Unexplored Potentials of Epigenetic Mechanisms of Plants and Animals—Theoretical Considerations

Istvan Seffer¹, Zoltan Nemeth¹,², Gyula Hoffmann³, Robert Matics², A. Gergely Seffer⁴ and Akos Koller²,⁵

¹Seffer-Renner Medical Clinic, Budapest, Hungary. ²Department of Pathophysiology and Gerontology, Medical School, and Szentagothai Res Centre, University of Pecs, Pecs, Hungary. ³Institute of Biology, Faculty of Sciences, University of Pecs, Pecs, Hungary. ⁴Surgery Clinic, Medical School, University of Pecs, Pecs, Hungary. ⁵Department of Physiology, New York Medical College, Valhalla NY, USA. Corresponding author email: zoltan.nemeth@aok.pte.hu

Abstract: Morphological and functional changes of cells are important for adapting to environmental changes and associated with continuous regulation of gene expressions. Genes are regulated—in part—by epigenetic mechanisms resulting in alternating patterns of gene expressions throughout life. Epigenetic changes responding to the environmental and intercellular signals can turn on/off specific genes, but do not modify the DNA sequence. Most epigenetic mechanisms are evolutionary conserved in eukaryotic organisms, and several homologs of epigenetic factors are present in plants and animals. Moreover, in vitro studies suggest that the plant cytoplasm is able to induce a nuclear reassembly of the animal cell, whereas others suggest that the ooplasm is able to induce condensation of plant chromatin. Here, we provide an overview of the main epigenetic mechanisms regulating gene expression and discuss fundamental epigenetic mechanisms and factors functioning in both plants and animals. Finally, we hypothesize that animal genome can be reprogrammed by epigenetic factors from the plant protoplast.

Keywords: epigenetic mechanisms, environmental signals, DNA methylation, histone acetylation, gene expression, reprogramming, protoplast
Epigenetics—A Brief History
In recent years, a new research field has emerged known as epigenetics, which studies the factors that influence the function of genes. The term “epigenetics” was suggested by the developmental biologist Waddington in 1942, who used this phrase as a “study of the processes by which genotype gives rise to phenotype” without changes at the level of the gene itself. However, the word “epigenetics” was used by Heinemann in the 19th century. The original concept can be traced back to Aristotle, who proposed a new theory known as epigenesis, which means to grow upon genesis, the opposite of preformation. Today, according to the most accepted definition, epigenetics is the study of alterations in gene expression without changes in the DNA sequence, hence the name epigenetics.3

One example of epigenetic changes in eukaryotic biology is the process of cellular differentiation by which a single totipotent egg cell develops into various pluripotent cell lines of the embryo, which in turn become fully differentiated cells. Epigenetics also examines the role of the environment in gene expression to determine how the environment can influence the expression of genes.4

This review, after describing some of the common epigenetic mechanisms of plant and animal cells, proposes potential epigenetic reprogramming mechanisms between plant and animal cells that have not been discussed in such reviews.

Epigenetic Regulation of the Genome
It has been well-established that DNA is organized by histones and non-histone proteins into chromatin. Approximately 146 base pairs of DNA wraps around a complex structure of eight histone proteins (octamer) to form one bead on a chain of bead-like nucleosomes connected by 80-base pair linker-DNA. Histones are responsible for protection of DNA as well as maintaining the shape and structure of a nucleosome. There are five families of histones known to date, including H1/H5, H2A, H2B, H3, and H4. Histones H2A, H2B, H3, and H4 are the core histones, while linker DNA is associated histones H1 and H5. Nucleosomes act as a physical barrier to transcription factors that bind to certain regions of DNA. However, specific acetylation can remove the positive charge on the lysine amino group that is acetylated, so that the nucleosome becomes loosened on the DNA.9

It has long been hypothesized that the linker histones H1 and H5 are essential for chromatin condensation; however, this dogma has not been supported by studies. Knockout experiments in Tetrahymena and Aspergillus nidulans showed that H1 is not essential for nuclear assembly. Moreover, H1 was found to control gene expression through activation and repression mechanisms.10,11 Each of the histones has an N-terminal tail with a specific sequence of amino acids, but the H2A also has a C-terminal tail.12 The C-terminus forms a globular docking domain that is packaged into the core. Several studies have demonstrated the importance of the histone tails for nucleosome remodeling by ATP-dependent chromatin remodeling factors.14,15

Histone N-termini undergo posttranslational modifications that alter their interaction with DNA and nuclear proteins. Such modifications include methylation, acetylation, phosphorylation, sumoylation, ubiquitination, and ADP-ribosylation.16 These modifications determine the interaction between the histone and other proteins, which may in turn regulate chromatin structure and transcription.

Among core histones, the H2A family exhibits the highest sequence divergence, resulting in the largest known number of variants. These variants, found in nearly all organisms, include H2A.Z and H2A.X.22 H2A.Z is associated with the promoters of actively transcribed genes and is also involved in the prevention of the spread of silent heterochromatin. It has also been found that the chromatin remodeling complex SWR1 catalyzes ATP-dependent exchange of H2A in the nucleosome for H2A.Z.24

In the other hand, H2AX, another histone variant contributes to the detection, signaling and repairing of DNA double-strand breaks.25 Plants exhibit a special class of H2A isoforms with an extended C-terminus comprising SPKK motifs.26 Histone H3 and H4 are nearly identical in plants and animals. For instance, only two amino acids of the 102 amino acids of histone H4 differ between pea and calf thymus.28 The linker histones are similarly found in all eukaryotes. The chromatin structure is therefore essential for both preventing of DNA and regulating gene expression, thereby preventing/enhancing
the binding of transcription factors, activators, and chromatin remodeling complexes to DNA.39

**Fundamental Epigenetic Mechanisms**

Epigenetic mechanisms are responsible for several phenomena, such as X-inactivation, genomic imprinting, and reprogramming.30,31 There are several epigenetic processes, such as methylation, acetylation, and others that modify chromatin structure.32 The main epigenetic processes are summarized in Figure 1. Generally, methylation is associated with heterochromatic gene silencing, while acetylation is associated with euchromatic gene activation.33,34

A notable exception to general rule is methylation of some lysine and arginine residues of histones that leads to gene expression.35,36 DNA and histone modifications by methylation/demethylation influence gene expression by making DNA inaccessible (by adding a methyl group to the DNA or histone tail) or accessible (by removing it) for transcription factors and other proteins. DNA methylation is implicated in fundamental processes such as genomic imprinting, X-chromosome inactivation, and in some diseases.37 In fact, during ontogenesis, these processes regulate differentiation and determine which embryonic stem cell lines should differentiate from the totipotent zygote. The main epigenetic mechanisms regulating gene expression include the modification of DNA, the modification of histone proteins, and the chromatin remodeling.

**DNA modification**

DNA methylation is a crucial epigenetic modification of the genome that involves the addition of a methyl group to the N6 position of adenine or N4 or C5 position of cytosine.38 DNA methylation is involved in regulating many cellular processes including embryonic development, chromatin structure, X-chromosome inactivation, genomic imprinting, and chromosome stability.30,31,39 This mechanism is catalyzed by DNA methyltransferases (DNMTs) that transfer a methyl group to DNA by using S-adenosyl methionine (SAM) as the methyl donor. Operation of DNMTs leads to conversion of cytosine to 5-methylcytosine, which suppresses gene expression. DNA methylation is performed by “de novo” methyltransferases that methylate previously unmethylated cytosines, while maintenance of methylation is performed by “maintenance methyltransferases”. Maintenance of methylation refers to maintaining the methylation pattern once it is established.40,41

There are some diseases associated with aberrant DNA methylation, such as hyperhomocysteinemia, characterized by a high level of homocysteine in the blood, leading to vascular inflammation.42 Metabolic disorders, such as diabetes (and obesity), have also been linked to aberrant DNA methylation;43 moreover, it is involved in neurodegenerative disorders.44 Several data suggest that mechanisms of epigenetic regulation are general among eukaryotes, and even in prokaryotes. Enzymes that catalyze the mechanisms are highly conserved among eukaryotes.45
DNMTs catalyzing DNA methylation can be divided into three different groups, including those that generate N6-methyladenine (m6A), N4-methylcytosine (m4C), and C5-methylcytosine (m5C), each widely used by prokaryotes, fungi, plants, and animals. The m6A and m4C DNMTs are found primarily in prokaryotes; however, the presence of m6A in certain fungi, algae, and several ciliates has been demonstrated. The m5C DNMTs can be found in prokaryotes and eukaryotes, with 10 conserved motifs found in the catalytic domain of all DNMTs, suggesting a common origin.

Based on sequence homology, DNMTs can be divided into at least 6 distinct classes, the DNMT1/methyltransferase 1 (MET1) class, DNMT2 class, DNMT3/domains rearranged methyltransferase (DRM) class, chromomethylases (CMT) class, MASC1/RID class, and MASC2/DIM2 class. DNMT1 was first identified in animals; however, a homolog is also found in plants. In mammals, DNMT1 is thought to be a maintenance methyltransferase, while methylation in plants is maintained by a DNMT1 homolog methyltransferase MET1. DNMT2 is the most conserved DNMT in eukaryotes that contains all the conserved methyltransferase motifs and is involved in methylation of tRNA. DNMT2 was found to have the same function in mammals and flowering plants. Interestingly, DNMT2 is also involved in histone deacetylation in Arabidopsis thaliana, a favorite model for plant biologists, suggesting that it participates in epigenetic regulation in plants. Nevertheless, very little is known regarding the function of DNMT2 in epigenetic regulation in plants and in animals. Recognition of hemimethylated DNA is catalyzed by variant in methylation (VIM) proteins in plants and ubiquitin-like, with PHD and RING finger domains 1 (UHRF1) proteins in animals.

Unlike mammalian DNMT1, members of the DNMT3 subfamily (eg, DNMT3a and DNMT3b) as de novo methyltransferases are responsible for establishing cytosine methylation patterns at unmethylated DNA. In plants, DNA methylation is established by DRM2, which is a DNMT3 homolog.

Demethylation of the DNA can take place through passive and active processes. Passive DNA demethylation occurs when cells fail to maintain their methylation state during DNA replication. Active DNA demethylation is primarily established by a small group of glycosylases, eg, repressor of silencing1 (ROS1), Demeter (DME) and Demeter-like3 (DML3) in plants, and 5-methylcytosine hydroxylases in animals, which introduce an abasic site.

Epigenetic factors involved in DNA modification found in plants and animals are summarized in Table 1. It was reported in Arabidopsis, a regulator of DNA demethylation, ID1M, is required for preventing DNA hypermethylation, whereby binding methylated DNA at chromatin sites lacking histone methylation and acetylation protects genes from silencing. In animals, active DNA demethylation occurs after a sperm enters an egg. It was recently reported that expression of unmethylated plasmids was detected in a mouse embryo <12 h after in vitro methylated plasmid injected into the zygote. The expression of methylated plasmids was delayed until the 8 cell-stage. This suggests that DNA demethylation plays a critical role in regulating development both in plants and animals.

**Histone modification**

Acetylation is catalyzed by histone acetyltransferases (HATs). Histone acetylation enhances transcription by converting the positively charged lysine residues in the N-terminal tail into neutral residues, resulting in the loosening of the bond between DNA and the histone (Fig. 1). HATs acetylate N-terminal lysines on histones H2B and H3. Nuclear HATs are classified into several families, including the GCN5 (general control non-repressed protein5)-related N-acetyltransferase (GNAT) family. A study found that one member of the three subfamilies of GNAT is present in plants, animals, and fungi, suggesting functional conservation.

Histone deacetylases (HDACs) remove acetyl groups from an N-acetyl lysine amino acid on a histone. In plants, histone deacetylase HDA2 is a homolog of the animal HDAC11. An HDAC class, designated as class 3, has been identified within the reduced potassium dependency3/histone deacetylase 1 (RPD3/HDA1) family found only in plants and animals by phylogenetic analysis.

**Chromatin remodeling**

Chromatin remodeling implies the assembly and disassembly of the nucleosomes, ATP-dependent chromatin remodeling, and modifications of histones. Nucleosome assembly factors, such as chromatin...
Table 1. Summary of DNA modifications in plants and animals.

| Epigenetic mechanism          | Factor                  | Function/comment                                                                 | Reference |
|-------------------------------|-------------------------|----------------------------------------------------------------------------------|-----------|
| Physical modifications        |                         |                                                                                  |           |
| Maintenance methylation      | MET1, VIM               | Transfer of a methyl group to DNA                                                | 55        |
|                               | DNMT1, UHRF family      | Establishment of DNA methylation patterns, recruitment of the maintenance        | 209       |
|                               |                         | Dnmt1/Met1 to hemimethylated DNA                                                 | 56,57,210 |
| De novo methylation          | DRM2                    | Dnm2 maintains CHH or asymmetrical methylation through a small interfering       | 41,211    |
|                               | DNMT3                   | RNA (siRNA)-driven signal in a process known as RNA-directed DNA methylation   |           |
| Demethylation                | DME (ROS1, DML2,3)      | Dme members have not yet been identified in animals                              | 210,212   |
|                               | DME                     |                                                                                  |           |
|                               | Gadd45a                 |                                                                                  |           |

Notes: In plants, DNA methylation commonly occurs at cytosine bases within all sequence contexts. CHH—Asymmetric CHH context, where H = A, T, or C. Abbreviations: Met1, Maintenance DNA methyltransferase1; DNMT1, DNA methyltransferase1; VIM, Variant in methylation; UHRF, Ubiquitin-like PHD and RING finger domain; DRM2, Domains rearranged methyltransferase2; DNMT3, DNA methyltransferase3; DME, Demeter; ROS1, Repressor of silencing1; DML2,3, Demeter-like2,3; Gadd45a, growth arrest and DNA damage-inducible protein 45.

assembly factor1 (CAF1) and nucleosome assembly protein1 (NAP1), facilitate transcriptional regulation through deposition of histones H3 and H4 onto DNA both in plants and animals.70 Chromatin-remodeling-enzymes are ATP-dependent and responsible for conformational changes in chromatin.71,72 The sub-units of chromatin-remodeling-complexes contain different domains (bromodomains, chromodomains, PHD fingers) that are involved in transcription. The members of the ATPase-dependent chromatin-remodeling-enzymes, for example the switch/sucrose nonfermentable2 (SWI2/SNF2), the imitation switch (ISWI), and the chromodomain-helicase-DNA-binding protein (CHD) groups, have ATPase domains that are responsible for their chromatin remodeling activity.73 Chromatin-remodeling-enzymes use nucleosomes as substrates and change positions of histone octamers and/or the topology of DNA that is wrapped around the nucleosome particles. The SWI/SNF family of chromatin-remodeling ATPases is conserved among the plants and animals; moreover, the SNF2 subfamily of the SWI/SNF complex is found in organisms from yeast to human.74 A summary of various epigenetic factors involved in histone modification and chromatin remodeling processes found in animal and plant cells are provided in Tables 2 and 3.

Homolog factors in plants and animals regulating gene expression

The order of the organs and body parts are determined genetically. Homeosis is the transformation of one body part into another arising from mutation of specific developmentally critical genes.75 Homeosis were first recognized in plants (Linnaeus, Goethe) and genetic studies on homeotic mutants of plants were carried out on Arabidopsis and Antirrhinum in the late 20th century.76 However, breakthrough discoveries were made in animals. Homeotic genes are conserved master genes that switch on early during ontogenesis and remain in a stable active or inactive state throughout life. These genes are involved in developmental patterns and sequences; for example, they are involved in determining when, where, and how body segments develop in flies.77 The proteins encoded by the Polycomb group (Pc-G) form structures similar to the heterochromatin and inactive specific genes such as Hox genes.

In animals, Pc-G and trithorax group (Tr-G) proteins are responsible for continuous activity/inactivity of homeotic genes: members of the Tr-G help to fix homeotic genes into the active state, while Pc-G proteins are in the inactive state.78 Some studies reported functional similarities between plant and animal Polycomb complexes. The Polycomb repressive complex 2 (PRC2) proteins enhancer of zeste [E(z)], extra sex combs (ESC), and suppressor of variegation [Su(z)12] of mammals are involved in repression of homeotic genes. In plants, proteins such as fertilization-independent endosperm (FIE), curly leaf swinger (CLF/SWN), multi-copy suppressor of ira (MSI), and embryonic flower2 (EMF2) form PRC2-like complexes have a very similar function: to maintain the repressive condition of plant homeotic genes.69,70 A PRC2 complex carries out trimethylation
Table 2. Summary of chromatin remodeling in plants and animals.

| Epigenetic mechanism | Factor | Function/comment | Reference |
|----------------------|--------|------------------|----------|
| Chromatin remodeling  | CAF1 (eg, FAS1,2), NAP1, MSI1, HIRA | Chromatin assembly, disassembly, in animals, HIRA functions as a chaperone of the variant histone H3.3 | 69,74,226,227 |
| SWI/SNF (eg, BRM, SYD), CHD (eg, PKL) | ISWI/ISWI (SNF2H) SWI/SNF (eg, BRM, BRG1, SWI2/SNF2, CDH (eg, CHD1-4,9, NURD) | Facilitate sliding of histone octamers on the DNA CHDs are both transcriptional repressors and activators | 228
| | | SWI/SNF complexes facilitate deacetylation of histones | 229–232 |

Abbreviations: CAF1, chromatin assembly factor1; FAS1,2, fasciata1,2; NAP1, nucleosome Assembly Protein1; MSI1, multicopy suppressor of ira1; HIRA, histone repression a factor; ISWI, imitation switch; SNF2H, sucrose nonfermenting 2 homolog; SWI/SNF, switch/sucrose nonfermentable; BRM, brahma; SYD, splayed; CHD, chromodomain-helicase-DNA-binding protein; PKL, pickle; BRG1, brahma-related gene1; SWI2/SNF2, switch2/sucrose nonfermentable2; CHD1-4,9, chromodomain-helicase-DNA-binding protein1-4,9; NURD, nucleosome-remodeling and histone deacetylase.

Table 3. Summary of histone modifications in plants and animals.

| Epigenetic mechanism | Factor | Function/comment | Reference |
|----------------------|--------|------------------|----------|
| Acetylation          | HATs (eg, GNAT, p300/CBP) | HATs not only specify histone modification, but also transcriptional function | 213–218 |
| Deacetylation        | HDAC1 (RPD3/HDA1) | RPD3/HDA1-like HDACs are found in all eukaryotic genomes | 68,219–221 |
| Methylation          | HMTs (SET domain proteins: CLF/SNF1, SWN/SNF1, MEA/SNF5) | SET domain found from yeast to human | 222,223 |
| Demethylation        | JMJC proteins (eg, KDM7B) | JHDM1 demethylates histone H3 at lysine 36; PKDM7B demethylates trimethyl H3K4 | 224,225 |

Abbreviations: HATs, histone acetyltransferases; GNAT, Gcn5-related N-acetyltransferase; p300/CREB, p300/CREB-binding protein; MYST, Named for the founding members MOZ (MYST3; MIM 601408), yeast YBF2 and SAS2, and TIP60 (HTATIP; MIM 601409); HAC1, Histone acetyltransferase1; HDAC1, Histone deacetylase1; RPD3, Reduced potassium dependency 3; HDA1, Histone deacetylase 1; HMTs, Histone methyltransferases; SET, [Su(var)3-9, E(z), Trx]; CLF/SNF1, Curly leaf/set domain group1; SWN/SNF1, Swinger/Set domain group1; MEA/SNF5, Medea/Set domain group5; SET1, [Su(var)3-9, E(z), Trx1]; ASH1, Discs absent, small, or homeotic-1; JMJC proteins, Jumonji domain-containing proteins; KDM7B, histone lysine (K) demethylase7B; JHDM1, JmjC domain-containing histone demethylase 1.
of H3Lys27, which correlates with the heterochromatic gene silencing in humans and possesses the evolutionary conserved SET domain.\textsuperscript{80,81}

The Su(var)3-9, E(z), Trx (SET) domain was first identified as a conserved sequence of three Drosophila proteins (Su(z), E(z), trithorax) and is highly conserved in all eukaryotes.\textsuperscript{82} The TrxG protein of SET domain catalyzes methylation of H3K4, which plays a role in transcription activation in both animals and plants.\textsuperscript{83–85}

The members of the SWI/SNF family, such as ATP-dependent chromatin remodeling complexes (CRCs), are highly conserved in both animals and plants.\textsuperscript{86} The ATP-dependent CRCs function depends on their ATPase and play crucial roles in regulating transcription (activation, repression), differentiation, and ontogenesis by controlling the accessibility of DNA sequences to transcription factors.\textsuperscript{87} There is a great similarity among SWI/SNF subunits, which are homologous with those in Saccharomyces cerevisiae SWI3 in mammals and plants.\textsuperscript{88} It has been demonstrated that mammalian SWI/SNF like BRG1-associated factors (BAFs) play a crucial role in the formation of embryonic toti- and pluripotent stem cells. Embryonic stem cells express a factor distinguished as esBAF, which is defined by the presence of human BAF155 genes. Mice homozygous to the null mutation of BAF155 die during the pre-implantation stage, and heterozygous mutants develop with neural tube defects.\textsuperscript{89} Mutation of an Arabidopsis homolog of BAF155, AtSWI3 leads to inhibited development at the globular stage.\textsuperscript{90,91}

The Jumonji transcription factor (Jmj) family was first identified in mouse whose members are involved in histone modification.\textsuperscript{92} It was reported that the JmjC domain containing transcription factors demethylate histones in both animals and plants. However, it was also shown that plant JmjC has both conserved and specific functions, in contrast to in mammals.\textsuperscript{93–95}

Specific markers, such as sex-determining region Y-box 2 (Sox2), octamer-binding transcription factor 4 (Oct4) and Nanog, can characterize pluripotent embryonic stem cells. As in animal cells, the plant meristematic cell state is maintained by transcription factors, including WUSCHEL (Wus), CLAVATA (Clv), and PLETHORA (Plt). A HAT complex GCN5 is essential for maintaining of root stem cell niche through the attenuation of Plt.\textsuperscript{96} In animals, the proto-oncogene c-Myc has a very similar function. In addition, it regulates the expression of GCN5 via binding to the GCN5 promoter.\textsuperscript{97}

\section*{Epigenetic Mechanisms Regulating Nuclear Reprogramming—Significance of Plasticity}

Epigenetics is strongly related to nuclear reprogramming; in fact, it can be considered as the base of genetic reprogramming. The term nuclear reprogramming is used to describe changes in gene activity that are induced naturally (fertilization) or experimentally by introducing nuclei into a new cytoplasmic environment.\textsuperscript{98} Experimentally induced nuclear reprogramming has a close link to cloning. The term clone (ancient Greek: κλώνος [klonos], meaning “twig”) had already been used since the beginning of the 20th century in reference to plants, and later to animals.\textsuperscript{99}

This can be done by removing cells from the roots of the plant and place them in a solution containing nutrients; thus, a large number of undifferentiated cells can be generated, known as the callus.\textsuperscript{100} Cells of the callus are totipotent, meaning that they have the ability to develop into any other cell type.\textsuperscript{101} Addition of plant hormones, such as auxins, cytokinins, and gibberellins to these cells results in the development of a whole plant that is genetically identical to the original plant.\textsuperscript{102}

Cloning of animals is a much more complex problem because differentiated animal cells are less susceptible to dedifferentiation. However, cloning is not only observed in plants, but also several animals (aphides, fishes, lizards, frogs, etc) can reproduce without fertilization under natural conditions, cloning themselves as a part of their natural life cycle. This means that even in animals, a type of “natural cloning” is possible, which is produced by mitosis of the germ line cells of the (female) parent.\textsuperscript{102–106}

The theory, originating from the great theoretician August Weismann (1834–1914) that cells forming tissues lose their reproductive ability and death becomes the natural part of their life cycle, persisted for a long time. The origin of this theory goes back to the end of the 19th century, when Weismann proposed the so called “germ plasma” (Keimplasma) theory, stating that germ line cells develop separately from somatic cells, thus indicating that acquired characteristics
cannot be inherited. In many animals, there are special granules containing ooplasmic determinants in the egg which are responsible for the determination of the germ line cells.

The German embryologist Wilhelm Roux (1850–1924) stated that when the first cleavage division separated the future right half of the embryo from the future left half, there would be a separation of “right” determinants from “left” determinants in the resulting blastomeres. To test the hypothesis, in 1888 Roux used two-cell frog embryos and killed one of the cells of each embryo with a hot needle. Thus, he obtained half-embryos. Based on these and theoretical deductions, the two great scientists created a long lasting, but incorrect hypothesis: according to the Roux-Weismann theory, the diversity of the cell fates is due to the segregation of nuclear determinants during cleavage divisions, so cell nuclei become different both quantitatively and qualitatively, ascribed to the loss of genetic material.

The development of nuclear transfer experiments overthrew this thesis. In the 1930s, it was examined whether genomes of terminally differentiated cells could be reprogrammed. To answer this question, the Nobel Prize Laureate German embryologist Hans Spemann proposed an experiment: differentiated cell nuclei should be transplanted into enucleated egg cells (considered science fiction at the time of the proposal). If each cell nucleus is genetically identical to the zygote, the transplanted nucleus should be able to initiate, drive, and control the development of a new organism. Unfortunately, until the early 1950s, the technical background was not available to carry out these experiments and test this idea. However, in 1952, Briggs and King successfully cloned 27 tadpoles from 104 nuclear transfers in northern leopard frogs. In 1958, John Gurdon transferred intact nuclei from somatic cells into a Xenopus oocyte and successfully cloned a frog. He stated that the nucleus of a fully differentiated cell can return to a pluripotent state. In the 1960s, he also produced frogs from gut epithelial cells, yet some scientists remained skeptical, debating the fact that gut cells were differentiated and suggested that they were primordial germ cells seated in the epithelium. Until now, these significant experiments were praised and attributed significantly to his earning of the Noble prize in 2012, whereby many independent studies showed that fully differentiated cells can regain their totipotency.

Gurdon’s experiments were the first demonstration in animals that the nucleus of a differentiated somatic cell can regain the potential to differentiate into any cell type. Additionally, regeneration experiments showed that mature cells can be transformed into other mature cells without going through an intermediate pluripotent state. The conversion of one cell to another is termed metaplasia and includes either conversions between stem cells or direct conversion of differentiated cells, respectively. Transdifferentiation (also known as lineage reprogramming) is a type of metaplasia defined as irreversible conversion of already differentiated cell to another cell type, resulting in the loss of one phenotype and the gain of another. For transdifferentiation, lens regeneration, also known as Wolffian regeneration (Wolff, 1895), was demonstrated as well as metaplasia liver-to-pancreas metaplasia. Also in the liver, for a previous study demonstrated transdifferentiation by converting hepatocytes into bile duct cells. It has recently been found that using ectopic transcription factors, adult dermal fibroblasts can be converted into neural progenitor cell-like cells (iNPCs) with similar properties as primary NPCS.

In 1996, the doctrine that the genetic material of fully differentiated cells is no longer able to produce an adult organism was finally disproved, when Scottish scientists, including the biologist Ian Wilmut, cloned a lamb successfully at the Roslin Institute using adult mammary epithelial cells incubated in depleted serum to “synchronize” to the mitotically “slow” oocyte, from a mature ewe as nucleus donor, and was transplanted to an enucleated oocyte. The cloning was easily verified because the phenotype and genotype of the cloned offspring could be clearly distinguished from the foster mother’s characters. The difficulty in these procedures was cleared by the fact that only 29 from the 270 nuclear transfers resulted in embryos, and just one survived. However, the only surviving sheep, Dolly, was able to produce healthy offspring, including Bonnie. Later, an entire series of mammals were successfully cloned. However, there are many negative aspects of cloning, including low rates and regulation problems. Cloning is very inefficient since most clones die soon after implantation. Even clones that survive...
often have serious abnormalities (e.g., increase of body weight, kidney hypertrophy), mutations, and shortened life spans, likely a corollary of the age of somatic cells used for cloning.\cite{123,125-127}

An important question arises: can a stem cell be created from a somatic cell without the need for human eggs? Two Japanese researchers, Takahashi and Yamanaka, demonstrated that ESC-like cells could be induced by some transcription factors, including Sox2, Oct4, Kruppel-like factor 4 (Klf4), and c-myc oncogene (c-Myc) pluripotency factors (also known as Yamanaka factors).\cite{128} Nuclear reprogramming using transcription factors may resolve the ethical problems related to embryonic stem cells. This method would enable development of pluripotent stem cell-based regenerative medicine. However, inducing of iPSC is very complicated and the risk of obtaining undesired cells indicates that further studies should be conducted before this method can be widely applied.\cite{129}

The importance of the discovery by Gurdon\cite{130} that specialization of cells is reversible and by Shinya Yamanaka\cite{128} that intact mature cells can be reprogrammed to become immature stem cells is acclaimed by award of Nobel Prize in Physiology or Medicine in 2012. Notably, there is a great difference in the cellular plasticity of plants and animals. Cellular plasticity is the ability of cells to change their structure or function to become a different type of cell, as we understand today, depending on the epigenetic regulation of gene expression (Fig. 2). Plasticity of plant cells to transdifferentiate into various types of cells is much higher than that of animal cells, which implies a much “looser” chromatin structure. This, however, should not be interpreted that the chromatin structure is less complex or that it is more complicated to regulate.\cite{131,132} Further in vitro epigenetic experiments and in vivo experiments, such as xenotransplantation, may reveal this phenomenon. Based on experimental results, it may be possible to reprogram a fully differentiated animal cell nucleus using a recipient plant protoplast, a hypothesis which should be verified by future research.

**Conserved Epigenetic Mechanisms in Cells of Plants and Animals**

The functional parallels between epigenetic elements of plant and animal development suggest that a high congruence in the epigenetic mechanisms is present in plants and animals. It should be mentioned, however, that although there is a high conservation of homeotic genes, the role of homeotic genes is dramatically different in the two groups.

In animals, the expression pattern of some ‘classical’ homeotic genes forming gene clusters is the basis for the concept “zootype”, which means that all animal phyla shared a particular pattern of gene expression. In plants, these genes are not homologous to “classical” Hox genes, suggesting that the functions of homeotic genes developed independently in the evolution of plants and animals.\cite{133,134} Comparing epigenetic patterns at the molecular level of plants and animals shows that they possess similar patterns, which are more pronounced at the molecular level than at the phenomenological level. Both taxons use the same processes for epigenetic regulation, and sometimes surprising similarities are present with respect to epigenetic factors. Several examples of proteomic analysis show that a homologous transcription factor present in one group can substitute for another that...
is absent.\textsuperscript{93–95} Some experiments have also demonstrated that the two distant epigenetic systems may be congruent to some extent.\textsuperscript{135,136}

Although several data suggest that the epigenetic regulation among plants and animals appears to be similar, an increasing amount of recent data has shown that there are many differences between the two groups, necessitating further studies.\textsuperscript{131,137}

**RNA Epigenetics**

It has been revealed that up to 90\% of eukaryotic genome is transcribed, but only 1\%–2\% of these transcripts encode for proteins, while the vast majority are transcribed as non-coding RNAs (ncRNAs). ncRNAs such as micro RNAs (miRNAs) are evolutionarily conserved, approximately 21 nucleotides in length, and play crucial role in development, stress responses, and chromatin states. RNA epigenetics also shows some similarities between animals and plants. In animals, such as humans, miRNAs are synthesized as single-stranded RNAs and cleaved by the RNAseIII enzymes Drosha and Dicer, producing precursor microRNAs (pre-miRNAs) and finally miRNA/miRNA duplexes.\textsuperscript{138} In plants, Dicer-like1 (DCL1) enzymes carry out these processes.\textsuperscript{139} In both plants and animals, miRNAs post-transcriptionally regulate gene expression via interactions with their target mRNAs. A major difference between plant and animal microRNA is observed for target recognition. Animal miRNAs repress gene expression by mediating translational attenuation, while nearly all plant miRNAs regulate their targets by directing mRNA cleavage at single sites in the coding regions.\textsuperscript{140} It has been demonstrated that miRNAs can also cause histone modification\textsuperscript{141} and direct DNA methylation.\textsuperscript{142,143} Interestingly, a recent study revealed that miRNAs of digested plants are present in the serum of healthy human.\textsuperscript{144}

To support the cross-kingdom similarity of miRNAs with regard to epigenetic regulation of the genome, Vaucheret and Chupeau demonstrated in a recently study that ingested plant small RNAs directly influence gene expression in animals.\textsuperscript{145}

**Genomic imprinting**

Genomic imprinting is an epigenetic process by which certain genes are expressed in a sex-dependent manner.\textsuperscript{146} It includes DNA and histone modification processes.\textsuperscript{147,148} Genomic imprinting has independently evolved in flowering plants and mammals;\textsuperscript{148,149} however, both in plants and animals, imprinting occurs in embryo-nourishing tissues, such as the placenta and the endosperm. Imprinted gene expression results from the sex-specific methylation of imprinted control regions (ICRs), such as differentially methylated regions (DMRs) in the parental germ lines both in plants and mammals.\textsuperscript{150,151} Imprinting is carried out by DNA methylation and Polycomb group-mediated trimethylation of histone H3 at lysine 27 (H3K27me3) in mammals\textsuperscript{152,153} as well as in plants.\textsuperscript{154–156} However, control of imprinting differs between plants and animals.\textsuperscript{157}

**Role of Microenvironment in Cell Fate, Differentiation, and Dedifferentiation**

In addition to epigenetic factors inside the cell, the fate of cell lineage and differentiation require continuous communications between the microenvironment of the cell, ie, extrinsic factors, extracellular matrix, and signals from neighboring cells, and the cell itself.\textsuperscript{158–160} Interactions between cells, physical conditions, and mechanical forces are also important for cell fate decision and differentiation. An interesting experiment modeled the surface geometric pattern, which affects the development of stem cells. According to this study, the shape of cells increases compressive forces in the cytoskeleton with the result that most of the flower-shaped cells form fat tissue, while star-shaped cells form bone tissue.\textsuperscript{161}

In a previous experiment, the human ear was successfully grown on the back of a mouse using bovine chondrocytes with a human ear-shaped degradable polymer as a scaffold, which served as a geometric signal.\textsuperscript{162} Changes in the environment may also affect differentiated cells. When a differentiated cell nucleus is transferred into a previously activated enucleated egg cell, genetic reprogramming is taking place. It is important to note that reprogramming is not one-sided, since when a cell nucleus is located in an atypical environment, the prevailing conditions exert inductive signals. This occurs when fully differentiated plant cells undergo cell wall degradation generating protoplasts which are totipotent.\textsuperscript{163} In vitro experiments suggest that cell shape can influence cell fate determination of mesenchymal stem
cells between chondrogenic and smooth muscle cell lineages through cell adhesion molecules-mediated pathways.\textsuperscript{164} Thus, extracellular stimuli, adhesion, and cell shape properties are critical determinants of cell fate and differentiation.

Epigenetic states of the cell can be modified by nutrition, behavior, stress, physical activity, and infections.\textsuperscript{165–167} It has been established that early stress effects can elicit changes in adult gene expression through epigenetic processes. Additionally, maternal stress can determine the gene expression pattern in the adult. Weaver et al. found that increased pup licking and grooming (LG) and arched-back nursing (ABN) by rat mothers altered the offspring epigenome at the glucocorticoid receptor (GR) gene promoter in the hippocampus.\textsuperscript{168}

In addition, a plethora of examples in plants demonstrates the importance of changes in gene expression through epigenetic regulation in response to stress adaptation.\textsuperscript{169–171} Additionally, a convincing example of adaptation to temperature stress by epigenetic regulation is the vernalization in plants growing at high altitudes.\textsuperscript{172} It has been revealed that activity of flowering locus (FLC) gene having a principal role in vernalization response state is controlled by DNA methylation, which allows the mitotically stable inheritance of the vernalized plant.\textsuperscript{173,174}

In animals, dietary supplements such as vitamins can also influence epigenetic processes by affecting enzymes that regulate methylation\textsuperscript{175} or by regulating methyl-group transfer.\textsuperscript{176} These effects influence the development of diseases, such as obesity.\textsuperscript{177,178} Lack of folic acid has been shown to be associated with genomic hypomethylation\textsuperscript{179} and neural tube defects.\textsuperscript{180} Physical exercise can also influence epigenetic mechanisms, as reviewed by number of papers.\textsuperscript{181,182} It has been revealed that physical activity may affect epigenetic regulation of tumor suppressor genes contributing to cancer survival.\textsuperscript{183,184} Environmental exposure-induced abnormal epigenetic processes have been observed in many types of human\textsuperscript{185–187} and plant\textsuperscript{167} tumors. It is also important to note that miRNAs acting as tumor suppressor genes are involved in various stages of carcinogenesis.\textsuperscript{188,189} Epigenetic upregulation of suppressor miRNAs, nutritional factors, particularly vitamins, such as vitamin A,\textsuperscript{190,191} vitamin D,\textsuperscript{192} vitamin E,\textsuperscript{193} and folate\textsuperscript{194} have been shown to prevent carcinogenesis.

**Interplay between Epigenetic Mechanisms of Plants and Animals—**

**In Vitro Chromosome Condensation and Nuclear/Nucleosome Assembly**

Successful xeno-transplantation or xeno-cloning, the transplantation of cells, tissues, or organs from one species to another, has been well-documented in replication and division. For instance, DNA transcription and division was observed in human nuclei, when they were injected into amphibian oocytes.\textsuperscript{195,196} The same phenomenon has not been documented between plants and animals. However, nuclear and chromatin assembly studies may deepen our understanding how to successfully conduct xeno-cloning between plant and animal.

As we described above, many transcription factors connected to the regulation of genes by rendering the chromatin state as active or silent are largely conserved in plants and animals. The ability of these transcription factors to access their binding sites depends on the structure of cellular chromatin.\textsuperscript{132,197,198} Cell shape can influence cell fate determination; therefore, cellular chromatin can be changed by the cell’s microenvironment.

In a previous study, nuclei from carrot were injected into maturing Xenopus oocyte as a recipient.\textsuperscript{199} In the control experiment, an immature oocyte was used. Prematurely condensed nuclei with premature chromosome condensation was observed after introduction of either Xenopus brain nuclei or carrot protoplast nuclei into an in vitro matured X. laevis egg immediately after germinal vesicle breakdown (GVBD). No chromosome condensation was observed after introduction of either Xenopus brain nuclei or carrot protoplast nuclei into Xenopus oocytes prior to GVBD.\textsuperscript{199} These findings suggest that chromosome condensation is restricted to mature oocytes that have undergone GVBD and that transplanted plant nuclei into Xenopus oocyte continues RNA synthesis, but this phenomenon was not observed when Xenopus somatic nuclei were injected into Xenopus oocytes. Breakdown of the nuclear membrane for both the plant and Xenopus nucleus by Xenopus cytoplasm
factors was also detected, suggesting that there is conservation between plants and animals regarding the enzymes involved in nuclear breakdown. However, it is possible the some nuclear damage also occurred during these procedures.

**Plant Cytoplasm and Animal Chromatin**

In vitro experimental evidence suggests that the plant cytoplasm is able to induce nuclear reassembly of the animal cell. For example, it was reported that carrot cytosol extract reassembled nuclear structure around a demembranated sperm chromatin from X. laevis. In this experiment, demembranated sperm cells and membrane vesicle purified from X. laevis was introduced into plant cell cytosol extract from carrot, which supplied an ATP-regenerating system. Immediately after introduction, the demembranated sperm chromatin was in a long, thin, and highly condensed form and strongly stained with 4’,6-diamidino-2-phenylindole (DAPI). Incubation at a specific temperature demembranated by lysolecithin sperm exhibited a series of structural and morphological changes including elongation, swelling, decondensation, changing to a round shape, and a nucleus-like structure, finally acquiring a continuous double-layered nuclear envelop with nuclear pores. After a long incubation, the newly assembled nuclei showed characteristics typical of normal nuclei. In the control, which contained DNase buffer, this phenomenon was not observed. Additionally, remodeling of the demembranated sperm chromatin based on the appearance of a typical DNA ladder after electrophoresis. Positive control freezing and thawing mouse liver nuclei showed a typical DNA ladder; as a negative control, lane 1 was loaded with sperm chromatin in DNase buffer. Using micrococcal nuclease did not result in DNA ladder in sperm, but a typical DNA ladder appeared in the carrot cell extract after micrococcal nuclease treatment, indicating that remodeling had occurred in this cell-free system. However, whether advanced structures developed, such as solenoids, remains unresolved.

Similarly, using a cell-free system purified from Nicotiana tabacum ovules and demembranated X. laevis sperm, chromatin decondensation and nuclear membrane assembly were observed. Demembranation was obtained in the same manner as in the study described above. In both cases, micrococcal nuclease digestion was used to verify nucleosome formation. Because Xenopus sperm is deficient in H1 histones, exposure to micrococcal nuclease leads to heterogeneous distribution of DNA fragment sizes. When Xenopus sperm nuclei were incubated with Nicotiana ovule extracts, the chromatin proteins could be replaced by histones derived from Nicotiana ovules, resulting in remodeling of the chromatin structure.

In both cases, nuclear remodeling and nucleosome assembly were observed, suggesting that transcription factors and/or cyclin-cdk complexes originating from the plant cytoplasm may contribute to the induction of nuclear reconstitution and chromatin formation. However, complex chromatin structures, such as solenoids, were not observed and no mitosis was detected.

**Animal Cytoplasm and Plant Chromatin**

A similar condition was applied when genetic reprogramming was carried out between an algae and an amphibian. In this experiment, chromosomes from the algae Crythecodium cohnii were incubated in cytoplasmic extracts of unfertilized X. laevis oocytes or C. cohnii cell extracts. Introduction in cell-free extract from X. laevis resulted in chromosome decondensation and recondensation, nuclear membrane formation, and nuclear reconstitution. The newly assembled nuclei were morphologically different from the normal algae nuclei. Electron micrographs showed that the nuclear envelope of C. cohnii was discontinuous. However, the reconstituted nuclei possessed a normal membrane with nuclear pores which was morphologically indistinguishable from that of normal higher eukaryotic interphase nuclei. In contrast to the highly condensed chromosomes attached to the dinoflagellate C. cohnii nuclear envelope, the chromatin in the newly assembled nuclei dispersed uniformly, similar to that of typical higher eukaryotic interphase nuclei. In addition, there was no nuclear assembly detected when C. cohnii chromosomes were introduced into cell-free extract from C. cohnii.

These experiments clearly showed that plants and animals can influence each other through their cytoplasm and show that induction of purified DNA/chromosomes with cell-free extract from other species can lead to nuclear and nucleosome/chromatin assembly. However, these results do not preclude the mechanical/chemical microenvironmental effects on chromatin caused by the enucleation and
nuclear transfer. In addition, each described only nuclear and nucleosome assembly as a result of purified chromosome induction with cell-free extracts, which is not extraordinary. Furthermore, in vitro nuclear assembly is independent of nucleosome/chromatin assembly. Early experiments demonstrated that cell-free extracts derived from species belonging to an amphibian class could induce formation of a nuclear envelope, chromatin decondensation, initiation of DNA synthesis, and chromosome condensation in sperm nuclei of X. laevis without membranes. The experiments described here only revealed changes in the morphology of chromatins, but not changes in DNA synthesis and mitosis.

Unicellular algae dinoflagellata C. cohnii lacks histones, which may explain why nuclear assembly did not occur when purified chromosomes from C. cohnii were introduced into cell-free extract from C. cohnii. In dinoflagellata, only three proteins possess similar biochemical traits as H4 in higher eukaryotes. Other experiments demonstrated that cytoplasm and purified chromosomes isolated from plant and from animal can induce chromatin assembly via cytoplasm factors involved in histone protein synthesis. The Xenopus egg extract possesses two histone variants, histone H2A. X and histone B4, which correspond to H2A and H1 histones found in eukaryotic somatic cells. In the experiments, the Xenopus egg was arrested in metaphase, indicating that full components or factors are necessary for chromatin decondensation and recondensation during nuclear assembly. However, the reasons for DNA replication failure remain unclear. However, it has already been reported that in animal cells, factors involved in chromosome condensation are associated with mitosis and meiosis.

**A Novel Hypothesis**

Based on the studies described above, we can hypothesize that the donor nucleus from an animal cell can reprogram the cell fate and develop into a special animal cell—“green cell”—through epigenetic mechanisms and factors of the plant protoplast. Furthermore, it can be hypothesized that external stresses, such as cell wall/membrane removal and enucleation, elicit protoplast induction/activation, resulting in the release of nuclear transcriptional regulators, thereby influencing chromatin states of the transferred nucleus. In Figure 3, a hypothetical experiment is described, in which one can transfer an animal nucleus to an enucleated plant cell, ie, protoplast, to reprogram, the donor nucleus, taking over the control of its development into differentiated animal cells. Thus, here we hypothesize that it is possible to reprogram a fully differentiated animal cell nucleus by transferring the nucleus to an enucleated protoplast (Fig. 3).

**Conclusions and Future Perspectives**

It is known that every cell in an adult individual, either animal or plant, possess a complete set of genes with genetic and biochemical potential, and under appropriate conditions these cells are able to dedifferentiate. However, only plants have the ability to regenerate complete individuals from one single isolated somatic cell. Therefore, plants have higher dedifferentiation plasticity and capacity than animals, and utilizing these features of plants may create new avenues for research and treatment of diseases. The fully differentiated plant cells can be isolated from the original tissue by removing the cell wall, resulting in protoplasts, in which repressed genes reactivate and encode molecules needed for initiation of the developmental processes. Several studies have shown that plants...
and animals use conserved epigenetic mechanisms to regulate gene expression, but many different enzymes catalyze the same mechanisms.\(^{137}\)

Thus, the main question to be answered in the future is why is complete regeneration is possible in plants, but not in animals. One possibility is that the epigenetic apparatus of plants is able to “open up”, whereas that of the animals cannot, due to its more “rigid” chromatin structure preventing the reactivation of repressed regions. However, it remains unclear whether plants have less “rigid” chromatin structure than animals or if they can utilize their epigenetic apparatus more efficiently for gene reactivation. These exciting issues need to be solved by future studies. As a further possibility for utilizing epigenetic mechanisms, more efficient methods can be designed to treat diseases that are currently incurable, such as the vast majority of cancers or neural disorders, such as Parkinson’s and Alzheimer diseases. However, diet, nutrition, and exercise also influence or control epigenetic mechanisms, and these may be used better to treat diseases such as obesity and cancer. In other areas, such as agriculture, preventing of crops from infections, or enhancing plants to adapt to stress and climate change, modification of epigenetic mechanisms could also be a target for future investigations.

In conclusion, an increased understanding of the details of epigenetic regulation of gene’s function and the use of more signaling models for detecting factors involved in regulating epigenetic processes may provide the potential to generate reprogrammed pluripotent or totipotent cells without the use of cancer genes or egg cells. These developments will help to design better treatments for human diseases by using the power of epigenetic factors and mechanisms.

**Author Contributions**

Wrote the first draft of the manuscript: IS, ZN, AK.
Contributed to the writing of the manuscript: IS, ZN, GH, RM, GS, AK. Agree with manuscript results and conclusions: IS, ZN, GH, RM, GS, AK. Jointly developed the structure and arguments for the paper: IS, ZN, GH, RM, GS, AK. Made critical revisions and approved final version: IS, ZN, GH, RM, GS, AK. All authors reviewed and approved of the final manuscript.

**Funding**

Supported by: SROP-4.2.2.A-11/1/KOV-2012-0024 SROP-4.2.2.A-11/1/KOV-2012-0017, Nat. Sci. Res. Fund.-OTKA K7159 and American Heart Association Founders Aff., 0555897T.

**Acknowledgment**

We thank Tibor A. Rauch for critical reading of the manuscript.

**Competing Interests**

Author(s) disclose no potential conflicts of interest.

**Disclosures and Ethics**

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

**References**

1. Jablonka E, Lammi E. Commentary: The epigenotype—a dynamic network view of development. *Int J Epidemiol*. 2012;41(1):16–20.
2. Hurd PJ. The era of epigenetics. *Brief Funct Genomics*. 2010;9(5–6):425–8.
3. Wu Ct, Morris JR. Genes, genetics, and epigenetics: a correspondence. *Science*. 2001;293(5532):1103–5.
4. Cortessis VK, Thomas DC, Levine AJ, et al. Environmental epigenetics: prospects for studying epigenetic mediation of exposure-response relationships. *Hum Genet*. 2012;131(10):1565–89.
5. Fischle W, Wang Y, Allis CD. Histone and chromatin cross-talk. *Curr Opin Cell Biol*. 2003;15(2):172–83.
6. Behe MJ. Histone deletion mutants challenge the molecular clock hypothesis. *Trends Biochem Sci*. 1990;15(10):374–6.
7. Wolff A. Regulation of Chromatin Structure and Function. Austin, TX: RG Landes; 1994.
8. Nelson DL, Cox MM, Lehninger AL. *Lehninger Principles of Biochemistry*. New York, NY: Freeman; 2005.
9. Goodsell DS. The molecular perspective: histone deacetylase. *Oncologist*. 2003;8(4):389–91.
10. Shen X, Gorovsky MA. Linker histone H1 regulates specific gene expression but not global transcription in vivo. *Cell*. 1996;86(3):475–83.
11. Ramón A, Muro-Pastor Ml, Scorzocchio C, Gonzalez R. Deletion of the unique gene encoding a typical histone H1 has no apparent phenotype in Aspergillus nidulans. *Mol Microbiol*. 2000;35(1):223–33.
Cross reprogramming between plant and animal cells: the green cell

12. Biswas M, Voltz K, Smith JC, Langowski J. Role of histone tails in structural stability of the nucleosome. *PLoS Comput Biol*. 2011;7(12):e1002279.

13. Wang Y, Aristizabal MJ, Ryan C, Krogan NJ, Kobor MS. Key functional regions in the histone variant H2A.Z C-terminal docking domain. *Mol Cell Biol*. 2011;31(18):3871–84.

14. Georgept PT, Tsukiyama T, Wu C. Role of histone tails in nucleosome remodelling by Drosophila NURF. *EMBO J*. 1997;16(15):4717–26.

15. Clapier CR, Länsjö G, Corona DF, Becker PB, Nightingale KP. Critical role for the histone H4N terminus in nucleosome remodelling by ISWI. *Mol Cell Biol*. 2001;21(3):875–83.

16. Bird A. DNA methylation patterns and epigenetic memory. *Genes Dev.* 2002;16(1):6–21.

17. Shahbazian MD, Grunstein M. Functions of site-specific histone acetylation and deacetylation. *Annu Rev Biochem*. 2007;76:75–100.

18. Loury R, Sassone-Corsi P. Histone phosphorylation: how to proceed. *Methods*. 2003;31(1):40–8.

19. Nathan D, Sterner DE, Berger SL. Histone modifications: Now summoning the genome. *EMBO J*. 2004;303(5658):644–9.

20. Cao J, Yan Q. Histone ubiquitination and deubiquitination in transcription, DNA damage response, and cancer. *Front Oncol*. 2012;2:26.

21. Martínez-Zamudio R, Ha HC. Histone ADP-ribosylation facilitates gene transcription by directly remodelling nucleosomes. *Mol Cell Biol*. 2012;32(12):2490–502.

22. Talbert PB, Henikoff S. Histone variants—ancient wrap artists of the genome. *Nat Rev Mol Cell Biol*. 2010;11(4):264–75.

23. Guillette B, Bataille AR, Gévry N, et al. Variant histone H2A.Z is globally localized to the promoters of inactive yeast genes and regulates nucleosome positioning. *PLoS Biol*. 2005;3(12):e384.

24. Wu WH, Alami S, Luk E, et al. Scc2 is a widely conserved H2A.Z-binding module essential for ATP-dependent histone exchange. *Nat Struct Mol Biol*. 2005;12(12):1064–71.

25. Chen WT, Alpert A, Leiter C, Gong F, Jackson SP, Miller KM. Systematic identification of functional residues in mammalian histone H2AX. *Mol Cell Biol*. 2013;33(1):111–26.

26. Rodrigues Jde A, Brandt WF, von Holt C. The amino acid sequence of wheat histone H2A(1): a core histone with a C-terminal extension. *Eur J Biochem*. 1985;150(3):499–505.

27. Yi H, Sardesi N, Fujinuma T, Chan CW, Veena, Gelvin SB. Constitutive expression exposes functional redundancy between the Arabidopsis histone H2A gene HTA1 and other H2A gene family members. *Plant Cell*. 2006;18(7):1575–89.

28. DeLange RJ, Farnbrough DM, Smith EL, Bonner J. Calf and pea histone IV-A. 389(6649):349–52.

29.坻田 DIR, D貳湖 D, 羽目 D, et al. Solving the Dnmt2 enigma. *EMBO J*. 2005;70(5):550–8.

30. Rogers SD, Rogers ME, Saunders G, Holt G. Isolation of mutants sensitive to 2-aminopurine and alkylating agents and evidence for the role of DNA methylation in Penicillium chrysogenum. *Curr Genet*. 1986;10(7):557–60.

31. Bharat S, Cheng X, Klimaszewski S, et al. The DNA (cytosine-5) methyltransferase methyltransferase. *Nucleic Acids Res*. 1994;22(1):1–10.

32. Posfai J, Bhagwat AS, Péfsi G, Roberts RJ. Predictive motifs derived from cytosine methylation. *Nucleic Acids Res.* 1989;17(7):2421–35.

33. Chen T, Li E. Structure and function of eukaryotic DNA methyltransferases. *Curr Top Dev Biol*. 2004;60:55–89.

34. Bartee L, Bender J. Two Arabidopsis methylation-deficiency mutations confer only partial effects on a methylated endogenous gene family. *Mol Biol Cell*. 2001;29(1):2127–34.

35. Ding F, Chaillet JR. In vivo stabilization of the Dnmt1 (cytosine-5) DNA methyltransferase AtDnmt2 associates with histone deacetylase AtHD2s activity. *Plant Mol Biol*. 2003;54:393–403.

36. He XJ, Chen T, Zhu JK. Regulation and function of DNA methylation in plants and animals. *Cell Res*. 2011;7(12):1649–51.

37. Paulsen M, Ferguson-Smith AC. DNA methylation in genomic imprinting, development, and disease. *J Pathol*. 2001;195(1):97–110.

38. Ponger L, Li WH. Evolutionary diversification of DNA methyltransferases in eukaryotic genomes. *Mol Biol Evol*. 2005;22(4):1119–28.

39. Robertson KD. DNA methylation and human disease. *Nat Rev Genet*. 2005;6(8):597–610.

40. Giannino D, Mele G, Cozza R, et al. Isolation and characterization of a maintenance DNA-methyltransferase gene from peach (Prunus persica [L.] Batsch): transcript localization in vegetative and reproductive meristems of three buds. *J Exp Bot*. 2005;54(393):2623–33.

41. Okano M, Bell DW, Haber DA, Li E. DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. *Cell*. 1999;99(3):247–57.

42. Jamaluddin MS, Yang X, Wang H. Hyperhomocysteinemia, DNA methylation and vascular disease. *Clin Chem Lab Med*. 2007;45(12):1660–6.
65. Qian W, Miki D, Zhang H, et al. A histone acetyltransferase regulates active DNA demethylation in Arabidopsis. Science. 2012;336(6087):1445–8.
66. Reik W, Dean W, Walter J. Epigenetic reprogramming in mammalian development. Science. 2001;293(5533):1089–93.
67. Zhang P, Su L, Wang Z, et al. The involvement of 5-hydroxymethylcytosine in active DNA demethylation in mice. Biol Reprod. 2012;86(4):104.
68. Pandey R, Muller A, Napoli CA, et al. Analysis of histone acetyltransferase and histone deacetylases families of Arabidopsis thaliana suggests functional diversification of chromatin modification among multicellular eukaryotes. Nucleic Acids Res. 2002;30(23):5036–55.
69. Shen WH, Xu L. Chromatin remodeling in stem cell maintenance in Arabidopsis thaliana. Mol Plant. 2009;2(4):600–9.
70. Enzer V, Gruissem W, Hennig L. Control of trichome branching by chromatin assembly factor-1. BMC Plant Biol. 2008;8:54.
71. Li E, Beard C, Jaenisch R. Role for DNA methylation in genomic imprinting. Nature. 1993;366(6453):362–5.
72. Sudarsanam P, Winston F. The Swi/Snf family nucleosome-remodeling complexes and transcriptional control. Trends Genet. 2000;16(8):345–51.
73. Saladi SV, de la Serna IL. ATP dependent chromatin remodeling enzymes in embryonic stem cells. Stem Cell Rev. 2010;6(1):62–73.
74. Kaya H, Shibahara KI, Taoka KI, Iwabuchi M, Stillman B, Araki T. FASCIATA genes for chromatin assembly factor-1 in arabidopsis maintain the cellular organization of apical meristems. Cell. 2001;104(1):131–42.
75. Akam M. Hox genes, homeosis and the evolution of segment identity: no need for hopeless monsters. Int J Dev Biol. 1998;42(3):445–51.
76. Weigel D, Meyerowitz EM. The ABCs of floral homeotic genes. Cell. 1994;78(2):203–9.
77. Gehring WJ, Hiromi Y. Homeotic genes and the homeobox. Annu Rev Genet. 1986;20:147–73.
78. Kennison JA. The Polycomb and trithorax group proteins of Drosophila melanogaster. Mol Cell Biol. 2000;20:147–73.
79. Rea S, Eisenhaber F, O’Carroll D, et al. Regulation of chromatin structure by site-specific histone H3 methyltransferases. Nature. 2000;406(6796):593–9.
80. Johnson CD, Bynum TE. Hypocacemia as a complication of jejunoileal bypass for morbid obesity. South Med J. 1976;69(5):616–8.
81. Alvarez-Venegas R, Pien S, Gasteck M, Grossniklaus U. FASCIATA genes for chromatin assembly factor-1 in arabidopsis maintain the cellular organization of apical meristems. Cell. 2001;104(1):131–42.
82. Barski A, Cuddapah S, Cui K, et al. High-resolution profiling of histone modification in the human genome. Cell. 2007;129(4):823–37.
83. Rea S, Eisenhaber F, O’Carroll D, et al. Regulation of chromatin structure by site-specific histone H3 methyltransferases. Nature. 2000;406(6796):593–9.
84. Aluminum-Venegas R, Pien S, Sadder M, Witmer X, Grossniklaus U. Polycomb group and trithorax group proteins in Arabidopsis. Biochim Biophys Acta. 2007;1769(5–6):375–82.
85. Bezhanis W, Winter C, Hershman S, et al. Uniqued, shared, and redundant roles for the Arabidopsis SWI/SNF chromatin remodeling ATPases BRAHMA and SPLAYED. Plant Cell. 2007;19(2):403–16.
86. Hargreaves DC, Crabtree GR. ATP-dependent chromatin remodeling: genetics, genomics and mechanisms. Cell Res. 2011;21(3):396–420.
87. Zhou C, Miki B, Wu K. CHD2, a member of the SWI3 gene family, is a global regulator in Arabidopsis. Plant Mol Biol. 2003;52(6):1125–34.
88. Yoo AS, Crabtree GR. ATP-dependent chromatin remodeling in neural development. Curr Opin Neurobiol. 2009;19(2):120–6.
89. Crosby MA, Miller C, Alon T, et al. The trithorax group gene moira encodes a brahma-associated putative chromatin-remodeling factor in Drosophila melanogaster. Mol Cell Biol. 2009;19(2):1159–70.
90. Sarnowski TJ, Rios G, Jäskel J, et al. SWI3 subunits of putative SWI/SNF chromatin-remodeling complexes play distinct roles during Arabidopsis development. Plant Cell. 2005;17(9):2454–72.
91. Motoyama J, Takeuchi T. The mouse embryogenesis of jumonji mutant obtained by gene-trap method. Tanpakushitsu Kakuszakoso. 1995;40(14):2152–61.
92. Lu F, Li G, Cui X, Liu C, Wang XJ, Cao X. Comparative analysis of JmJc domain-containing proteins reveals the potential histone demethylases in Arabidopsis and rice. J Integr Plant Biol. 2008;50(7):886–96.
93. Sun Q, Zhou DX. Rice JmJc domain-containing gene JM706 encodes H3K9 demethylase required for floral organ development. Proc Natl Acad Sci U S A. 2008;105(36):13679–84.
94. Tsukada Y, Fang J, Erdjument-Bromage H, et al. Histone demethylation by a family of JmJc domain-containing proteins. Nature. 2006; 439(7078):811–6.
95. Kornet N, Scheres B. Members of the GC55 histone acetyltransferase complex regulate PLETHORA-mediated root stem cell niche maintenance and transit amplifying cell proliferation in Arabidopsis. Plant Cell. 2009;21(4):1070–9.
96. Knoepfler PS, Zhang XY, Cheng PF, Gaffken PR, McMahon SB, Eisenman RN. Myc influences global chromatin structure. EMBO J. 2006; 25(12):2723–34.
97. Gurdon JB, Byrne JA, Simonsson S. Nuclear reprogramming and stem cell creation. Proc Natl Acad Sci U S A. 2003;100 Suppl 1:11819–22.
98. Gurdon JB, Colman A. The future of cloning. Nature. 1999;402(6763):743–6.
99. Steward FC, Caplin SM. A tissue culture from potato tuber: the synergistic action of 2,4-D and of coconut milk. Science. 1951;113(2940):518–20.
100. Schroeder CA, Kay E, Davis LH. Totipotency of Cells from Fruit Pericarp Tissue in vitro. Science. 1962;138(3540):595–6.
101. Dharmawardhana P, Brunner AM, Strauss SH. Genome-wide transriptome analysis of the transition from primary to secondary stem development in Populus trichocarpa. BMC Genomics. 2010;11:150.
102. Cullum AJ. Comparisons of physiological performance in sexual and asexual whiptail lizards (genus Cnemidophorus): implications for the role of heterozygosity. Am Nat. 1997;150(1):24–47.
103. Farkett K, Plantegenest M, Prunier-Leterme N, Mieuze L, Delmote F, Simon JC. Admixed sexual and facultatively asexual aphid lineages at mating sites. Mol Ecol. 2005;14(1):325–36.
104. Smith TG, Kim B, Hong H, Desser SS. Intraerythrocytic development of species of Heapospora infecting ritinga frogs: evidence for convergence of life cycle characteristics among apicomplexans. J Parasitol. 2000;86(3):451–8.
105. Schausch H, Tobler M, Plath M, Penn DJ, Schluupp I. Polymorphic MHC loci in an asexual fish, the amazon molly (Poecilia formosa; Poeciliidae). Mol Ecol. 2008;17(24):5220–30.
106. Gilbert SF. Developmental Biology. Sunderland, MA: Sinauer Associates; 2000.
107. Briggs R, King TJ. Transplantation of living nuclei from blastula cells into enucleated frogs’ eggs. Proc Natl Acad Sci U S A. 1952;38(5):455–63.
108. Gurdon JB, Elsdale TR, Fischberg M. Sexually mature individuals of Xenopus laevis from the transplantation of single somatic nuclei. Nature. 1958;182(4627):64–5.
109. Sun K, van Es JH, de Lau W, et al. Conversion of metamorphic Barrett’s epithelium into post-mitotic goblet cells by gamma-secretase inhibition. Dis Model Mech. 2011;4(1–2):104–10.
110. Barros R, Freund JN, David L, Almeida R. Gastric intestinal metaplasia revisited: function and regulation of CDX2. Trends Mol Med. 2012;18(9):555–63.
111. Enzer T. Forcing cells to change lineages. Trends Mol Med. 2009;15(5):1159–70.
112. Eberhard D, Tosh D. Transdifferentiation and metaplasia as a paradigm for understanding development and disease. Cell Mol Life Sci. 2008;65(1):33–40.
119. Horb ME, Shen CN, Tosh D, Slack JM. Experimental conversion of liver to pancreas. *Curr Biol.* 2003;13(2):105–15.

118. Nishikawa Y, Doi Y, Watanabe H, et al. Transdifferentiation of mature rat hepatocytes into bile duct-like cells in vitro. *Am J Pathol.* 2005;166(4):1077–88.

117. Tian C, Ambroz RJ, Sun L, et al. Direct conversion of dermal fibroblasts into neural progenitor cells by a novel cocktail of defined factors. *Carr Mol Med.* 2012;12(2):126–37.

116. Campbell KH, McWhir J, Ritchie WA, Wilmut I. Sheep cloned by nuclear transfer from a cultured cell line. *Nature.* 1996;380(6596):64–6.

115. Axtell MJ, Westholm JO, Lai EC. Vive la difference: biogenesis and function of plant microRNAs. *Genome Res.* 2004;14(10):1825–34.

114. Voinnet O. Origin, biogenesis, and activity of plant microRNAs. *Nat Rev Genet.* 2003;4(6):465–75.

113. Shimozawa N, Sotomaru Y, Eguchi N, et al. Phenotypic abnormalities observed in aged cloned mice from embryonic stem cells after long-term maintenance. *Reproduction.* 2006;132(3):435–41.

112. Wang Y, Hai T, Liu Z, et al. HSPC117 deficiency in cloned embryos causes placental abnormality and fetal death. *Biochem Biophys Res Commun.* 2010;397(3):407–12.

111. Takashaki K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell.* 2006;126(4):663–76.

110. Geoffhegan E, Byrnes L. Mouse induced pluripotent stem cells. *Int J Dev Biol.* 2008;52(8):1015–22.

109. Gurdon JB. The developmental capacity of nuclei taken from intestinal epithelium cells of feeding tadpoles. *J Embryol Exp Morphol.* 1962;10:622–40.

108. Avramova ZV. Heterochromatin in animals and plants. Similarities and differences. *Plants Physiol.* 2002;129(1):40–9.

107. Grafi G. How cells dedifferentiate: a lesson from plants. *Dev Biol.* 2004;268(1):1–6.

106. Theissen G, Becker A, Di Rosa A, et al. A short history of MADS-box genes in plants. *Plant Mol Biol.* 2000;42(1):115–49.

105. Warren RW, Nagy L, Selegue J, Gates J, Carroll S. Evolution of homeotic gene regulation and function in flies and butterflies. *Nature.* 1995;373(6513):451.

104. Liu XL, Shen Y, Chen EJ, Zhao ZH. Nuclear assembly of purified Crytocodinium cohnii chromosomes in cell-free extracts of Xenopus laevis eggs. *Cell Res.* 2000;10(2):127–37.

103. von der Haar B, Sperling K, Gregor D. Maturing Xenopus oocytes induce chromosome condensation in somatic plant nuclei. *Exp Cell Res.* 1981;134(2):477–81.

102. Feng S, Jacobsen SE, Reik W. Epigenetic reprogramming in plant and animal development. *Science.* 2010;330(6004):622–7.

101. Kim VN, Han J, Siorri MC. Biogenesis of small RNAs in animals. *Nat Rev Mol Cell Biol.* 2009;10(2):126–39.

100. Voinnet O. Origin, biogenesis, and activity of plant microRNAs. *Cell.* 2009;136(4):669–87.

99. Axtell MJ, Westholm JO, Lai EC. Vive la difference: biogenesis and evolution of microRNAs in plants and animals. *Genome Biol.* 2011;12(4):221.

98. Roccaro AM, Sacco A, Jia X, et al. microRNA-dependent modulation of histone acetylation in Waldenstrom macrogllobulinemia. *Blood.* 2010;116(9):1506–14.

97. Wu L, Zhou H, Zhang Q, et al. DNA methylation mediated by a microRNA pathway. *Mol Cell.* 2010;38(3):465–75.

96. Chavalil V, Tyagi SC, Mishra PK. MicroRNA-133a regulates DNA methylation in diabetic cardiomyocytes. *Biochem Biophys Res Commun.* 2012;425(3):668–72.

95. Zhang L, Hou D, Chen X, et al. Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA. *Cell Res.* 2012;22(1):107–26.

94. Vacheret H, Chapeau Y. Ingested plant miRNAs regulate gene expression in animals. *Cell Res.* 2012;22(1):3–5.

93. Iderabaddullah FY, Vigneau S, Bartolomei MS. Genomic imprinting mechanisms in mammals. *Mutat Res.* 2008;647(1–2):77–85.

92. Meaney MJ, Ferguson-Smith AC. Epigenetic regulation of the neural transcriptome: the meaning of the marks. *Nat Neurosci.* 2010;13(11):1313–8.

91. Feil R, Berger F. Convergent evolution of genomic imprinting in plants and mammals. Trends Genet. 2007;23(4):192–9.

90. Jiang H, Kohler C. Evolution, function, and regulation of genomic imprinting in plant seed development. *J Exp Bot.* 2012;63(13):4713–22.

89. Bartolomei MS. Genomic imprinting: employing and avoiding epigenetic processes. *Genes Dev.* 2009;23(18):2124–33.

88. Macdonald WA. Epigenetic mechanisms of genomic imprinting: common themes in the regulation of imprinted regions in mammals, plants, and insects. *Genet Res Int.* 2012;2012:585024.

87. Umlauf D, Goto Y, Cao R, et al. Imprinting along the Kcnq1 domain on mouse chromosome 7 involves repressive histone methylation and recruitment of Polycomb group complexes. *Nat Genet.* 2004;36(12):1296–300.

86. Edwards CA, Ferguson-Smith AC. Mechanisms regulating imprinted genes in clusters. *Curr Opin Cell Biol.* 2007;19(3):281–9.

85. Kinoshita T, Miura A, Choi Y, et al. One-way control of FWA imprinting in Arabidopsis endosperm by DNA methylation. *Science.* 2004;303(5657):521–3.

84. Baroux C, Gagliardini V, Page DR, Grossniklaus U. Dynamic regulatory interactions of Polycomb group genes: MEDEA autoregulation is required for imprinted gene expression in Arabidopsis. *Genes Dev.* 2006;20(9):1081–6.

83. Xiao W, Custard KD, Brown RC, et al. DNA methylation is critical for Arabidopsis embryogenesis and seed viability. *Plant Cell.* 2006;18(4):805–14.

82. Scott RJ, Spielman M. Genomic imprinting in plants and mammals: how life history constrains convergence. *Cytogenet Genome Res.* 2006;113(1–4):53–67.

81. Bai X, Yan Y, Song YH, et al. Both cultured and freshly isolated adipose tissue-derived stem cells enhance cardiac function after acute myocardial infarction. *Eur Heart J.* 2010;31(4):489–501.

80. Guiikar F, Cohen DM, Estes BT, Gimble JM, Liedtke W, Chen CS. Control of stem cell fate by physical interactions with the extracellular matrix. *Cell Stem Cell.* 2009;5(1):17–26.

79. Li N, Lu X, Zhao X, et al. Endothelial nitric oxide synthase promotes bone marrow stromal cell migration to the ischemic myocardium via upregulation of stromal cell-derived factor-1alpha. *Stem Cells.* 2009;27(4):961–70.

78. Kilian KA, Bugaria B, Lahn BT, Mrksich M. Geometric cues for directing the differentiation of mesenchymal stem cells. *Proc Natl Acad Sci U S A.* 2010;107(11):4872–7.

77. Cao Y, Vacanti JP, Paige KT, Upton I, Vacanti CA. Transplantation of chondrocytes utilizing a polymer-cell construct to produce tissue-engineered cartilage in the shape of a human ear. *Plast Reconstr Surg.* 1997;100(2):297–302.

76. Zhao J, Moroznova N, Williams L, Libs L, Avivi Y, Grafi G. Two phases of chromatin decondensation during dedifferentiation of plant cells: distinction between competence for cell fate switch and a commitment for S phase. *J Biol Chem.* 2001;276(25):22772–8.

75. Gao L, McBeath R, Chen CS. Stem cell shape regulates a chondrogenic versus myogenic fate through Rac1 and N-cadherin. *Cell Biol Int.* 2007;31(8):750–60.

74. Mathers JC, Strathdee G, Kelton CL. Induction of epigenetic alterations by dietary and other environmental factors. *Adv Genet.* 2010;71:3–39.

73. Alegria-Torres JA, Baccarelli A, Bollati V. Epigenetics and lifestyle. *Epigenomics.* 2011;3(3):267–71.

72. Biener H, Hamon M, Cossart P. Epigenetics and bacterial infections. *Cold Spring Harb Perspect Med.* 2012;2(2):a010272.

71. Weaver IC, Corvoni N, Champagne FA, et al. Epigenetic programming by maternal behavior. *Nat Neurosci.* 2004;7(8):847–54.

70. Mirouze M, Paszkowski J. Epigenetic contribution to stress adaptation in plants. *Curr Opin Plant Biol.* 2011;14(3):267–74.
170. McCue AD, Nuthikattu S, Reeder SH, Slotkin RK. Gene expression and stress response mediated by the epigenetic regulation of a transposable element small RNA. PLoS Genet. 8(2):e1002474.

171. Chinnusamy V, Zhu JK. Epigenetic regulation of stress responses in plants. Curr Opin Plant Biol. 2009;12(2):133–9.

172. Sheldon CC, Finnegan EJ, Rouse DT, et al. The control of flowering by vernalization. Curr Opin Plant Biol. 2000;3(5):418–22.

173. Sheldon CC, Rouse DT, Finnegan EJ, Peacock WJ, Dennis ES. The molecular basis of vernalization: the central role of FLOWERING LOCUS C (FLC). Proc Natl Acad Sci U S A. 2000;97(7):3753–8.

174. Xi S, Xu H, Shan J, et al. Cigarette smoke mediates epigenetic repression of the mammalian epidermal growth factor receptor. J Cell Biochem. 2011;113(3):445–58.

175. Brunaud L, Alberto JM, Ayav A, et al. Effects of vitamin B12 and folate deficiencies on DNA methylation and carcinogenesis in rat liver. Clin Chem Lab Med. 2003;41(8):1012–9.

176. Niculescu MD, Zeisel SH. Diet, methyl donors and DNA methylation: interactions between dietary folate, methionine and choline. J Nutr. 2002;132(Suppl 8):2335–5.

177. Vucetic Z, Kimmel J, Reyes TM. Chronic high-fat diet drives postnatal epigenetic regulation of µ-opioid receptor in the brain. Neuropsychopharmacology. 2011;36(6):1199–206.

178. Milagro FI, Mansego ML, De Miguel C, Martinez JA. Dietary factors, epigenetic modifications and obesity outcomes: Progresses and perspectives. Mol Aspects Med. 2013;34(4):782–812.

179. Pufulete M, Al-Ghanim R, Khashal A, et al. Effect of folate acid supplementation on genomic DNA methylation in patients with colorectal adenoma. Gut. 2005;54(5):648–53.

180. Blom HJ. Folic acid, methylation and neural tube closure in humans. Birth Defects Res A Clin Mol Teratol. 2009;85(4):295–302.

181. Sanchis-Gomar F, Garcia-Gimenez JL, Perez-Quiles C, Gomez-Cabrerac MC, Pallardo FV, Lippi G. Physical exercise as an epigenetic modulator: Eustress, the “positive stress” as an effecter of gene expression. J Strength Cond Res. 2012;26(12):3469–72.

182. Schwarzenbach H. Impact of physical activity and doping on epigenetic gene regulation. Drug Test Anal. 2011;3(10):682–7.

183. Chen X, Wang J, Shen H, et al. Epigenetics, microRNAs, and carcinogenesis: functional role of microRNA-137 in uveal melanoma. Invest Ophthalmol Vis Sci. 2011;52(3):1193–9.

184. Xie S, Xu H, Shan J, et al. Cigarette smoke mediates epigenetic repression of miR-487b during pulmonary carcinogenesis. J Clin Invest. 2013;123(3):1241–61.

185. Rossi A, D’Urso OF, Gatto G, et al. Non-coding RNAs change their expression profile after Retinoid induced differentiation of the promyelocytic cell line NB4. BMC Res Notes. 2010;3:24.

186. Garzon R, Pichierri F, Palumbo T, et al. MicroRNA gene expression during retinoic acid-induced differentiation of human acute promyelocytic leukemia. Oncogene. 2007;26(28):4148–57.

187. Peng X, Vaishnav A, Murillo G, Alimrah F, Torres KE, Mehta RG. Protection against cellular stress by 25-hydroxyvitamin D3 in breast epithelial cells. J Cell Biochem. 2010;110(6):1324–33.

188. Gaedicke S, Zhang X, Schmelzer C, et al. Vitamin E dependent microRNA regulation in rat liver. FEBS Lett. 2008;582(23–4):3542–6.
218. Deng W, Liu C, Pei Y, Deng X, Niu L, Cao X. Involvement of the histone acetyltransferase AtHAC1 in the regulation of flowering time via repression of FLOWERING LOCUS C in Arabidopsis. Plant Physiol. 2007;143(4):1660–8.

219. Yang XJ, Seto E. The Rpd3/Hda1 family of lysine deacetylases: from bacteria and yeast to mice and men. Nat Rev Mol Cell Biol. 2008;9(3):206–18.

220. Fu W, Wu K, Duan J. Sequence and expression analysis of histone deacetylases in rice. Biochem Biophys Res Commun. 2007;356(4):843–50.

221. Chen LT, Luo M, Wang YY, Wu K. Involvement of Arabidopsis histone deacetylase HDA6 in ABA and salt stress response. J Exp Bot. 2010;61(12):3345–53.

222. Hallson G, Hollebakken RE, Li T, et al. dSet1 is the main H3K4 di- and tri-methyltransferase throughout Drosophila development. Genetics. 2012;190(1):91–100.

223. Cheung P, Lau P. Epigenetic regulation by histone methylation and histone variants. Mol Endocrinol. 2005;19(3):563–73.

224. Yang W, Jiang D, Jiang J, He Y. A plant-specific histone H3 lysine 4 demethylase represses the floral transition in Arabidopsis. Plant J. 2010;62(4):663–73.

225. Klose RJ, Zhang Y. Regulation of histone methylation by demethylimation and demethylation. Nat Rev Mol Cell Biol. 2007;8(4):307–18.

226. De Koning L, Corpet A, Haber JE, Almouzni G. Histone chaperones: an escort network regulating histone traffic. Nat Struct Mol Biol. 2007;14(11):997–1007.

227. Ach RA, Taranto P, Grussiem W. A conserved family of WD-40 proteins binds to the retinoblastoma protein in both plants and animals. Plant Cell. 1997;9(9):1595–606.

228. Noh YS, Amasino RM. PIE1, an ISWI family gene, is required for FLC activation and floral repression in Arabidopsis. Plant Cell. 2003;15(7):1671–82.

229. Knizewski L, Gintuński K, Jerzmanowski A. Sfn2 proteins in plants: gene silencing and beyond. Trends Plant Sci. 2008;13(10):557–65.

230. Mlynárová L, Nap JP, Bisseling T. The SWI/SNF chromatin-remodeling gene AtCHR12 mediates temporary growth arrest in Arabidopsis thaliana upon perceiving environmental stress. Plant J. 2007;51(5):874–85.

231. Farrona S, Hurtado L, Bowman JL, Reyes JC. The Arabidopsis thaliana SNF2 homolog AtBRM controls shoot development and flowering. Development. 2004;131(20):4965–75.

232. Wagner D, Meyerowitz EM. SPLAYED, a novel SWI/SNF ATPase homolog, controls reproductive development in Arabidopsis. Curr Biol. 2002;12(2):85–94.

233. Marfella CG, Imbalzano AN. The Chd family of chromatin remodelers. Mutat Res. 2007;618(1-2):30–40.