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Epigenomics and gene regulation in mammalian social systems

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Abstract

Social epigenomics is a new field of research that studies how the social environment shapes the epigenome and how in turn the epigenome modulates behavior. We focus on describing known gene–environment interactions (GEIs) and epigenetic mechanisms in different mammalian social systems. To illustrate how epigenetic mechanisms integrate GEIs, we highlight examples where epigenetic mechanisms are associated with social behaviors and with their maintenance through neuroendocrine, locomotor, and metabolic responses. We discuss future research trajectories and open questions for the emerging field of social epigenomics in nonmodel and naturally occurring social systems. Finally, we outline the technological advances that aid the study of epigenetic mechanisms in the establishment of GEIs and vice versa.

Key words: epigenetics, DNA methylation, histone modification, rank, social status, social systems

Mammals show a broad range of social systems, characterized by diverse social interactions in terms of their frequency, type (affiliative or agonistic), flexibility, or complexity. Following the definition of mammalian social systems proposed by Kappeler et al. (2013), here we define social systems in terms of their social organization and structure. Social organization refers to the size, composition, cohesion, and genetic structure of a social unit and includes adult individuals which are solitary, form pairs to coordinate their activities with a member of the opposite sex, or form groups to coordinate their activities with 2 or more conspecifics (Kappeler et al. 2013). Social structure refers to the frequency and patterns of interactions between members of a group, which can be influenced by individual traits (e.g., age, sex, social status, or personality) and the degree of despotism between group members (Kappeler et al. 2013).

Group-living animals express a diversity of social behaviors dependent on their environment (Robinson et al. 2008). In turn, this diversity of behaviors is supported by complex physiological processes including neuroendocrine, locomotor, and metabolic responses (Cushing and Kramer 2005; Robinson et al. 2008; Seebacher and Krause 2019). The molecular control of these environmental cue-based physiological responses is orchestrated by gene expression changes (Robinson et al. 2008; Jensen 2013). Therefore, the interactions between genotypes and environmental factors, including the social environment (gene–environment interactions [GEIs] Runcie et al. 2013; Godar et al. 2019) are likely to play a pivotal role during these processes. Consequently, ascertaining the regulatory mechanisms involved in GEIs can help identifying the extent to which GEIs underpin behaviors and social systems.

Although there is an increasing number of studies on the molecular basis of social behaviors, mostly conducted on model species under controlled laboratory conditions (e.g., Weaver et al. 2004; Champagne et al. 2006; Hao et al. 2011; Meaney et al.

2013), little is known about the relationships between behaviors expressed in naturally occurring social systems and gene regulatory mechanisms (Runcie et al. 2013; Rogers 2018; Seebacher and Krause 2019).

At the molecular level, the epigenetic mechanisms react and embed environmental cues into the genome. These properties make them ideal targets for tracking how GEIs induce physiological and behavioral changes (Landecker and Panofsky 2013). As such we define epigenetic mechanisms as chemical modifications and molecules which are triggered by said environmental cues (either endogenous/ microenvironmental or exogenous/ macroenvironmental) and modulate and maintain alternative states of gene expression without changing the underlying DNA sequence (modified from Cavalli and Heard 2019). The sum of all epigenetic mechanisms at a genome-wide scale is the so-called epigenome, which is cell type specific (Cavalli and Heard 2019). The systematic study of the epigenome is therefore termed epigenomics (Bonetta 2008). Furthermore, the integration of epigenomics and its applications into the study of social behavior has given rise to the field of social epigenomics. We refer to social epigenomics as the study of how the social environment shapes the epigenome, and how in turn, epigenetic modifications modulate behavior (Banaudha et al. 2018).

Here, we review the progress made toward identifying GEIs and the role of epigenetic mechanisms in different types of mammalian social systems. We discuss alternative states of gene expression and epigenetic mechanisms associated with different types of social interactions occurring throughout the lifetime of individuals (e.g., from early-life maternal care to social interactions between adults), including those in solitary and group-living mammals. To illustrate how epigenetic mechanisms integrate GEIs, we highlight examples in which epigenetic mechanisms are associated with social behaviors and with its perpetuation mainly through neuroendocrine, locomotor, and metabolic responses. We also discuss future research trajectories and open questions brought about as the field of social epigenomics gains more attention in nonmodel and naturally occurring social systems. We close with a brief outline of the technological advances that are aimed at accelerating our understanding of the involvement of epigenetic mechanisms in the establishment of GEIs and vice versa.

Epigenetic Mechanisms

Epigenetic mechanisms respond dynamically to environmental cues, including nutrition, climatic and seasonal conditions, the social environment, etc. (Beck et al. 2017; Cavalli and Heard 2019; Kubsad et al. 2019). These responses can remain stable over cell divisions and can be transmitted to subsequent generations through germline embedding (Beck et al. 2017; Cavalli and Heard 2019; Kubsad et al. 2019). The epigenetically regulated cell-type-specific responses modify gene expression, thereby activating diverse neuroendocrine, locomotor, and metabolic circuits that result in behavioral outcomes (Landecker and Panofsky 2013; Rogers 2018). For a better understanding of these processes, we first briefly describe the main epigenetic mechanisms.

Epigenetic mechanisms can be classified based on the level at which they act to regulate gene expression. They can affect 1) DNA accessibility by changing the chromatin compaction state, 2) post-transcriptional/pretranslational interference via noncoding (nc) RNAs, and 3) gene transcription via molecular tags of which DNA methylation is the best-studied mechanism.

The chromosomal DNA folds around proteins known as histones and forms packing units called nucleosomes. These nucleosomes are further compacted and the resulting DNA-protein complex is called chromatin. The chromatin has variable degrees of compaction which are tightly coupled with gene expression. As such, tightly compacted chromatin (heterochromatin) is transcriptionally inactive, whereas the less compacted chromatin (euchromatin) is transcriptionally active, allowing gene expression (Peterson and Laniel 2004; Nelson and Monteggia 2011). Chemical modifications on these histones (e.g., by acetylation, phosphorylation, mono-, di-, trimethylation, ubiquitylation, and SUMOylation) lead to changes in the chromatin compaction state, altering DNA accessibility, and thus gene expression (Champagne et al. 2006).

A well-studied histone modification is the transfer of an acetyl group to lysine by the enzyme histone acetyltransferase. This acetylation neutralizes the positive charge of the lysine, weakens the interaction between histones and DNA, thus reducing chromatin compactness. Other important enzymes are the histone lysine methyltransferase and protein arginine methyltransferase, which may act as activators or repressors (Palumbo et al. 2018).

ncRNAs are a diverse group that comprises small non-coding RNAs (also often called sncRNAs) and long ncRNAs. ncRNAs regulate gene expression by interacting with gene transcription (Choudhuri 2010; Stuwe et al. 2014). One class of ncRNAs often used in behavioral studies is micro RNAs (miRNAs; Issler and Chen 2015; Allen and Dwivedi 2020). Untranslated small RNA transcripts bind to the 3′ untranslated region of their target messenger RNAs (mRNA). After binding, gene expression is regulated through a silencing complex and/or by destabilization of the mRNA. miRNAs can either fully block gene expression or can act as "fine tuners" of gene expression levels (Choudhuri 2010; Issler and Chen 2015). The latter is a very active process in the mammalian adult brain, where the structure and function of neuronal networks are influenced by miRNAs via such fine-tuning of gene expression (Issler and Chen 2015).

DNA methylation is an epigenetic modification that remains stable over cell divisions, conveys transgenerational effects and mediates cellular memory (Tung et al. 2012; Stuwe et al. 2014). DNA methylation is very important during embryogenesis (e.g., silencing of retrotransposons, genomic imprinting, and X-chromosome inactivation), as well as in dynamically modulating physiological pathways during the lifetime. It is known, for instance, that the alterations in gene expression that follow neuron depolarization on environmental stimuli are accompanied by modifications of the epigenome that include DNA methylation changes (Guo et al. 2011; Moore et al. 2012).

The effects of DNA methylation strongly depend on the genomic region where these changes occur. DNA methylation at promoters generally decreases transcriptional activity (Glaser and Kiecolt-Glaser 2005), whereas the function of DNA methylation at gene bodies remains poorly understood (Moore et al. 2012). Opposing evidence suggests that depending on cell type, DNA methylation at gene bodies associates with either an increase in gene transcription or with gene silencing (Moore et al. 2012). Consequently, DNA methylation at promoters is more commonly studied as a marker of gene expression regulation (Cavigelli and Chaudhry 2012; Moore et al. 2012). It is known that DNA methylation mediates gene expression primarily by recruiting repressive methyl-binding proteins and/or by inhibiting the access of the transcription machinery to the DNA (Moore et al. 2012). Additionally, DNA methylation can

downregulate gene expression by promoting the formation of heterochromatin (Champagne et al. 2006).

DNA methylation is performed by specialized DNA methyltransferases (DNMTs). DNMT-1 is a methyltransferase responsible for the maintenance of DNA methylation during cell division, whereas both DNMT-3a and DNMT-3b catalyze de novo methylation. These enzymes methylate cytosines, preferably in cytosine–guanine dinucleotides (CpGs). Most CpGs are grouped in specific loci, such as regulatory regions like promoters, as well as in exons, and to a lower extent in introns. These groups are known as CpG islands (CGIs; Moore et al. 2012). Over 2/3 of mammalian promoters reside within CGIs (around 70%), and practically all known housekeeping genes have CGI nested promoters. DNA methylation at CGIs is, therefore, one of the most important epigenetic markers (Pelizzola and Ecker 2010; Moore et al. 2012). De novo methylation is known to be highly active during early embryogenesis, highlighting the potential susceptibility of this stage to environmental stimuli (see below). The dynamic nature of DNA methylation gives place to both active and passive demethylation. Active demethylation occurs via a group of enzymes called ten-eleven translocation enzymes, whereas passive demethylation occurs by dilution on DNA replication after each cell division (Vincenzetti et al. 2019). Akin to the term epigenome, the methylome comprises the genome-wide DNA methylation profile of a cell, tissue, or organism (Pelizzola and Ecker 2010).

The interplay between all epigenetic mechanisms orchestrates both stable and transient gene expression changes (Moore et al. 2012). Such plasticity is necessary to regulate higher-order physiological responses, and ultimately behavior. Furthermore, due to the extensive epigenetic reprogramming that occurs during embryonic and fetal development, the genome is particularly susceptible to stimuli during these stages, a susceptibility that continues well into the perinatal stage (Skinner and Guerrero-Bosagna 2009; Szyf 2011). To emphasize its importance, this period of increased susceptibility has been coined as the "early-life window" (Jirtle and Skinner 2007; Skinner and Guerrero-Bosagna 2009). The "early-life window" is a paramount target to study GEIs in the context of behavior, as we discuss below.

Social Interactions and Epigenetic Mechanisms

Immediate and long-lasting effects of maternal care

The conditions experienced during early life, the period from conception to developmental maturity (Lindström 1999), strongly shape the phenotypes of organisms. During this period, hormones and receptors are organized as the central nervous system develops. As a result, environmental cues during early life can have both immediate and long-lasting influences on susceptibility to stress and diseases, metabolism, or on evolutionary (fitness) components such as fertility, growth, and longevity (Cushing and Kramer 2005; Monaghan 2008). One main factor of an offspring's environment that can have particularly pronounced and long-lasting effects is the environment provided by its parents (Mousseau and Fox 1998). In mammals, females usually invest more time and energy than males for the pre- and postnatal development of offspring (Broad et al. 2006). Therefore, parental effects are usually more likely to result from mothers than fathers (Bernardo 1996; Maestripieri and Mateo 2009) and are often referred to as maternal effects. Maternal effects constitute pathways by which the maternal phenotype affects the expression of the offspring phenotype (Mousseau and Fox 1998; East et al. 2009). Genes involved in social interactions are listed in Table 1.

A pioneer study by Weaver et al. (2004) showed that rat mothers that exhibit higher levels of pup-licking and grooming caused a reduction in DNA methylation of the hippocampal glucocorticoid receptor (*GR*) gene in the offspring and that this behavior is passed on from mothers to their offspring. The increase in *GR* expression was accompanied by an increase in histone acetylation and in NGFI-A transcription factor binding to the *GR* gene promoter. Cross-fostering experiments reversed the degree of pup-licking and grooming behavior, and epigenetic signatures were maintained into adulthood (Weaver et al. 2004).

Another study from the same research group showed that early-life stress and deprivation of maternal care in rats caused a long-lasting downregulation in the expression of hippocampal *GR* genes (Meaney et al. 2013). In adolescent rats, the quantity of licking and grooming behavior, as well as the sex composition of the litter was linked to methylation patterns of the μ-opioid receptor (*Oprm1*) in the hippocampus and *nucleus accumbens* (Hao et al. 2011). Intense pup-licking/grooming by female rats during the first week postpartum lead to an increased estrogen receptor-α (*ER-α*) expression in the medial preoptic area of their female offspring (Champagne et al. 2006), and this increased expression is transmitted across generations (Matsuda 2014 and references therein).

These results underline that environmental cues experienced during early-life may result in important epigenetic and behavioral modifications. These effects in turn may have important consequences for behavior later in life and may be transmitted to subsequent generations via DNA methylation and histone modifications (Matsuda 2014). Environmental signals may cause an epigenetic reprogramming of the germline only during a narrow developmental phase (Skinner and Guerrero-Bosagna 2009), but generally very little is known about the size of early-life windows in nonmodel species and free-ranging wildlife populations.

Studies investigating the transmission of traumatic information (e.g., maternal care deprivation) via sncRNA demonstrated that male mice that had experienced reoccurring early-life stress showed an increase in 9 specific miRNAs (Rodgers et al. 2013). When sncRNA was isolated from the sperm of males that had experienced deprived maternal care and was then injected into fertilized naive oocytes, these sncRNAs transmitted the traumatic experiences and metabolic alterations from father to offspring (Gapp et al. 2014).

In rhesus macaques *Macaca mulatta*, the deprivation of maternal care in early life led to high methylation of promoters of frontal cortex genes, resulting in their reduced expression. This downregulation remained stable into adulthood (Massart et al. 2014). In comparison, in peer-reared offspring, the binding of histone 3, trimethylated at lysine 4 (H3K4me3), was reduced in regions of genes critical to behavioral stress response in the hippocampus (Baker et al. 2017). Because H3K4me3 is associated with actively transcribed genes (Ruthenburg et al. 2007), a reduction of its binding leads to a less effective stress response. In particular, the transcription activity for the oxytocin receptor gene was reduced. Oxytocin is a neuropeptide that is very important during parturition and for mother–offspring bonding. It is also very important for social affiliation, caregiving, social separation response, stress response, learning, and memory (Baker et al. 2017; Perkeybile and Bales 2017).

Interestingly, fathers and offspring might also influence the extent of maternal care. During pregnancy female mammals are primed for providing maternal care, and some evidence suggests that this is partly induced by placentally-secreted hormones. In

laboratory mice, the paternal allel of the gene *pleckstrin* homology-like domain family A member 2 (*Phlda2*) is silenced by epigenetic imprinting. It has been shown that female mice pregnant with offspring carrying the imprinted *Phlda2* display increased maternal care, whereas the opposite effect was observed when offspring carries two active (non-imprinted) alleles (Creeth et al. 2018). This evidence suggests that maternal care may be influenced by the father's genome, as well as profound effects of normal or aberrant genomic imprinting.

Puberty and aggressive behavior during puberty and adulthood

Puberty is often considered another sensitive window in an organism's life, as the effects of environmental cues on phenotype may be particularly marked and have long-term consequences when occurring during this period. In many mammals, aggressive behavior increases with the onset of reproductive activity and is associated with modified hormone levels, especially for testosterone and serotonin (Jarrell et al. 2008; Batrinos 2012). The role of the serotonin transporter (*5-HTT*) in this process has been investigated in several mammalian species. The effects differed depending on the allele studied, and there was no clear behavioral association with a certain genotype (in baboons: Kalbitzer et al. 2016; in female rhesus macaques: Jarrell et al. 2008; van der Kooij and Sandi 2015; Wilson and Kinkead 2008; in dogs and grey wolves: Koch et al. 2016; Banlaki et al. 2017).

The absence of a purely genetic cause despite the detected genetic variation suggests the action of epigenetic mechanisms. In humans, several epigenetic signatures of the serotonin pathway are known. They are linked to early-life aversive experiences and exert changes that increase the risk of developing aggressive or antisocial behaviors (Palumbo et al. 2018). Similarly, fear induction experiences in peripubertal rats lead to an elevated and maintained expression of monoaminooxidase A (*MAOA*) caused by an increased histone 3 (H3) acetylation at the *MAOA* promoter (Márquez et al. 2013).

Epigenetic regulation also plays a role in the secretion of the gonadotropin-releasing hormone (GnRH). GnRH is important for the development of reproductive function as it controls the secretion of pituitary hormones such as gonadotropins. GnRH secretion is activated at mammalian puberty and epigenetically influenced via histone acetylation at the hypothalamic *Kiss1* gene locus (coding for *kisspeptin*). The regulation of the *Kiss1* gene expression in the two populations of hypothalamic kisspeptin neurons (located in two different areas of the brain) is crucial for the onset of puberty and subsequent reproductive performance (Uenoyama et al. 2016).

A study in humans showed that DNA methylation patterns in peripheral blood reflect the pubertal development (Almstrup et al. 2016). In the hypothalamus, the *embryonic ectoderm development* (*Eed*) gene and the *Chromobox* (*Cbx*) gene are silenced by DNA methylation at the onset of puberty. This has also been observed in female rats (Lomniczi and Ojeda 2016).

Aggressive behavior and social support have been observed in wild house mice *Mus musculus domesticus*. Wild house mice forms social hierarchies in which dominant males defend territories harboring subordinate males, females, and pups, whereas other (subordinate) males experience severe social exclusion, accompanied by physical aggression by dominant males (Fickel and Weyrich 2011; Krause et al. 2015). Such social exclusion is considered to be a very severe stressor (Krause et al. 2015). A study on the epigenetic effects of such social exclusion revealed important differences in concentrations of lysine 4-trimethylated histone-3 (H3K4me3) and lysine 27-acetylated histone-3 (H3K27ac) in chromatin regions of numerous metabolic genes in the liver (e.g., *Cyp4a14*, *Gapdh*, and *Nr3c1*). These differences clearly distinguished socialized from socially excluded mice (Krause et al. 2015). As the test was performed with adult mice, it remains to be elucidated if such "histone patterns of social exclusion" emerged during adulthood or earlier, and if they are additionally accompanied by phenotypic, physiological, or epigenetic differences.

Another gene that is involved in the establishment of social status in mice is the growth factor receptor-bound protein gene *Grb-10*, which in the brain isonly paternally expressed (i.e. maternally imprinted, whereas the maternal allele is silenced) from fetal life into adulthood. It has been experimentally shown that mice lacking the expression of this allele exhibit increased social dominance. These mice were more likely to prevail in forced encounters than mice carrying the normal allele and were responsible for grooming their cage mates (Garfield et al. 2011). Both of these behaviors are considered expressions of dominance in laboratory mice. This was the first time that an imprinted gene was described to regulate a behavioral trait (Garfield et al. 2011). In proximity to the *Grb-10* locus resides the gene for DOPA decarboxylase (*DDC*), an enzyme that is essential for producing dopamine, noradrenaline, adrenaline, and serotonin (Hodgetts and O'keefe 2006; van der Kooij and Sandi 2015). In humans, this gene and its epigenetic regulation have been studied in models that try to explain the perpetuation of a family's socioeconomic status and social dominance across generations via the synthesis of catecholamines and indolamines (Hodgetts and O'keefe 2006; van der Kooij and Sandi 2015). A similar regulation might also be involved in the transmission of molecular mechanisms associated with social status in other mammal species.

Pair bonding and (sexual) partner preference

Affiliation is a positive kind of social behavior that brings animals together (Carter 2014). Such complex behavior is governed by endocrine and neuromodulatory systems that are intensely studied to understand the contribution of genes to the evolution of behavior and GEIs (Phelps and Young 2003).

The major hormones studied in this context are oxytocin (see above) and vasopressin. The peptide hormone vasopressin and its receptor (V1aR) are modulating recognition of individuals, communication, aggression, paternal care, and pair-bonding in monogamous species. Expression patterns of the *V1aR* are shared among the monogamous prairie vole *Microtus ochrogaster* and the pine vole *M. pinetorum*, but differ in their promiscuous congeners, the meadow vole *M. pennsylvanicus* and the montane vole *M. montanus* (Phelps and Young 2003). The molecular mechanism behind these patterns of expression is a single-nucleotide polymorphism (SNP), a variation at a single nucleotide position in the DNA sequence haplotype, which is strongly associated with *V1aR* density in the retrosplenial cortex, an area involved in spatial memory and sexual fidelity. The SNP variant occurring in *M. ochrogaster* and *M. pinetorum* was correlated with an increased monomethylation of Histone 3 at lysine 4 (H3K4me1; Okhovat et al. 2015). Besides histone acetylation, DNA methylation is also involved in the developmental regulation of V1aR abundance. This was demonstrated by investigating different receptor alleles containing different frequencies of CpG sites (Okhovat et al. 2018).

The role of histone acetylation in partner preference and pair bonding was further tested by the injection of histone deacetylase inhibitors (sodium butyrate and trichostatin A) into the brains of female prairie voles *M. ochrogaster* (Wang et al. 2013). The effect was

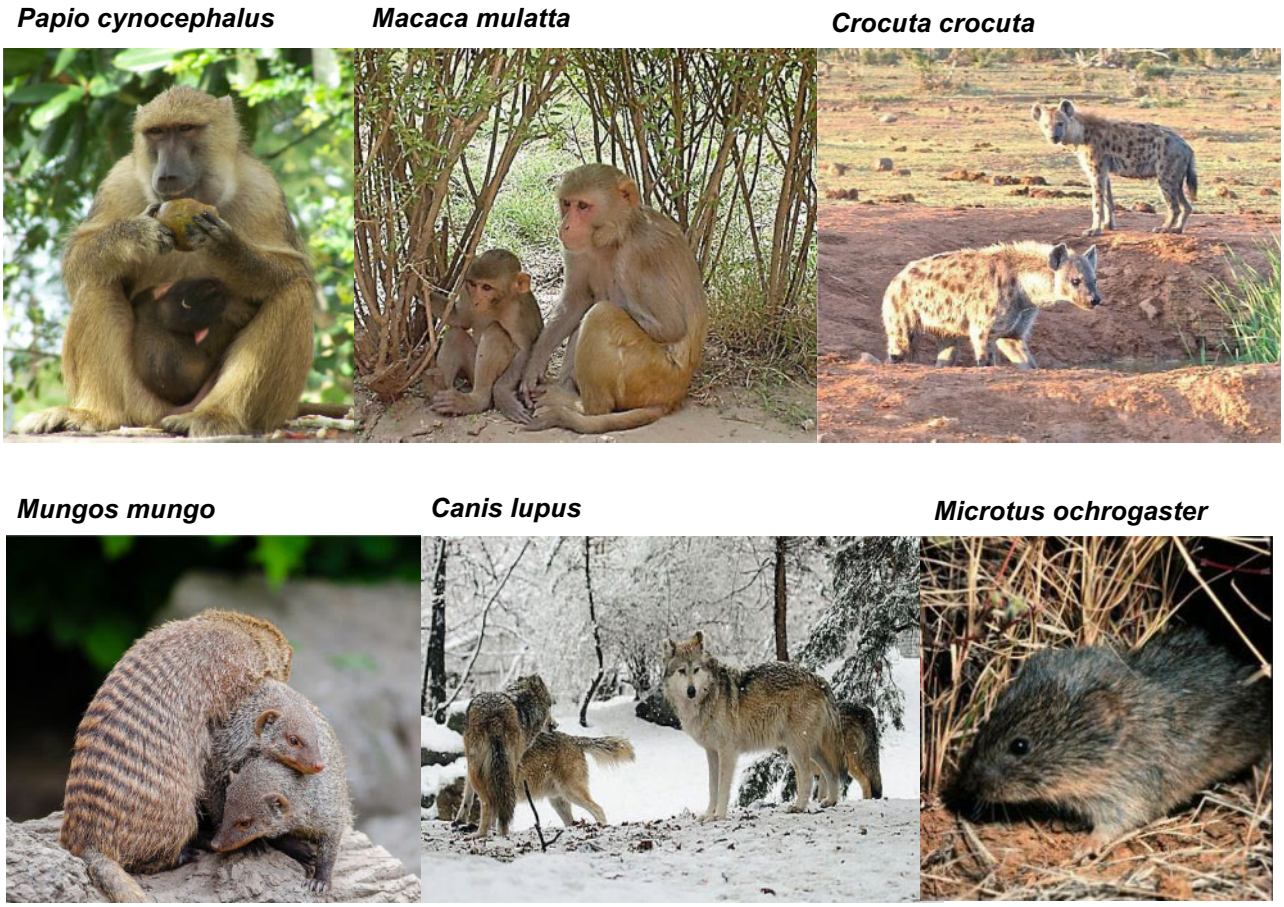

Figure 1. Illustration of the diversity of mammalian social and breeding systems (from upper left to lower right): yellow baboons *P. cynocephalus,* rhesus macaques *M. mulatta,* and spotted hyenas *Crocuta crocuta* in groups structured by a stable linear dominance hierarchy, wild banded mongooses *M. mungo* in groups with cooperative breeding, wolves *Canis lupus* in a pack with one reproducing pair and prairie voles *M. ochrogaster* in communal groups with lifelong pair-bonding. (© Pictures were taken from Wiki Commons.)

striking, as it induced a permissive state through an increased histone acetylation at the oxytocin receptor locus and the vasopressin receptor promoter in the nucleus accumbens, resulting in the enhanced expression of the corresponding genes. This result was the first evidence for an epigenetic regulation of pair-bonding (Wang et al. 2013).

Social systems and social status

In mammalian social systems (see Figure 1 for examples), the social status of an individual is often considered a behavioral trait, which is determined by the individual's interactions with its social environment (Watts 2010; Clutton-Brock 2016; Vullioud et al. 2019). More specifically, the social status of an individual refers to its position in a given dominance hierarchy. The acquisition and maintenance of social status can result from several processes, including intrinsic attributes such as body size or fighting ability, social support, or winner and loser effects (East et al. 2009; Vullioud et al. 2019).

The social status of an individual may profoundly effect its access to resources, physiological or immune processes or fitness. In stable and highly-structured social systems, individuals with a high social status enjoy priority access to resources, a privilege that strongly affects their life history (Stearns 1989) and increases their fitness (survival and lifetime reproductive success), compared with individuals with a low social status (Silk 2007; Kerhoas et al. 2014).

These status-related differences in life history traits may also be accompanied by status-related differences in physiology. In stable social hierarchies, in which dominant animals are not socially challenged by subordinate individuals and in which subordinates receive intense aggression by dominants, circulating concentrations of glucocorticoids (GC) are usually higher in subordinates than in dominants (Creel 2001; Abbott et al. 2003; Goymann and Wingfield 2004; Sapolsky 2005; Benhaiem et al. 2013) and may impair immune processes (Glaser and Kiecolt-Glaser 2005). In line with life history theory (McNamara and Houston 1996; Glaser and Kiecolt-Glaser 2005), inferior access to food resources causes low-status individuals to reduce their internal allocation of energy to immune processes (Archie et al. 2012; East et al. 2015; Marescot et al. 2018).

These status-related differences suggest the involvement of gene regulatory mechanisms. With the exception of a series of pioneer studies in captive rhesus macaques (Tung et al. 2012; Snyder-Mackler et al. 2016a, 2016b), only few studies have revealed the specific molecular mechanisms linking social status and physiological responses (Bossdorf et al. 2007).

New cost-effective DNA sequencing technologies now allow focusing on more genes (as further discussed in Section

'Conclusionas and future trajectory of social epigenomics'), their allelic variants and their regulatory mechanisms, including epigenetic mechanisms. Behavioral variation correlates with gene variants and their different expression (Jensen 2013), but is also strongly influenced by GEIs (Runcie et al. 2013). For some neurobiological and metabolic pathways, the physiological responses associated with these processes are known from model organisms, such as for the hypothalamic–pituitary–adrenal axis, for elements of the sympathetic nervous system (Cushing and Kramer 2005; Jensen 2013), and for steroid hormones (Cushing and Kramer 2005). Examples, again, are the neuropeptide oxytocin (Dantzer et al. 1987) and the prohormone vasopressin (Phelps and Young 2003; see also 'Puberty and agressive behavior during puberty and adulthood'). When studying the relationships between social status and epigenetics, at least two scenarios have to be considered: 1) social status is behaviorally "inherited" during postnatal development and 2) social status is acquired (or changed) during adulthood.

Female Philopatry and Linear Dominance Hierarchies

Hereafter, we describe recent findings on the relationships between social interactions and epigenetic mechanisms in three mammalian species living in complex societies, structured by a linear dominance hierarchy; rhesus macaques, yellow baboons, and spotted hyenas (Figure 1). In all three species, as in most mammals, females are philopatric and males disperse (Greenwood 1980). Philopatry promotes the emergence of potentially important social bonds and social support among (adult) females. Social relationships among adult females can also be "negative," e.g. during competitive interactions (e.g. von Holst et al. 2002; Wasser et al. 2004; McLoughlin et al. 2006). In all three species, daughters acquire a social rank which is just below that of their mother and above that of their older siblings, and which as acquired through a process of maternal behavioral (social) support during interactions with other group members (Bernstein and Williams 1983; Bernstein and Ehardt 1986; East et al. 2009; Maestripieri and Hoffman 2011). In spotted hyenas, a species with low sexual dimorphism, female dominance was recently found to emerge from female philopatry and a disparity in social support in favor of this sex (Vullioud et al. 2019).

Rhesus macaques

Most of the work on social epigenomics in non-rodent organisms was done in captive rhesus macaques, both because they are a model species in neurobiology and because they form complex social structures (Chang et al. 2013). In this species, CpG methylation patterns are associated with social status. For example, placental DNA methylation patterns in high and low-status female rhesus macaques differed significantly in genes of essential pathways such as cellular growth and proliferation, apoptosis, and molecule transport (Massart et al. 2017). DNA methylation patterns in peripheral blood cells also differed between females of high and low status, as did the expression of genes for GC-mediated signaling and for the immune and pro-inflammatory response (Tung et al. 2012). Experimental alteration of an individual's social status changed cell-specific gene expression (Snyder-Mackler et al. 2016b). Thus, both DNA-methylation patterns (Tung et al. 2012; Massart et al. 2017) and gene expression (Snyder-Mackler et al. 2016b; Massart et al. 2017) are affected by the social environment.

Yellow baboons

A few studies on social epigenetics have also been conducted in non-model species. Two studies in free-ranging baboons of the Amboseli basin of Kenya (one focusing on yellow baboons *Papio cynocephalus* [Lea et al. 2018a] and one on pure yellow baboons *P. cynocephalus* and some hybrids with anubis baboons *P. anubis* [Runcie et al. 2013]) have included long-term behavioral data and genomic approaches to study GEIs. In these species, a male social status is typically determined by its fighting ability. Social environment characteristics, as well as sex and age, were found to strongly influence gene expression dynamics in yellow baboons (Runcie et al. 2013). Group size and social connectedness in adulthood were related to consistent and socially-mediated GEIs, both in females and males. As males typically disperse, thereby encountering new social environments, they are likely to experience more frequent epigenetic modifications and gene expression changes (as suggested by Weyrich et al. (2015). In addition, factors associated with access to mates (e.g. tenure in a group, testosterone and glucocorticoid levels) may then become more relevant than early-life experiences. In females, the absence of maternal social status-mediated GEIs was a surprising finding (Runcie et al. 2013), given previous evidence that maternal social status drives growth, the timing of reproductive and social maturation, and ultimately the social status females finally achieve (Alberts 2018). The authors did not (yet) test for genome-wide epigenetic modifications (see below). Therefore, though GEIs occur in social environments, the regulatory mechanisms underpinning the observed behavioral phenotypes are still poorly understood.

In yellow baboons, many of the differentially expressed genes that are influenced by the social environment strongly relate to immune function (Tung et al. 2012; Runcie et al. 2013). A study focusing on male Amboseli baboons, showed that high-social status males have a faster wound healing than low social status ones (Archie et al. 2012). Gene expression analyses (RNA-Seq) were used in wild baboons to study the expression of immune genes (Lea et al. 2018a). More than 2,000 social status-associated genes were identified in males, considerably less in females. In high social status males, increased expression of innate immunity genes was correlated to a preferential activation of the NF-κB-mediated pro-inflammatory pathway. Interestingly, this pathway was associated with low status in female rhesus macaques (Slavich and Cole 2013).

The study by Lea et al. (2018a) provides evidence that high social status-associated gene expression patterns are precursors and not consequences of high social status in males, supporting the concept that physiological conditions and regulation of gene expression may precede the achievement of high social status in wild social mammals under some conditions. Lea et al. (2018a) also drew attention to highly context-dependent relationships between social status and the regulation of gene expression. For instance, captive female rhesus macaques with a low social status have more euchromatin in regions of transcription factor genes related to inflammatory response (Snyder-Mackler et al. 2018), whereas high social status captive females exhibited more accessible binding sites for transcription factor genes related to an anti-inflammatory response (Lea et al. 2018a). In contrast, free-ranging female baboons had no social status dependent differences in their expression of innate immunity and inflammation-related genes, whereas in males such associations existed. High social status males exhibited an increased expression of innate immunity genes and a preferential activation of the NF-κB-mediated pro-inflammatory pathway. These striking differences may occur because free-ranging females in this species have the opportunity to protect themselves from status-associated stressors by

Table 1. Genes and epigenetic markers identified in social behaviors across species

Gene ID	Environmental effect and epigenetic mark	Species	References
Cbx	Puberty, silenced by DNA methylation at the onset of puberty	Humans, female rats	Lomniczi and Ojeda (2016); Almstrup et al. (2016)
Cyp4a14, Gapdh, Nr3c1	H3K4me3 and H3K27ac change chromatin compaction in gene regions, which distinguish socialized from socially excluded mice	Mice	Krause et al. (2015)
ER-α	Maternal care investment	Rats	Champagne et al. (2006)
5-HTT	Social dominance and subordination	Rhesus macaques, humans	Wilson and Kinkead (2008)
	Aggressiveness	Dogs and wolves	Koch et al. (2016); Banlaki et al. (2017)
GR	Reduced mDNA and increased expression as a consequence of high maternal care	Rats	Weaver et al. (2004); Meaney et al. (2013)
Grb-10	Its absence or downregulation associates to reduced social dominance. Possibly in combined action with DOPA decarboxylase (*DDC*) gene, encoding an enzyme essential for producing dopamine, noradrenaline, adrenaline, and serotonin	Mice	van der Kooij and Sandi (2015)
Kiss1	Puberty and reproductive performance, regulating GnRH secretion	Mammals, incl. rodents and humans	Uenoyama et al. (2016)
MAOA	Aggressiveness increased H3 acetylation at MAOA promoter relates to peripubertal aversive experiences.	Baboons, rats	Márquez et al. (2013); Kalbitzer et al. (2016)
Oprm1	Changes in mDNA in response to quantity of licking and grooming behavior	Rats	Hao et al. (2011)
Pleckstrin/Phlda2	Maternal care, imprinted genes	Mice	Creeth et al. (2018)
V1aR	Recognition, communication, aggression, paternal care, and pair bonding in monogamous species. SNP variant associates to increased monomethylation of Histone 3 at lysine 4 (H3K4me1).	Voles	Phelps and Young (2003); Okhovat et al. (2015)
Other findings			
MicroRNA	ncRNAs germline transmission of traumatic behavior and metabolic alterations	Mice	Rodgers et al. (2013); Gapp et al. (2014)
Global DNA methylation differences	Global promoter methylation and reduced expression of cortex genes plus reduced H3K3me3	Macaques	Massart et al. (2014); Baker et al. (2017)
Global DNA methylation differences	Global DNA methylation differences, higher CCGG methylation associated with high social status	Spotted hyena	Laubach et al. (2019)

investing in social bonds with kin, whereas in captivity, animals are typically housed apart from kin, causing acute status-associated chronic stress (Lea et al. 2018a).

To gain a general overview of the influence of social status on nutrition and access to resources, genome-wide, whole-blood DNA-methylation levels were measured in two groups of wild baboons exposed to different diets: one group of wild-feeding baboons foraging in their natural savanna environment, and a second group which was fed with human food scraps (Lea et al. 2016). More than 1,000 CpG sites were differentially methylated between the two groups, mostly affecting gene expression levels at metabolism-related genes.

Spotted hyenas

A recent study in free-ranging spotted hyenas *Crocuta crocuta* in the Masai Mara National Reserve in Kenya associated global DNA methylation changes with socioecological factors in three age classes (Laubach et al. 2019). The results indicate associations between maternal rank, anthropogenic disturbance and prey availability early in life with later life global DNA methylation. Cubs born to mothers of high social status had a 2.75% higher global methylation than cubs of mothers of low social status. DNA methylation is highly targeted at specific genes and gene pathways dependent on specific environmental factors (Weyrich et al. 2015, 2018, 2019). As the method applied in this study did not allow for the identification of the genes underlying these differences, the functional relevance of this increased methylation in high-born cubs remains unclear.

Highly Cooperative Behavior

Although most knowledge on the interactions between social behavior and epigenetic mechanisms in free-ranging social mammals is based on species where groups are structured by a linear dominance hierarchy (see 'Female philopatry and linear hierarchies'), epigenetic mechanisms are expected to also play a role in other species showing high levels of cooperative behaviors, as we illustrate in this section.

Banded mongooses

To our knowledge, no study ever investigated the relationships between epigenetic mechanisms and the typical behaviors observed in mammalian cooperative breeding systems. We detail below why and under which conditions such relationships would be expected. Cooperative breeding is a type of social system, where offspring are raised by their parents and by additional members of the group, often called "helpers" (Lukas and Clutton-Brock 2012). Banded mongooses *Mungos mungo* are an interesting example of cooperative breeders in mammals.

Depending on the mean ecological conditions encountered during their early life and adolescence, male wild banded mongoose may adopt a "live fast—die young" or "live slow—die old"

strategy, resulting in similar fitness (Marshall et al. 2017). Interestingly, "silver spooned" males had globally a lower fitness than males who experienced bad or variable early-life ecological conditions, and such effects were not observed in females (Marshall et al. 2017).

In another study on banded mongooses, lifelong fitness was increased for juveniles that had been cared for by adult helper mongooses that were not their parents, in one-to-one relationships. These benefits were detected in both male and female recipients (Vitikainen et al. 2019). Although in males these fitness effects depended on body mass (the heavier the greater the benefits), females always profited from helpers care independently of the body mass they had when reaching maturity. Because in rats such care (i.e., grooming/licking) has an epigenetic basis (Weaver et al. 2006; Cameron et al. 2008), similar mechanisms of epigenetic inheritance may also be in place in banded mongooses (Vitikainen et al. 2019). Studying these phenomena with an epigenomics approach might elucidate relevant circuits and provide valuable insights beyond the traditional medical-oriented (e.g., anxiety, stress susceptibility, behavioral disorders, etc.) concept of early-life experiences.

Wolves

Wolves live in social groups called packs and show cooperative hunting. Wolf packs consist of one reproductively dominant alpha-couple and their offspring, with pack sizes of 5–8 wolves (Miklosi 2016). Offspring disperse with the onset of puberty (Mech and Boitani 2003). Genome-wide gene expression profiles of whole blood cells were analyzed for rank-effects in wolves from the Yellowstone National Park, accounting for age, social rank, disease status, and sex, while controlling for genetic relatedness (Charruau et al. 2016). Surprisingly, the study found no effect of rank on gene expression, possibly because of the relatively tolerant relationships between pack members. Wolf packs are usually families, where *alpha* denotes the breeding pair, typically the parents of all other pack members. Therefore, differences in stress levels and in resource access, or in received aggression from other group members are less severe, which in turn might lead to similar gene expression patterns. Second, a wolf's social status and age are positively correlated and may have crossing effects on biological pathways (Snyder-Mackler et al. 2014), which could have limited the statistical power to detect social status effects independently of age.

Conclusions and Future Trajectory of Social Epigenomics

Social epigenomics is making its way into the study of GEIs in the context of behavior and social interactions, both in model and non-model organisms. The examples discussed here show that social behaviors can be traced to the molecular governing of physiological responses and in turn to epigenetic mechanisms. There are important epigenetic pattern associations for age classes (e.g., macaques), sex (e.g., baboons), and social status (e.g., hyenas).

Given the different responses to environmental stimuli between sexes, investigating differences at the epigenetic regulation of neuroendocrine responses between sexes is worth pursuing by social epigenomics. Similarly, the study of the epigenetic mechanisms and physiological pathways that associate with social status represents one of the most appealing avenues for the study of GEIs and social epigenomics. Furthermore, in order to understand the extent to which GEIs underpin social systems, it would be very valuable to be able to ascertain the epigenetic mechanisms that associate with the maitenance and dynamics of social status, spanning different naturally occurring social systems.

We believe that beyond the individual-centered approach (e.g., how maternal care affects DNA methylation levels associated with anxiety and stress susceptibility; histone modifications associated with submissiveness in mice, etc.) a GEIs-epigenomics perspective can be applied to either challenge or support classical findings in evolutionary ecology. For instance, epigenetic marks can potentially be associated with seen effects of good early-life, ecological conditions and fitness outcomes (e.g., silver spoon effect, Grafen 1988; environmental matching of early and adult life in short-lived species, Monaghan 2008), or other forms of long-term consequences of early-life conditions (see e.g., Marshall et al. 2017; Danchin et al. 2019). Furthermore, it would be interesting to assess the stability of such epigenetic markers along different timescales. We propose a combination of ecological methods and epigenomics to shed light on the molecular underpinnings of life history physiological and behavioral adjustments that are ubiquitous among social mammals.

To understand the interplay between plasticity and environmental constraints in the evolution of social behavior it is necessary to develop and to validate methods that test how epigenetic regulation influences behavior under naturally occuring social systems (Kappeler et al. 2013; Runcie et al. 2013). Thereby, in the last sections, we discuss open questions inherent to the field of epigenomics and technical developments that can help fill in those gaps.

Open questions and challenges

Despite big advances in the field of epigenomics, a relevant question that remains to be addressed is to what extent environmentally-responsive molecular mechanisms can be generalized across similar contexts, tissues, or species (Snyder-Mackler and Lea 2018). Environmental fluctuations trigger epigenetic changes that are assimilated primarily on the tissue or system that is directly involved in the response to the stimulus and subsequently, these changes are also systemically integrated to activate higher-order physiological responses. Due to the systemic cascade of gene expression regulation that follows these processes, it is a common practice to monitor these changes in proxy-like tissues (surrogate tissues), such as peripheral blood cells (e.g., Tung et al. 2012) or exfoliated cells from buccal swabs (Snyder-Mackler et al. 2014). However, this is challenging because, while systemic, the epigenetic mechanisms might elicit different gene regulatory effects depending on the tissue and the time at which they are captured. Therefore, to overcome this shortcoming it would be necessary to trace the epigenetic changes that act at each level, which might be indicators of the studied system or pathway (Landecker and Panofsky 2013; Weyrich et al. 2020). For behavioral studies, efforts could focus on shifts at neuroendocrine and locomotor responses (Landecker and Panofsky 2013).

Causality between environmentally-sensitive epigenetic mechanisms and changes in phenotypes has so far been poorly tested (Snyder-Mackler and Lea 2018). This is particularly the case in wild and free-ranging species, where experimental settings to reduce confounding variables and to test causality are usually unrealistic. Nevertheless, with the development of novel inferential tools, these problems may become solvable in the near future (Snyder-Mackler and Lea 2018). For example, such approaches have been used to test GEIs at a finer-scale, using a combination of machine learning (e.g., to select potentially functional genetic variants) with mixed-linear models selected based on techniques for model selection, such as the

Akaike information criterion (Czamara et al. 2019). Additionally, Mendelian randomization, which uses well-characterized genetic variants as proxies for testing causal effects (Richardson et al. 2018) could be adapted for its use on social epigenomics settings.

Another important aspect that merits further research is ascertaining the phases in life when animals are most sensitive or receptive to social or physical environmental inputs. It is still greatly unknown which specific environments organisms integrate into the genome during the early-life window versus dynamic responses during their lifespan (Snyder-Mackler and Lea 2018). Addressing this aspect is key to enable the translation of epigenomic knowledge into potential interventions for environmental improvements or enrichments at the right moment. In this regard, we would encourage a focus on longitudinal studies in nonmodel species that would allow measuring the spatiotemporal dynamics of epigenetic markers in response to environmental inputs and the resulting phenotypes.

From an evolutionary perspective, perhaps one of the most intriguing avenues that the newfound pivotal role of GEIs has opened is that of the possibility that the evolution of complex mammalian social structures has also an effect on the ways in which genetic variation is maintained and expressed (Runcie et al. 2013). Some of these questions might be solved by the increasing incorporation of social epigenomics into diverse naturally occurring social systems. Technical developments will allow tackling specific questions at unprecedented scales as we discuss in the final section.

Technical developments

The increasing amount of epigenomic studies on a broader range of taxa and the parallel advances in high-throughput sequencing technologies depict a promising future for social epigenomics. We anticipate that it will be possible to create a "landmark map" of epigenetic signatures associated with behavioral traits across a wide range of species and social structures. For example, transcriptomic data of certain social stressors of the "conserved transcriptional response to adversity" are available for model organisms and partially for some wild species (Cole 2013; Rittschof and Robinson 2016). Furthermore, leveraging novel epigenomics and other *omics* technologies (e.g., transcriptomics, proteomics, metabolomics, and microbiomics) can unravel GEIs, and enable the development of tools to predict the triggers of physiological responses and ultimately behavioral traits. We have emphasized that this approach is valuable to address evolutionary and ecological questions. Additionally, we see the potential to assist in management decisions because there are implications for animal health and welfare.

Until recently, many phenotypic changes arising as a consequence of GEIs were labeled as "unexplained effects." The progress in the field of epigenomics is changing this view and is offering a molecular mechanistic explanation to these formerly unexplained effects (Deichmann 2016; Kukekova et al. 2018). Incorporating epigenomics into behavioral investigations will allow studying complex ecological models more comprehensively. This will also contribute to better explain complex phenotypes, whose differences failed to be solely explained by underlying gene variants (e.g., SNP; Madlon-Kay et al. 2018).

A technical challenge for studies in wildlife has always been the difficult access to samples of the species of interest. In epigenetic research, conventional sample material includes buccal cells and peripheral blood cells (Roth 2013; Chagnon et al. 2015; Lowe et al. 2015; Walton et al. 2015; Banlaki et al. 2017). However, these specimens require human–animal interaction, which is a disturbance for the animals involved. Moreover, access to appropriate sample material is hindered by the need to account for the cell-specific epigenetic signatures. Future research in nonmodel species should, therefore, prioritize validating additional noninvasive sampling schemes (e.g., exfoliated intestinal epithelial cells from feces [Whitfield-Cargile et al. 2017] and cell sorting from hair-snares [Henry et al. 2011]).

Similarly, to pave the way for epigenomics applications in wildlife research it is useful to improve and develop reliable and robust tools as alternatives to techniques that rely fully on the availability of reference genomes and high-coverage sequencing to measure epigenetic markers (e.g., single-nucleotide resolution via bisulfite conversion and sequencing, Clark et al. 1994; methylated DNA binding proteins-based sequencing, Serre et al. 2010). For instance, the reduced representation bisulfite sequencing (Meissner et al. 2005) decreases the number of reads required to obtain sufficient CpG coverage and has been successfully used in nonmodel mammalian species (e.g., wild guinea pigs, Weyrich et al. 2015). However, because the bisulfite treatment degrades DNA, the availability of high amounts of good quality genomic DNA is a limiting factor. The LUminometric Methylation Assay (Karimi et al. 2006) to assess global methylation without the need of an annotated reference genome, has also been used in wildlife (Head et al. 2014; Laubach et al. 2019). This method provides information on genome stability, although it has the shortcoming that it does not allow identifying changes at specific genes and pathways (Karimi et al. 2006; Laubach et al. 2019). Thus, there is an urgent need to further improve these and similar tools with the potential to outcompete the conventional and less-accessible approaches.

The validation of novel sampling schemes to gain access to specific cell types is an investment worth working for because it will unlock the potential to use more sophisticated methods such as single-cell sequencing technologies. Single-cell experiments could be powerful to characterize tissue-specific responses across related species. Furthermore, single-cell experiments would allow defining specific epigenetic markers at fine-scale resolution. An additional promising development is the cell-type-specific analysis without the need for cell-sorting nor for single-cell experiments, which aid in dropping the technical costs of conventional single-cell sequencing (Rahmani et al. 2019). Lastly, an unattended area in nonmodel mammalian species' epigenomics is the incorporation and consequently, the lack of technical developments to assess epigenetic markers other than DNA methylation, such as histone modifications (Krause et al. 2015; Okhovat et al. 2015) and ncRNAs. This might be due to the higher technical demands required to assess these markers. However, as technologies that allow measuring epigenetic markers and other gene regulatory elements in parallel (Vu et al. 2017) are refined and becoming accessible, this trend might shift in upcoming years.

Regarding the interpretation of the many emerging associations between epigenetic markers and trait variations, a quantitative approach was developed by Lea et al. (2018b). This high-throughput approach quantifies the effects of DNA methylation on regulatory element function and predicts DNA methylation-gene expression correlations in primary cells. This approach could also be used in combination with the analytical tools mentioned earlier (see Section 'Open questions and challenges').

We highly recommend that the use of these new technologies should be in close cooperation between disciplines such as molecular biology, bioinformatics, and evolutionary biology in order to make the best out of the available technical capabilities and the data output.

We have discussed epigenetic mechanisms underlying the molecular processes that respond to GEIs, as well as how GEIs may give rise to a rich diversity of behaviors in (wild) mammals. We, therefore, propose that social epigenomics should be adopted to tackle questions regarding the epigenetic based perpetuation of behavior and social structures. Social epigenomics should also aim to understand human–wildlife interactions and how anthropogenic activities affect the social interactions and behavior of wild mammals. In recent years, the value of such knowledge is being recognized for conservation actions planning and mitigating human–animal conflicts (Ramos et al. 2019; Rey et al. 2020).

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Conflicts of Interest

The authors declare no competing financial interests.

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