Environmental Epigenomics and Its Applications in Marine Organisms

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Abstract Although epigenetics is still a relatively new discipline, its development during the last 10 years has revolutionized the current understanding of genome structure and function. The present chapter provides an insight on the exciting field of environmental epigenetics (i.e., the cause-effect relationships between environmental signals and epigenetic modifications altering phenotypes) and its potential applications for different types of studies in the marine environment. In the first part of this chapter, this work focuses on defining epigenetics, the different mechanisms involved in the epigenetic regulation of gene expression, as well as their potential role during the evolution of life on Earth. In the second part, this chapter moves into the potential applications of epigenetics in marine organisms, using current research projects on model species ranging from marine invertebrates to large marine megafauna as references. Overall, the present contribution underscores the importance of environmental epigenetic studies in marine organisms to better understand how organisms respond to their surrounding environment,

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fostering the development of a new generation of biomarkers enhancing restoration, conservation, and management efforts.

Keywords Biomonitoring · Chromatin · DNA methylation · Epigenetics · Mechanisms · ncRNAs · Population parameters · Restoration

1 Introduction

1.1 What Is Epigenetics?

The word "epigenetics" was originally coined by Conrad Waddington in 1942, referring to how genotypes give rise to phenotypes during development (Waddington 1942). Since then, the definition of epigenetics has been reshaped multiple times in order to keep up with the advances in biological knowledge. In this book chapter, epigenetics will be referred to as "The study of phenomena and mechanisms that cause chromosome-bound, heritable changes to gene expression that are not dependent on changes to DNA sequence" (Deans and Maggert 2015). In this context, heritability is defined as involving both mitotic and meiotic inheritance, and thus, epigenetic mechanisms need not be confined to processes that are inherited across generations (Metzger and Schulte 2016).

One of the most important challenges associated with the differentiation of the eukaryotic cell was organizing an extremely large genome within the reduced space of the cell nucleus (e.g., human diploid DNA is approximately 2 m long and needs to be packed within a cell nucleus of 6 μm of diameter). Such a high degree of condensation is achieved through the association of DNA with chromosomal proteins, forming a structure known as chromatin (van Holde 1989). The structural determinants of chromatin are extremely conserved across eukaryotes, underscoring their critical roles (Malik and Henikoff 2003; Ammar et al. 2012). However, chromatin also plays a functional role by regulating access to DNA in a well-coordinated and tightly regulated manner. Thus, this polymer can be defined as a highly dynamic structure where numerous proteins, transcription factors (TF), chemical marks (e.g., DNA methylation and histone posttranslational modifications), and other molecules (e.g., noncoding RNAs) work together to modify the architecture and accessibility to the DNA and, ultimately, regulate gene expression (Luger et al. 2012; Magistri et al. 2012; Table 1 and Fig. 1).

Chromatin provides a framework for the study of epigenetics, with this constituting an exciting frontier to understand how the environment influences the regulation of DNA function and the resulting phenotypic variation (i.e., phenotypic plasticity) observed in living organisms (Cortessis et al. 2012; Bollati and Baccarelli 2010; Suarez-Ulloa et al. 2015). The cause-effect relationships between environmental changes and epigenetic variation constitute the basis for environmental epigenetic studies (Feil and Fraga 2012). This discipline provides a powerful approach to study environmental responses in different ecosystems, notably in

Table 1 Main epigenetic mechanisms shaping the regulatory landscape of eukaryotic cells in response to environmental signals

Epigenetic mechanism	Definition	References
DNA methylation	Covalent incorporation of a methyl group to a DNA base. In metazoans, this often occurs on the 5 carbon of a cytosine	Jones (2012), Okano et al. (1999), Tahiliani et al. (2009), Li and Zhang (2014)
Histone posttranslational modifications and incorporation of histone variants	DNA is wrapped around nucleosomes formed by protein octamers of core histones (H2A, H2B, H3 and H4). Histones are subject to posttranslational modifications (PTMs) altering DNA-nucleosome interactions. Chromatin structure can be also altered by incorporation of histone variants replacing their canonical counterparts. Overall, histones regulate the access to the DNA by modifying chromatin structure	Ausio (2006), Kouzarides (2007), Henikoff and Ahmad (2005), Bannister and Kouzarides (2011)
Noncoding RNAs	RNAs transcribed from DNA but not translated into proteins, these RNAs generally function in controlling gene expression. There are many types of noncoding RNA (ncRNA) such as miRNA, siRNA, piRNA, and lncRNA. RNAs can be methylated, as part of the epitranscriptome	Palazzo and Lee (2015), Vidigal and Ventura (2015), Zhang et al. (2014), Carthew and Sontheimer (2009)

marine ecosystems subject to the harmful effects of global climate change (i.e., changes in water temperature, pH, salinity, and anthropogenic pollutants; Harley et al. 2006). Yet, while there is evidence supporting an epigenetic basis for the acquisition and transgenerational inheritance of acclimatized phenotypes in response to environmental changes, the mechanisms underlying such responses remain unclear (Vignet et al. 2015; Marsh and Pasqualone 2014; Greco et al. 2013; Navarro-Martín et al. 2011; Vandegehuchte et al. 2009). More precisely, our knowledge about how these mechanisms occur in response to specific stressors during different developmental stages, as well as how they interconnect and set the foundations for longer-term adaptation processes, is still very limited.

The present contribution will discuss foundational works in the field of environmental epigenetics, along with actual research defining the current understanding of epigenetics and the potential application of epigenetic studies in the marine environment. The first section of this work will introduce the main epigenetic mechanisms, how they can be influenced by the environment, as well as their potential for inheritance within and across generations. Subsequently, Sect. 2 will highlight specific fields of application for epigenetics with particular emphasis on the marine environment.

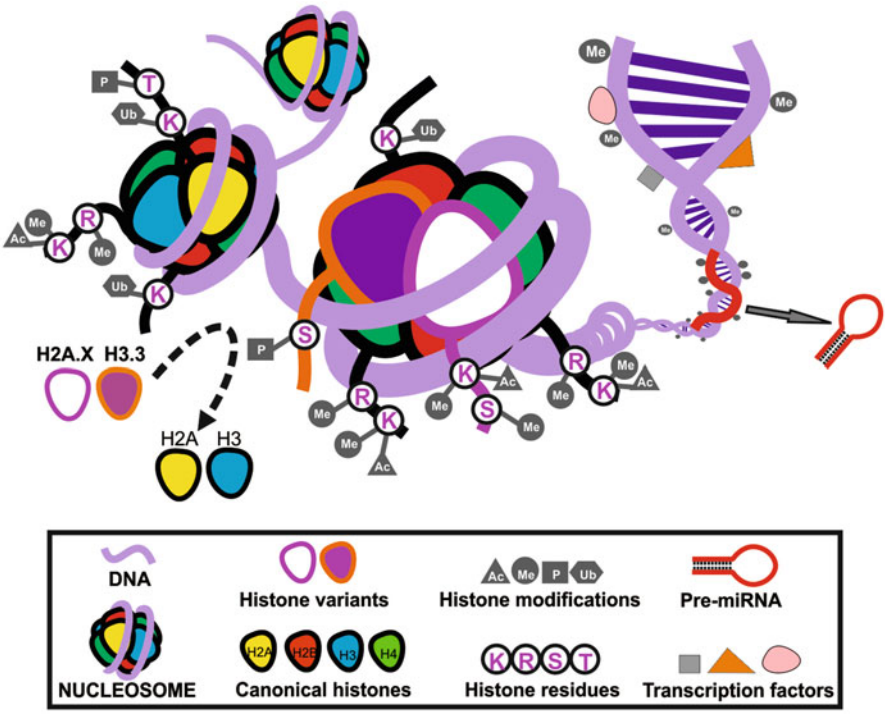

Fig. 1 Chromatin structure as a framework for epigenetic mechanisms. Various mechanisms have the potential to encode epigenetic information and regulate gene expression including DNA methylation (Me), the replacement of canonical histones by specialized histone variants in nucleosomes (e.g., H2A and H3 by H2A.X and H3.3, respectively), posttranslational modifications of histone residues (e.g., *Ac* acetylation, *Me* methylation, *P* phosphorylation, *Ub* ubiquitination), noncoding RNAs (e.g., miRNAs) or binding of transcription factors to the DNA

1.2 Main Epigenetic Mechanisms

1.2.1 DNA Methylation

DNA methylation is arguably the most studied epigenetic mark, involving the covalent incorporation of methyl groups to DNA bases (Table 1). DNA methylation marks have been described in genomes of organisms belonging to all domains of life, especially in the metazoan lineage within eukaryotes. The most common form of DNA methylation occurs at the fifth carbon of a cytosine, typically in the context of CpG dinucleotides, establishing a 5-methylcytosine (5mC) residue (Jones 2012). The reaction resulting in the addition of a methyl group to the carbon 5 of a cytosine is catalyzed by DNA methyltransferase (DNMT) enzymes (Okano et al. 1999). In mammals, DNMT3A and DNMT3B establish de novo DNA methylation patterns during embryonic development. Meanwhile, the enzyme DNMT1 binds to hemimethylated DNA and maintains those methylation marks after each cell

division, taking advantage of the symmetry of the CpG motif. DNA methylation is thus propagated unless removed by active [e.g., by ten-eleven translocation (TET) proteins (Tahiliani et al. 2009)] or passive mechanisms [e.g., lack of DNMT1 activity (Li and Zhang 2014)].

Genome Distribution and Regulatory Role of DNA Methylation

Despite its ancient origin and widespread occurrence, there is considerable variation in the 5mC distribution patterns and functions among taxa. Accordingly, even important model species show no detectable (e.g., *Caenorhabditis elegans* and *Saccharomyces cerevisiae*) or very low levels (e.g., *Drosophila melanogaster* displays low methylation levels detected only at early stages of development) of 5mC (Capuano et al. 2014; Bird 2002). Within metazoans, the genomes of vertebrate organisms are generally heavily methylated, with most CpGs exhibiting methylation marks, with the exception of those located at CpG islands (CGIs) which remain mostly unmethylated (Suzuki and Bird 2008). In contrast with this global distribution, most invertebrate genomes exhibit a mosaic pattern of 5mC distribution, with long stretches of highly methylated DNA interspersed with unmethylated regions (Tweedie et al. 1997; Feng et al. 2010). Interestingly, DNA methylation occurs mainly in gene bodies in invertebrates (including exons and introns of protein-coding regions, Suzuki et al. 2007; Zemach et al. 2010), while vertebrate genomes are commonly methylated also in intergenic regions, promoters, and transposable elements (Feng et al. 2010).

The functional effect of DNA methylation is highly dependent on the genomic context. Accordingly, high levels of methylation in proximal upstream promoters and enhancers are usually linked to transcriptional repression, through association with methyl-binding domain (MBD) proteins or through inhibition of transcription factor binding (Klose and Bird 2006; Deaton and Bird 2011). In contrast, gene body methylation is highly correlated with actively transcribed genes, reduction of transcriptional noise, and regulation of alternative splicing (Jones 2012; Huh et al. 2013; Shukla et al. 2011). Thanks to its regulatory role, DNA methylation is involved in critical biological processes such as cell differentiation and embryonic development (Smith and Meissner 2013). Furthermore, DNA methylation is also necessary to maintain genome integrity and even for defense purposes, as it is involved in the silencing of transposable elements in some species, as well as X-chromosome inactivation and genomic imprinting in mammals (Suzuki and Bird 2008; Jones 2012).

DNA Methylation Responses in Marine Environments

Although most of the current knowledge concerning DNA methylation derives from studies in mammalian model organisms, similar distribution patterns and transcriptional regulatory roles for this epigenetic mark have been shown in other chordates

(Peat et al. 2017; Metzger and Schulte 2016). Accordingly, the recent publication of the DNA methylome of the elephant shark *Callorhinchus milii* shows a global distribution of DNA methylation marks and a correlation with gene expression similar to that described in other vertebrates (Peat et al. 2017). Although functional information in non-model invertebrates is still scarce, several reports focused on marine species have contributed to filling this gap, including studies in the Pacific oyster (*Crassostrea gigas*) evidencing a correlation between gene body DNA methylation and high levels of gene expression (Gavery and Roberts 2013), as well as roles for DNA methylation in the regulation of alternative splicing (Gavery and Roberts 2013; Song et al. 2017) and embryonic development (Riviere et al. 2017).

Dynamic changes in DNA methylation are dependent on intrinsic genetic factors but also environmental factors (Feil and Fraga 2012; Fraga et al. 2005). Indeed, there is increasing evidence suggesting that changes in 5mC states can be triggered by changes in environmental conditions, contributing to phenotypic plasticity in organisms during subsequent responses (Kelly et al. 2012; Foo and Byrne 2016). Several works in marine animals further illustrate the links between DNA methylation and environmental changes. For instance, Marsh and Pasqualone reported that Antarctic polychaete embryos raised at different temperatures showed striking differences in DNA methylation patterns upon reaching adulthood, with increased DNA methylation levels on those raised at higher temperatures (Marsh and Pasqualone 2014). In a global climate change context, a study simulating ocean acidification conditions reported increased levels of global DNA methylation in the scleractinian coral *Pocillopora damicornis* after exposure to high pCO_2 conditions (Putnam et al. 2016). Similarly, DNA methylation changes have also been observed in the eastern oyster, *Crassostrea virginica*, in response to toxin-producing harmful algal blooms (González-Romero et al. 2017), although in this case DNA methylation decreased during exposure to increased levels of toxins. Interestingly, another recent report described lower levels of DNA methylation during the initial expansion phase of the invasive pygmy mussel *Xenostrobus securis*, potentially increasing phenotypic plasticity facilitating settling in the new environment (Ardura et al. 2017).

Among fishes, freshwater species such as the model zebrafish have dominated the literature (Metzger and Schulte 2016; Gavery and Roberts 2017). However, there are an increasing number of studies in marine species analyzing changes in DNA methylation in response to different conditions. For instance, DNA methylation in response to thermal variation has been studied in species such as the European sea bass, *Dicentrarchus labrax* (Anastasiadi et al. 2017); the Atlantic salmon, *Salmo salar* (Burgerhout et al. 2017); the Atlantic cod, *Gadus morhua* (Skjærven et al. 2014); the Senegalese sole, *Solea senegalensis* (Campos et al. 2013); and the tongue sole, *Cynoglossus semilaevis* (Shao et al. 2014). Of note here is the work by Varriale and Bernardi (2006) analyzing DNA methylation levels in 75 species of fish living at different latitudes and reporting higher 5mC levels in those living at lower temperatures (Varriale and Bernardi 2006). Changes in DNA methylation have also been observed in response to salinity variation in the tongue sole, *Cynoglossus semilaevis* (Li et al. 2017); cadmium exposure in the European eel, *Anguilla anguilla* (Pierron et al. 2014); hexabromocyclododecane and 17β-estradiol exposure in the three-

spined stickleback, *Gasterosteus aculeatus* (Aniagu et al. 2008); tributyltin and triphenyltin exposure in the sea ruffe, *Sebastiscus marmoratus* (Wang et al. 2009); and even environmental-caused tumorigenesis in the common dab, *Limanda limanda* (Mirbahai et al. 2011). In addition, changes in DNA methylation during development were also studied in the Atlantic salmon, *Salmo salar* [early maturation stages (Morán and Pérez-Figueroa 2011)]; the sea lamprey, *Petromyzon marinus* [metamorphosis (Covelo-Soto et al. 2015; Metzger and Schulte 2016)]; or the European eel, *Anguilla anguilla* [metamorphosis (Trautner et al. 2017)]. Overall, the number of publications applying DNA methylation analyses in marine species has increased dramatically in recent years. However, its use in other areas such as population studies remains largely unexplored. In this sense, DNA methylation could be used for species differentiation, behavior analysis, or estimation of demographic parameters such as age or sex of specific individuals in a population. The state of the art of these and other potential applications will be discussed in subsequent sections.

1.2.2 Histones, Histone Variants, and Histone Posttranslational Modifications

The chromatin fiber is constituted by fundamental subunits known as nucleosomes, each consisting of an octamer of architectural chromosomal proteins known as histones associated with DNA. Two copies of each core histone (H2A, H2B, H3, and H4) interact to form the nucleosome core particle (NCP), around which two left-handed super helical turns of DNA are wrapped (van Holde 1989, Table 1). Adjacent nucleosomes are joined together by short irregular stretches of linker DNA that interact with linker H1 histones, resulting in an additional folding of the chromatin fiber. Histones are small basic proteins with high affinity for the acidic DNA. They contain two structurally differentiated regions: a globular domain facilitating histone-histone interactions during nucleosome assembly and two unstructured tails (N- and C-terminal) that protrude from the nucleosome particle (Luger et al. 1997). Importantly, histones are not mere structural components of the chromatin but also critical determinants of its functionality (Allis et al. 2015). Indeed, histones can profoundly affect chromatin structure and its functional state by changing its local environment. This can be achieved in several ways. On the one hand, histones can be posttranslationally modified (PTM) at specific residues (Bannister and Kouzarides 2011) altering their electrostatic properties and, consequently, their affinity for DNA and other proteins. On the other hand, the replacement of canonical histones with specialized histone variants affects even to a greater extent the structure of the chromatin (Ausio 2006). Overall, the combination of histone variability and the different PTMs generate an enormous diversity in the nucleosome composition, creating a great variety of chromatin environments and transcriptional states (Henikoff and Ahmad 2005; Kouzarides 2007).

Histone- and Chromatin-Mediated Environmental Responses

In recent years, evidence has accumulated supporting the role of histone variants and histone modifications in environmental responses (Talbert and Henikoff 2014; Kasinsky et al. 2011). For instance, some environmental stressors can affect the DNA causing double-strand breaks (DSB). Upon damage, histone variant H2A.X undergoes rapid phosphorylation constituting a focus surrounding the damaged area. Along with modifications in other variants such as H2A.Z, macroH2A, or H3.3, these events constitute the earliest responses activating DNA repair pathways in the cell (Talbert and Henikoff 2014; Li et al. 2005). Histone H2A.Z has also been associated with responses to other environmental cues such as temperature (Kumar and Wigge 2010) or seasonal changes (Simonet et al. 2013) by regulating the expression of environmentally responsive genes (Adam et al. 2001; Coleman-Derr and Zilberman 2012; Wan et al. 2009). Additionally, PTMs such as acetylation (Wan et al. 2009) or ubiquitination (Simonet et al. 2013) targeting H2A.Z are involved in these responses. The histone variant macroH2A has also been involved in the seasonal acclimatization of the carp fish through the transcriptional regulation of the ribosomal cistron (Araya et al. 2010). In addition, although not an epigenetic feature in sensu stricto, histones also display an effective antimicrobial activity, and the extracellular release of histones is a widespread mechanism involved in the defense against pathogens that has been described in several marine organisms (Patat et al. 2004; Smith et al. 2010; Poirier et al. 2014; Sathyan et al. 2012; Destoumieux-Garzón et al. 2016).

Despite their critical roles during environmental epigenetic responses, detailed studies addressing the role of chromatin structural components are still lacking in non-model marine organisms. This is essentially due to the lack of knowledge about their chromatin structure, as well as to the absence of specific antibodies enabling the dynamic study of these proteins genome-wide. During the last decade, however, several studies have advanced in the description of chromatin components in marine animals, especially bivalve molluscs [reviewed in (González-Romero et al. 2012a, b; Suarez-Ulloa et al. 2015)], evidencing a high degree of conservation (Rivera-Casas et al. 2016a, b; González-Romero et al. 2012a, b) but also intriguing divergence in some cases (Rivera-Casas et al. 2016a, b). Detailed guidelines for the study of chromatin-associated proteins in bivalves have been recently published based on these studies (Rivera-Casas et al. 2017) paving the way to expand this type of analysis. In addition, studies in bivalve molluscs have shown the involvement of histone variants and PTMs in environmental-triggered responses. Accordingly, it has been recently reported that histone variant H2A.X is rapidly phosphorylated in the eastern oyster *C. virginica* during responses to harmful algal blooms and toxin exposure (González-Romero et al. 2017) and that histone methylation is influenced by changes in temperature during the development of the Pacific oyster *C. gigas* (Fellous et al. 2015). Overall, although the number of studies in marine organisms

analyzing the role of histone variants and histone modifications in environmental responses is still very scarce, the studies above evidence the need to put more effort in the characterization of the protein component of the chromatin.

1.2.3 RNA-Mediated Regulation of Gene Expression

Many eukaryotic genomes are characterized as concentrating protein-coding DNA regions within a very limited space of the overall genome (e.g., 1–2% in humans), compared to the proportion of DNA formerly considered as "genomic junk." However, it is now known that most of the DNA in eukaryotic genomes is indeed transcribed and potentially functional, producing different types of noncoding RNAs (ncRNA) which can play fundamental roles in the cell (Palazzo and Lee 2015), including structural functions and regulation of gene expression (Vidigal and Ventura 2015; Zhang et al. 2014). Regulatory activity might take place either through direct mechanisms (e.g., mRNA interference, splicing, or degradation) or through the modulation of other epigenetic mechanisms, notably DNA methylation and histone modifications (Carthew and Sontheimer 2009). In fact, one of the best-known roles of ncRNA in epigenetics is the regulation of genetic imprinting, where genes are selectively silenced by heavy DNA methylation depending on their maternal or paternal origin.

The RNA-mediated regulation of gene expression is considered to have evolved convergently in animals, plants, and protists independently, based on the high level of evolutionary conservation and the remarkable responsiveness to environmental stress found in regulatory ncRNA molecules across taxa (Zhang et al. 2011). The different types of ncRNA can be broadly classified based on their size into short ncRNA [sncRNA $<$30 nucleotides (nt)] and long ncRNA (lncRNA $>$200 nt). The former group comprises three major classes, short interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs), and microRNAs (miRNAs), all of them with specific functions in epigenetic mechanisms (Holoch and Moazed 2015). The present section focuses particularly on miRNAs, the most widely studied type of small ncRNA, which are approximately 22 nt long and can block the translation of mRNA by hybridizing with imperfect complementary sequences at 3′-UTR of their targets. Optimized sequencing methods allow for the characterization of these short noncoding RNA transcripts in any organism, facilitated by the high level of conservation they display within metazoans. Moreover, predictive models have been developed to identify potential targets among protein-coding transcripts (mRNA), streamlining the characterization of regulatory networks. Interestingly, despite the relatively high evolutionary conservation of miRNA sequences, a high rate of gene turnover and different regulatory mechanisms have been proposed for cnidarians in contrast to bilaterian animals (Moran et al. 2014). These observations resemble the relevant differences existing between miRNA in animals vs. plants, where miRNA regulates the expression of target mRNA through cleavage and plays a role in directing DNA methylation events (Wu et al. 2010).

Epigenetic Role of miRNAs During Environmental Responses

Interestingly, recent findings suggest that miRNAs might be instrumental in cellular intercommunication, since these molecules can be observed in extracellular fluids inside vesicles or as part of protein complexes (Zhang et al. 2015). Thus, these findings lead to another critical question: Do miRNAs participate in the transgenerational epigenetic inheritance by carrying environmental information from somatic cells to the germ line? (Zhang et al. 2015; Cossetti et al. 2014). Similarly, the possibility of a miRNA-based communication between microbiota and host organism adds further interest to this specific type of ncRNA. While most studies have been focused in model vertebrates, miRNAs have been also identified in several non-model organisms, including marine vertebrates and invertebrates. Accordingly, miRNA transcriptomes have been identified and characterized in fish (Li et al. 2016), in marine mammals (Segawa et al. 2016), and also in invertebrates such as molluscs (Xu et al. 2014; Picone et al. 2017; Jiao et al. 2014), cnidarians (Gajigan and Conaco 2017; Liew et al. 2014), and sponges (Liew et al. 2016).

Similar to the case of other epigenetic mechanisms, the role of miRNAs during environmental responses is starting to be deciphered, supporting their value to study acclimatory responses under rapidly changing environments and their biomarker potential. For instance, specific miRNAs have been shown to participate in fish responses to hypoxia (Lau et al. 2014) and thermal stress (Bizuayehu et al. 2015). In addition, the role of environmentally responsive miRNAs has been linked to crucial physiological processes including reproduction in fishes (Juanchich et al. 2013; Tse et al. 2016). The key regulatory role of miRNAs during environmental responses has been demonstrated in marine invertebrates (Huo et al. 2017; Zhao et al. 2016a, b), as well as in marine microorganisms (Gierga et al. 2012). In particular, the potential of miRNA to be transferred extracellularly via vesicles or protein complexes makes them particularly promising to understand host-microbe interactions like in the case of coral-dinoflagellate symbiosis, where the latter have been shown to produce miRNAs complementary to mRNAs in the coral host (Lin et al. 2015).

1.2.4 Epigenetic Regulatory Networks

The regulation of eukaryotic gene expression is possible thanks to the complex coordinated action of different genetic and epigenetic mechanisms. Although still largely unknown, recent reports have identified the interplay among some types of ncRNA (e.g., siRNA or lncRNA) as critical mediators of DNA methylation and histone modifications. For instance, lncRNAs have been repeatedly reported to initiate DNA methylation events through the interaction with DNA methyltransferases (Zhao et al. 2016a, b). However, both long and short noncoding RNAs other than miRNAs (e.g., lncRNA, siRNA, piRNA) have been also associated with methylation of histone tails through different mechanisms, leading to different chromatin states including heterochromatinization (i.e., global silencing of genes by increased chromatin

compaction; Joh et al. 2014). On the other hand, it has been reported that DNA methylation marks at promoters of metazoan miRNA genes exert an indirect, although critical, effect in gene regulation by modulating the expression of this interference mechanism, illustrating the complexity of this multilevel epigenetic regulatory network (Parodi et al. 2016).

DNA methylation in promoters is usually excluded from regions containing nucleosomes with transcriptionally active marks such as H3 methylation (H3K4me2 and H3K4me3) or presence of H2A.Z (Gu et al. 2015; Zilberman et al. 2008). In this sense, work in mammals has shown that methylation of H3K4 strongly inhibits the initiation of the de novo methylation process (Ooi et al. 2007). Overall, the modeling of these regulatory networks has been attempted using a systems biology approach and computational methods in biomedical research (Artyomov et al. 2010; Chen and Li 2016). Despite the general lack of these kinds of studies using marine organisms, these studies convey the promise of more specific biomarkers for disease or environmental stress obtained through the combination of heterogeneous epigenetic data that can inform about the health of the organism or populations. Moreover, they have the potential to be used as a proxy to inform about subtle changes in the environment working as bioindicators of the quality of ocean waters.

1.3 Inheritance of Epigenetic Modifications

A critical aspect to consider when analyzing the contribution of epigenetic mechanisms to phenotypic plasticity is their inheritance and whether this is referring to mitotic cellular divisions or the meiotic transmission to further generations. While some epigenetic marks can persist in a cell for decades [e.g., DNA methylation-mediated gene silencing (Klose and Bird 2006)] or be transmitted transgenerationally [e.g., DNA methylation marks (Kuhlmann et al. 2014), small RNAs (Chen and Li 2016)], other epigenetic modifications can rapidly change between modified and unmodified states depending on environmental cues [e.g., histone acetylation (Turner 2000)]. The highly dynamic nature observed in epigenetic modifications has motivated the differentiation of two types of approaches for their study: intragenerational epigenetics (contributing to intragenerational plasticity, IGP; see Fig. 2) and transgenerational epigenetics (contributing to transgenerational plasticity, TGP; see Fig. 2; Burggren 2016). Accordingly, the first is primarily focused on the mechanistic basis underlying gene expression changes produced by epigenetic marks and its persistence in an individual (e.g., epigenetics of diseases). On the other hand, transgenerational epigenetics is interested in the persistence of particular epigenetic marks across generations, more precisely, the transmission of epigenetic marks beyond the F2 generation, ruling out a direct environmental effect in primordial germ cells (Feil and Fraga 2012). Thus, transgenerational epigenetics constitutes a very innovative and powerful tool to study adaptation and population modeling (Etchegaray and Mostoslavsky 2016). Yet, despite the evident appeal of the transgenerational approach, our understanding of the basic mechanisms by which

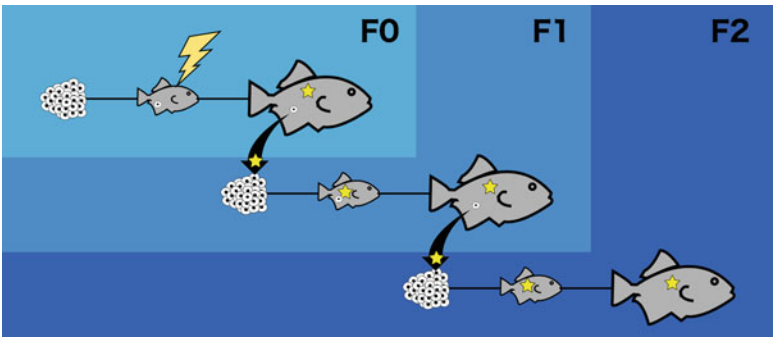

Fig. 2 Intragenerational plasticity (IGP) and transgenerational plasticity (TGP) phenomena triggered by environmental signals. Environmental signals may influence the phenotype of an organism through epigenetic modifications regulating gene expression, even at later stages in life long after exposure (considering F0 only). The phenotypic outcome of these environmentally induced epigenetic modifications may be acclimatory or deleterious (e.g., disease) and can be referred to as intragenerational plasticity (IGP). This environmental information can be transmitted to subsequent generations (F1–onward) by means of stable epigenetic marks in the germ line. In order to qualify as transgenerational plasticity (TGP), this transmission must occur until at least F2 in the case of non-eutherian fish, or until at least F3 in the case of viviparous species. This is because exposure of the gestating female (F0) that modify the epigenome could result in simultaneous direct exposure of the developing embryo (F1) and the developing germ line of the embryo (F2) (Mirbahai and Chipman 2014)

epigenetic marks persist, modulate expression, and survive reprogramming events in the zygote is still very limited and can lead us to erroneous assumptions about their role in inherited phenotypes.

1.3.1 Epigenetic Reprogramming

Epigenetic reprogramming events have been best characterized in the germ line and during early stages of mammalian embryogenesis. Such events represent major barriers for the transmission of epigenetic marks to the next generation, since the majority of DNA methylation marks and practically all of histones and their PTMs are removed from chromatin and replaced by protamines during male gametogenesis (Eirín-López and Ausió 2009), only to be restored afterward during cell differentiation (Morgan et al. 2005). Studies of DNA methylation during zebrafish development revealed similar patterns to those observed in mammals, supporting and expanding these observations to other vertebrates (Riviere et al. 2013). Oppositely, extensive epigenetic reprogramming events have not been observed in plants nor in most invertebrate species (with the exception of social insects). These observations have led to hypothesize that transgenerational inheritance of DNA methylation marks would be more plausible in these taxonomic groups (Sano and Kim 2013; Hauser et al. 2011).

An interesting perspective on the application of epigenetics in ecology and evolution of marine organisms was put forward by Verhoeven et al. (2016), emphasizing the relevance of transgenerational epigenetics for the development of such fields. There, DNA methylation was designated as the only mechanism able to carry epigenetic information transgenerationally, dismissing the already confirmed roles of small RNAs (Chen and Li 2016) and chromatin modifications (e.g., Siklenka et al. 2015). It is important to point out that such dismissal could be motivated by a lack of information or precise knowledge about the contribution of these mechanisms to this process. Indeed, the transgenerational transmission of epigenetic information does not need to occur by the direct transmission of a specific mark (generally reset at some stage), but instead it could involve the translation of such information across diverse epigenetic marks. It is therefore fundamental to continue to investigate the relationships between different epigenetic mechanisms over the base of specific marks and elicited changes in gene expression patterns as well as the environmental factors triggering those epigenetic marks in the first place (Cortessis et al. 2012). By doing so, it would be possible to move toward identifying the nature and inheritance of these modifications and their implication in adaptive responses (Tricker 2015).

1.4 Epigenetic Determinants of Evolutionary Change

Understanding the contribution of epigenetic mechanisms to organismal acclimatization and adaptation under rapidly changing environments constitutes one of the current greatest challenges in modern biology. The potentially heritable nature of epigenetic modifications (and their subsequent contribution to the inheritance of environmentally acquired phenotypes) is revolutionizing the current understanding of the mechanisms underlying evolutionary change. Indeed, through epigenetic modifications, it is possible to provide a mechanistic basis for well-known evolutionary phenomena including phenotypic plasticity (PP) (Rando and Verstrepen 2007). In addition, epigenetic diversity may act as a compensatory mechanism in populations where genetic diversity is low, increasing phenotypic variability. This mechanism has been shown to be critical for the establishment and success of invasive species in new environments as has been seen in marine invertebrates (Ardura et al. 2017; Pu and Zhan 2017). More importantly, epigenetic modifications could facilitate extremely rapid and acclimatized phenotypic responses to global climate change in much shorter time scales than those required for the fixation of genetic variants providing increased fitness (Rando and Verstrepen 2007). Given the rapid pace of global climate change and its critical impact on marine environments, the characterization of the role played by epigenetic mechanisms during acclimatization and adaptation will help develop better population assessment and management strategies.

The contribution of epigenetic modifications to rapid acclimatization and adaptation may be even closer to classical mutation-selection theories than previously

thought. This is best illustrated by studies finding high mutation rates (up to tenfold compared with non-methylated DNA) at hypermethylated CpG sites. Although this observation has been linked to altered cancer states, it could also contribute to adaptation and evolution (Guerrero-Bosagna et al. 2005). Therefore, epigenetics provides an attractive framework to explain mechanisms of rapid evolution, offering great potential for conservation efforts. These ideas have been considered by coral researchers proposing an innovative concept coined as "assisted evolution" (van Oppen et al. 2017). This approach suggests the implementation of selective breeding and preconditioning treatments artificially increase tolerance of organisms to environmental stress through the manipulation of environmental conditions. This notion is supported by the concept of priming hormesis (the environmental "priming" of certain physiological processes can improve their functioning later in life) as a nonlinear dose-response relationship where beneficial consequences of low-level exposure to environmental stress or pollution may increase the organism's tolerance to higher levels of such pollution or stress later in life (Costantini 2014).

2 Environmental Epigenetic Applications in Marine Ecosystems: Current and Future Perspectives

The present section summarizes some of the most relevant research directions illustrating the current relevance of environmental epigenetic studies in marine organisms. For that purpose, examples encompassing a broad range of taxa have been chosen. Since epigenetics research is still in its infancy in non-model organisms, especially in the marine environment, many of the studies discussed below are still efforts in progress.

2.1 Epigenetic Assessment of Health and Stress in Marine Organisms

Genetic disorders can be identified, and in many instances treated, through analyses revealing alterations in the DNA sequence. However, these analyses have intrinsic limitations at the time of revealing direct changes in gene function motivated by heterogeneous environmental conditions. Environmental epigenetic analyses fill that gap (Bollati and Baccarelli 2010), providing a framework for developing sensible epigenetic biomarkers. Such approach has been pioneered in human health sciences for a while now, notably linked to cancer biology (Sharma et al. 2010). Overall, the combination of genetic and epigenetic analyses is ushering basic research and applied therapies into the age of personalized medicine, incorporating genetic and environmental diversity into current studies. Importantly for ecological and toxicological research, the information currently being generated in model

organisms can be readily expanded to different taxa across different environments, thanks to the evolutionary conservation of the fundamental components of epigenetic machinery (Feng et al. 2010; Lee et al. 2010; Goll and Bestor 2005; Lowdon et al. 2016).

2.1.1 Epigenetic Biomarkers of Disease

Epigenetic modifications are becoming a popular new source of health biomarkers in humans. These biomarkers have been linked to ongoing conditions, such as in the case of cancer-specific hypermethylation of CpG islands (Herman and Baylin 2003). In addition, epigenetic biomarkers identifying disease susceptibility have also been defined in cases where the disruption of epigenetic marks results in detrimental mutations and transcriptional changes leading to disease. This latter type is best illustrated by the "epigenetic progenitor model" (Mirbahai and Chipman 2014; Mirbahai et al. 2011a, b; Portela and Esteller 2010), suggesting that epigenetic changes occur as early as in progenitor cells and facilitate the progression of carcinogenesis (Pogribny 2010; Sharma et al. 2010; Feinberg et al. 2006). This model found support in marine studies combining methylated DNA immunoprecipitation (MeDIP) with de novo high-throughput sequencing to investigate DNA methylation changes in the non-model common flatfish dab (Mirbahai et al. 2013). Accordingly, an unusually high incidence of liver tumors (20% affected in some areas) was found in these organisms, displaying a 1.8-fold decrease in the DNA methylation of adenoma liver tissue cells. Based on these results, it was suggested that chronic exposure to pollutants (including endocrine disruptors and heavy metals) was responsible for the epigenetic changes observed (Bollati and Baccarelli 2010; Huang et al. 2008; Reichard et al. 2007).

The observed cause-effect relationship between environmental stress, epigenetic modifications, and the risk of developing disease later in life supports the relevance of environmental epigenetic studies in aquatic organisms. Although this approach is still hampered by the lack of detailed knowledge regarding epigenetic regulation, some species such as zebrafish and medaka are starting to emerge as model systems (Kim et al. 2016; Mudbhary and Sadler 2011), facilitating the study of transgenerational epigenetics and the impact of environmental stressors on population dynamics. On the other hand, the study of marine mammals can easily benefit from (and even complement) technologies and molecular tools specifically developed in human health research. Accordingly, the use of miRNA in biofluids (e.g., blood and plasma) has already been proposed for biomonitoring and early disease diagnosis of dolphins in aquaria (Segawa et al. 2016). Also, since high levels of circulating nucleosomes have been associated with several types of cancer and other conditions in humans (Chen et al. 2014; McAnena et al. 2017), liquid biopsies targeting histone modifications as potential early biomarkers of different diseases could also be a promising approach in the case of marine mammals (Bauden et al. 2015; Gezer et al. 2015; Abrams et al. 2013). Although the application of these methodologies in ecological studies could be challenging, their implementation in

captive and wild animals would critically contribute to individual and population assessment, supporting management and conservation efforts.

2.1.2 Epigenetic Biomarkers of Stress Exposure

The study of epigenetic biomarkers constitutes a very powerful approach to identify early exposure to pollutants and other environmental stressors, based on the plasticity and sensibility of epigenetic modifications (Jaenisch and Bird 2003). Both genomic and mitochondrial DNAs represent good sources of epigenetic biomarkers, as suggested by studies revealing germ line mutations, DNA damage, and global hypermethylation in mice exposed to particulate air pollution in an urban/industrial location (Byun et al. 2013; Yauk et al. 2008). In marine environments, anthropogenic pollutants are often found in tissues of marine organisms, including polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDE), and several other chemicals (Tanabe et al. 1983; Stuart-Smith and Jepson 2017; Lascelles et al. 2014). Heavy metals constitute another widely quantified stressor in marine environments (Boening 1999), whose effects include altered DNA methylation states (Baccarelli and Bollati 2009). These elements represent a common threat during dredging associated with the development of coastal areas. During this procedure, the sediment is introduced (along with the pollutants deposited in the soil, particularly trace heavy metals (Calmano et al. 1996)) into the surrounding water column. Under certain conditions these pollutants become bioavailable and subsequently incorporated into the food chain (Latimer et al. 1999; Eggleton and Thomas 2004; Burton et al. 2010), critically impacting species using shallow coastal bay and estuary areas as nurseries, including fish, shrimp, and predatory species such as sharks.

The work toward finding epigenetic biomarkers of exposure for marine organisms has been pioneered by several studies addressing the effects of exposure to various stressors including parasites (Farias et al. 2017), pollutants (Wang et al. 2009), and harmful algal blooms (Suárez-Ulloa et al. 2013; González-Romero et al. 2012a, b). Most of these studies focused on DNA methylation changes with exposure to the various stressors, and all used molluscs as the model organism. Given the intra- and transgenerational persistence of some epigenetic modifications, their study could potentially provide an insight into the variety of environmental exposures that an individual has experienced during its life (Mirbahai and Chipman 2014). With current technology capabilities (i.e., next-generation sequencing, microarrays, bisulfite treatment sequencing), biomarkers of exposure can be identified in species without a reference genome. Simply identifying changes in the epigenome can improve our ability to identify early exposures to detrimental stressors. As more reference genomes become available, biomarker identification will be further facilitated in other marine species as well as our ability to determine the health effects of these stressors upon the organisms and their populations.

2.2 *Epigenetic Study of Population Parameters in Marine Organisms*

Biological conservation requires efficient methods to identify endangered populations in a timely fashion. However, this task is often hindered by the difficulty to record different species attributes. For instance, the study of populations belonging to highly mobile species is more complicated due to their vagility, as it is the case for many marine species. In those scenarios, molecular techniques have proven to be extremely valuable, being in many cases the only approach possible to gather certain types of information, such as sex or populations dynamics. Yet, the information provided by genomic analyses is still limited in many instances. The present section discusses potential applications of epigenetic strategies for gathering additional types of information for population analyses, notably age and sex.

2.2.1 Epigenetic Estimation of Age

Determining the age of individuals is critical to understand their demography and population dynamics (see Fig. 3). Unfortunately, the influence of this trait on trophic interactions (e.g., Lahaye et al. 2006) and on environmental responses (Mashburn and Atkinson 2004; Poloczanska et al. 2016) is generally unknown for many species. This is mainly due to the inherent difficulty in estimating age in these organisms. Consequently, several areas of study (e.g., ecology, physiology, toxicology, etc.; see Fig. 3) would greatly benefit from the incorporation of age into their datasets, improving the resolution of these analyses (Yang et al. 2015; Horvath 2013; Jarman et al. 2015). Large marine mammals such as dolphins and whales are among these difficult species to study. Although different methods have been developed to sample and estimate biological parameters, the age estimation method most widely used in cetaceans is counting growth layer groups (GLGs) on teeth (Perrin and Myrick 1980). This method requires the removal of a tooth from the animal which, in addition of being extremely invasive, is not feasible in the case of population studies involving several animals or in the case of very large species (e.g., large whales).

Molecular methods of age estimation have been therefore developed, notably the analysis of telomere lengths (Fagagna et al. 2003; Hedrick and Lacy 2015). Unfortunately, the high levels of intraindividual variation observed make this approach unreliable for age estimation (Hedrick and Lacy 2015; Olsen et al. 2012). Alternatively, it has been demonstrated that the study of epigenetic modifications such as DNA methylation can provide a reliable method for age estimation (Horvath 2013), based on the correlation between methylation of CpG sites and age (see Fig. 3a, b). This technique has even been calibrated for use with humpback whales, using noninvasive skin tissue samples (Polanowski et al. 2014). More precisely, the humpback epigenetic age assay (HEAA) targets three genes whose DNA

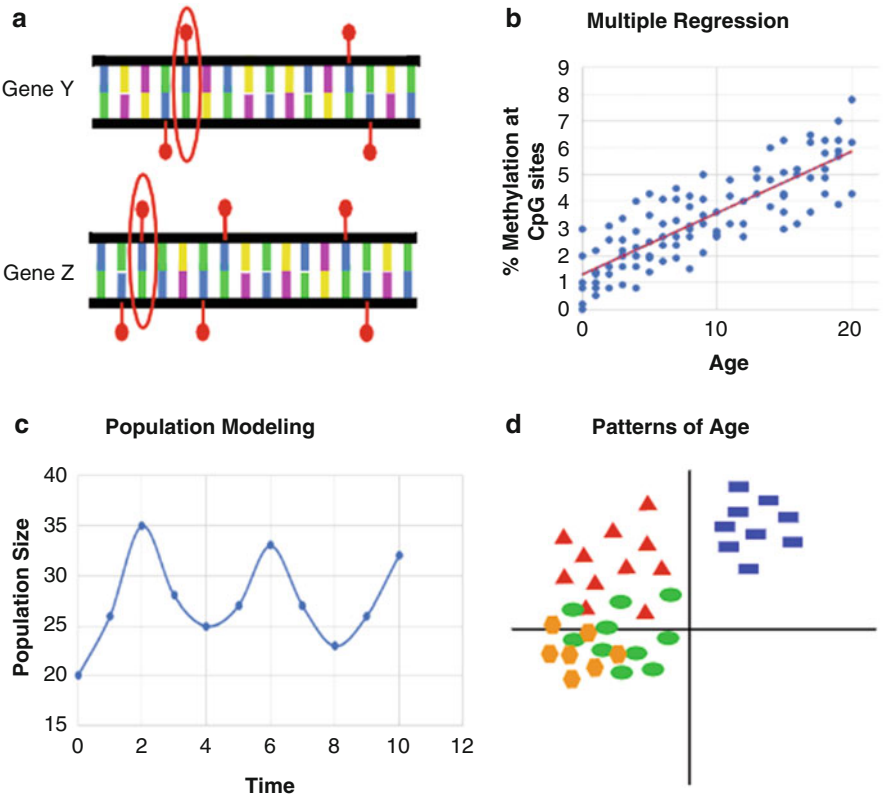

Fig. 3 Epigenetic estimation of age and implications for population ecology. Epigenetics can be used to estimate the age of individuals based on DNA methylation patterns at age-associated loci. (**a**) In mammals, the amount of DNA methylation at specific CpG sites (indicated with red circles) displays a strong correlation with age. (**b**) Using multiple regression based on CpG sites whose DNA methylation changes with age, a model can be created to identify the age of unknown individuals. (**c**) Age identification supports and informs conservation efforts in endangered populations (e.g., helping model and predict population growth through identifying how many individuals are of reproductive age). (**d**) This principal component analysis shows a scenario in which age makes sense of the different groups (e.g., juveniles, blue rectangles; subadults, red triangles; adults, green circles; older nonreproductive individuals, yellow hexagons); this could be a feasible analysis for several fields such as toxicology, DNA methylation patterns and exposures/different environments, or other types of data that may be different across age groups

methylation is highly correlated with aging. The applicability of this tool is not only evident in this species, but it also provides a framework for developing species-specific assays able to efficiently determine age in keystone marine mammals (Hannum et al. 2013). Nonetheless, this goal requires the availability of a reference genome for the targeted species. In case that is not available, the use of high-throughput sequencing might help in finding age markers through massive genome scanning.

2.2.2 Identification of Cryptic Subpopulations Using Epigenetic Markers

One of the most important challenges in conservation biology is to identify when speciation is occurring and to properly manage the incipient subpopulations. Accordingly, when two subpopulations become reproductively isolated, it is expected that genetic mutations will begin to accumulate between the two populations, due to the low gene flow (Bateson 1909; Dobzhansky 1936; Muller 1942). However, little or no genetic differentiation will be evident during the early stages of this process due to not enough time having elapsed since isolation (i.e., mutation rate is low and differentiation is slow). This hinders the correct identification and management of subpopulations of endangered species. Nonetheless, whether population isolation is due to physical barriers or geographical preferences, it is expected that each population will be subject to different environmental conditions, triggering different epigenetic responses. That prediction, which has been supported by studies developed on human monozygotic twins subject to different environments (Fraga et al. 2005), underscores the potential of epigenetic analyses to identify early speciation events and their relevance for management and conservation purposes. This strategy is even more important in populations in which cohorts or social groups may exist which may influence isolation of reproduction, such as dolphins (Viricel and Rosel 2014).

Epigenetics may even contribute to speciation (Blevins et al. 2017). As previously mentioned, rapid acclimatory responses influenced by environmentally responsive epigenetic modifications might provide a basis for rapid adaptation and evolution. For instance, DNA methylation at CpG islands increases the rate of mutation at these sites by as much as tenfold, encompassing implications not only for disease but also for speciation (Sved and Bird 1990; Guerrero-Bosagna et al. 2005). In Blevins et al. (2017), an epiallele for the HISN6 was found that silenced the gene in *Arabidopsis thaliana*. Individuals of the specific ecotype that had this epiallele were found to be incompatible in making viable offspring with individuals of a different ecotype that had a genetic mutation in the gene, HISN6A, that was nonfunctioning. This study evidences that both genetic and epigenetic variation among subpopulations is contributing to their incompatibility. This particular scenario of speciation falls under the mechanism of speciation proposed by Lynch and Force (2000), where gene duplications often lead to the inactivation of one of the duplicates (as a resolution to the duplication). Thus, incompatibilities can occur between individuals from populations with opposing resolutions to gene duplications. Based on this observation, it is now important to look not only at the genotype but also at the epigenotype of populations, in order to identify causes of reduced gene flow. This could be extended into breeding programs to help severely endangered populations such as corals or in the extreme situation where only a handful of individuals of a population remains and captive breeding becomes the only option such as in the case of the attempts to resque the Vaquita (Taylor et al. 2016).

2.2.3 Other Populational and Ecological Applications

There are potentially many different ways in which epigenetics can contribute to the current ecological understanding of marine populations. Thus, when studying a population, it is critical to monitor changes in the genome and also in the epigenome to learn how species respond to their environment. For instance, the study of DNA methylation provides a relatively easy and inexpensive strategy (i.e., storage and handling of samples is less stringent and expensive for DNA vs. RNA) for ascertaining how gene expression is being modified under different environmental regimes. Accordingly, Morán and Pérez-Figueroa (2011) found that epigenetic changes (DNA methylation) participate in the early maturation of male Atlantic salmon (*Salmo salar*) in response to low population densities. Additionally, DNA methylation studies in the three-spined stickleback found that several genes encoding ion channels were differentially methylated between freshwater and saltwater stickleback. They found that genes harboring genetic and epigenetic changes between the two ecotypes were different suggesting that DNA methylation was a complementary mechanism to the adaptation to freshwater (Artemov et al. 2017).

Epigenetics can also help in predicting population parameters or health status in future generations. For example, in European sea bass (*Dicentrarchus labrax*), DNA methylation changes have been found to affect sex determination in response to changes in temperature (Navarro-Martín et al. 2011). More precisely, increased DNA methylation of the promoter region of the aromatase (cyp19a1) gene at higher temperatures decreases its expression, thereby accumulating increased levels of androgen and promoting the formation of testis and a male-biased sex ratio. This is similar to sex differentiation mechanisms found in some reptiles (Matsumoto et al. 2013), and it has been suggested that temperature-dependent sex determination could be inherited transgenerationally (Warner et al. 2013). Knowing this kind of information could help with predicting what new generation population parameters will be like and allow for a better estimation of the breeding population. In addition to predicting sex as a parameter of populations, it can also be informative to be able to just identify the sex of individuals for several fields of study. In species that are hard to differentiate between males and females, epigenetic markers of sex could come in handy. Several studies have documented significant differences in DNA methylation between the sexes (Boks et al. 2009; El-Maarri et al. 2007).

In marine fish, other ecologically relevant traits have been found to be mediated by the epigenome (Bizuayehu and Babiak 2014; Metzger and Schulte 2016). For instance, sea lamprey (*Petromyzon marinus*) go through a metamorphosis from being a filter feeder to a tissue-consuming organism, and it was found that DNA methylation changes were associated with this process in muscle tissue (Covelo-Soto et al. 2015). Similarly, it was found in rainbow trout (*Oncorhynchus mykiss*) alevins that major changes in metabolic gene expression and miRNAs were correlated with the transition from endogenous (yolk sac) to exogenous feeding (Mennigen et al. 2013). miRNAs are thought to contribute greatly to growth in Nile tilapia (*Oreochromis niloticus*). This was demonstrated when skeletal muscle miRNAs were found to be significantly different

between fast- and slow-growing strains (Huang et al. 2012). miRNAs were also found to target IGF-1 in Nile tilapia indicating that they may be of importance to the hypothalamic-pituitary pathway (Yan et al. 2013). Temperature-induced phenotypic plasticity of growth in Senegalese sole (*Solea Senegalensis*) was found to have expression changes in miRNAs as well (Campos et al. 2013). Application of this knowledge could help in the selection of faster-growing individuals for aquaculture. In addition, miRNAs have been found to contribute greatly in immune response of teleost fish similarly to how they have been identified to be important in mammals (Andreassen and Høyheim 2017). Studying this aspect of immunology may provide insights to keeping aquaculture fish healthy or even choosing individuals that have strong immune responses.

2.3 Epigenetic Approaches to Restoration and Management

The primary goal of species reintroductions is to stop population decline and artificially increase the rate of population growth (Seddon et al. 2007). Population decline could be caused by habitat deterioration or loss of population members due to overexploitation. In the latter case, better population management may be enough (Myers et al. 1995) and should be used when the genetic diversity of the population is a concern (Gaffney 2006). On the contrary, the case of habitat deterioration is more complex since the success of reintroduction will depend in the chances of restoring the habitat (Miller and Hobbs 2007; Seaman 2007) or the capacity of the species to acclimate and adapt to the new habitat condition. Because of this and despite its wide implementation, many reintroduction projects have failed to fulfill the aim of establishing self-sustainable populations in marine organisms (Mercado-Molina et al. 2015; Okubo and Omori 2001). Commonly, this failure is attributed to the environmental conditions of the specific site that do not promote species establishment and persistence (Seddon et al. 2007). Unfortunately, under the current pace of climate change, it is possible that those "favorable" conditions are already gone in most regions, deeming restoration a futile effort if organismal acclimatization capabilities are not considered and somehow enhanced.

The role of epigenetic modifications improving acclimatory capabilities has been observed across diverse environmental scenarios. For instance, a role for epigenetic modifications has been proposed in response to invasions (i.e., invasive species, Ardura et al. 2017). Similarly to species reintroduced in a hostile environment, invasive species need to overcome challenges in order to successfully establish self-sustaining populations. Thus, epigenetic modifications were initially proposed as a way to explain how invaders compensate the reduced genetic diversity, derived from the low number of individuals starting the population (Chown et al. 2015; Pérez et al. 2006). Further experimental evidence supporting epigenetic responses to environmental changes, and promoting acclimation/adaptation responses, is also available in terrestrial (Lämke and Bäurle 2017; Sgrò et al. 2016; Galván et al. 2017) and aquatic organisms (Norouzitallab et al. 2014; Palumbi et al. 2014;

Putnam et al. 2016). Based on these results, a change in paradigm for restoration and reintroduction of species populations is starting to be envisioned (van Oppen et al. 2017; Jones and Monaco 2009). The identification and selection of individuals displaying a better ability to respond to environmental stressors or even the induction of "preconditioned" or "hardened" epigenomes constitute one of the central pillars of this new approach.

2.3.1 Epigenetic Basis of Coral Reef Restoration

The application of this strategy (i.e., reintroductions) to marine organisms is best illustrated by coral restoration programs. Hermatypic (i.e., reef-building, stony) corals constitute the structural basis of reef ecosystems, supporting most of marine and coastal biodiversity. Corals are particularly affected by changes in temperature and chemical composition of the oceans (Cai et al. 2016; Hume et al. 2016), evidencing their susceptibility in a global change scenario. Out-planting constitutes one of the principal coral reef restoration strategies implemented by scientists, managers, and local stakeholders in trying to revert the current rate of coral cover loss (Hoegh-Guldberg et al. 2007). Despite being widely implemented, this approach is hampered by the low survival rates of out-planted fragments in many programs worldwide (Okubo and Omori 2001), decreasing significantly after the third year post-out-planting (Garfield 2016). These programs generally select genotypes showing more rapid growth, disregarding other important traits as endurance and resilience. Non-genetic processes such as changes in the microbiome (Hauser et al. 2011; Hernandez-Agreda et al. 2016) and epigenetic mechanisms can accelerate the rate of phenotypic change beyond the limits of genetic adaptation (Fig. 4), helping corals develop traits that permit effective responses to a rapidly changing climate and result in increased survival post-out-planting (Putnam et al. 2016; Roberts and Gavery 2012).

Despite the potential to manipulate epigenetic marks to increase restoration success, little is known about how these non-genetic mechanisms respond to different stressors and their interaction with standing genetic variation to produce acclimatized phenotypes in marine invertebrates (Suarez-Ulloa et al. 2015; Crespi et al. 2012; Beaulieu and Costantini 2014). More so, in many cases, we lack understanding about the mechanisms and their potential to mediate intragenerational plasticity (IGP) and transgenerational plasticity (TGP), critical processes mediating acclimation and adaptation as discussed earlier in this work. Epigenetic analyses in corals have been almost exclusively focused on DNA methylation analyses and its relationship with gene expression (Marsh et al. 2016; Dixon et al. 2014) during responses to environmental change (Dixon et al. 2014; Dimond and Roberts 2016) and the consequences on phenotypic plasticity (Putnam and Gates 2015). These studies showed rapid acclimatory responses in corals during thermal stress (Palumbi et al. 2014; Barshis et al. 2013), including transcriptomic and epigenetic changes in response to nutrient enrichment (Rosic et al. 2014), as well as modifications in DNA methylation levels in response to ocean warming and acidification (Putnam et al. 2016; Putnam and Gates

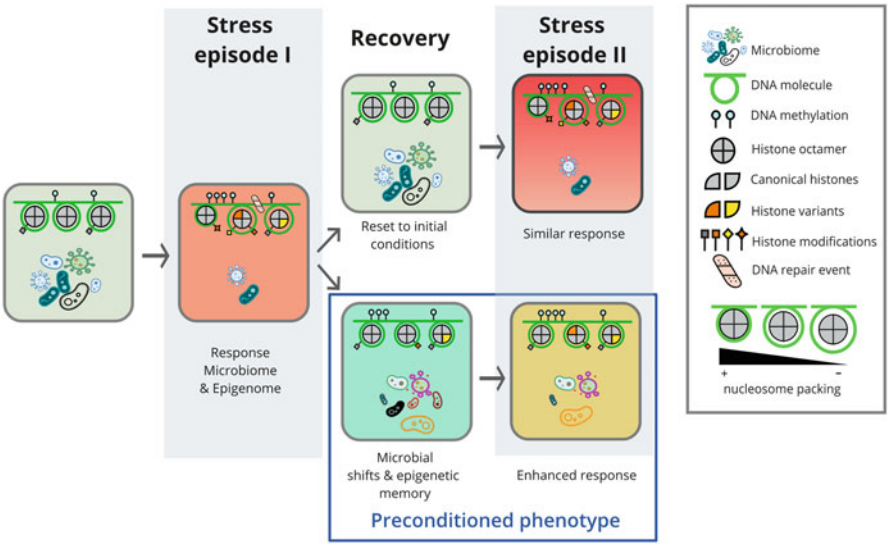

Fig. 4 Epigenetic contribution to environmental preconditioning. Both epigenetic memory and microbiome shifts have the potential to create preconditioned phenotypes displaying enhanced responses to repetitive stress episodes. A stress event will trigger non-genetic responses (epigenetic and microbial shifts) that could be reset to initial conditions or generate persistent changes potentially enhancing organism responses to environmental stress. The present figure depicts these potential scenarios under two pulses of similar stressors

2015). In such a way, they have strengthened the links between DNA methylation and transcriptional plasticity, although the genome-wide distribution of such marks (DNA methylome) and their role in the onset of transgenerational epigenetic memory and adaptive responses are still not clear. Other epigenetic mechanisms, such as noncoding RNAs, histone variants, and their posttranslational modification, have received less attention. This constitutes a research priority based on the very promising results obtained on related species and other marine invertebrates (Moran et al. 2014; Rivera-Casas et al. 2016a, b; Fraune et al. 2016; Reddy et al. 2017) and the implication these mechanisms can have on "preconditioning" of corals.

Several lab-based experiments have increased thermal tolerance of corals through controlled heat-stress exposures (Cunning et al. 2015), mainly promoting thermally tolerant symbionts. However, it is unknown how these manipulations can affect the physiology of the coral holobiont. Towle et al. (2016) showed an increased susceptibility to bleaching in coral preconditioned to increased CO_2. Changes in gene expression (Barshis et al. 2013; Bellantuono et al. 2012) and microbiome composition, derived from the preconditioning, could have a positive effect driving acclimatory processes but at the same time could have unknown negative effects. Further efforts are required to evaluate different strategies for preconditioning both in laboratory and field settings, including the analysis of the interaction between genome, epigenome, and microbiome in the response within and between

generations. Overall, determining whether this "preconditioning" can enhance coral demographic performance in an ecological context constitutes the final step for the development of successful coral reef restoration.

3 Conclusions

Epigenetic analyses encompass many potential applications in the field of marine sciences. Current studies based on DNA methylation analyses are paving the way for the incorporation of epigenetic research into different disciplines within the marine realm, as evidenced by the numerous examples discussed in the present work. Moving forward, there is a need for identifying marine organisms that will represent a new generation of ecologically and environmentally relevant model organisms. These will be fundamental for elucidating how epigenetic mechanisms work, how they change in response to environmental stressors, and how epigenetic signatures are inherited and contribute to phenotype diversity across generations. Currently, little work has been done on assessing epigenomic variation between species and populations for marine organisms, mainly due to the lack of complete genomes for most species as well as because of the high costs associated with single nucleotide resolution studies. In addition, the few works developed were conducted using different methodologies and different types of samples, hampering the comparison of results and making assessment of differences between these species unclear and unreliable (Hofmann 2017). As mentioned earlier, the work comparing three-spined sticklebacks from freshwater and saltwater environments probably constitutes the more comprehensive example of population epigenomic studies in marine organisms. Results from this research suggest that epigenetic adaptation may act as a compensatory regulatory mechanism for the lack of genetic variation, complementing the selection of genetic variants and enhancing phenotypic plasticity in different environments (Artemov et al. 2017).

The current ability to effectively record complex biological traits such as age or sex through epigenetic analyses can potentially revolutionize several research fields, notably ecotoxicology, ecology, and genetics. Within the current context of a highly paced global climate change, it is now evident that epigenetic mechanisms play a key role during organismal acclimatization and adaptation. Further development of marine epigenomics will facilitate a better understanding of how organisms respond to their environment, allowing for stronger restoration efforts to occur as well as fostering the development of a new generation of biomarkers and tools that can be used for conservation.

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