramatic increase in the number of species of which the genomes have been sequenced. This is yielding large amounts of genomic information that can be used to tackle many questions in genetics and genomics from a comparative perspective: the structure and composition of genomes in relation to the environment, how speciation occurs, the processes of domestication, responses to stress and so on. However, although classical genetic analyses and the 'omic' technologies (transcriptomic, proteomic, metabolomic and so on) will continue to provide important information, new and unexpected information may also result from studying epigenetic processes (DNA methylation, histone modifications, RNA interference), which do not change the sequence of the DNA itself, but modify the way genes are expressed during development. Analyzing the large amount of data available about epigenomes (genome-wide profiling of DNA methylation and histone modifications) is a major challenge involving biologists, bioinformatics specialists and computer biologists, because there is increasing evidence of differences in epigenetic patterns between individuals (Lister *et al*., 2009), and even between different tissues and cell types. Recent research into the contribution of epigenetics to the differential regulation of gene expression, imprinting (differential gene expression depending on the parent-of-origin), gene silencing and the involvement of transposable elements (TEs) in these processes, have all shed fresh light on the relationships between genotype and phenotype. In this special issue, we provide a selection of reviews that covers epigenetic processes occurring at several different levels and in various organisms.

DNA methylation is an epigenetic mark that is often associated with histone modifications (methylation, acetylation, phosphorylation and so on), chromatin conformation and RNA interference, all of which are processes that regulate gene transcription during embryonic and subsequent development. Gibney and Nolan review the overall role of epigenetics in influencing gene expression during differentiation and development; Teixeira and Colot then summarize the effects of DNA methylation in plants, in which cytosines are methylated in all sequence contexts, whereas in animals it is mostly CGs that are methylated (Feng *et al*., 2010; Law and Jacobsen, 2010); Dambacher, Hahn and Schotta present cutting-edge research about the part played by histone lysine methylation in regulating development, and Rountree and Selker review the impact of DNA methylation on the formation of heterochromatin in *Neurospora crassa*, revealing the close interrelationships that exist between the methylation of histone H3 lysine 9 (H3K9me3) by histone methyltransferase and heterochromatin protein 1. Epigenetic differences within natural populations and between various ecotypes have been linked to variation in DNA methylation (Johannes *et al*., 2009) and even seem to be directed by small interfering RNAs that match to specific genomic regions (Zhai *et al*., 2008). Several hundred regions of the DNA of mammalian genomes have been found to be differentially methylated, with their methylated status depending on *cis*-acting factors (Schilling *et al*., 2009), suggesting that they may influence the overall phenotype. Indeed, it has been clearly shown that deficiencies in DNA methylation are deleterious and usually lead to early embryo mortality, and that any surviving unmethylated mutants exhibit developmental aberrations of progressive severity (Mathieu *et al*., 2007). This indicates that any mutation that leads to the misexpression of genes involved in epigenetic control will have a major effect throughout development and may even lead to the onset of diseases in adulthood, including some tumors.

For epigenetics to have an important role in populations, epigenetic marks and epigenetic alterations need to be handed down from parents to offspring, and so transmitted down the generations. In mammals, most epigenetic marks are erased between generations, but epigenetic reprogramming occurs early in embryogenesis, and it is now clear that this erasure is incomplete. A good example of epigenetic transmission during development and across generations is that of the 'imprinted genes'. The expression of these genes depends on their parent-of-origin and they produce their effects during embryonic development or later on in development. The mechanisms involved in this imprinting phenomenon and its evolution are reviewed by Hudson, Kulinski, Huetter and Barlow in the mouse and by Koehler and Weinhofer-Molisch in plants. The parent-of-origin expression of the imprinting genes is regulated by specific regions known as imprinting control regions (ICRs). These ICRs acquire their DNA methylation pattern in the male germline, and the paternal imprint is protected against demethylation in the paternal genome of the zygote. The methylated imprint is thus maintained throughout development (Kacem and Feil, 2009) in the somatic cell lineage. One important characteristic of ICRs is that maternally methylated ICRs can exert promoter activity on the paternal allele and sometimes silence it. This kind of interallelic talk resembles the paramutations that have been reported in plants and in the mouse, in which the two parent-of-origin alleles can influence each other's expression. These epigenetic modifications are also known to be transmitted to the offspring. Misexpression of imprinted genes has been shown to be associated with early embryonic lethality and post-natal development in mammals, and has recently also been identified in plants (Bayer *et al*., 2009). Around 100 imprinted genes

clustered in 25 genomic regions, have been identified in mice and humans. Hudson, Kulinski, Huetter and Barlow show that the different patterns of imprinted gene expression observed in embryonic tissues and extra-embryonic tissues, such as the placenta in mammals, can be explained by differences in DNA methylation and repressive histone modifications. They conclude that genes displaying imprinted expression only in extra-embryonic tissues may be regulated by different epigenetic mechanisms than genes with widespread expression. As Koehler and Weinhofer-Molisch describe, plants are known to display genomic imprinting in the endosperm, which is not restricted to this tissue but extends to tissues that contribute to the next generation. The authors then summarize the roles of histone methylation and of the polycomb group proteins. They suggest mechanisms that could explain how epigenetic marks are reprogrammed in gametes. Although this discussion clearly shows that imprinted genes have an important role in the developmental process, recent studies have also reported differential DNA methylation between alleles at nonimprinted loci in human autosomes, which seems to involve about 10% of all genes (Schilling *et al*., 2009; Zhang *et al*., 2009). Understanding the exact role of these genes is likely to be of the utmost relevance for our understanding of how genomes are regulated.

It is well known that early in female development, in mammals, one of the two X chromosomes is transcriptionally silenced, which compensates for the unequal copy number of X-linked genes in males and females. Leeb and Wutz summarize the mechanistic concepts in X inactivation that underlie this dosage compensation in mammals. Random X inactivation depends on the noncoding *Xist* RNA in the inactive X chromosome (Xi) and seems to be conserved among placental mammals, but seems to differ in other mammals. The silencing of genes on the Xi is mediated by various epigenetic factors, such as the histone variant macroH2A, which are associated with silent chromatin. Leeb and Wutz conclude that genes and nongenic sequences undergo similar epigenetic modifications on the Xi. The authors then show how the cell counts and chooses the appropriate number of X chromosomes to inactivate, how chromosome-wide gene repression is coordinated and how a stable inactive X chromosome is established. They detail the conservation and divergence of this mechanism in different mammalian species. It is not clear whether the mechanism underlying X inactivation is specific to mammal or also occurs in other species and this warrants further investigation.

DNA methylation, DNA-associated protein modifications and RNA interference, are all epigenetic processes that are closely connected to chromatin structure. In their review, Chioda and Becker summarize the role of nucleosome remodeling factors in regulating DNA accessibility within chromatin, notably during transcription initiation, and explore the impact of the newly emerging ideas, suggesting that remodeling complexes shape the epigenome during development and stem cell differentiation; Desvoyes, de la Paz Sanchez, Ramirez-Parra and Gutierrez (2010) then review the impact of nucleosome dynamics and histone modifications on cell proliferation during Arabidopsis development. Because aspects such as posttranslational modifications of histones and the constituents of nucleosomes are known for to affect DNA accessibility in genes and regulatory elements and the specification of chromosomal domains, the review focuses mainly on the less obvious effects of ATP-dependent nucleosome remodeling enzymes. These enzymes have been shown to disrupt the ionic association of DNA with histones in nucleosomes or nucleosome assembly intermediates and to endow chromatin with flexibility, allowing it to respond to environmental clues. Finding out how an organism integrates such chromatin changes into its development promises to yield new insights into genotype–environment interactions.

One important clue to the nature of epigenetic phenomena is that they seem to involve TEs. Indeed, imprinted genes often contain repeated sequences, such as TEs, and by recruiting the epigenetic machinery, these sequences could mark the ICRs defined above, thus determining the epigenetic status of the affected alleles. Moreover, epigenetic processes involving DNA methylation–demethylation, histone modifications and RNA interference, are all known to influence the expression of various TEs during development. Because TEs are known to be able to activate–deactivate various genes and to regulate host genes differentially during embryonic development, as reported in the mouse (Peaston *et al*., 2004), many changes in individual phenotypes are expected. This is consistent with reports that epigenetic processes, which often involve the decrease in DNA methylation 1 (DDM1) chromatin remodeling protein that controls TE expression, may contribute to loss of fitness in Arabidopsis and to meiotic failure in mouse spermatocytes. It is thus believed that organisms have developed defense mechanisms, mostly based on interfering RNAs as discussed by Teixeira and Colot, intended to thwart the effects of TEs. Because the epigenetic repression of TEs is relaxed in the early-developing germline, TEs may take this opportunity to transpose at a high rate and thus invade the host genome. Why then are TEs not entirely repressed in the germline? Zamudio and Bourc'his give support to the idea that this time-limited loss of repression allows the genome to detect rogue elements and force them into repression. The germline can therefore be seen as playing an insidious trick on the TEs by forcing them to reveal their existence and their capacity to injure the genome and subsequent generations. However, the alternative hypothesis that TEs simply exploit the open chromatin to transpose cannot be entirely ruled out.

By their effects modifying the genomic methylation state and changing the structure of chromatin, the environmental conditions encountered during the development and lifetime of an organism have been reported to have a major impact on the expression of various genes, including TEs, and their effects have even been observed even in subsequent generations (see Kristensen *et al*., 2009). Diets or exposure to chemicals that interfere with the DNA-methylating enzymes involved may have major effects both on normal physiology and on the manifestation of diseases such as cancers. In their review, Bollati and Baccarelli identify a number of environmental toxicants, such as metals, phytoestrogens, hydrocarbons, dioxin, biphenyls, phthalates and several classes of pesticide that can alter epigenetic states and may therefore have health-related effects. They therefore discuss the available evidence of transgenerational environmental effects, which have been clearly shown to occur in mouse and plants, but which are still contentious in human beings, even though

epigenetic effects implying repeated sequences and TEs are known to occur. We must therefore be aware that the environment during one developmental stage can have a strong impact on subsequent stages and even in adulthood. Further studies are therefore required to help decipher the mechanisms involved. Such studies will be confronted by the high level of epigenomic variation observed between individuals within populations and between different genomic regions, as reported in the review by Johnson and Tricker, which outlines the great potential and possible pitfalls of population epigenomics (Johannes *et al*., 2008; Vieira *et al*., 2009), which can be expected to provide a plentiful supply of data that will be difficult to analyze. The authors then argue that the conventional use of model species could bias the analysis and propose that epigenetic analyses should be extended to nonmodel systems, which may be more representative of biological normality.

This special issue ends with two examples of the epigenetic regulation of tissue development. Covic, Karaca and Lie summarize recent evidence that behavior and environment influence neurogenesis in the adult hippocampus through epigenetic mechanisms. It has indeed been shown that new neurons are generated in the hippocampus throughout life, and because this tissue is associated with learning, memory and emotional control, any effect of the environment is therefore of great importance for our understanding of human behavior. The authors highlight the dynamic role of DNA methylation and histone methylation through the Polycomb and Trithorax complexes. Cvekl and Mitton summarize the roles of sequence-specific DNA-binding transcription factors in the recruitment to specific chromosomal regions of chromatin remodeling enzymes, and their impact on extracellular signaling and cellular differentiation during vertebrate eye development and associated diseases. The authors show how changes in the nucleolar organization, in the expression of noncoding RNAs and in DNA methylation all contribute to regulating the development of the lens and retina. The epigenetic regulatory mechanisms involved in neurogenesis and ocular tissues are good illustrations of an exciting new field of research, which should help us to decipher the relationships between the environment and development of normal tissue through epigenetic mechanisms and also to understand diseases related to aging and to changes in the environment in terms of genome size and composition and population structure. The last review in this issue deals with the search for the epigenetic processes that underpin tumor biology, with the aim of finding new therapeutic approaches and using epigenetic patterns as prognostic and predictive biomarkers in cancer therapy. Finally, Claes, Buysschaert and Lambrechts promote pharmacoepigenomics, pointing out that DNA methyltransferases and histone deacetylase inhibitors are beginning to be accepted as potential candidates for cancer treatment. These agents may reactivate silenced tumor suppressor and apoptotic genes, as well as influencing the tumor environment.

Although classical genetic techniques and the high-throughput sequencing of genomes of various species (including invertebrates, in which DNA methylation seems to have functions different from those it has in plants and vertebrates, and which are not covered in this issue) will continue to furnish new and important knowledge about how genotype leads to phenotype, the reviews published in this special issue clearly show that we have already entered the epigenetic area. We think that it is in the fields presented above, and by means of a comparative approach involving both model and nonmodel species, that the most stimulating discoveries will be made in the future.

Conflict of interest

The author declares no conflict of interest.

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