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Marine Environmental Epigenetics

Jose M. Eirin-Lopez[1,*] and Hollie M. Putnam[2,*]

[1]Environmental Epigenetics Laboratory, Center for Coastal Oceans Research, Institute for Water and Environment, Florida International University, North Miami, Florida 33181, USA; email: jeirinlo@fiu.edu

[2]Department of Biological Sciences, University of Rhode Island, Kingston, Rhode Island 02881, USA; email: hputnam@uri.edu

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*Both authors contributed equally to this article

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Abstract

Marine organisms' persistence hinges on the capacity for acclimatization and adaptation to the myriad of interacting environmental stressors associated with global climate change. In this context, epigenetics—mechanisms that facilitate phenotypic variation through genotype–environment interactions—are of great interest ecologically and evolutionarily. Our comprehensive review of marine environmental epigenetics guides our recommendations of four key areas for future research: the dynamics of wash-in and wash-out of epigenetic effects, the mechanistic understanding of the interplay of different epigenetic marks and the interaction with the microbiome, the capacity for and mechanisms of transgenerational epigenetic inheritance, and the evolutionary implications of the interaction of genetic and epigenetic features. Emerging insights in marine environmental epigenetics can be applied to critical issues such as aquaculture, biomonitoring, and biological invasions, thereby improving our ability to explain and predict the responses of marine taxa to global climate change.

1. INTRODUCTION

1.1. What Is Epigenetics?

The word epigenetics, derived from the Aristotelian word epigenesis, was coined by Conrad Waddington in 1942 and refers to how genotypes give rise to phenotypes during development. During the last 50 years, advances in molecular biology have driven a permanent reshaping of the definition of epigenetics. The most widely accepted contemporary definition of epigenetics (sensu Deans & Maggert 2015) is the study of phenomena and mechanisms that cause chromosome-bound, heritable (mitotically and/or meiotically) changes to gene expression that are not dependent on changes to DNA sequence (Deans & Maggert 2015). Nonetheless, a broader sense of epigenetics is still used [e.g., by the NIH Roadmap Epigenomics Mapping Consortium (**http://www.roadmapepigenomics.org**)] that includes long-term alterations in the transcriptional potential of a cell that are not necessarily heritable (Metzger & Schulte 2016). This broader, more inclusive definition will be used as a reference throughout the present work. Epigenetic research is rapidly developing, broad ranging, and of immense interest with respect to its role as a modulator of environmental "memory."

1.2. Epigenetic Effects Versus Epigenetic Inheritance

The study of epigenetics represents a departure from traditional views of acclimatization and adaptation, moving the discussion of these processes away from a strictly gene-centered neo-Darwinian framework to encapsulate portions of the Lamarckian framework [i.e., the inheritance of acquired characteristics (Jablonka & Raz 2009)]. Consequently, it is important to consider the transmission of epigenetic states in the soma and the germline within this context (**Figure 1**; see also the sidebar titled Future Challenges and Questions).

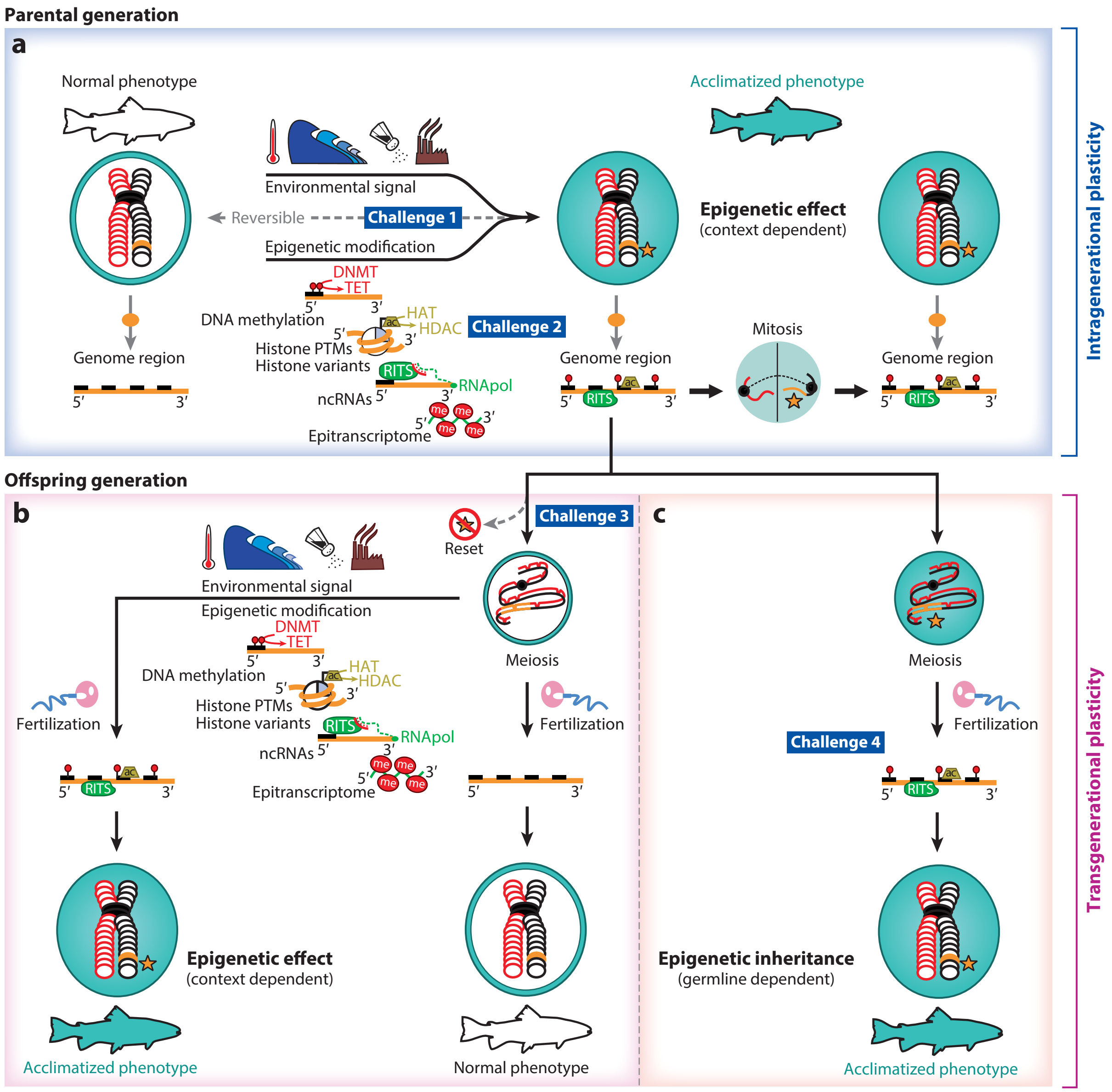
While it is still uncertain whether and (if so) how epigenetic changes acquired by somatic adult cells can be transmitted to the germ cell (Baccarelli & Bollati 2009), the fact that the possibilities of both epigenetic effects on somatic cells and epigenetic inheritance through the germline cells exist and have functional consequences for organisms means that epigenetics is a critical area of study. However, in order to fully understand how epigenetic inheritance functions in both cellular scenarios, it is important to understand that the boundaries governing DNA organization and regulation in germ cells are very different from those operating on somatic cells (Kota & Feil 2010). This is best illustrated by spermatozoa, in which DNA is stripped from most of its nucleosome-based structure so that it can be packaged in an extremely specialized manner (i.e., hypercondensed and inactivated through its association with chromosomal sperm proteins; see Section 2.2) (Eirin-Lopez & Ausió 2009). Overall, the interest in epigenetic studies is further reinforced by the capacity of both soma and germline to be affected by dynamic biotic and abiotic conditions (**Figure 1**), providing mechanisms for acclimatization and adaptation that may be advantageous in a time of rapid environmental change.

1.3. Environmental Epigenetics

Anthropogenic impacts (primarily greenhouse gas emissions) are driving global change at an unprecedented pace, with oceans in particular experiencing increased and multiple ecosystem stressors and enhanced biological invasions, which together are negatively affecting the abundance of marine taxa and their functionality (Lotze et al. 2006). Overall, this combination of stressors generates dire consequences for the world's oceans and dependent human populations

(Hoegh-Guldberg & Bruno 2010). It is well established that exposure to different environmental factors can modulate the ensemble of functionally relevant modifications in the genome that do not involve changes in the sequence of the DNA—in other words, the epigenome (Bollati & Baccarelli 2010). The growing field of environmental epigenetics focuses on elucidating the cause–effect relationships among the exposure to these environmental stressors, the modifications in epigenetic states, and the subsequent changes in the phenotypes of organisms.

With substantial evidence for rapid and significant anthropogenic climate change (IPCC 2014), the contribution of epigenetic mechanisms to phenotypic plasticity and acclimatization during



(Caption appears on following page)

Figure 1 (*Figure appears on preceding page*)

Epigenetic responses to environmental change. (*a*) Climatic changes trigger epigenetic modifications that modulate alternative and reversible phenotypic manifestations of the genotype. The mitotic transmission of epigenetic marks participates in the propagation of environmentally or developmentally induced states, described as epigenetic effects. The relationship between the magnitude, duration, and type of environmental signals and the specific type, stability, and longevity of epigenetic marks remains to be fully elucidated (challenge 1 in the sidebar titled Future Challenges and Questions). Although epigenetic mechanisms are currently being studied in marine organisms, a detailed understanding of their function and interactions is still lacking (challenge 2 in the sidebar). (*b*) One of the possibilities for the meiotic transgenerational transmission of epigenetic information, or "memory," across generations (sexual offspring) requires the persistence of stimuli supporting feedback loops, maintaining epigenetically induced phenotypes or context-dependent epigenetic effects. Yet the mechanisms underlying the communication of signals between soma and germline and their ability to endure the reorganization of chromatin during gametogenesis remain obscure (challenge 3 in the sidebar). (*c*) Alternatively, true epigenetic transgenerational inheritance (i.e., the transmission and persistence of specific epigenetic modifications in the germline) could occur without the persistence of the causative environmental conditions across generations, or germline-dependent inheritance. While animal model experiments are consistent with the possibility of both (e.g., the agouti locus in mice), the existence of true transgenerational inheritance and its evolutionary implications remain contentious (challenge 4 in the sidebar). Abbreviations: ac, acetylation; DNMT, DNA methyltransferase; HAT, histone acetyltransferase; HDAC, histone deacetylase; me, methylation; ncRNA, noncoding RNA; PTM, posttranslational modification; RITS, RNA-induced transcriptional silencing; RNApol, RNA polymerase; TET, ten eleven translocation.

rapid acclimatory and adaptive responses is beginning to emerge as a significant factor (Torda et al. 2017). More precisely, the role of epigenetic mechanisms in generating a temporal buffer, or enhancing or retarding acclimatization and/or adaptation (Kronholm & Collins 2016), constitutes a key topic in environmental epigenetic research. Furthermore, the development of environmental epigenetic studies also fosters epigenetic footprinting analyses, facilitating the retrospective assessment of stress exposures on populations of critical interest for biomonitoring purposes (Mirbahai & Chipman 2014). Environmental epigenetic analyses can therefore inform our capacity to understand the environmental resistance and resilience of marine organisms (Torda et al. 2017), consequently enhancing our ability to examine the interplay of genetic and epigenetic mechanisms, reducing uncertainty in our ability to forecast ecological and evolutionary processes (Kronholm & Collins 2016), and potentially contributing to conservation, restoration, and aquaculture practices (Gavery & Roberts 2017, van Oppen et al. 2015) in the Anthropocene.

Against a backdrop of intense anthropogenic pressures on the oceans and rapid advancements in our technological capacity to investigate genetic and epigenetic factors (**Table 1**), we are now poised to address many essential gaps in our understanding of marine environmental epigenetics. Among those, the inheritance of epigenetic marks constitutes a fundamental point of discussion (probably the most important and surely the most controversial), raising many questions about the mechanisms mediating their transmission, persistence, and effects on phenotype (see the sidebar titled Future Challenges and Questions). If heritable epigenetic variations can underlie evolutionary change, then a broader concept of heredity, along with the recognition that natural selection may act on several different types of heritable variation (Darwinian and Lamarckian), is necessary (Jablonka & Lamb 2002).

1.4. Article Overview

Comprehensive reviews exist for many aspects of epigenetics, notably the mechanistic basis, functional consequences, and potential inheritance of different types of epigenetic signals in traditional model organisms (Allis & Jenuwein 2016, Burggren 2015, Feil & Fraga 2012). However, a growing number of environmentally and ecologically relevant organisms are currently being incorporated into epigenetic studies in diverse ecosystems, providing critical insights into the molecular mechanisms linking global climate change to subsequent acclimatory and adaptive responses on these populations. Here, we do not attempt to encompass all material, but focus on environmental

FUTURE CHALLENGES AND QUESTIONS

- Challenge 1: Elucidating cause–effects relationships among environmental signals, epigenetic modifications, and the dynamics of wash-in and wash-out of epigenetic effects.
    a. How are environmental signals transduced into epigenetic responses? Do these differ with environmental predictability?
    b. Does susceptibility to epigenetic effects vary with developmental stage?
    c. What are the temporal dynamics of epigenetic marks and their physiological and ecological legacies?
    d. Can epigenetic profiling and conditioning be efficiently used as a tool for improving management or production in aquaculture and fisheries?
- Challenge 2: Generating a detailed mechanistic understanding of epigenetic mechanisms and their interplay.
    a. What are the roles of DNA methylation with respect to gene expression regulation?
    b. How do different epigenetic mechanisms interact to determine different epigenetic landscapes?
    c. Is there really an epigenetic code? If so, is it dependent on the peculiarities of genomic landscapes found across different eukaryotic taxa?
    d. Are environmentally acquired modifications in the epigenome linked to the microbiome? Do changes in the epigenome influence the microbiome community and/or function?
- Challenge 3: Demonstrating the capacity for and mechanisms of transgenerational epigenetic inheritance.
    a. Are acquired epigenomic states transmitted across generations in the form of transient environment-dependent epigenetic effects, or do they constitute true germline-dependent epigenetic inheritance?
    b. Can somatic epigenetic modifications be carried to germinal cells for transgenerational transmission? If so, what is the mechanistic basis underlying such communication?
    c. How do different types of epigenetic mechanisms contribute to transgenerational epigenetic inheritance?
    d. Are there specific life history traits that are more prone to the effect of transgenerational epigenetic inheritance?
- Challenge 4: Clarifying the interplay of genetic and epigenetic features and evolutionary consequences.
    a. How does the (epi)genomic landscape affect selection of (epi)alleles under different environments?
    b. Does phenotypic plasticity generated through epigenetic means enhance or retard evolutionary rates under climate change?
    c. Are some combinations of epigenetic mechanisms more or less likely to generate maladaptive plasticity under rapid climate change?
    d. Can epigenetics contribute to evolutionary processes that facilitate marine conservation and restoration?

epigenetic studies in marine taxa. To this end, we present mechanistic descriptions of epigenetic processes, provide illustrative examples of epigenetic approaches taken in marine systems to date (where possible), and indicate contrasting views in this emerging field. Furthermore, we discuss the utility (and limitations) of epigenetic processes in a global change context with respect to aspects such as biomonitoring, aquaculture, and restoration. Finally, we highlight the complex interplay of the variety of epigenetic mechanisms as a necessary future direction to understand emergent epigenetic consequences for marine organisms' persistence in a rapidly changing world.

2. EPIGENETIC MECHANISMS

The understanding of the role of epigenetics in an ecological and evolutionary framework depends on the mechanistic understanding of the variety of epigenetic processes and their interactions, which influence gene expression throughout the genome and determine epigenomic states that

Table 1 Techniques for assessing epigenetic marks

Approach	Description[a]	Level of detail	Difficulty[b]	Cost[c]	Advantages	Disadvantages	References[d]
DNA methylation							
CpG O/E	Methylated cytosine has a tendency to undergo deamination to thymine. This can leave a signature of cytosine depletion in the genome that can be quantified by looking at the ratio of observed CpG to expected CpG in silico.	Single-base-pair resolution of historical methylation status	#	$	Can utilize existing data sets	Cannot examine dynamic or inducible methylation changes	Gardiner-Garden & Frommer 1987 Dimond & Roberts 2016, Dixon et al. 2010, Gavery & Roberts 2010
HPLC and LC-MS/MS	An HPLC or LC-MS/MS instrument can detect global DNA methylation following digestion of the DNA.	Methylation relative to cytosines in DNA or total DNA	#	$	Quick and easy	Global signal, low resolution, no ability to assess sequence	Kuo et al. 1980, Song et al. 2005 Mirbahai et al. 2011, Varriale & Bernardi 2006 (HPLC); none found (LC-MS/MS)
ELISA	Enrichment and quantification of global DNA methylation can be done through the addition of a capture antibody for methylated DNA and a detection antibody, followed by colorimetric or fluorescent detection.	Methylation relative to total DNA	#	$	Quick and easy	Global signal, low resolution, no ability to assess sequence	NA Dabe et al. 2015, García-Fernández et al. 2017, Kuc et al. 2017, Putnam et al. 2016
MSP	MSP is used to quantify methylation within CpG islands through the dual amplification of loci from bisulfite-converted DNA using primers for methylated and unmethylated DNA.	Single-base-pair resolution	##	$	Provides enhanced base-pair-level detection within CpG islands	Requires primer design, requires predicting the occurrence of CpG islands within the promoter region of the target	Herman et al. 1996 Gavery & Roberts 2010

(*Continued*)

Table 1 *(Continued)*

Approach	Description[a]	Level of detail	Difficulty[b]	Cost[c]	Advantages	Disadvantages	References[d]
MSAP	MSAP generates banding patterns indicative of differentially methylated regions through the comparison of DNA fragments after cutting with methylation-sensitive (*HpaII*) and methylation-insensitive (*MspI*) restriction enzymes.	Genome-region-level information	##	$$	Provides information on multiple loci simultaneously	Uses broad profiling that does not provide extensive mechanistic information	Yaish et al. 2014 García-Fernández et al. 2017, Li et al. 2017b, Trautner et al. 2017, Y. Zhao et al. 2015
EpiRAD-seq	DNA methylation is detected through a restriction-site-associated DNA-sequencing-based method that includes a double-digest approach with one methylation-sensitive and one methylation-insensitive restriction enzyme.	Single-base-pair resolution following CCGG recognition sites	###	$$$	Provides information on multiple loci and single-base-pair resolution	Does not represent the whole genome, requires genotypic information to remove bias	Schield et al. 2016 Dimond et al. 2017
bsRAD-seq	bsRAD-seq provides a genome-wide capacity to investigate DNA methylation with single-base-pair resolution at a consistent set of loci across all samples.	Single-base-pair resolution for a reduced representation of the genome	###	$$$	Provides more information than EpiRAD-seq, does not require a genome	Does not represent the whole genome	Trucchi et al. 2016 Metzger et al. 2018, Watson et al. 2018
RRBS	Methylated DNA represents a small fraction of the genome, and thus sequencing at the whole-genome level can be cost prohibitive. RRBS, MBD-seq, and MeDIP-seq enrich for methylated areas through sequence detection of CCGG in order to target areas such as CpG islands (RRBS) and through the nontargeted enrichment of methylated DNA in general (MBD-seq and MeDIP-seq).	Single-base-pair resolution for a reduced representation of the genome	###	$$$	Provides information on more than just the cut sites	Does not represent the whole genome	Gu et al. 2011, Meissner et al. 2008 Baerwald et al. 2016, Le Luyer et al. 2017, Metzger & Schulte 2017

(Continued)

Table 1 (*Continued*)

Approach	Description[a]	Level of detail	Difficulty[b]	Cost[c]	Advantages	Disadvantages	References[d]
MBD-seq	MBD-seq enriches methylated DNA through the binding of methyl-binding domain proteins to methylated DNA. These regions can then be sequenced and compared with the unbound fraction (region comparisons) or subject to bisulfite conversion and sequencing (single-base-pair comparisons).	Several hundred base pairs for an enriched fraction of genome (single-base-pair resolution if followed by bisulfite conversion)	####	$$$	Does not damage DNA with bisulfite treatment	Biased enrichment of regions with higher CpG density, does not provide single-base-pair resolution unless followed by bisulfite conversion	Harris et al. 2010, Serre et al. 2010 Dixon et al. 2016, 2017; Gavery & Roberts 2013
MeDIP-seq	MeDIP-seq enriches methylated DNA through the immunoprecipitation of methylated DNA using a 5-methylcytosine-specific antibody. These regions can then be sequenced and compared with the unbound fraction (region comparisons) or subject to bisulfite conversion and sequencing (single-base-pair comparisons).	Several hundred base pairs for an enriched fraction of genome (single-base-pair resolution if followed by bisulfite conversion)	####	$$$	Has higher sensitivity for lower CpG density than MBD-seq, does not damage DNA with bisulfite treatment	Level of capture not 100%, does not provide single-base-pair resolution unless followed by bisulfite conversion	Jacinto et al. 2008 Mirbahai et al. 2011, Riviere et al. 2017, Zou et al. 2018
WGBS	A global picture of DNA methylation with single-base-pair resolution gives the optimal capacity to test hypotheses that go beyond genes or regions to genomic architecture. These data are generated by whole-genome fragmentation, bisulfite conversion, DNA library preparation, and sequencing.	Base pair or whole genome	#####	$$$$$	Provides a complete picture of methylation with single-base-pair resolution, facilitates higher-order analyses	Can potentially damage DNA with bisulfite treatment, has a high cost of sequencing for very-low-percentage methylation	NA Dabe et al. 2015; Li et al. 2018; Liew et al. 2018a,b; Rondon et al. 2017; Wang et al. 2014

(*Continued*)

Table 1 *(Continued)*

Approach	Description[a]	Level of detail	Difficulty[b]	Cost[c]	Advantages	Disadvantages	References[d]
Polymerase kinetics	A global picture of DNA methylation with single-base-pair resolution gives the optimal capacity to test hypotheses that go beyond genes or regions to genomic architecture. These data are generated by library preparation and sequencing that detects methylation through changes in polymerase kinetics.	Base-pair or whole-genome quantitative data	####	$$$	Has single-base-pair resolution, facilitates higher-order analyses, does not require bisulfite conversion	Signal small and may be difficult to detect, methods not yet commonly used	Flusberg et al. 2010 None found
Histone chromatin level							
Histone extraction and immuno-detection	Acidic extractions can selectively extract histones and PTMs that are subsequently resolved using methods such as PAGE, HPLC, and Western blot detection.	Qualitative or quantitative data for an organism, tissue, or cell	###	$	General approach is revealing, does not require genomic data, is applicable in all organisms	Does not provide gene or single-base-pair resolution	Karch et al. 2013 Rivera-Casas et al. 2017
ChIP-seq	The immunodetection of histones and their PTMs allows the identification of specific DNA regions targeted during the regulation of epigenetic responses, facilitating their genome-wide mapping.	Single-nucleotide quantitative data using multiple derivative techniques	#####	$$$$$	Provides histone variant and PTM distributions in chromatin with single-base-pair resolution	Requires highly specific antibodies and individual cells, is not feasible for large amounts of samples	Barski et al. 2007, O'Geen et al. 2011 Li et al. 2018, Lin et al. 2012, Veluchamy et al. 2015
ATAC-seq	ATAC-seq transposes sequencing adapters into native chromatin, identifies regions of open chromatin and nucleosome-bound and nucleosome-free positions in regulatory regions, and infers the positions of DNA-binding proteins.	Single-nucleotide quantitative data	####	$$$$	Fast, requires only a small number of cells, has simple library preparation, does not require antibodies	Requires individual cells, requires optimizing cell density for appropriate transposition levels	Buenrostro et al. 2015, Dekker 2006 None found

(*Continued*)

Table 1 (*Continued*)

Approach	Description[a]	Level of detail	Difficulty[b]	Cost[c]	Advantages	Disadvantages	References[d]
ncRNA							
Regulatory RNA characterization	This method characterizes ncRNA molecules and specific RNA and DNA targets.	Single-nucleotide quantitative data	###	$$$	Quick, easy RNA sequencing, does not require substantial input material	Requires additional studies to corroborate functional regulatory roles	Kashi et al. 2015, Ozsolak & Milos 2011 Boltaña et al. 2016, Mennigen et al. 2013, Paneru et al. 2016, Yu et al. 2016
RNA methylation							
Epitranscriptome characterization	RNAs can be methylated just like DNA and in a highly specific way. These modifications are detected using specific antibodies and/or chemical transformations coupled to high-throughput sequencing technologies.	Single-nucleotide quantitative data	####	$$$	Allows for different techniques, does not require antibodies, is highly accurate	Provides poor specificity in some cases, produces false positives, requires substantial input material	Helm & Motorin 2017, Li et al. 2016 None found

Abbreviations: ATAC-seq, assay for transposase-accessible chromatin with high-throughput sequencing; bsRAD-seq, bisulfite restriction-site-associated DNA sequencing; ChIP-seq, chromatin immunoprecipitation sequencing; CpG, cytosine-phosphate-guanine; ELISA, enzyme-linked immunosorbent assay; EpiRAD-seq, epigenetic restriction-site-associated DNA sequencing; HPLC, high-performance liquid chromatography; LC-MS/MS, liquid chromatography–electrospray ionization tandem mass spectrometry; MBD-seq, methyl-binding domain sequencing; MeDIP-seq, methyl-DNA immunoprecipitation sequencing; MSAP, methyl-sensitive amplification polymorphism; MSP, methylation-specific polymerase chain reaction; NA, not applicable; ncRNA, noncoding RNA; O/E, observed/expected; PAGE, polyacrylamide gel electrophoresis; PTM, posttranslational modification; RRBS, reduced-representation bisulfite sequencing; WGBS, whole-genome bisulfite sequencing.

[a] For detailed discussion of methodologies, we refer readers to several extensive reviews (Harris et al. 2010, Kurdyukov & Bullock 2016, Laird 2010, Olova et al. 2018).

[b] The number of # symbols indicates how difficult the approach is to use, ranging from # (easy to use) to ##### (very difficult to use).

[c] The number of $ symbols indicates how expensive the approach is, ranging from $ (low cost) to $$$$$ (very high cost).

[d] Within each row, the top cell indicates the primary methods reference(s) (or NA if there is no primary reference), and the bottom cell indicates reference(s) that used that approach in a marine organism (if any were found by a literature search for the approach name along with the terms “marine” and “ocean,” or from citations of the original method).

can vary from cell to cell, producing different phenotypic outcomes (**Figure 2**). Here, we discuss dominant patterns that have emerged from the literature but acknowledge the incomplete state of knowledge in this field, in particular with respect to nonmodel and marine organisms, making epigenetic research in marine systems a particularly exciting scientific frontier (Hofmann 2017).

CpG: cytosine-phosphate-guanine

2.1. DNA Methylation

DNA methylation provides an environmentally triggered and potentially heritable epigenetic mark involved in the regulation of gene expression, with functional consequences for phenotypic plasticity and acclimatization. This epigenetic mechanism has been the focus of many early marine environmental epigenetics studies.

2.1.1. The mechanistic basis of DNA methylation. Perhaps the best-studied epigenetic mechanism to date is DNA methylation, which was first identified as 5-methylcytosine (Wheeler & Johnson 1904). Most commonly, it is cytosine that is methylated in animals (Doskočil & Šorm 1962), specifically in a cytosine-phosphate-guanine (CpG) sequence. Methylation also occurs in other contexts (e.g., CHG and CHH), with a higher frequency of non-CpG methylation in plants (Suzuki & Bird 2008). Overall, methylated DNA is a minor component of the genome and generally occurs in approximately 60–90% of CpG sequences in mammals (Jeltsch 2002) but substantially fewer in invertebrates (Feng et al. 2010). The hypothesized function of DNA methylation emerged in the 1960s (Doskočil & Šorm 1962) with the identification of the palindromic (and therefore self-complementary) nature of CpG sequences, providing a system for copying information that is derived not from the DNA bases themselves or their sequence, but epigenetically.

The DNA methylation reaction involves the enzyme-assisted transfer of a methyl group from *S*-adenosylmethionine to the C5 position of cytosine. Several enzymes called DNA methyltransferases (DNMTs), including DNMT3a, DNMT3b, and DNMT1 (Jeltsch 2002), play roles in establishing (DNMT3a and DNMT3b) and maintaining (DNMT1) methylation patterns within the genome. They can, however, also act in concert to methylate both strands, and there is some evidence for a de novo role for DNMT1 (Jeltsch & Jurkowska 2014). DNA methylation is not permanent but may be reverted by both passive demethylation (loss of methylation during replication, returning cytosine to an unmethylated state) and active demethylation [through the activity of ten eleven translocation (TET) proteins] (**Figures 1** and **2**), which oxidize 5-methylcytosine to generate 5-hydroxymethylcytosine, 5-formylcytosine, and 5-carboxylcytosine (Ito et al. 2011). These intermediates can be further broken down through thymine-mediated excision and base excision repair to unmethylated cytosine. Additionally, there is a propensity for methylated cytosine to mutate to thymine through deamination, resulting in a base change, which base excision repair can subsequently correct. The capacity for dynamic or transient DNA methylation in response to biotic and abiotic factors is present in many organisms (Feil & Fraga 2012), maintaining the functional consequences of this epigenetic mark under changing environments. The rates of active methylation and active and passive demethylation are not known for many species, particularly nonmodel organisms, where they constitute a knowledge gap (see the sidebar titled Future Challenges and Questions).

2.1.2. DNA methylation and the regulation of genome function. DNA methylation is posited as a dynamic system for cellular memory through the regulation of gene expression and thus the developmental or tissue-specific fate of the cell. This role is supported, for example, by the connection of DNA methylation with development, disease, and environmentally induced plasticity

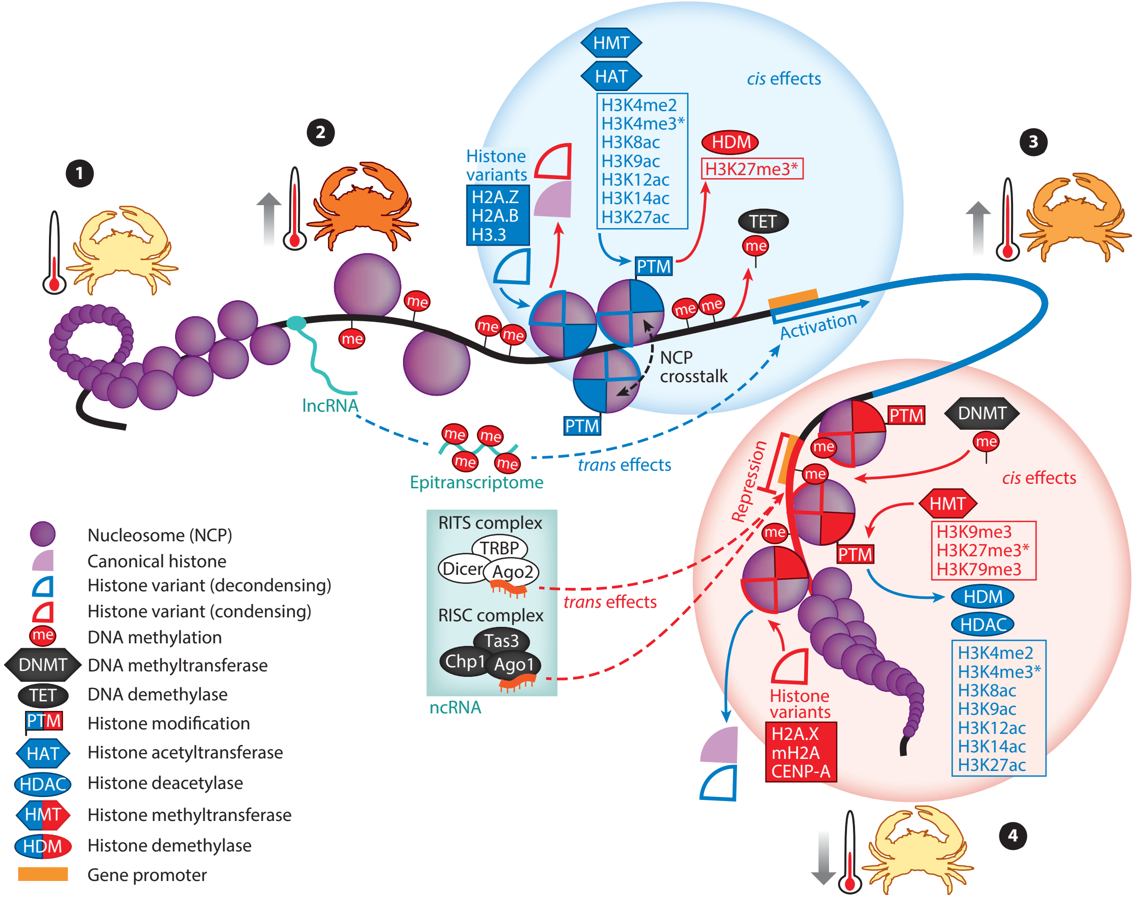


Figure 2

Example of interactions among different epigenetic mechanisms during responses to environmental stress. A transient increase from (❶) normal to (❷) high water temperature elicits the epigenetic regulation of genes involved in the thermal stress response. Accordingly, different chromatin segments harboring such genes may be enriched in transcriptionally active marks, including DNA demethylation at gene promoters or in gene bodies, histone H3 methylation and acetylation, and the recruitment of histone variants involved in chromatin decondensation (indicated in *blue*). The balance of bivalent histone modifications (i.e., functionally opposite histone marks, indicated with *asterisks*) results in different transcriptional states. These epigenetic marks are written or erased by enzymes and chaperone proteins with dedicated functions (HAT/HDAC, HMT/HDM, etc.), and together with the contributions of long and short ncRNAs and their modifications (i.e., the epitranscriptome), they promote the onset of (❸) the acclimatized phenotypes. Upon return to normal temperature levels, most epigenetic marks are reversed, including DNA methylation, transcriptionally active marks (which are removed and/or replaced with repressive marks), and histone variants involved in chromatin condensation (indicated in *red*). This process can be assisted by RNA-associated mechanisms, including RITS and RISC, promoting (❹) the cessation of the acclimatized phenotype. The flexibility of these epigenetic parameters in response to exogenous influence allows for the stable propagation of gene activity states from one cellular generation to the next. Abbreviations: ac, acetylation; DNMT, DNA methyltransferase; HAT, histone acetyltransferase; HDAC, histone deacetylase; HDM, histone demethylase; HMT, histone methyltransferase; lncRNA, long noncoding RNA; me, methylation; NCP, nucleosome core particle; ncRNA, noncoding RNA; PTM, posttranslational modification; RISC, RNA-induced silencing complex; RITS, RNA-induced transcriptional silencing; TET, ten eleven translocation.

(Feil & Fraga 2012). Regulation of gene expression through DNA methylation can occur through interactions of the methyl group with the major groove of the DNA helix, which does not interfere with base pairing but can enhance or block DNA-binding proteins, thereby providing some control on transcription. Further control of gene expression may occur through methylated CPG recruitment of methyl-binding domain proteins, which in turn can generate a repressive chromatin state (Feil & Fraga 2012).

The location of DNA methylation in the genome is critical to its function. For instance, in the vertebrate system, repetitive CpG sequences (CpG islands) can be found located upstream in promoter regions, and here the presence of methylation can silence transcription by blocking the binding of transcription factors (but see Ford et al. 2017). Additionally, DNA methylation can commonly be found in gene bodies, where it hypothetically contributes to the reduction of transcriptional variation, reduction of spurious transcription, and facilitation of alternative splicing (reviewed in Roberts & Gavery 2012). Beyond the coding portions of the genome, DNA methylation can also be associated with intergenic regions and transposable elements, contributing to the silencing of transposable elements and viral elements that would otherwise result in genome disruption by sequence and DNA mutation (Rey et al. 2016).

There has been a strong focus to date on the role of DNA methylation in transcriptional control and phenotypic plasticity and therefore its potential to facilitate acclimatization and/or adaptation to chronic and stochastic environmental perturbations in the marine environment (Hofmann 2017). Given the multistressor nature of climate change in the oceans, symbiotic and calcifying organisms are particularly susceptible to increased temperature and ocean acidification (Hoegh-Guldberg & Bruno 2010). Therefore, reef-building corals and shellfish have been an early focus for DNA methylation research with respect to environmental epigenetics. The link between phenotypic plasticity and DNA methylation is supported by the exposure of an environmentally sensitive coral to ocean acidification conditions for six weeks, revealing a decline in growth, changes in metabolomic profiles, and an increase in the proportion of methylated DNA (Putnam et al. 2016). Sequencing of methylation-enriched fractions and whole-genome bisulfite sequencing provides further mechanistic clarification regarding coral responses to transplantation between different thermal environments [*Acropora millepora* (Dixon et al. 2017)] and exposure to low-pH environments [*Stylophora pistillata* (Liew et al. 2018b)]. Additionally, several works have described a role for DNA methylation in Pacific oysters [*Magallana* (*Crassostrea*) *gigas*], including transcriptional control (Gavery & Roberts 2010, Olson & Roberts 2014), patterns of oyster DNA methylation through development (Riviere et al. 2013, 2017), a role for methylation in alternative splicing (Song et al. 2017), and the potential for functionally important promoter methylation (Saint-Carlier & Riviere 2015).

Marine vertebrate DNA methylation is less well studied in an environmental epigenetics and climate change context. This literature has focused primarily on the role of DNA methylation in developmental variation, sex determination, and hatchery rearing (Metzger & Schulte 2016). For example, Covelo-Soto et al. (2015b) detected substantially different methylation patterns between larval and adult life stages when they examined the development of sea lamprey using a methylation-sensitive amplified polymorphism (MSAP) approach (**Table 1**). Sex determination in the half-smooth tongue sole (*Cynoglossus semilaevis*) (Shao et al. 2014) and temperature-mediated sex determination in fish (Ellison et al. 2015, Navarro-Martín et al. 2011) and sea turtles (Venegas et al. 2016) are linked to differential DNA methylation patterns. Recently, the comparison of hatchery- and wild-reared Pacific salmon has highlighted the role of environmentally induced epigenetic reprogramming through DNA methylation (Le Luyer et al. 2017), with implications for the use of epigenetic conditioning (or environmental hardening) practices in hatchery and restoration (Gavery & Roberts 2017, Putnam et al. 2017, van Oppen et al. 2015). A detailed examination of the link between transgenerational plasticity and DNA methylation in a nonmodel marine vertebrate characterized significant differential methylation and transcriptional patterns of the coral reef fish *Acanthochromis polyacanthus* following exposure to ocean warming conditions for two generations. Here, DNA methylation patterns are linked to both transcriptional changes in genes involved in mitochondrial function and energy homeostasis (among other functions) and a more efficient phenotype for aerobic performance (Ryu et al. 2018).

Overall, the presence, patterning, and inducible capacity of DNA methylation supports a role in phenotypic plasticity and acclimatization. DNA methylation not only marks the bases for a more direct role in the regulation of gene expression but can also be involved with higher-order packaging organization and can therefore contribute to additional epigenomic modifications. The link between DNA methylation and phenotype is steadily emerging (Metzger & Schulte 2016, Roberts & Gavery 2012). This emergence is further fueled by the development of genomic resources for nonmodel systems and the availability of technical approaches that do not require full genomic resources for epigenetic analyses (**Table 1**).

2.2. Chromatin Organization

Chromatin provides a framework for the study of epigenetics and constitutes an exciting frontier for understanding how the environment influences the regulation of DNA function and the resulting phenotypic variation (i.e., phenotypic plasticity) observed in living organisms (Bollati & Baccarelli 2010, Suarez-Ulloa et al. 2015).

2.2.1. Histone variants and posttranslational modifications. Histone proteins constitute key structural elements that facilitate the packing of the long eukaryotic DNA within the limited space of the cell nucleus and therefore modulate access to different regions in the genome. These proteins are small and very basic, forming histone octamers that associate with the DNA and give rise to the nucleosome, the fundamental subunit of chromatin (van Holde 1989) (**Figure 2**). Histone proteins have evolved subject to a birth-and-death process under strong purifying selection (Eirin-Lopez et al. 2009), leading to the diversification of different histone families that encompass functionally specialized types known as histone variants (Talbert et al. 2012). Some of these variants have been identified in marine invertebrates, including H2A.X, H2A.Z, and macroH2A, which are involved in critical roles in the epigenetic regulation of DNA structure and metabolism (González-Romero et al. 2012, Moosmann et al. 2011).

Histone proteins are also amenable to more than 10 types of posttranslational modifications at multiple conserved residues (Allis & Jenuwein 2016) (**Figure 2**). These modifications (notably acetylation, methylation, and phosphorylation) not only participate in the regulation of chromatin structure but also help recruit proteins and chromatin-remodeling complexes that influence transcription as well as many other DNA processes, such as repair, replication, and recombination (Bannister & Kouzarides 2011). Combined with histone variants, histone posttranslational modifications also play critical roles in chromatin metabolism and epigenetic memory (Feil & Fraga 2012), contributing to major evolutionary transitions in eukaryotes (Eirin-Lopez & Ausió 2009).

Histone variants and their modifications participate in environmental responses (Talbert & Henikoff 2014). However, their study in environmentally and ecologically relevant marine organisms has been hampered by the experimental complexity of chromatin-related techniques in nonmodel systems (**Table 1**), as well as by the difficulty of accommodating population analyses consisting of large sample sizes. Nonetheless, the role of histone variants and their modifications during the development of marine annelids (Gibson et al. 2012), as well as in mediating responses to marine pollution in molluscs (González-Romero et al. 2017) and diatoms (Veluchamy et al.

2015), has been described. Among marine organisms, histone H2A.Z is the most studied histone variant; structural and regulatory analyses have been performed in basal chordates, annelids, and molluscs (Arenas-Mena et al. 2007, González-Romero et al. 2012, Rivera-Casas et al. 2016). Histone H2A.X is another variant intensively studied due to its involvement in the maintenance of genome integrity, as shown by its study in molluscs (González-Romero et al. 2017) and cnidarians (Reddy et al. 2017). Similarly, the presence of histone macroH2A, a variant involved in gene repression at heterochromatic regions, has also been corroborated in marine organisms (Rivera-Casas et al. 2016). The presence of additional histone posttranslational modifications linked to gene regulation has also been identified in marine fishes, including histone acetylation in response to butyrate exposure in teleost fish, upregulating the activity of specific genes (Terova et al. 2016).

ncRNA: noncoding RNA

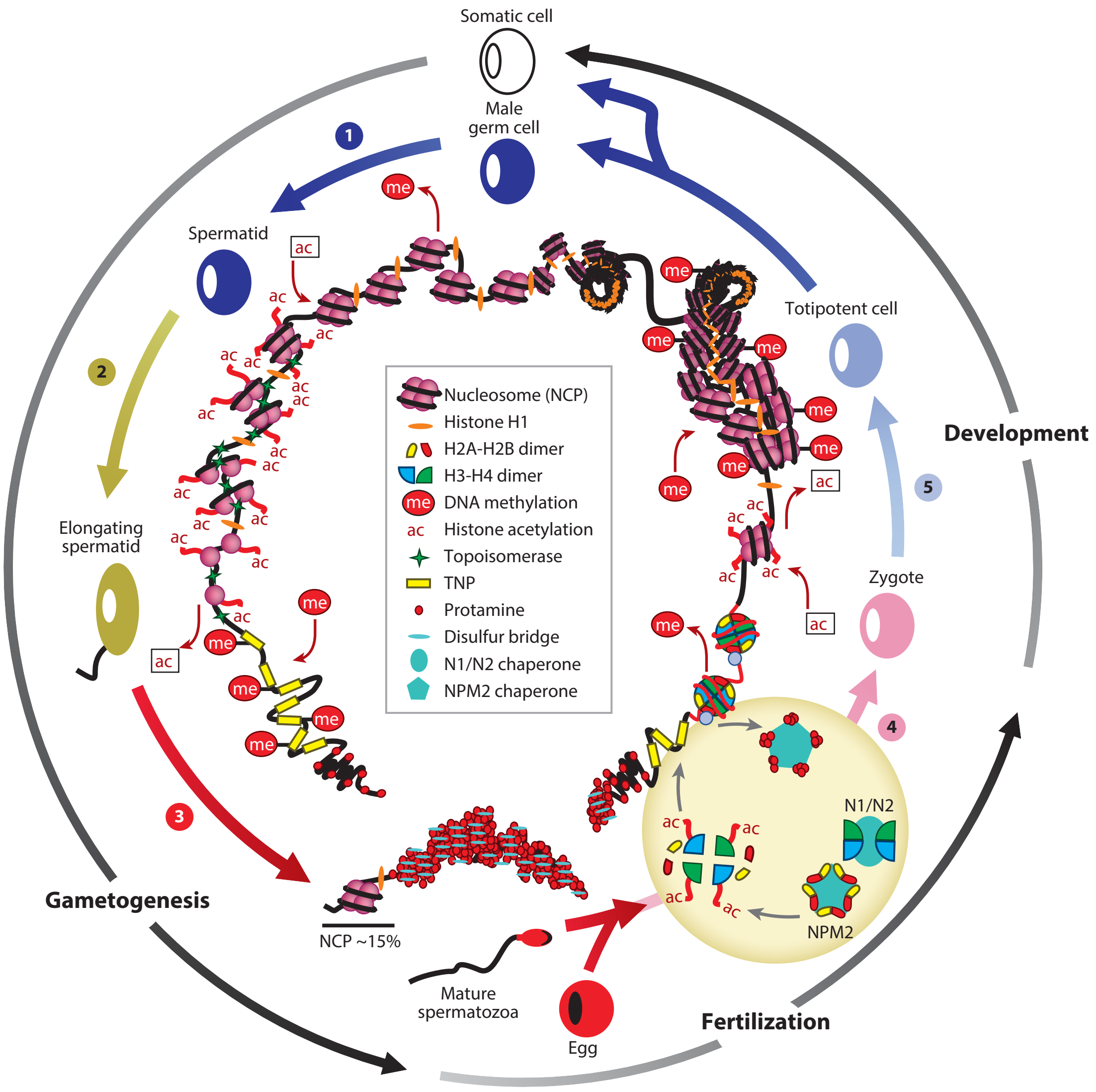
miRNA: microRNA

2.2.2. Unique characteristics of germinal chromatin. Germinal cells have the unique capacity to start a new life upon fertilization. Their development is controlled by unique gene expression programs that involve highly specialized epigenetic reprogramming (Kota & Feil 2010), show striking differences between males and females, and prepare germ cells for fertilization (**Figure 3**). In order to be vertically transmitted to the offspring, epigenetic modifications need to be present in the germline and endure the extreme reorganization of chromatin during gametogenesis, especially in the case of males. Since nucleosomes are disassembled and histones are widely replaced by protamines in mature spermatozoa (Eirin-Lopez & Ausió 2009), the epigenetic contributions of sperm chromatin to embryo development have been considered highly limited (**Figure 3**). However, a small fraction of the sperm chromatin retains a nucleosome configuration, including loci of developmental importance, such as imprinted gene clusters, microRNA clusters, HOX gene clusters, and the promoters of stand-alone developmental transcription and signaling factors (Hammoud et al. 2009). While the mechanisms underlying such transmission are still obscure, an intriguing possibility is the potential regulatory role that noncoding RNAs (ncRNAs), which are transported in the chromatoid bodies of gametes, could play in germ cells before and after fertilization (Kimmins & Sassone-Corsi 2005).

2.3. Noncoding RNAs

ncRNAs have emerged as key regulators of chromatin structure and gene expression in eukaryotic cells (Holoch & Moazed 2015), displaying conserved functional features across different taxa (Ulitsky & Bartel 2013). The regulatory role of ncRNAs involves the formation of RNA structures that facilitate the recruitment of chromatin-modifying complexes into specific chromatin regions, determining and maintaining specific epigenetic states (Holoch & Moazed 2015) (**Figure 2**). It has also been suggested that various classes of RNAs could be transferred horizontally across neighboring cells through extracellular vesicles, promoting environmental signal transduction, as well as potentially altering the epigenome of neighboring cells by carrying RNA-binding proteins (i.e., chromatin modifiers and transcription factors riding ncRNAs) (Di Liegro et al. 2017). Interestingly, RNAs (ncRNA and mRNA) can be methylated just like DNA, and these epigenetic modifications in what is now defined as the epitranscriptome (**Table 1**) may be key in the regulation of ncRNAs (Esteller & Pandolfi 2017). Overall, while the epigenetic potential of ncRNAs seems to be well justified, the characterization of the molecular mechanisms underlying the participation of these molecules in epigenetic regulatory processes awaits further characterization.

The different types of ncRNA can be broadly classified into short ncRNAs (<30 nucleotides) and long ncRNAs (>200 nucleotides). The former group comprises three major classes: short interfering RNAs and microRNAs (miRNAs), which are part of the same control machinery (Ulitsky & Bartel 2013), as well as Piwi-interacting RNAs, which specifically target germline transposons, among other roles (Iwasaki et al. 2015). miRNAs are ubiquitous short RNA molecules (18–26 nucleotides) that potentially bind mRNA transcripts from up to 200 different genes and modulate their expression by inhibiting mRNA translation or enhancing mRNA decay (Ulitsky & Bartel 2013). The miRNA transcriptome has been explored in marine organisms such as cnidarians (Moran et al. 2013), platyhelminthes (Resch & Palakodeti 2012), molluscs (Rosani et al. 2016), and teleost fishes (Bizuayehu & Babiak 2014). The results obtained by these studies suggest that miRNAs play critical regulatory roles during development, including mediating stem cell function. In addition, genes encoding miRNAs are expressed at a high level during development but display low and noninducible expression levels in adult organisms. Finally, evolutionary analyses are consistent with an ancient origin for the miRNA biogenesis machinery.



(Caption appears on following page)

Figure 3 (*Figure appears on preceding page*)

Transitions in chromatin structure and epigenetic marks during gametogenesis. Haploid DNA experiences an extensive reorganization before being packed inside the nucleus of gametes, especially in spermatozoa. This process starts with (❶) a wave of DNA demethylation, accompanied by massive histone acetylation and the incorporation of histone variants linked to chromatin decondensation. Mechanical tensions in DNA structure are reduced by DNA topoisomerases and chromatin-remodeling factors, facilitating (❷) nucleosome disassembly and the replacement of histones by a specialized group of TNPs. This process is followed by a stop in gene transcription, the repair of DNA breaks necessary for meiotic crossing-over, and increased DNA methylation. During (❸) the elongation of spermatids, TNPs are replaced by highly specialized protamines, completing the packing of the sperm DNA within the sperm nucleus. Only 4% (humans) to 15% (mice) of sperm DNA retains a nucleosomal organization (potentially carrying parentally acquired epigenetic information), notably at loci of developmental importance. In contrast to spermatozoa, oocytes preserve a nucleosomal organization throughout oogenesis (*outer circle*). Upon (❹) fertilization, the reversion of the process starts with the reduction of disulfide bonds that cross-link protamines and their replacement for histones, a process mediated by histone chaperones NPM2 and N1/N2, which act as reservoirs of H2A-H2B and H3-H4, respectively, in the egg cytoplasm. The process is followed by a wave of DNA demethylation and histone acetylation, assisted by chromatin-remodeling factors assembling zygote nucleosomes. Finally, (❺) the zygote chromatin is assembled and DNA selectively methylated, facilitating cell division and gene expression during development. Abbreviations: ac, acetylation; me, methylation; NCP, nucleosome core particle; NPM2, nucleoplasmin 2; TNP, transition protein.

The high levels of conservation displayed by ncRNAs suggest that a considerable set of mRNAs are also under their modulation in marine organisms (Bizuayehu & Babiak 2014). Accordingly, gene regulation mediated by ncRNAs has been linked to development, sex determination, and reproduction in oysters (Yu et al. 2016) and teleost fishes (Bizuayehu et al. 2012a,b, 2015; Cochrane et al. 2011, Mennigen et al. 2013, Robledo et al. 2017). A role for ncRNAs was also proposed during environmental responses to stress in marine organisms, including responses to virus and bacterial infection in Atlantic salmon (Boltaña et al. 2016) and rainbow trout (Paneru et al. 2016). miRNA participation during responses to thermal stress has also been identified in Atlantic cod, although a study of DNA methylation in the promoters of differentially expressed miRNAs had inconclusive results (Bizuayehu et al. 2015). Beyond marine species, the role of miRNAs during other responses, such as osmoregulation and reactions to oxidative stress, osmotic stress, and toxins, has been revealed in freshwater teleost fishes (Bizuayehu & Babiak 2014).

2.4. Mitochondrial Epigenetics

The majority of the literature to date has focused on nuclear epigenetic mechanisms, with limited and disparate evidence available for epigenetic features in mitochondrial DNA (mtDNA). Thus, the nature of mtDNA epigenetic mechanisms, their location, and their function remain underexplored and contentious due to the unclear presence and role of mitochondrial DNMTs (Maresca et al. 2015), the potentially limited specificity of nuclear DNMTs for mtDNA (Ghosh et al. 2014), and the lack of histones associated with mtDNA (D'Aquila et al. 2017). Yet DNA methylation may still act as a mitochondrial epigenetic mechanism, as mtDNA appears to include both methylcytosines and hydroxymethylcytosines (D'Aquila et al. 2017). For example, bisulfite sequencing of human mtDNA provides a map of the mitochondrial methylome (Ghosh et al. 2014). By contrast, another study has concluded that the secondary structure of mtDNA impedes complete bisulfite conversion, leading to an overestimation of mtDNA methylation when measured through a bisulfite sequencing approach (Mechta et al. 2017). With respect to epigenetic mechanisms beyond DNA methylation, the lack of a chromatin-based packing in mtDNA (mtDNA is organized in loosely compartmentalized nucleoides containing several molecules of mtDNA and associated proteins) makes the presence of mechanisms based on histone variants and posttranslational modifications unlikely. On the other hand, the presence of nuclear-encoded miRNAs has been documented within, or associated with, the mitochondria and may play a role in the regulation of mitochondrial transcripts (Castegna et al. 2015).

Overall, the various potential areas of mitochondrial epigenetic investigations are still in their infancy. One potentially fruitful avenue of study is the significant crosstalk between mitochondrial function and epigenetic mechanisms associated with nuclear DNA, or mitoepigenetics (sensu Manev & Dzitoyeva 2013). Accordingly, it has been suggested that signals of mitochondrial (dys)function may act to trigger or reinforce epigenetic patterns in nuclear DNA (Castegna et al. 2015). For example, acetyl-coenzyme A (acetyl-CoA) generated from citrate cleavage during the citric acid cycle can be used for histone acetylation by histone acetyltransferases (HATs). Thus, acetyl-CoA fluctuations as a result of mitochondrial activity may drive changes in histone acetylation, influencing chromatin relaxation (acetylation) and condensation (deacetylation). Furthermore, since mitochondrial activity controls the production of *S*-adenosylmethionine, it may also drive changes in nuclear DNA methylation through the regulation of DNMT activity (Castegna et al. 2015). Although no mitochondrial epigenetics studies have yet been conducted in marine organisms, mitoepigenetics may constitute an interesting frontier of study for marine taxa.

2.5. Epigenetic Interplay

Far from being structurally and functionally isolated, different types of epigenetic modifications act in coordination to shape the epigenome across different cells (**Figure 2**). Although still largely unknown, the notion of interplay among different epigenetic mechanisms was already suggested in the early 2000s through the concept of the histone code, suggesting that specific combinations of histone modifications would be involved in recruiting regulatory complexes that modulate gene expression (Strahl & Allis 2000). For instance, it seems that the role of histones and their modifications in chromatin structure and epigenetics relies on crosstalk among different nucleosomes that harbor posttranslational modifications at different histones, which in turn determines the specific chromatin states at different genome regions, defines regions of the nucleus preferentially occupied by particular chromosomes, and ultimately regulates cell fate and metabolism. Indeed, it seems that epigenetic information might be encoded not at the level of individual nucleosomes but rather in groups of nucleosomes with coupled modification states (Erdel 2017). This notion was expanded into the epigenetic code by incorporating modifications in DNA methylation (Turner 2007). The consistent relationship among different types of modifications and their functional outcomes provides support for the epigenetic code hypothesis (**Figure 2**). For instance, it is now clear that the regulatory activity of different types of ncRNAs takes place through the modulation of other epigenetic mechanisms, notably DNA methylation and histone modifications (Carthew & Sontheimer 2009). In addition, recent findings suggest that miRNAs might be instrumental in cell communication, since these molecules can be observed in extracellular fluids inside vesicles, or as part of protein complexes (Zhang et al. 2015). These findings raise important questions about the roles of miRNAs in transgenerational epigenetic inheritance and in mediating communication between microbiotas and host organisms (see the sidebar titled Future Challenges and Questions). That notion is further reinforced by recent results suggesting that DNA methylation provides an epigenetic mechanism of transcriptional homeostasis during symbiosis (Li et al. 2018).

3. THE EPIGENETIC BASIS OF ENVIRONMENTAL ACCLIMATIZATION

Acclimatization is the short-to-intermediate-timescale cellular response of organisms to changing biotic and abiotic conditions (Hochachka & Somero 2002). These responses often include the modulation of gene expression or protein expression and posttranslational modifications, which can occur through epigenetic mechanisms. Acclimatization through epigenetic regulation provides potential for environmental memory beyond a single life stage or season, which has ecological consequences. Thus, research on epigenetic acclimatization in response to anthropogenic environmental perturbation has gained substantial traction in recent years (Hofmann 2017, Richards et al. 2017).

Acclimatization studies have focused on phenotypic plasticity, or the capacity for an organism to display a variety of phenotypes as a function of the environment. This examination of phenotypic plasticity has primarily been at two scales: intragenerational plasticity (IGP) and transgenerational plasticity (TGP). IGP is generated by signals occurring within the organism's life, while TGP is induced by signals set prior to fertilization that modulate the offspring reaction norms in different ways (Salinas & Munch 2012) (**Figure 1**). These processes have the potential to provide environmental legacy effects, which to date have not often been considered despite the growing acknowledgment of their importance in a time of intense and abrupt climate change (Torda et al. 2017).

IGP: intragenerational plasticity

TGP: transgenerational plasticity

3.1. Acclimatization Through Epigenetic Effects

IGP can occur on a spectrum ranging from transient to enduring results. On the dynamic end of the spectrum is the mode of reversible acclimatization through IGP. This shorter-term environmental memory could facilitate beneficial acclimatization but may be transient in nature (Burggren 2015) (**Figure 1**). Accordingly, an environmental parameter would induce an epigenetic effect that remains for some period of time and within that time incurs phenotypic consequences. While studies of methylation dynamics in marine systems are few and focus only on several time points (Dixon et al. 2017, Liew et al. 2018b, Putnam et al. 2016), a role for epigenetics in reversible acclimatization is clear in other model systems (Feil & Fraga 2012). This flexibility in phenotype may provide a buffer against rapid environmental change, but the uncertainty of the role of epigenetics and acclimatization in climate change response comes from the wash-in and wash-out nature of these effects (Burggren 2015). The details by which the type, magnitude, and duration of a signal and the life stage at which exposure occurs contribute to a dynamic or potentially canalized response are largely unknown (see the sidebar titled Future Challenges and Questions).

A mode of IGP on the more enduring end of the spectrum is developmental acclimatization, where the signals from the developmental environment set a trajectory toward a phenotype in anticipation of such conditions later in life. For example, the thickness of the fur coat of the meadow vole (*Microtus pennsylvanicus*) is generated by maternal environmental sensing of day length, which is translated as a hormonal signal to the developing offspring that primes a thick-coat phenotype, which should be matched to cooler conditions later in life (Lee & Zucker 1988). If environmentally induced epigenetic imprinting acts in an analogous way to the hormonal signal, a developmental trajectory could be epigenetically set. This is the case in the mammalian system, where the thrifty phenotype can be generated epigenetically by nutritional status during early development (Feil & Fraga 2012). Evidence for developmental IGP is common in the responses of marine calcifiers to ocean acidification (Ross et al. 2016), but to date, few examples exist in the marine system that have been linked to epigenetic mechanisms (Anastasiadi et al. 2017). The danger of a more fixed anticipatory response, especially in light of the rate of environmental change demonstrated and predicted in the oceans, is the potential mismatch of the phenotype generated by developmental conditions and the novel environmental conditions experienced later in life.

Scaling out across generations, a wealth of data on maternal effects and ecological TGP in marine taxa exists at the organismal level (Donelson et al. 2018, Ross et al. 2016, Torda et al.

2017), with the majority of aquatic invertebrates and fish showing positive TGP, in comparison with negative or null TGP (Donelson et al. 2018). In organisms with rapid generation times, such as the marine polychaete *Ophryotrocha labronica*, studies indicate some positive performance in offspring in response to parental preconditioning to increased temperature and reduced pH up to the F6 generation (Gibbin et al. 2017). In barnacles (*Striatobalanus amaryllis* and *Amphibalanus amphitrite*) and gastropod (*Volegalea cochlidium*) species, exposure of parents to increased temperatures increased the critical thermal maximum (i.e., the upper limits of thermal sensitivity) in the F1 and F2 generations above that of the parental generation (Morley et al. 2017). A variety of marine fish display TGP in response to both ocean warming and acidification. In particular, a strong positive response to adult preconditioning to ocean acidification has been documented in reef clownfish (*Amphiprion melanopus*) in terms of survival, size traits, and metabolic rate and a suite of movement and swimming metrics (reviewed in Donelson et al. 2018), supporting the capacity for beneficial traits to emerge through TGP.

3.2. Acclimatization Through Epigenetic Inheritance

In comparison with the clear occurrence of phenotypic plasticity due to parental exposure, the mechanistic evidence for transgenerational epigenetic inheritance (**Figure 1*b***) is less clear. In reef-building corals, there is evidence for the inducibility of DNA methylation in an environmentally sensitive brooding coral (*Pocillopora damicornis*) following exposure to ocean acidification (Putnam et al. 2016). This same species shows beneficial acclimatization of the offspring at the larval stage following adult exposure during brooding (Putnam & Gates 2015) and beneficial effects of adult exposure to low pH on the settlement, survivorship, and growth of larvae months after adult exposure (Putnam et al. 2018). Transgenerational alterations have been described in the marine tubeworm *Hydroides diramphus* in response to salinity stress (Jensen et al. 2013), in the bryozoan *Bugula neritina* upon exposure to copper (Marshall 2008), and in the offspring of Pacific oysters exposed to the herbicide diuron (Rondon et al. 2017). The transmission of physiological responses to high $p\mathrm{CO}_2$ through the F1 and F2 generations has been reported in the copepod *Pseudocalanus acuspes* (Feil & Fraga 2012). Together, these studies indicate a role for epigenetic mechanisms in beneficial TGP. New work examining the patterns of DNA methylation in adults, gametes, and larvae in the spawning brain coral *Platygyra daedalea* provided a further indication of transgenerational epigenetic inheritance (Liew et al. 2018a), although no phenotypic test of acclimatization was provided with the epigenetic data.

To date, tests of epigenetic mechanisms in intragenerational epigenetic effects and transgenerational epigenetic inheritance remain rare and are often equivocal in marine organisms. Furthermore, the ecological and evolutionary roles of phenotypic plasticity are complex and heavily debated (Pfennig et al. 2010). Theory predicts that both the direction (i.e., adaptive or maladaptive) and extent (i.e., complete or incomplete) of plasticity contribute to its evolutionary role (Kronholm & Collins 2016, Pfennig et al. 2010). In this light, the role of epigenetic mechanisms with respect to acclimatization to novel environmental conditions through IGP and TGP may have wide-ranging implications not only ecologically but also evolutionarily.

4. GENETIC–EPIGENETIC INTERPLAY

While epigenetic marks occur outside of the DNA bases, there is an inherent connection to genetic variation in both a causative and responsive role. With respect to DNA methylation, genetic aspects such as CG content and CpG density provide both the substrate for methylation and the outcome of persistent methylation presence that leads to sequence mutation (e.g., 5-methylcytosine deamination to thymine). Furthermore, the positions (Gertz et al. 2011) and abundance of single-nucleotide polymorphisms and the positions of transposable elements (Rey et al. 2016) can contribute to differences in the propensity for methylation or chromatin modification (Taudt et al. 2016). The full suite of mechanisms and the extent of genetic–epigenetic interplay are still unclear, but evidence from mammals and plants indicates a genotype-based tendency for differential methylation (Feil & Fraga 2012) and the potential for selection to occur based on epigenetic marks. In the reverse direction, genetic sequence may be a result of DNA methylation contributing to mutation through CpG deamination to thymine, which in turn may lead to codon bias. This notion is supported by the correlation between gene body methylation (in CpG dinucleotides) and codon bias (differences in the frequency of preferred synonymous codons) in a single coral methylome, as a result of the hypermutability of methylated cytosines leading to an increase of TpGs and CpA dinucleotides (Dixon et al. 2016). This genetic–epigenetic interaction is an understudied area that may generate evolutionary consequences and as such should be the focus of future study in marine organisms (see the sidebar titled Future Challenges and Questions).

The potential for genetic information to be influenced by epigenetic states is possible through several mechanisms. Genetic variation influences chromatin state, and this state can act in *cis* or *trans* to influence epigenomic variation (Taudt et al. 2016). For instance, the profiling of human histone posttranslational modifications reveals a large bias toward gene regions, with interindividual variation prevalent at enhancer or repressive states. Association mapping experiments identified multiple potential modes of epigenetic influence beyond histone modifications, notably by influencing nucleosome positioning and chromatin accessibility (McVicker et al. 2013). It is therefore possible to generate heritability estimates of epigenetic features through the use of quantitative trait loci, where the epigenetic variation is treated as a quantitative trait. These approaches include examination of histone quantitative trait loci and methylation quantitative trait loci, which could be used to quantify epigenetic heritability.

In light of the dire ecological forecast for marine ecosystems (Lotze et al. 2006), the need to understand acclimatory buffers and the evolutionary implications of climate change has promoted the study of linkages between plasticity and adaptation. One such linkage is genetic accommodation, or the enhancement of a novel phenotype through the genetic consequences of selection on environmentally induced phenotypic responses (Schlichting & Wund 2014). In this way, epigenetically generated phenotypic plasticity, as the target of selection, has the potential to direct evolutionary outcomes, thereby potentially buffering or exacerbating negative ecological performance and also retarding or potentiating adaptive evolution.

The importance of the genetic–epigenetic interplay in a marine organism was recently revealed through experimental evolution via manipulation of the genome and epigenome in the green alga *Chlamydomonas reinhardtii*. Strains with genetically and chemically modified epigenetic variation displayed reduced evolution of growth rate, demonstrating the role of epigenetic variation in facilitating adaptation (Kronholm et al. 2017), as predicted by theoretical models of adaptation that include epigenetic variation (Kronholm & Collins 2016). As there have been few empirical studies of the interaction between the genotype and epigenotype with respect to evolutionary processes, and the generation times of many marine organisms are substantially longer than those of *Chlamydomonas*, predictions of the evolution in future ocean conditions are still tested primarily through theoretical means (Day & Bonduriansky 2011, Kronholm & Collins 2016) and must be informed by additional empirical findings (see the sidebar titled Future Challenges and Questions). With respect to evolutionary outcomes in the ocean, areas of uncertainty (but significant interest) include the potential for epigenetic traps (Consuegra & Rodríguez López 2016), the possibility for epigenetics to activate speciation (Vogt 2017), and the capacity for epigenetic mechanisms to enhance rapid adaptation to novel environments that facilitates biological invasions (Hawes et al. 2018, Huang et al. 2017) (see the sidebar titled Future Challenges and Questions).

5. THE APPLIED POTENTIAL OF EPIGENETIC ANALYSES

While it is now evident that the epigenome is altered by environmental exposures, a formal framework describing how different epigenetic mechanisms interact to shape regulatory responses to environmental signals is still lacking (Bollati & Baccarelli 2010). The investigation of the cause–effect relationship between specific environmental effects, subsequent epigenetic modifications, and their functional consequences at different levels will facilitate the incorporation of epigenetics-based assays into risk assessments (Suarez-Ulloa et al. 2015), including retrospective assessments of environmental stress exposure through epigenetic footprinting (Mirbahai & Chipman 2014). The latter could help identify exposure to stressors and predict risk and susceptibility to disease (Baccarelli & Bollati 2009).

Epigenetic biomarkers can be defined as any epigenetic mark or altered epigenetic mechanism that is stable and reproducible during sample processing and can be measured in the body fluids or tissue preparations (García-Giménez et al. 2017). They must be robust, affordable, easy to use, and accurately measurable across individuals and populations. Although the biomarkers are emerging as promising tools for the study of disease in humans (e.g., cancer) and have obvious advantages compared with genetic biomarkers, their development is still in its infancy due to the complexity and time-consuming nature of most epigenetic techniques. Indeed, only a handful of papers have compared the same markers using the same assays in similar specimens (García-Giménez et al. 2017), and many of the more popular epigenetic assays (e.g., MSAP) are either nonquantitative or semiquantitative and thus are prone to reproducibility problems. Consequently, in order to successfully complement genetic biomarkers, epigenetic biomarkers still require increased standardization and improved validation, design, and optimization methods, along with rigorous quality and contamination control (Lorincz 2011).

5.1. Epigenetic Biomonitoring of Environmental Stress in Marine Ecosystems

The development of epigenetic and epigenomic approaches for biomonitoring affords great potential for developing fast and sensible environmental biomonitoring programs in diverse ecosystems (Metzger & Schulte 2016, Suarez-Ulloa et al. 2015). In marine organisms, studies focused on DNA methylation constitute the most abundant biomonitoring efforts (Díaz-Freije et al. 2014; Gavery & Roberts 2013, 2014; González-Romero et al. 2017), followed by the characterization of small RNAs developed mostly in fishes (Bizuayehu & Babiak 2014) and their parasites (Gallardo-Escárate et al. 2017), as well as in some bivalves (Rosani et al. 2016, Yu et al. 2016). In comparison, chromatin-based studies are less abundant due to the requirement of genomic tools and species-specific molecular tools (e.g., specific antibodies) (Rivera-Casas et al. 2017). Some of the earliest studies illustrating the potential of epigenetic analyses for biomonitoring were developed in marine fishes exposed to environmental toxins (Metzger & Schulte 2016). Epigenetic alterations were also monitored in marine invertebrates (i.e., bivalve molluscs) exposed to toxins produced by harmful algal blooms, revealing decreased levels of DNA methylation and phosphorylation of histone H2A.X (González-Romero et al. 2017). Additional studies have linked DNA methylation and thermal stress in other invertebrates, such as polychaetes (Marsh & Pasqualone 2014), as well as in teleost fishes (Anastasiadi et al. 2017, Burgerhout et al. 2017).

Altered DNA methylation levels have also been observed in corals subject to ocean acidification conditions (Putnam et al. 2016) and nutrient stress (Rodriguez-Casariego et al. 2018) and in response to changes in salinity in fish (Li et al. 2017a) and heavy metals in fish and other marine organisms (Mirbahai et al. 2013, Pierron et al. 2014, Zuo et al. 2009). Beyond DNA methylation, histone variants (H2A.Z and macroH2A) have also been associated with thermal acclimatization in the carp *Cyprinus carpio*, potentially involving different histone posttranslational modifications (Araya et al. 2010, Simonet et al. 2013). Specific miRNAs have also been involved in fish responses to thermal stress (Bizuayehu et al. 2015) and hypoxia (Lau et al. 2014), as well as in responses to osmotic stress response in oysters (Zhao et al. 2016). Overall, environmental aggressions trigger functional epigenomic changes, which have the potential to be used as biomarkers supporting ecological, evolutionary, and genetic approaches toward improving conservation and management actions in marine populations. However, the development and application of epigenetic biomarkers is contingent not only on overcoming the inherent weaknesses mentioned above (standardization, reproducibility, etc.) but also on clarifying key predictive aspects, such as the specificity of cause–effect relationships between particular stressors and epigenetic marks, or the temporal dynamics of these marks (wash-in and wash-out) upon initiation, exposure, and cessation of different stress types and intensities.

5.2. Epigenetic Biomonitoring of Marine Population Parameters

Beyond the effect of stress, epigenetic modifications can also provide information about other parameters linked directly or indirectly to environmental changes. For instance, epigenetic modifications affecting development and growth during cell differentiation along with changes in epigenome profile may act as a memory, predisposing individuals to certain disease conditions (Mirbahai & Chipman 2014). In marine organisms, changes in DNA methylation have been linked to alterations in the early development, metamorphosis, and growth of teleost fishes (Covelo-Soto et al. 2015b, Morán & Pérez-Figueroa 2011, J.L. Zhao et al. 2015). Similarly, it has been recently suggested that the DNA methylome modulates transcription regulation and that histone methylation is influenced by changes in temperature during Pacific oyster development (Fellous et al. 2015, Riviere et al. 2017). The epigenetic biomonitoring of growth has also been put into practice in marine mammals, where DNA methylation analyses served as the basis for developing a tool to estimate age in population samples from humpback whales (Polanowski et al. 2014).

The applicability of epigenetic biomonitoring can be translated to other parameters, notably the identification of sex in population samples, especially in cases of species displaying environmental sex determination (Navarro-Martín et al. 2011). Accordingly, specific DNA methylation patterns were linked to sex determination and identity in different teleost fishes (Metzger & Schulte 2016). Since diet influences methyl donors and the enzymatic activity of epigenetic modulators and affects gene expression (Etchegaray & Mostoslavsky 2016), this parameter represents another potential target for epigenetic biomonitoring efforts. Finally, the correlation between epigenetic modifications and other ecological processes, such as biological invasions, has been described in marine organisms (Ardura et al. 2017), providing an exciting opportunity to explore the functional relevance of DNA methylation for identifying and tracking successful biological invasions (Hawes et al. 2018).

6. EMERGING TOPICS

6.1. Epigenome–Microbiome Crosstalk

Within a marine context, the study of microbial diversity and stability has exploded over recent years, identifying a substantial role of the microbiome in organism function and an additional source of rapid adaptation (Torda et al. 2017). For instance, the microbiome may have a potential role in TGP, and this is exemplified by systems such as reef-building corals, where the microbiome (as constituents of the metaorganism) can enhance adaptive capacity and environmental stress tolerance (Webster & Reusch 2017). This is apparent more broadly in rodent models, where epigenetic features and their prokaryotic microbiome are linked, as DNA methylation underlies normal gut development, which differs with variation in gut microbiota (Yu et al. 2015). Mechanistically, these epigenetic differences could be triggered by signaling from metabolites generated by various microbial community members (Donohoe & Bultman 2012), as seen in humans through maternal and metabolic programming (Mischke & Plösch 2013). These metabolic differences are clearly possible in marine metaorganisms as well (Sogin et al. 2017). Emergent properties of the interaction between epigenetic mechanisms and dynamic microbial communities provide fertile grounds for rapid adaptation through nongenetic means (see the sidebar titled Future Challenges and Questions).

6.2. Epigenetics in Fisheries, Aquaculture, and Conservation

The current predictions of global climate change depict a near-future scenario where a sharp increase in aquaculture will be necessary to satisfy food demand. This goal requires the incorporation of alternative species and methods, including not only genetic selection but also epigenetic analyses. Although this knowledge is still scarce in marine organisms, recent studies have linked epigenetic mechanisms with commercially important traits in aquaculture (Gavery & Roberts 2017), and given that production efficiency has large effects on profitability, the ability to control these traits using epigenetic programming would be highly desirable. Mass selection studies of the Pacific oyster *Crassostrea gigas* revealed that epigenetic selection does not induce reductions in genetic diversity or large modifications in global DNA methylation levels. However, punctual differences in DNA methylation are found at specific genes, suggesting that epigenetic variation might be partly dependent on the genetic context (Jiang et al. 2013). This is further supported by changes in DNA methylation at loci potentially involved in the maintenance of polyploidy in fishes (Covelo-Soto et al. 2015a) and molluscs (Jiang et al. 2016). Similarly, the characterization of egg-predominant miRNAs in fishes opens the door for the development of egg-quality biomarkers of interest for aquaculture (Ma et al. 2012). Accordingly, miRNAs can potentially be used as markers for specific functional and diagnostic applications to control health in aquaculture production, since polymorphisms in miRNA genes and their target sites may underlie phenotypic variation in quantitative traits of value for selective breeding (Andreassen et al. 2013).

Within aquaculture, two key areas where epigenetics could make a major contribution have been defined as (*a*) the selection of epigenetic markers that improve brood-stock holding or conditioning and (*b*) environmental manipulation, notably during larval development and during brood-stock conditioning to facilitate environmental hardening (Gavery & Roberts 2017). The latter is especially interesting, as the identification of a programming window could be leveraged during husbandry activities and potentially used to transmit environmentally induced epigenetic modifications from parents to offspring (Gavery & Roberts 2017, Putnam et al. 2017). Nutrition and diet are also critical for aquaculture, potentially affecting phenotypes later in life, as revealed by a study showing that early short-term exposure of rainbow trout fry to a plant-based diet improved acceptance and utilization of the same diet when given at later life stages (Geurden et al. 2013). Similarly, it was suggested that a salt-enriched diet induces epigenetic modifications that can be important for the transformation of gills during salinity acclimatization in the brown trout (*Salmo trutta*) (Morán & Pérez-Figueroa 2011). However, an absence in evident global epigenetic signatures was found in other cases, although differential gene expression was still observed (Geay et al. 2012).

Overall, these results support the potential application of epigenetic selection and environmental manipulation for stress hardening to improve aquaculture practices. However, elucidating how epigenetic determinants and genetic context interact to promote positive or negative phenotypes established during programming windows (Geurden et al. 2013) remains a major challenge, although the potential benefits may motivate commercial industries to develop further epigenetic studies (Li & Leatherland 2012) (see the sidebar titled Future Challenges and Questions).

7. FUTURE CHALLENGES

Substantial threats to marine systems are apparent in the Anthropocene (Lotze et al. 2006), and these novel environmental conditions have uncovered plasticity in marine organisms' responses, caused in part by a variety of epigenetic mechanisms. Many challenges remain in this dynamic field of environmental epigenetics, including the limited mechanistic understanding of most epigenetic marks and their consequences for many marine species (which is unavoidable, given the dearth of genomic resources), the cost of performing epigenetic studies, and the collaborative expertise necessary for many of these projects (oceanographic, chemical, ecological, molecular, bioinformatic, etc.). These limitations are clear from the rarity of population-level analyses, the lack of integration of multiple epigenetic marks, and the infrequent use of methodologies for approaches common in other systems [e.g., assay for transposase-accessible chromatin with high-throughput sequencing (ATAC-seq), chromatin immunoprecipitation sequencing (ChIP-seq), and whole-genome bisulfite sequencing]. We suggest advancing approaches such as (*a*) developing a marine epigenetics research consortium or research coordination network (such as the Epigenomics of Plants International Consortium), (*b*) making concerted efforts around model organisms with broad translational capacity (e.g., *Crassostrea*, *Nematostella*, and *Aiptasia*) to facilitate technology transfer to nonmodel taxa, and (*c*) creating open-source protocols, bioinformatic pipelines, and statistical code to facilitate reproducible and efficient analyses. We further highlight areas of critical need and exciting potential as necessary next steps in our understanding of marine environmental epigenetics (see the sidebar titled Future Challenges and Questions). Marine environmental epigenetics represents an emerging research frontier, with the potential to revolutionize our understanding of ecological and evolutionary dynamics at a critical climate change juncture, in an invaluable marine setting.

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