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Epigenetics and Neuroendocrinology

Clinical Focus on Psychiatry, Volume 2

Springer

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Foreword

The field of neuroendocrinology has evolved from initial studies on the hypothalamic control of pituitary secretion to the study of multilayered reciprocal interactions between the central nervous system (CNS) and the endocrine system. Together, they serve to coordinate a vast range of physiological responses in order to maintain homeostasis. At the same time, neuroendocrine systems can undergo dynamic, potentially lasting, adjustments in preset thresholds and regulatory set points during critical periods of development and beyond. Such adjustments, commonly thought of as adaptation, can enhance the capacity of an organism to cope with recurrent challenges but may also increase the risk for certain diseases. Importantly, molecular epigenetic mechanisms are increasingly recognized for their role both in the development and maturation of the neuroendocrine system as well as for their role as a molecular interface in the mediation of multifaceted gene-environment interactions.

Epigenetics and Neuroendocrinology – Focus on Psychiatry – addresses current advances in the understanding of molecular epigenetic mechanisms for the function and adjustment of neuroendocrine systems and their impact on trauma- and stress-related psychiatry disorders.

With the beginning of the last century, experimental hypophysectomy (Crowe et al. 1910) and stereotactic hypothalamic lesions (Hetherington and Ranson 1940) demonstrated a close interaction between the hypothalamus and the pituitary. These and following studies clearly established that an intact hypothalamus is necessary for normal endocrine function although the mechanisms mediating these effects remained obscure.

This gap was filled when several groups, namely, the one of Ernst and Berta Scharrer (Scharrer 1987), discovered that neurons in the hypothalamus are the origin of the axons that constitute the neural, posterior lobe. Further refined anatomical studies (Wislocki and King 1936) revealed the role of pituitary portal vessels in linking the median eminence of the hypothalamus and the anterior pituitary and grounded today's hypophyseal-portal-chemotransmitter hypothesis.

The decades to follow witnessed major progress in the identification of the factors that mediate the communication between the hypothalamus and the pituitary

and were crowned by the isolation of several putative peptide hormone releasing factors by Andrew Schally and Roger Guillemin (Guillemin 1978; Schally 1978). These neuropeptides turned out to be the long-sought functional link between the CNS and the endocrine systems in the control of reproduction, growth, metabolism, and the stress response. Epigenetic regulation of these releasing factor genes during critical time windows of development and their relevance for the onset, progression, and course of major depression and trauma presents an important aspect of this book (vol 1, Part I).

Following on, the cloning and characterization of specific G protein-coupled receptors bound by hypothalamic releasing factors enabled elucidation of the underlying signaling pathways and opened up the prospect of tailored treatments (Griebel and Holsboer 2012). Experience-dependent epigenetic (de)regulation of the encoding receptor alleles has emerged as an important step in the pathology of several psychiatric disorders (vol 2, Part I).

Although the discipline of neuroendocrinology has focused traditionally on the clinical function of hypothalamic releasing factors in reproduction and development, metabolism, fluid balance, and stress, the field has expanded over the last decades to embrace the multilayered interactions of the endocrine and nervous system in the control of homeostasis. Within this framework the concept of endocrine psychiatry emerged at the beginning of the twentieth century as a new discipline with Manfred Bleuler as one of its leading protagonists (Bleuler 1965). This development also gave birth to the field of psychoneuroendocrinology comprising the clinical study of hormone fluctuations and their relationship to human behavior. Certain mood disorders were shown to be associated with neuroendocrine or hormonal changes affecting brain function while otherwise certain endocrine disorders were shown to associate with psychiatric diseases. New areas in these research fields include, among others, neurosecretion, neurotransmission, receptor pharmacology, transcriptional regulation, and most recently molecular epigenetics (Allis et al. 2015).

Homeostatic systems integrate endocrine, autonomic, and behavioral outcomes by connecting classical neuroendocrine axes to neuronal inputs and refined feedback loops to maintain a dynamic equilibrium (vol 1, Part I). In the classical stress concept this well-balanced state is challenged by certain physical and psychological events termed “stressors” (Fink 2007). These stressors also trigger neuroendocrine and behavioral responses with the aim to reinstate homeostasis. Excessive, inadequate, or enduring stress responses can trigger epigenetic mechanisms that inscribe long-lasting memory traces into the methylome of exposed individuals and may act in conjunction with certain genetic predispositions as risk factors for various psychiatric diseases (vol 1, Part I and vol 2, Parts I–III).

Early life comprises a period of both great vulnerability and great opportunity for brain development (Shonkoff and Phillips 2000). A growth-promoting environment filled with attentive social interactions prepares the highly plastic developing brain to evolve optimally. Conversely, adverse early life experiences can result in faulty brain circuitry and leave lasting, if not lifelong, molecular epigenetic footprints at the hypothalamic-pituitary-adrenal axis (vol 1, Part I and vol 2, Parts I–III).

Persuasive evidence has been gained for a role of experience-dependent molecular epigenetic marks in the mediation between early life adversity and later psychopathology (Heim and Binder 2012; Hoffmann and Spengler 2012).

Our sex plays a fundamental role in our daily lives and the timing of onset, prevalence, clinical course, and treatment response for various mental disorders (vol 1, Part II). Sexual differentiation of the brain occurs during a perinatal-sensitive time window as a result of gonadal hormone-driven activational and organizational effects on neuronal templates. Molecular epigenetic mechanisms contribute to these processes and are themselves under the control of sex hormones (vol 1, Part II). Epigenetic programming of neuroendocrine and behavioral phenotypes is sex dependent (vol 1, Parts I–II and vol 2, Parts I–III), indicative of a tight interplay between sex differences in molecular brain epigenetics and gonadal hormones. In support of this view, loss of transcriptional repression is a key mechanism underlying the onset of puberty in females and is triggered by molecular epigenetic cues (vol 1, Part II).

Integrated analysis of neuroendocrine systems can advance our insight into the relationship from epigenetically mediated adaptation to disease (Choi 2010). In positive feedback systems, the controlled variable increases hormone output but decreases it in case of negative feedback systems. The hypothalamic-pituitary-adrenal axis presents a classical example where glucocorticoid receptors, encoding ligand-gated transcription factors (Bunce and Campbell 2010), sense the concentration of steroid hormones and terminate the output of the system (vol 1, Part I). Receptors of classical steroids, the glucocorticoid, mineralocorticoid, progesterone, androgen, and estrogen receptors reside in the cytoplasm in a complex with chaperon proteins. Following ligand binding, they translocate to the nucleus to bind predominantly as homodimers at well-defined response elements. Subsequently, they confer transcriptional regulation by the combinatorial recruitment of multiple cofactor complexes containing various enzymatic activities catalyzing site-specific histone modifications underlying an “open” (transcriptionally active) or “closed” (transcriptionally inactive) chromatin structure (vol 1, Part I). The expression of nuclear receptors can be epigenetically programmed by early-life experiences in a tissue-specific manner and represents an important risk factor for the development of various psychiatry disorders (vol 2, Part III). Similarly, allele-specific epigenetic marking of FKBP51, encoding a key chaperon for glucocorticoid receptor function, has been discovered as a molecular mechanism underlying gene-environment interactions in stress-related psychiatric disorders (vol 2, Part I). Moreover, the DNA methylation status at glucocorticoid receptor response elements can regulate cell-type specific enhancer activity (vol 1, Part I). Together, these findings exemplify how molecular epigenetic mechanisms can operate at multiple levels to control negative feedback regulation of the hypothalamic-pituitary-adrenal axis.

For the past 60 years, the genome has been viewed as an immutable master plan that has been laid down with the inception of our lives with DNA as the heritable molecule that carries information about phenotypes from parent to offspring (Jablonka et al. 2005). Experimental studies in different animal models and observational findings in humans suggest, however, that stressful exposures during

pregnancy, birth, or adolescence can be passed down to the offspring (intergenerational) and subsequent generations (transgenerational) to affect sex-dependently neuroendocrine and behavioral responses (vol 2, Part II). Some routes require the continuous presence of the initial trigger and result from behavioral and social transfer while others may uncouple from the initial trigger and rely solely on the molecular transfer through the germ cells. Molecular epigenetic mechanisms seem to underpin these effects, and diffusible factors, in particular hormonal signals and possibly RNAs, might explain epigenetic inheritance via the gametes. The impetus of such transmissible effects for the chemistry of our children's DNA and for evolutionary medicine awaits still careful investigations (Gluckman et al. 2010).

A concluding open question is how to alleviate epigenetically encoded disease risks in psychiatric disorders. Epigenetic biomarkers offer a promising tool to identify individuals at risk and for outpatient monitoring (vol 2, Part III). If social experiences and adverse stressors are important determinants, this may be good news; physiological stress responses that depend strongly on epigenetic programming may be more amenable to psychotherapeutic interventions than hardwired genetic factors. Therapeutic approaches that aim to revise perceptions psychologically may complement personalized pharmacological treatments, and possibly there are interactive psychological and pharmacological interventions that work better than either type of approach alone.

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Glossary

Acetylation The introduction, via an enzymatic reaction, of an acetyl group to an organic compound, for instance to *histones* or other proteins.

Agouti gene The agouti gene (A) controls fur colour through the deposition of yellow pigment in developing hairs. Several variants of the gene exist, and for one of these (Agouti Variable Yellow, A^{vy}) the expression levels can be heritably modified by *DNA methylation*.

Alleles Different variants or copies of a gene. For most genes on the chromosomes, there are two copies: one copy inherited from the mother, the other from the father. The DNA sequence of each of these copies may be different because of genetic polymorphisms.

Assisted reproduction technologies (ART) The combination of approaches that are being applied in the fertility clinic, including *IVF* and *ICSI*.

5-Azacytidine A cytidine analog in which the 5 carbon of the cytosine ring has been replaced with nitrogen. 5-azacytidine is a potent inhibitor of mammalian *DNA methyltransferases*.

Bisulfite genomic sequencing A procedure in which bisulfite is used to deaminate cytosine to uracil in genomic DNA. Conditions are chosen so that 5-methylcytosine is not changed. PCR amplification and subsequent DNA sequencing reveals the exact position of cytosines which are methylated in genomic DNA.

Bivalent chromatin A chromatin region that is modified by a combination of histone modifications such that it represses gene transcription, but at the same time retains the potential of acquiring gene expression,.

Brno nomenclature Regulation of the nomenclature of specific histone modifications formulated at the Brno meeting of the NoE in 2004. Rules are: <Histone > <amino-acid position > <modification type > <type of modification>. Example: H3K4me3 = trimethylated lysine-4 on histone H3

Bromo domain Protein motif found in a variety of nuclear proteins including transcription factors and HATs involved in transcriptional activation. Bromo domains bind to histone-tails carrying acetylated lysine residues.

Cell fate The programmed path of differentiation of a cell. Although all cells have the same DNA, their cell fate can be different. For instance, some cells develop into brain, whereas others are the precursors of blood. Cell fate is determined in part by the organisation of *chromatin* – DNA and the histone proteins – in the nucleus.

Cellular memory (epigenetic) Specific active and repressive organisations of chromatin can be maintained from one cell to its daughter cells. This is called *epigenetic inheritance* and ensures that specific states of gene expression are inherited over many cell generations.

ChIP See *chromatin immuno-precipitation*.

ChIP on chip After chromatin immunoprecipitation, DNA is purified from the immunoprecipitated chromatin fraction and used to hybridise arrays of short DNA fragments representing specific regions of the genome.

ChIP Seq Sequencing of the totality of DNA fragments obtained by ChIP to determine their position on the genome. Sequencing is usually preceeded by PCR amplification of ChIP derived DNA to increase its amount.

Chromatid In each somatic cell generation, the genomic DNA is replicated in order to make two copies of each individual chromosome. During M phase of the cell cycle, these copies – called chromatids – are microscopically visible one next to the other, before they get distributed to the daughter cells.

Chromatin The nucleo-protein-complex constituting the chromosomes in eukaryotic cells. Structural organisation of chromatin is complex and involves different levels of compaction. The lowest level of compaction is represented by an extended array of *nucleosomes*.

Chromatin immuno-precipitation (ChIP) Incubation of chromatin fragments comprising one to several nucleosomes, with an antiserum directed against particular (histone) proteins or covalent modifications on proteins. After ChIP, the genomic DNA is purified from the chromatin fragments brought down by the antiserum and analysed.

Chromatin remodelling Locally, the organisation and compaction of chromatin can be altered by different enzymatic machineries. This is called chromatin remodelling. Several chromatin remodelling proteins move *nucleosomes* along the DNA and require ATP for their action.

Chromo domain (chromatin organization modifier domain) Protein-protein interaction motif first identified in *Drosophila melanogaster HP1* and *polycomb group proteins*. Also found in other nuclear proteins involved in transcriptional silencing and heterochromatin formation. Chromo domains consist of approx. 50 amino acids and bind to histone tails that are methylated at certain lysine residues.

Chromosomal domain In higher eukaryotes, it is often observed that in a specific cell type, chromatin is organised (eg, by *histone methylation*) the same way across hundreds to thousands of kilobases of DNA. These 'chromosomal domains' can comprise multiple genes that are similarly expressed. Some chromosomal domains are controlled by *genomic imprinting*.

CpG dinucleotide A cytosine followed by a guanine in the sequence of bases of the DNA. *Cytosine methylation* in mammals occurs at CpG dinucleotides.

CpG island A small stretch of DNA, of several hundred up to several kilobases in size, that is particularly rich in *CpG dinucleotides* and is also relatively enriched in cytosines and guanines. Most CpG islands comprise promoter sequences that drive the expression of genes.

Cytosine methylation In mammals, DNA methylation occurs at cytosines that are part of *CpG dinucleotides*. As a consequence of the palindromic nature of the CpG sequence, methylation is symmetrical, i.e., affects both strands of DNA at a methylated target site. When present at promoters, it is usually associated with transcriptional repression.

Deacetylation The removal of acetyl groups from proteins. Deacetylation of histones is often associated with gene repression and is mediated by histone deacetylases (HDACs).

"de novo" DNA-methylation The addition of methyl groups to a stretch of DNA which is not yet methylated (acquisition of 'new' DNA methylation).

Disomy The occurrence in the cell of two copies of a chromosome, or part of a chromosome, that are identical and of the same parental origin (uniparental disomy).

DNA-demethylation Removal of methyl groups from DNA. This can occur 'actively', i.e. by an enzymatically mediated process, or 'passively', when methylation is not maintained after DNA replication.

DNA-methylation A biochemical modification of DNA resulting from addition of a methyl group to either adenine or cytosine bases. In mammals, methylation is essentially confined to cytosines that are in *CpG dinucleotides*. Methyl groups can be removed from DNA by DNA-demethylation.

DNA methyltransferase Enzyme which puts new (***de novo***) methylation onto the DNA, or which maintains existing patterns of DNA methylation.

Dosage compensation The X chromosome is present in two copies in the one sex, and in one copy in the other. Dosage compensation ensures that in spite of the copy number difference, X-linked genes are expressed at the same level in males and females. In mammals, dosage compensation occurs by inactivation of one of the X chromosomes in females.

Early-life adversity (ELA) Parental maladjustment (mental illness (frequently MDD), substance abuse, violence, and criminality), maltreatment (sexual abuse, physical abuse, or neglect), interpersonal loss (parental death or divorce, separation from parents or caregivers), life threatening childhood physical illness in the respondent, or severe childhood family financial distress are leading sources of ELA and typically associate with early-life stress (ELS).

Most studies have focused on childhood trauma, in particular sexual and physical abuse though neglect during early childhood is the most common form of maltreatment, accounting for more than three quarters of all maltreatment cases. ELA is a strong risk factor for the development of various psychiatric diseases, particularly major depressive disorder.

Embryonic stem (ES) cells Cultured cells obtained from the inner cell mass of the blastocyst, and for human ES cells, possibly also from the epiblast. These cells are totipotent; they can be differentiated into all different somatic cell lineages.

ES-like cells can be obtained by dedifferentiation *in vitro* of somatic cells (see *iPS cells*).

Endocrine disruptor A chemical component which can have an antagonistic effect on the action of a hormone (such as on estrogen) to which it resembles structurally. Some pesticides act as endocrine disruptors and have been found in animal studies to have adverse effects on development, and for some, to induce altered *DNA methylation* at specific loci. A well characterised endocxrine disruptor is *Bisphenol-A*, a chemical used for the productions of certain plastics.

Enhancer A small, specialised sequence of DNA which, when recognised by specific regulatory proteins, can enhance the activity of the promoter of a gene(s) located in close vicinity.

Epi-alleles Copies of a DNA sequence or a gene which differ in their epigenetic and/or expression states without the occurrence of a genetic mutation.

Epigenesis The development of an organism from fertilisation through a sequence of steps leading to a gradual increase in complexity through differentiation of cells and formation of organs.

Epigenetics The study of heritable changes in gene function that arise without an apparent change in the genomic DNA sequence. Epigenetic mechanisms are involved in the formation and maintenance of cell lineages during development, and, in mammals, in *X-inactivation* and *genomic imprinting*, and are frequently perturbed in diseases.

Epigenetic code Patterns of DNA methylation and histone modifications can modify the way genes on the chromosomes are expressed. This has led to the idea that combinations of epigenetic modifications can constitute a code on top of the genetic code which modulates gene expression.

Epigenetic inheritance The somatic inhertance, or inheritance through the germ line, of epigenetic information (changes that affect gene function, without the occurrence of an alteration in the DNA sequence).

Epigenetic marks Regional modifications of DNA and chromatin proteins, including *DNA methylation* and histone methylation, that can be maintained from one cell generation to the next and which may affect the way genes are expressed.

Epigenetic reprogramming The resetting of *epigenetic marks* on the genome so that these become like those of another cell type, or of another developmental stage. Epigenetic reprogramming occurs for instance in *primordial germ cells*, to bring them back in a 'ground state'. Epigenetic reprogramming and dedifferentiation also occur after *somatic cell nuclear transfer*.

Epigenome The epigenome is the overall epigenetic state of a particular cell. In the developing embryo, each cell type has a different epigenome. Epigenome maps represent the presence of DNA methylation, histone modification and other chromatin modifications along the chromosomes.

Epigenotype The totality of epigenetic marks that are found along the DNA sequence of the genome in a particular cell lineage or at a particular developmental stage.

Epimutation A change in the normal epigenetic marking of a gene or a regulatory DNA sequence (e.g., a change in DNA methylation) which affects gene expression.

Euchromatin A type of chromatin which is lightly staining when observed through the microscope at interphase. Euchromatic *chromosomal domains* are loosely compacted and relatively rich in genes. The opposite type of chromatin organisation is *heterochromatin*.

Genomic imprinting An epigenetic phenomenon which affects a small subset of genes in the genome and results in mono-allelic gene expression in a parent-of-origin dependent way (for a given pair of alleles uniformly either the maternally or paternally derived copy is active).

Germ line specific stem cells Cells derived from undifferentiated germ cells which can be maintained without alterations in their characteristics through many cell divisions.

Glucocorticoid (GC) Main stress hormones released from the adrenal glands following activation of the hypothalamic-pituitary-adrenal axis. Typical glucocorticoids are corticosterone in animals, and cortisol in humans. Sustained up-regulation of GCs is found following exposure to early-life adversity and during the course of major depressive disorders.

Heterochromatin A type of chromatin which is darkly staining when observed through the microscope at interphase., Heterochromatic chromosomal domains, found in all cell types, are highly compacted, rich in repeat sequences, and show little or no gene expression. Extended regions of heterochromatin are found close to centromeres and at telomeres.

Histone acetylation Post-translational modification of the ε-amino group of lysine residues in histones catalyzed by a family of enzymes called *histone acetyltransferases (HATs)*. Acetylation contributes to the formation of decondensed, transcriptionally permissive chromatin structures and facilitates interaction with proteins containing *bromo domains*.

Histone acetyltransferase (HAT) An enzyme that acetylates (specific) lysine amino acids on histone proteins.

Histone code Theory that distinct chromatin states of condensation and function are marked by specific histone modifications or specific combinatorial codes (see also epigenetic code).

Histone deacetylase (HDAC) An enzyme that removes acetyl groups from histone proteins. This increases the positive charge of histones and enhances their attraction to the negatively charged phosphate groups in DNA.

Histone-demethylase (HDM) Proteins catalysing the active enzymatic removal of methyl groups from either lysine or arginine residues of histones. Prominent examples are LSD1 and Jumonji proteins.

Histone methylation Post-translational methylation of amino acid residues in histones catalysed by *histone methyltransferases (HMTs).* Histone methylation is found at arginine as mono- or di-methylation and lysine as mono-, di- or trimethylation. Modifications are described depending on the position and type

of methylation (mono, di, tri-methylation) according to the *Brno nomenclature*. Different types of methylation can be found in either open trancriptionally active or silent (repressive) chromatin (*histone code*). Methylated lysine residues are recognized by proteins containing *chromo domains*.

Histone methyltransferase (HMT) Enzymes catalysing the transfer of methyl groups from S-adenosyl-methionine (SAM) to lysine or arginine residues in histones.

Hypothalamic-pituitary-adrenal axis (HPA axis) Activated in response to stress, neurons in the hypothalamus release two neuropeptides called corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). Their release triggers the subsequent secretion and release of another factor called adrenocorticotropin (ACTH) from the pituitary gland, situated at the basis of the brain. When ACTH is secreted by the pituitary gland, it travels in the blood and reaches the adrenal glands, which are located above the kidneys, and triggers secretion of the so-called stress hormones. There are two main stress hormones, the glucocorticoids, and the catecholamines (epinephrine and norepinephrine).

Imprinted genes Genes that show a parent-of-origin specific gene expression pattern controlled by epigenetic marks that originate from the germ line.

Imprinted X-inactivation Preferential inactivation of the paternal X-chromosome in rodents (presumably also humans) during early embryogenesis and in the placenta of mammals

Imprinting See *genomic imprinting*

Imprinting control region (ICR) Region that shows germ line derived parent of origin dependent epigenetic marking which controls the imprinted expression of neighbouring imprinted genes

Induced pluripotent stem cells (iPS) Cells derived from differentiated somatic cells by in vitro reprogramming. Reprogramming is triggered by the activation of pluripotency factor genes and cultivation in ES-cell medium. iPS cells are capable to generate all cell types of an embryo.

Inner cell mass (ICM) Cells of the inner part of the blastocyst forming the embryo proper. Inner cell mass cells are the source for ES cells.

Intracytoplasmic sperm injection (ICSI) Capillary mediated injection of a single sperm into the cytoplasm of an oocyte followed by activation to promote directed fertilization.

In vitro fertilisation (IVF) Fertilisation of a surgically retrieved oocyte in the laboratory, followed by a short period of in vitro cultivation before the embryo is transferred back into the uterus to allow development to term.

Isoschizomers Restriction enzymes from different bacteria which recognize the same target sequence in DNA. Often these enzymes respond differently to methylation of bases within their target sequence, which may make them important tools in DNA-methylation analysis. Thus, *Msp*I cuts both CCGG and C5mCGG, whereas *Hpa*II cuts only the unmethylated sequence.

Locus control region (LCR) Region marked by insulator functions and DNase hypersensitive sites. LCRs contain binding sites for insulator proteins and enhancer binding proteins. LCRs control the domain specific developmentally regulated expression of genes by long range interactions with gene promoters.

Major depressive disorder (MDD) A world-wide leading mood disorder (also known as major depression (MD), unipolar depression, or as recurrent depression in case of repeated episodes) characterized by a pervasive and persistent low mood that is accompanied by low self-esteem and by a loss of interest or pleasure in normally enjoyable activities. MDD is a disabling condition that adversely affects a person's family, work or school life, sleeping and eating habits, and general health.

Maternal effects Long-term effects on the development of the embryo triggered by factors in the cytoplasm of the oocyte.

Methyl-binding domain (MBD) Protein domain in Methyl-CpG-binding proteins (MBPs) responsible for recognizing and binding to methylated cytosine residues in DNA. Proteins containing MBDs form a specific family of proteins with various molecular functions.

Methyl-CpG-binding proteins (MBPs) Proteins containing domains (such as MBD) binding to 5-methyl-cytosine in the context of CpG dinucleotides. MBPs mostly act as mediators for molecular functions such as transcriptional control or DNA repair.

Non-coding RNA (ncRNA) RNA transcripts that doe not code for a protein. ncRNA generation frequently involves RNA processing.

Non-Mendelian inheritance Inheritance of genetic traits that do not follow Mendelian rules and/or cannot be explained in simple mathematically modelled traits.

Nuclear periphery Region around the nuclear membrane characterized by contacts of the chromosomes with the nuclear lamina.

Nuclear (chromosomal) territory Cell type specific areas within the nucleus occupied by specific chromosomes during interphase (G1).

Nucleolus Specific compartments within the nucleus formed by rDNA repeat domains. Nucleoli are marked by specific heterochromatic structures and active gene expression.

Nucleosome Fundamental organisational unit of chromatin consisting of 147 base pairs of DNA wound around a histone octamer.

Pluripotency Capacity of stem cells to form all cell types of an embryo including germ cells.

Polycomb group proteins Epigenetic regulator proteins forming multiprotein complexes (PRCs = polycomb repressive complexes). Polycomb group proteins posess enzymatic properties to control the maintenance of a suppressed state of developmentally regulated genes, mainly through histone methylation and ubiquitination.

Position effect variegation (PEV) Cell/tissue specific variability of gene expression controlled by the temporal inheritance of certain epigenetic states. PEV is a consequence of variable formation of heterochromatin across the respective gene. A classical example of PEV is found in the certain mutations leading to variegated eye pigmentation in *Drosophila* eyes.

Posttraumatic stress disorder (PTSD) This condition may develop after a vulnerable person is exposed to one or more traumatic events, such as major stress, sexual assault, terrorism, or other threats on a person's life. Characteristic symptoms

comprise disturbing recurring flashbacks (re-experiencing symptoms), avoidance or numbing of memories of the event, and hyperarousal, which continue for more than a month after the occurrence of a traumatic event.

Primordial germ cell Mammalian cells set aside during early embryogenesis which migrate through the hind gut of the developing mammalian embryo into the "Gonadenanlagen" to form founder cells of the latter germ line.

Protamines Small, arginine-rich proteins that replace histones late in the haploid phase of *spermatogenesis* (during *spermiogenesis*). They are thought to be essential for sperm head condensation and DNA stabilization. After fertilization protamines are removed from paternal chromosomes in the mammalian zygote.

RNA interference (RNAi) Posttranscriptional regulatory effects on mRNAs (control of translation or stability) triggered by processed ds and ss small RNA (si-, mi-, pi RNAs) molecules. Effects are propagatesd by enzymatic complexes such as RISC containing the small RNAs bound by Argonaute proteins.

SAHA Suberoylanilide hydroxamic acid, an inhibitor of ertain histone deactylases, leading to enhanced levels of histone acetylation. See also *TSA*.

S-adenosylhomocysteine (SAH) Hydrolysed product formed after the methylation reaction catalyzed by DNA- and *histone methyltransferases* using SAM as methyl group donor. SAH is a competitive inhibitor of SAM for most methyltransferases.

S-adenosyl methionine (SAM) A cofactor for all DNA- (DNMTs) and histone-methyltransferases (HMTs) providing the methyl group added to either cytosines (DNA) or histones (arginine or lysine).

SET domain A domain found in virtually all lysine-specific *histone methyltransferases (HMTs)*. A protein-protein interaction domain required for HMT activity and modulation of chromatin structure, frequently associated with cysteine-rich Pre-SET and Post-SET domains.

Silencer Element in the DNA to which proteins bind that inhibit transcription of a nearby promoter. Silencer elements are recognized and bound by silencer proteins.

siRNAs Small interfering RNAs, RNAs in the size range of 21–24 nucleotides derived from double stranded long RNAs cleaved by Dicer. siRNAs are incorporated into the RISC complex to be targeted to complementary RNAs to promote cleavage of these mRNAs.

Somatic cell nuclear transfer (SCNT) Transfer of the nucleus of a somatic cell into an enucleated oocyte using a glas capillary to form an SCNT-zygote. After activation of the zygote the genome of the nucleus derived from the somatic cells become reprogrammed to start development.

Spermatogenesis The process by which spermatogonia develop into mature spermatozoa. Spermatozoa (sperm) are the mature male gametes. Thus, spermatogenesis is the male version of gametogenesis.

Spermiogenesis The final stage of spermatogenesis which sees the maturation of spermatids into mature, motile spermatozoa (sperm). During this stage, cells no longer divide and undergo a major morphological transformation. In addition, at most of the genome, histone proteins are replaced by the more basic *protamines*.

Stem cell Non-committed cell which has the capacity to self renew and divide many times giving rise to daughter cells which maintain the stem cell function. Stem cells have the property to differentiate into specialized cells.

Stress A stressor is any event that can activate a physiological stress response, e.g., the body's reaction to the event. Consequently, stress is an inferred internal state, based on the physiological stress response. When a situation is interpreted as being stressful, e.g., novel and possibly threatening (inferred state), this triggers a stress response that is typically represented by the activation of the HPA-axis (see hypothalamic-pituitary-adrenal axis).

Totipotency Capacity of stem cells to produce all cell types required to form a mammalian embryo, i.e. embryonic and extraembryonic cells ***(see Pluripotency)***. Totipotent cells are formed during the first cleavages of the embryo.

Trithorax group proteins Proteins containing a thritorax like bromo-domain: They are usually involved in recognizing histone modifications marking transcriptionally active regions and contribute to maintenance of activity.

Trophoblast Cells of the blastoderm forming the placental tissues in mammals.

TSA ***Trichostatin-A***, an inhibitor of certain types of histone-deacetylases.

X chromosome inactivation Epigenetically controlled form of *dosage compensation* in female mammals resulting in transcriptional silencing of genes on surplus X-chromosomes. X-chromosome inactivation is triggered by the non-coding RNA Xist and manifested by various epigenetic modifications including histone methylation, histone deacetylation and DNA-methylation.

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