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RECEIVED 15 December 2025

REVISED 28 January 2026

ACCEPTED 30 January 2026

PUBLISHED 04 March 2026

CITATION

Johnson EC and Wong JM (2026) From stress to response: a systematic review of epigenetic pathways underlying gene expression and phenotypic plasticity in aquatic invertebrates.
Front. Mar. Sci. 13:1767697.
doi: 10.3389/fmars.2026.1767697

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From stress to response: a systematic review of epigenetic pathways underlying gene expression and phenotypic plasticity in aquatic invertebrates

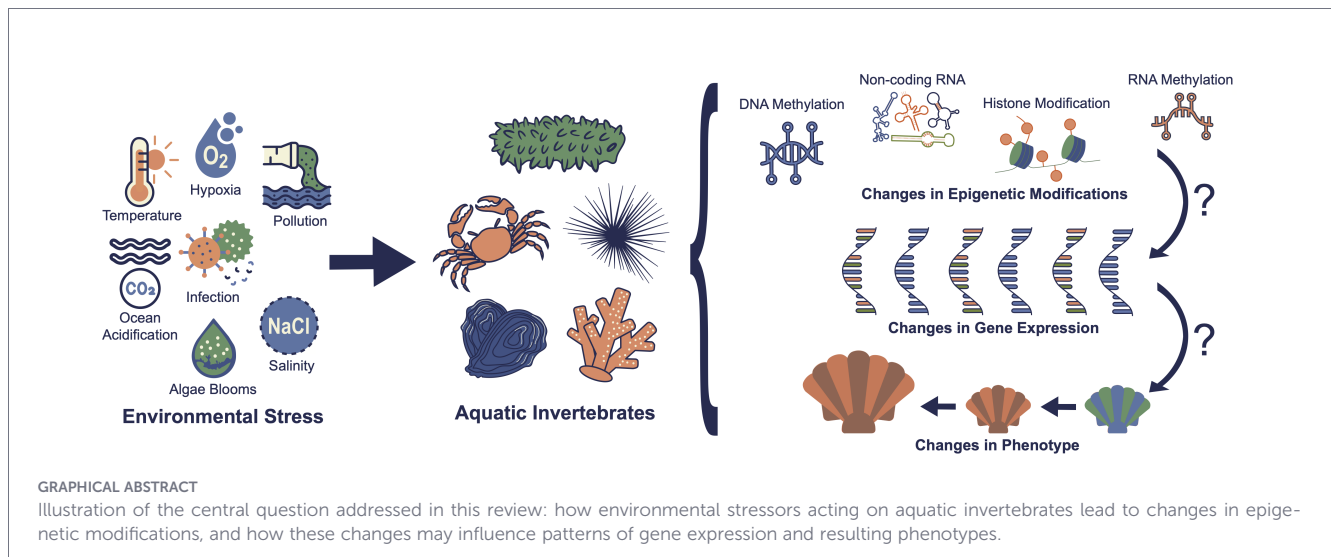
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Marine and freshwater ecosystems are undergoing rapid transformations propelled by human activity, placing unprecedented pressure on aquatic species and threatening critical ecosystem services. Aquatic invertebrates, which underpin aquaculture industries, shape habitat structure, and contribute to biomedical discovery, are particularly vulnerable, yet their capacity to respond to environmental change remains understudied. Epigenetic mechanisms have emerged as potential mediators of rapid acclimatization, but their roles in aquatic invertebrates are not well defined. In this review, we systematically analyzed 223 studies that examined epigenetic responses of aquatic invertebrates to environmental or anthropogenic stress. For each study, we recorded taxonomic representation, stressor type, exposure duration, experimental design, and major molecular and phenotypic outcomes. DNA methylation was the most frequently investigated mechanism, mollusks were the dominant study phylum, and infection was the most common stressor; however, substantial variation and ongoing debate were evident across molecular findings. Epigenetic processes are increasingly recognized as key regulators of gene expression and phenotypic plasticity, yet their functional significance, temporal stability, and heritability in aquatic invertebrates remain uncertain. By synthesizing existing evidence and compiling a comprehensive database of current research, this review establishes a foundation for advancing environmental epigenetics toward a predictive, mechanistic framework capable of informing conservation, aquaculture, and ecosystem management under accelerating global change.

KEYWORDS

acclimatization, aquatic invertebrates, environmental stress, epigenetics, phenotypic plasticity, gene expression



1 Introduction

Marine and freshwater ecosystems are experiencing rapid and far-reaching environmental change. From shifts in temperature and ocean acidification to heightened pollution levels and rising instances of disease, many of these stressors are caused and exacerbated by anthropogenic sources (Doney et al., 2012; Lafferty et al., 2004; Lotze et al., 2006; Vikas and Dwarakish, 2015). Rapid changes can occur at temporal scales that outpace the slower rate of mutation-based evolution by natural selection, potentially leaving species unfit for novel environmental conditions (Hofmann, 2017; Martin et al., 2023). This is a particular concern for aquatic invertebrates, which support major aquaculture industries, function as foundation and keystone species in diverse habitats, and continue to provide valuable biomedical insights (Eisenhauer and Hines, 2021; Ellison, 2019; Kunselman et al., 2024; Romano et al., 2022; Wilson-Sanders, 2011). While geographic redistribution (e.g., tropicalization) may occur via dispersive larval stages, this process offers limited protection for post-settlement, sessile invertebrate taxa (e.g., oysters, mussels) and it may not be sufficient to ensure persistence under new or intensified environmental stress (Chen, 2021; Zarzycny et al., 2024). This raises the critical question: can aquatic invertebrate species persist under novel environmental changes, and if so, how?

Epigenetics is an emerging area of inquiry in rapid organismal acclimatization to environmental stress. While definitions vary, this review follows the framework proposed by Deans and Maggert (2015), with two key modifications: we exclude the requirement of heritability (consistent with the NIH Roadmap Epigenomics Mapping Consortium) and expand beyond the chromosome-bound criterion to include non-coding RNAs, resulting in a broader and more inclusive definition. Here, epigenetics is defined as mechanisms that modify chromatin or regulate gene expression without altering DNA sequence and act either directly on chromatin or indirectly through post-transcriptional regulation. Within this framework, we additionally define epitranscriptomics as chemical modifications to RNA that regulate RNA function without

altering nucleotide sequence (Meyer and Jaffrey, 2014; Roundtree et al., 2017; Zaccara et al., 2019). Therefore, this review focuses on four major mechanisms: DNA methylation, chromatin organization (e.g., histone modification), non-coding RNA (ncRNA), and RNA methylation. Each has been implicated in gene regulation and may underlie forms of phenotypic plasticity in which identical genotypes produce divergent and potentially adaptive phenotypes in response to environmental conditions (Eirin-Lopez and Putnam, 2019).

In vertebrates, particularly mammals, the role of epigenetics in development and cell differentiation is well established. For example, promoter DNA methylation and microRNAs are commonly associated with transcriptional repression, whereas histone acetylation is generally linked to transcriptional activation (Gibney and Nolan, 2010). In contrast, although similar trends have been predicted and, in some cases, demonstrated in invertebrates, their epigenetic architecture remains far less understood. Notably, several invertebrate model organisms (i.e., *Caenorhabditis elegans* and *Drosophila melanogaster*) lack components of canonical epigenetic machinery, leading to early uncertainty about whether certain epigenetic mechanisms operated in these taxa at all (Gowher et al., 2000; Klughammer et al., 2023; Simpson et al., 1986). Additional distinctions between vertebrates and invertebrates emerge when comparing their epigenomic landscapes. Vertebrate genomes typically exhibit globally high levels of DNA methylation, whereas invertebrate genomes often display a mosaic or reduced methylation pattern, with methylation concentrated largely within gene bodies (Klughammer et al., 2023; Suzuki and Bird, 2008). Differences in the timing and extent of DNA methylation reprogramming during development have also been observed, raising questions about the epigenetic basis of heritability in invertebrates versus vertebrates (Xu X. et al., 2019). Histone modifications and non-coding RNAs further underscore these divergences, revealing variation in chromatin dynamics and regulatory mechanisms that may reflect taxon-specific epigenetic functions that differ between invertebrates and vertebrates (Chen and Kim, 2024; Guan et al., 2025; Ho et al., 2014; López-Hernández

et al., 2025). Perhaps the most striking disparity, however, is the comparatively limited scope of research on invertebrate epigenetics, which has left substantial gaps in our understanding of how these mechanisms contribute to genome regulation, developmental plasticity, and environmental responsiveness in aquatic systems.

As the impacts of climate change on aquatic ecosystems intensify, elucidating the mechanisms that enable invertebrates to persist has become increasingly urgent (Mather, 2013). Although mounting evidence indicates that environmental stressors can induce changes in epigenetic profiles, the downstream effects of these modifications on gene regulation and phenotypic plasticity in invertebrates remain inadequately understood and actively debated (Kim et al., 2024a). Recent methodological advancements, however, have begun to clarify these relationships. Epigenetics is a relatively young yet rapidly expanding field; since a horizon scan conducted nine years ago (see Hofmann, 2017), the number of publications and the sophistication of sequencing analyses have increased substantially. Building on this progress, we synthesize the current state of knowledge on how epigenetic mechanisms contribute to environmental stress responses in freshwater and marine invertebrates and compile a comprehensive database of current research to guide future work.

We focus on studies that have examined epigenetic modifications following exposure to environmental stressors, with heightened interest in studies that also recorded changes in gene expression and phenotypic outcomes. Our goal is to address three central questions: (1) What empirical evidence supports the role of epigenetic modifications in regulating gene expression and shaping phenotypic plasticity in aquatic invertebrates under environmental change? (2) How do factors such as timing of sampling, the material used for molecular analysis (e.g., cell type, tissue type, etc.), and transgenerational exposure influence our interpretation of these responses? (3) What are the most pressing knowledge gaps and research priorities needed to advance this field? By addressing these questions, this review aims to clarify the role of epigenetics in mediating rapid, non-genetic acclimatization in aquatic invertebrates, a growing area of relevance for predicting species resilience and informing conservation strategies in the face of accelerating climate change.

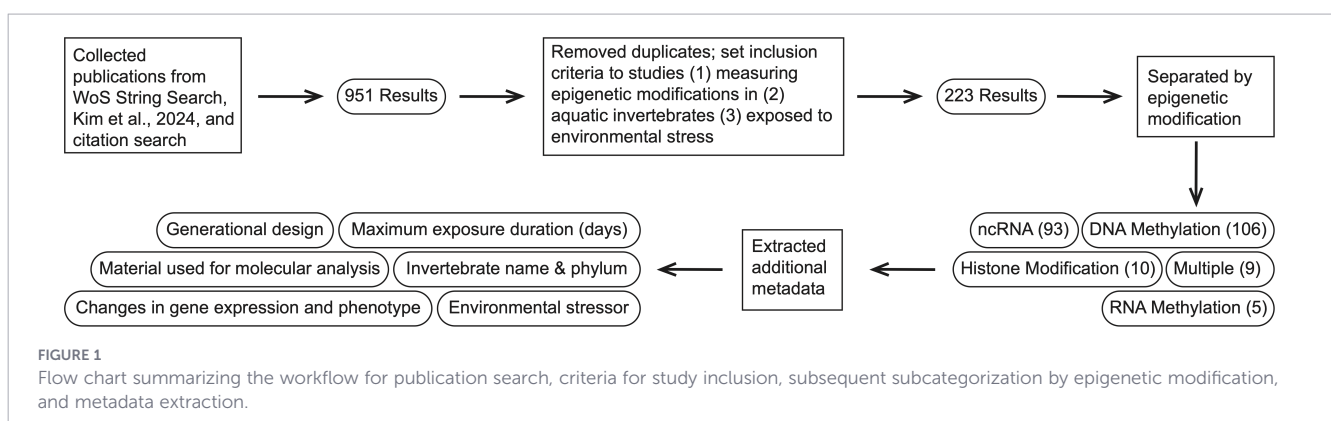
2 Materials and methods

To identify relevant studies, a comprehensive literature search was conducted in the Web of Science (WoS) Core Collection (Science Citation Index Expanded, 2000–present) on November 4th, 2025. The search string combined terms for epigenetic mechanisms, aquatic environments, invertebrate taxa, and environmental stress (Supplementary Figure 1). The initial WoS search yielded 862 publications, with additional publications incorporated from Kim et al. (2024a; $n = 64$) and a citation search ($n = 25$). Duplicate publications were removed, and inclusion requirements were applied, retaining only studies that (1) measured epigenetic modifications in (2) aquatic invertebrates (3) exposed to environmental stress, resulting in a final dataset of 223 publications (see PRISMA; Supplementary Figure 2).

Each study was further categorized by the epigenetic modification analyzed and metadata were manually extracted from each publication. Specific metadata included taxonomic information (phylum and species), environmental stressor, maximum exposure duration (recorded in days), source of material used for molecular analysis (i.e., tissue, cell, or body fluid), generational design (single-generation exposure, multigeneration exposure, or multigeneration with parent-only exposure), and key molecular and phenotypic findings (Figure 1). Particular interest was given to studies that recorded response types beyond epigenetic modification (i.e., gene expression and phenotype). To be included in the dataset, studies had to report at least one epigenetic modification, therefore, all papers measured at least one response type. If studies also reported changes in gene expression or phenotype, they were classified as measuring two response types. Studies that recorded epigenetic changes, gene expression changes, and phenotypic changes were classified as measuring all three response types.

3 Results

Among the 223 publications included in this review, the majority ($n = 106$) investigated changes in DNA methylation,



followed by studies examining ncRNAs ($n = 93$), histone modification ($n = 10$), multiple modifications ($n = 9$), and a small subset ($n = 5$) that measured RNA methylation (Figure 2A; Supplementary Tables 1-5). The majority of experiments were conducted within a single generation ($n = 197$); however, a subset ($n = 26$) employed transgenerational designs, either exposing only the parental generation ($n = 10$) or both parent and offspring to environmental stress ($n = 15$), with one study incorporating both parent-only exposure and combined parent-offspring exposure (Figure 2B). Mollusca was the most common invertebrate phylum ($n = 90$), followed by Arthropoda ($n = 53$), Echinodermata ($n = 45$), Cnidaria ($n = 19$), Chordata ($n = 19$), Annelida ($n = 4$), and Rotifera ($n = 2$), with one study including multiple phyla (Figure 2C). The most common stressor was infection ($n = 50$), followed by pollution ($n = 36$) and temperature ($n = 28$). Studies also examined site-specific environmental stress ($n = 21$), defined here as comparisons among environmentally distinct field sites and often incorporating reciprocal transplant or common garden experiments. Additional stressor categories included mixed stressors ($n = 20$), pH ($n = 18$), salinity ($n = 13$), hypoxia ($n = 9$), nutrition ($n = 5$), and range expansion ($n = 2$). An “other stressors” category ($n = 18$) encompasses less frequently studied conditions, including harmful algal blooms ($n = 4$), injury ($n = 3$), upwelling ($n = 3$), aestivation ($n = 2$), multiple stressors ($n = 2$), radiation ($n = 2$), desiccation ($n = 1$), and light availability ($n = 1$; Figure 2D). Mixed stressors refers to studies in which more than one stressor was tested simultaneously, whereas multiple stressors denotes studies in which two or more stressors were tested separately within a single publication. Maximum exposure time (recorded in days) ranged from under thirty minutes to two years. However, when studies analyzed field-collected tissue samples or when exposure duration was unclear in the publication, exposure time could not be accurately documented

and was therefore marked as ‘-’ for these studies (Supplementary Tables 1-5).

3.1 DNA methylation

DNA methylation was the most extensively studied epigenetic modification, investigated as the sole mechanism in 106 of the reviewed publications. Two primary approaches were used: global DNA methylation assessments and base-pair resolution methods, including both reduced representation and genome-wide techniques. Pollution exposure was the most common environmental stressor. Exposure durations varied widely, ranging from one hour to two years, with an average of approximately 105 days. Tissue-specific DNA methylation was assessed in nine studies, and twenty employed transgenerational designs. Phenotypic variation in response to stress was reported in 59 studies (Table 1; Supplementary Table 1).

3.2 ncRNA

Ninety-three studies examined ncRNA, primarily investigating microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). Studies measured both differential ncRNA expression and the predicted influence and targets of individual ncRNAs. Infection was the most common stressor, with 37 studies examining the effect. Fourteen studies assessed tissue-specific ncRNA expression, with one study analyzing up to seven distinct tissues. Only two studies employed a transgenerational design: one with parent-only exposure and the other involving both parent and offspring exposure. Phenotypic changes were documented in 25 studies, with exposure durations ranging from 40 minutes to 60 days, with an approximate average of 5.3 days (Table 1; Supplementary Table 2).

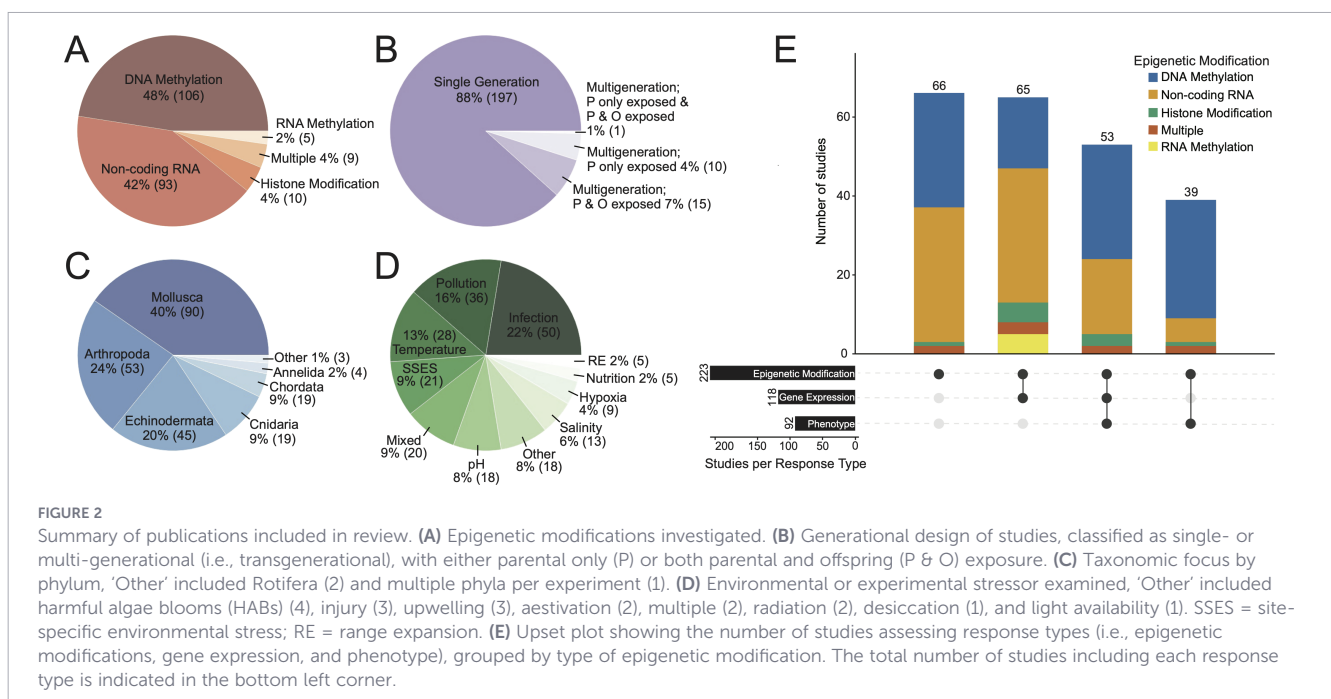


TABLE 1 Summary of included publications.

Epigenetic modification	Phylum	Stressor	Exposure duration (days)	Response types recorded	Generational design
DNA Methylation (106)	Annelida (3), Arthropoda (21), Chordata (7), Cnidaria (13), Echinodermata (12), Mollusca (49), Multiple (1)	Aestivation (2), HABs (2), infection (5), injury (1), mixed (8), multiple (2), nutrition (3), pH (12), pollution (26), radiation (1), range expansion (5), salinity (5), SSES (18), temperature (14), upwelling (2)	Min = 0.042, max = 730, average = 105.12	EM only (29), EM and GE (18), EM and Phenotype (30), EM, GE, and Phenotype (29)	Single-generation exposure (86), multigeneration – P (7), multigeneration – P & O (12), multigeneration – P & O; P (1)
ncRNA (93)	Arthropoda (27), Chordata (2), Cnidaria (3), Echinodermata (26), Mollusca (34), Rotifera (1)	Desiccation (1), HABs (1), hypoxia (9), infection (37), injury (2), mixed (9), nutrition (2), pH (4), pollution (9), salinity (8), SSES (3), temperature (8)	Min = 0.025, max = 60, average = 5.34	EM only (34), EM and GE (34), EM and Phenotype (6), EM, GE, and Phenotype (19)	Single-generation exposure (91), multigeneration – P (1), multigeneration – P & O (1)
Histone Modifications (10)	Annelida (1), Arthropoda (1), Cnidaria (2), Echinodermata (1), Mollusca (4), Rotifera (1)	Infection (2), light availability (1), pH (2), temperature (5)	Min = 0.021, max = 8, average = 2.36	EM only (1), EM and GE (5), EM and Phenotype (1), EM, GE, and Phenotype (3)	Single-generation exposure (8), multigeneration – P (0), multigeneration – P & O exposure (2)
RNA Methylation (5)	Arthropoda (1), Echinodermata (2), Mollusca (2)	Infection (3), mixed (1), pollution (1)	Min = 1, max = 7, average = 2.8	EM only (0), EM and GE (5), EM and Phenotype (0), EM, GE, and Phenotype (0)	Single-generation exposure (5), multigeneration – P (0), multigeneration – P & O exposure (0)
Multiple (9)	Arthropoda (3), Cnidaria (1), Echinodermata (4), Mollusca (1)	HABs (1), infection (3), mixed (2), radiation (1), temperature (1), upwelling (1)	Min = 1, max = 120, average = 22.67	EM only (2), EM and GE (3), EM and Phenotype (2), EM, GE, and Phenotype (2)	Single-generation exposure (7), multigeneration – P (2), multigeneration – P & O (0)

The total number of publications contributing to each category are listed in parentheses. HABs, harmful algae blooms; SSES, Site-specific environmental stress; EM, epigenetic modification; GE, gene expression; P, parent; P & O, parent and offspring.

3.3 Histone modification

Ten studies focused exclusively on histone modifications or chromatin accessibility. Methods typically involved chromatin immunoprecipitation (ChIP) sequencing or assay for transposase-accessible chromatin (ATAC) sequencing. The most common environmental stressor examined was temperature, with five studies focusing on this. Exposure durations ranged from 30 minutes to eight days, with an average of 2.4 days. Two studies employed a transgenerational design, both examining multigenerational exposure. Phenotypic changes were reported in four studies; however, none assessed tissue-specific epigenetic modifications (Table 1; Supplementary Table 3).

3.4 RNA methylation

Five studies investigated RNA methylation, a form of epitranscriptomics, with all studies measuring N6-methyladenosine (m6A) methylation. Infection was the most common stressor examined. Exposure durations ranged from one to seven days, with an average of 2.8 days. All experiments occurred within a single generation, and none recorded changes in phenotype or assessed tissue-specific epigenetic modifications (Table 1; Supplementary Table 4).

3.5 Multiple modifications

Among the nine studies that investigated more than one epigenetic mechanism, the combinations included DNA methylation paired with either histone modifications or chromatin accessibility, and ncRNA with RNA methylation. Notably, none of these studies assessed non-coding RNA or RNA methylation in conjunction with DNA methylation or histone modification. Exposure durations ranged from one to 120 days, with an average of 22.7 days. Two studies employed transgenerational designs involving parent exposure only. Phenotypic changes were reported in four studies; however, none assessed tissue-specific epigenetic modifications (Table 1; Supplementary Table 5).

3.6 Response types examined

A central objective of this systematic review was to assess how changes in epigenetic modifications relate to other response types, including shifts in gene expression and phenotype. To evaluate these relationships, each study was categorized based on the response types measured (i.e., epigenetic modifications, gene expression, and phenotypic responses). All studies included in the review assessed epigenetic modifications, as this was an inclusion

criterion. The most common scenario was studies measuring only epigenetic changes ($n = 66$), closely followed by 65 studies that measured both epigenetic modifications and gene expression. Fifty-three studies assessed all three response types (epigenetic modifications, gene expression, and phenotype) and 39 measured both epigenetic modifications and phenotype (Figure 2E). This distribution provided a substantial foundation for examining potential correlations among molecular and phenotypic responses to environmental stress in aquatic invertebrates.

4 Discussion

Across the diverse studies reviewed, thematic groupings emerged that allowed for broader trends to be evaluated across epigenetic mechanisms. DNA methylation, non-coding RNAs, histone modifications, RNA methylation, and studies examining multiple mechanisms, contained numerous examples that demonstrated the potential to regulate gene expression in response to environmental stress, though only a few studies questioned the extent of this influence. This discussion synthesizes patterns across these epigenetic mechanisms, highlighting evidence for their role in shaping transcriptional responses and phenotypic plasticity. Commonly measured traits are examined alongside associated changes in gene expression and epigenetic profiles. Additional themes include the temporal dynamics of epigenetic modifications, variation among materials used for molecular analysis, and the potential for transgenerational inheritance. The discussion concludes with knowledge gaps and future research directions needed to advance our understanding of how epigenetic regulation contributes to phenotypic acclimatization in aquatic invertebrates.

4.1 DNA methylation and its impact on gene expression

DNA methylation was the most extensively studied epigenetic modification with numerous reviews (e.g., Dixon et al., 2016; Hofmann, 2017; Roberts and Gavery, 2012) having examined its role in regulating gene expression and facilitating phenotypic plasticity in aquatic invertebrates, a level of synthesis that remains limited for other epigenetic mechanisms.

Functionally, DNA methylation entails the covalent addition of a methyl group to the fifth carbon of cytosine, typically within cytosine–phosphate–guanine (CpG) dinucleotides, although non-CpG contexts such as CHG and CHH ($H = A, C, \text{ or } T$) also occur (Suzuki and Bird, 2008). This reaction is catalyzed by DNA methyltransferases (DNMTs), which transfer a methyl group from *S*-adenosylmethionine to cytosine. The *de novo* methyltransferases DNMT3A and DNMT3B establish new methylation patterns, while DNMT1 maintains them during DNA replication (Jeltsch, 2002). DNA methylation is reversible through both passive and active demethylation processes. Passive demethylation occurs when methylation is lost during replication, restoring cytosines to an unmethylated state, whereas active

demethylation is mediated by ten–eleven translocation (TET) proteins that oxidize 5-methylcytosine to generate 5-hydroxymethylcytosine, 5-formylcytosine, and 5-carboxylcytosine (Ito et al., 2011). Methylated cytosines can also deaminate to thymine, introducing mutations that over evolutionary time contribute to reduced CpG density across genomes.

In invertebrates, a few more distinctions in DNA methylation arise. For example, in many aquatic invertebrate taxa, including mollusks (e.g., *Crassostrea* spp.), cnidarians (e.g., *Acropora millepora*) and echinoderms (e.g., *Strongylocentrotus purpuratus*), tracts of methylated CpGs are interspersed with unmethylated regions across the genome, forming a mosaic pattern, with methylation predominantly enriched within gene bodies, particularly exons (Dixon et al., 2018; Keller et al., 2016; Riviere et al., 2017; Roberts and Gavery, 2012; Suzuki et al., 2007; Suzuki and Bird, 2008; Wang et al., 2014). Likewise, when examining gene body methylation, it can be seen to divide into two groups of either lowly or highly methylated genes, creating a “bimodal” distribution, with gene function hypothesized to determine the distinction (Sarda et al., 2012). When analyzing DNA methylation, multiple levels of analytical resolution can be applied, and its functional consequences vary depending on genomic context and location. The following section outlines these different levels of resolution and highlights context-dependent influences across the genome.

4.1.1 Global DNA methylation influences on gene expression

Quantifying global DNA methylation provides a low-resolution but cost-effective overview of methylation dynamics, requiring fewer resources and less specialized equipment than base-resolution approaches (Eirin-Lopez and Putnam, 2019). It is commonly measured using techniques such as methylation-sensitive amplified polymorphism (MSAP) or ELISA-based assays, which are particularly advantageous for non-model organisms as they do not require a reference genome. Global assays are also valuable for preliminary assessments, such as determining whether a species exhibits DNA methylation and evaluating population-level methylome diversity relative to underlying genomic diversity. Here, many of the publications used global DNA methylation as the primary epigenetic modification investigated.

Global-scale approaches have been widely applied to investigate DNA methylation responses to environmental stressors, producing highly variable results (Supplementary Table 1; Hofmann, 2017; Kim et al., 2024a). Across diverse taxa, stressors, and exposure durations, studies have reported increases, decreases, or no significant changes in overall methylation levels. A recurring hypothesis is that reductions in global DNA methylation may enhance transcriptional plasticity, particularly during range expansions or biological invasions. This pattern, observed in multiple invasive species, may reflect a mechanism facilitating rapid acclimatization to novel environments (Ardura et al., 2017; Hawes et al., 2019). Supporting this hypothesis, reduced gene body methylation has been associated with increased transcriptional variability in several invertebrate taxa, including mollusks,

arthropods, and cnidarians (Downey-Wall et al., 2020; Johnson et al., 2020; Lee et al., 2022; Liew et al., 2018; Rodriguez-Casariago et al., 2022). Furthermore, global DNA methylation assays provide an efficient means of assessing population-level epigenetic variation, and in certain cases, methylome differentiation even exceeds underlying genetic structure (Johnson and Kelly, 2020; Zhang et al., 2018).

A key limitation of global DNA methylation assays, however, is their inability to localize methylation changes to specific genomic regions, preventing direct inference of functional relationships between DNA methylation and gene expression. Consequently, when feasible, base-resolution analyses are better suited to uncover the mechanistic links underlying environmentally responsive DNA methylation.

4.1.2 Location-specific DNA methylation influences on gene expression

Base-resolution approaches offer a more detailed view of DNA methylation patterns but are technically demanding, resource-intensive, and costly. A few of the most common techniques include whole-genome bisulfite sequencing (WGBS) and reduced representation bisulfite sequencing (RRBS), methyl-CpG-binding domain sequencing (MBD-seq), and methylated DNA immunoprecipitation sequencing (MeDIP-seq). However, despite the cost and difficulty challenges, such high-resolution methods enable more informative analyses, particularly when investigating mechanistic links between DNA methylation and gene regulation.

The most common way to examine correlation is to look at differentially expressed genes (DEGs) and differentially methylated genes, regions, or loci (DMG, DMR, DML respectively). When the same gene is both differentially expressed and differentially methylated, there is predicted to be a relationship between the two. Genes can be up- or down-regulated and genomic regions can be hyper- or hypomethylated, both in relation to the control. Often, the location of DNA methylation, in addition to the quantity, is believed to dictate its function and influence on gene expression. It is often stated that methylation in the gene body promotes gene expression, while methylation in the promoter region inhibits gene expression, a finding more common in vertebrates (Chang et al., 2023; Feng et al., 2010; Zemach et al., 2010). First gene body DNA methylation is discussed, before moving into studies that examine promoter DNA methylation.

4.1.2.1 Gene body methylation

Gene body methylation (GBM) refers to the methylation of cytosines within the coding regions (introns and exons) of genes, rather than in upstream promoter or downstream regulatory regions. It represents the predominant form of DNA methylation in aquatic invertebrates, although its precise function remains debated (Keller et al., 2016). Early studies demonstrated a positive association between GBM and gene expression (Feng et al., 2010; Zemach et al., 2010), with the hypothesis that higher levels of gene body methylation are associated with constitutively expressed genes while lower levels of gene body methylation are associated with

environmentally responsive gene categories (Roberts and Gavery, 2012; Song et al., 2017). As such, it is possible that genes showing a decrease in gene body methylation may lead to an increase in plasticity of that gene.

Several investigations included here followed that hypothesis and reported genome-wide positive correlations between GBM and transcriptional activity (Downey-Wall et al., 2020; Johnson et al., 2020; Lee et al., 2022; Liew et al., 2018; Rodriguez-Casariago et al., 2024; Strader et al., 2020). However, once gene-level correlation analyses were conducted, it was revealed that this relationship often weakened or disappeared (Downey-Wall et al., 2020; Rodriguez-Casariago et al., 2022, 2024; Strader et al., 2020). In many cases, the overlap between differentially expressed genes (DEGs) and differentially methylated genes (DMGs) was minimal, sometimes to the extent that correlations were considered coincidental (Johnson et al., 2022). When overlap did occur, there were a variety of findings with studies reporting a majority of positive correlations (Dang et al., 2022), a majority of negative correlations (Chang et al., 2023), and associations roughly balanced between positive and negative correlations (Huang et al., 2021; Yang et al., 2023; Zhang et al., 2024). Nonetheless, functional enrichment analyses have occasionally revealed similarities between DEGs and DMRs, even when gene overlap was limited, suggesting that methylation and expression changes may act on functionally related gene sets (Dixon et al., 2018; Liew et al., 2018; Strader et al., 2020).

Beyond direct effects on transcription, GBM has also been proposed to stabilize gene expression by reducing transcriptional noise or spurious intragenic transcription, particularly during environmental stress (Downey-Wall et al., 2020; Johnson et al., 2020; Lee et al., 2022; Liew et al., 2018; Rodriguez-Casariago et al., 2022). Indeed, numerous studies report positive correlations between GBM and mean gene expression, coupled with negative correlations between GBM and expression variance. However, the inconsistency of these relationships at the individual gene level underscores ongoing uncertainty about the direct regulatory role of DNA methylation. A recent meta-analysis found no consistent correlation between GBM and expression changes in either Anthozoa or Hexapoda, concluding that any transcriptional regulation by DNA methylation likely depends on additional factors or regulatory influences (Dixon and Matz, 2022). This interpretation is echoed across multiple studies, which suggest that DNA methylation alone does not fully explain observed transcriptional patterns and must be considered alongside other regulatory processes such as chromatin accessibility, histone modifications, and alternative splicing (Asselman et al., 2017; Bogan et al., 2023; Chandra Rajan et al., 2021). Additionally, GBM has been hypothesized to limit transposable element (TE) mobilization, thereby maintaining genomic stability, with two studies observing increased methylation within TE sites (Johnson et al., 2022; Rodriguez-Casariago et al., 2022).

4.1.2.2 Promoter methylation

With respect to promoter DNA methylation, the relationship to gene expression appeared more direct, but still variable. Promoter methylation is classically understood to suppress gene expression by

altering chromatin structure, preventing transcription factor binding, and recruiting methyl-binding proteins that promote a repressive chromatin state (Campanero et al., 2000; Joulie et al., 2010; Deaton and Bird, 2011). While promoter methylation is more commonly documented in vertebrates, it was observed in several invertebrate studies included in this review. Two studies supported the overarching hypothesis that stress-induced hypermethylation of promoter regions led to significant downregulation of genes (Jiang et al., 2024; Tang et al., 2023). Further, two studies employed targeted *in vitro* manipulations of promoter methylation and demonstrated that increased promoter methylation directly reduced transcription under specific environmental stressors, including nutrient limitation in mollusks (Sun et al., 2023) and heat and hypoxia exposure in echinoderms (Wu et al., 2021). However, other studies reported mixed or even significant positive correlations between promoter methylation and gene expression, emphasizing the variability in control (Li et al., 2015; Liu et al., 2023, 2025; Yang et al., 2023; Zhang et al., 2024).

Together, these findings indicate that the relationship between DNA methylation and gene expression, across both gene bodies and promoter regions, is more complex than traditionally described. The field would benefit in moving beyond the binary model of gene-body methylation as activating and promoter methylation as repressing and instead move towards a more integrative framework that accounts for genomic and environmental context, interactions with other epigenetic modifications, suppression of transcriptional noise, modulation of transposable elements, alternative splicing control, and regulatory roles independent of changes in expression level.

4.2 ncRNAs and their impact on gene expression

Non-coding RNAs (ncRNAs) represent an important yet comparatively underexplored layer of epigenetic regulation, encompassing diverse mechanisms that modulate gene expression and influence chromatin architecture, with functional roles broadly conserved across taxa (Holoch and Moazed, 2015; Ulitsky and Bartel, 2013). Previously, regulatory ncRNAs were classified primarily by size, with RNA species <200 nucleotides (nt) considered short ncRNAs and those >200 nt classified as long non-coding RNAs (lncRNAs) (Connerty and Lock, 2023). However, length-based definitions have been recognized as largely arbitrary and provide limited insight into ncRNA function. Accordingly, we adopt the classification framework proposed by Mattick et al. (2023), which delineates three categories: (1) small ncRNAs (<50 nt); (2) medium-length transcripts (~50–500 nt), including transcripts synthesized by RNA polymerases III and V in plants, as well as small RNA polymerase II-derived transcripts; and (3) long ncRNAs (>500 nt).

Small ncRNAs include microRNAs (miRNAs) and small interfering RNAs (siRNAs), which bind to complementary mRNA transcripts to repress translation or promote degradation (Ulitsky and Bartel, 2013). Also, within this group are Piwi-interacting RNAs (piRNAs), which primarily silence transposons

in germline cells (Iwasaki et al., 2015). Medium-length ncRNAs encompass a diverse set of regulatory transcripts, including small nucleolar RNAs (snoRNAs), small nuclear RNAs (snRNAs), transcription initiation RNAs (tiRNAs), and smaller RNA polymerase II-derived transcripts that have often been classified as lncRNA. Despite their established roles in gene regulation, these ncRNAs have received comparatively less focused attention in the literature, as they are frequently discussed under broader classifications rather than as a distinct category (Boivin et al., 2019). The lncRNAs and circular RNAs (circRNAs) serve diverse functions, including the regulation of chromatin organization and transcription, RNA splicing, translation, localization, and stability, processes often responsive to environmental stressors, although their direct influence on gene expression remains less well defined (Mattick et al., 2023). Non-coding RNAs are typically identified via total RNA extraction followed by small-RNA sequencing (for small RNAs) or by computational filtering of transcriptome data to identify lncRNAs and circRNAs based on predicted structural features (Eirin-Lopez and Putnam, 2019).

Across 93 studies investigating ncRNA responses to environmental stress, miRNAs were the most commonly analyzed. As with mRNA, differentially expressed miRNAs, lncRNAs, and circRNAs are typically identified between control and treatment groups, and their target genes are predicted using bioinformatic methods. These predicted targets are then subjected to functional enrichment analyses to infer biological significance. Numerous studies have applied this approach to explore ncRNA responses to various stressors, revealing diverse regulatory effects on predicted mRNA targets (see Supplementary Table 2; e.g., He et al., 2019; Huo et al., 2021a; Pan et al., 2021; Pereiro et al., 2021; Zhao et al., 2019). To integrate these findings, several studies constructed interaction networks combining differentially expressed ncRNAs and mRNAs. Multiple studies developed competitive endogenous RNA regulatory networks that modeled miRNA–lncRNA–mRNA interactions, one of which also incorporated circRNAs, to examine miRNA utilization and the associated functional pathways (Han et al., 2023; Ibrahim et al., 2023). Other studies directly assessed miRNA–mRNA relationships.

Although miRNAs are often described as repressors that reduce mRNA abundance, results vary: two studies observed both positive and negative correlations between miRNAs and their target genes, with individual miRNAs exerting divergent effects across different targets (Chen et al., 2019; Han et al., 2023). In contrast, one study reported exclusively inverse relationships following stress exposure, consistent with the canonical repressive role of miRNAs (Chang et al., 2022). Another investigation further validated these interactions using a dual-luciferase reporter assay, demonstrating that a specific miRNA suppressed gene expression while simultaneously binding a lncRNA, implicating its dual regulatory role under stress (Huo et al., 2020). Collectively, these findings highlight the complexity and context dependence of ncRNA-mediated regulation and underscore the need for further research, particularly on lncRNAs and circRNAs, to elucidate their functional roles during environmental stress responses.

4.3 Histone modifications and their impact on gene expression

Histone modifications play a central role in chromatin organization and gene accessibility, thereby potentially influencing transcriptional activity (Bollati and Baccarelli, 2010). These modifications are known to respond rapidly to environmental stress across various aquatic invertebrate taxa; however, their direct role in regulating gene expression remains to be fully elucidated. Histone proteins can undergo numerous types of posttranslational modifications, including acetylation, methylation, ubiquitination, phosphorylation, ADP-ribosylation, propionylation, neddylation, glycosylation, butyrylation, carbonylation, biotinylation, and SUMOylation, which collectively regulate chromatin accessibility and gene expression in a highly context-dependent manner (Allis and Jenuwein, 2016; Sadakierska-Chudy and Filip, 2015; Shanmugam et al., 2017). Broadly, it has been described that acetylation and phosphorylation generally lead to chromatin relaxation and increased gene expression, while deacetylation and dephosphorylation results in chromatin condensation and reduced gene expression (Xu et al., 2022). In contrast, histone methylation is typically associated with transcriptional repression, whereas demethylation can activate chromatin (Fellous et al., 2015). Ubiquitination is the most context-dependent, with influence on gene expression highly dependent on specific histone and modification location (Oss-Ronen et al., 2022).

To measure these modifications, common methods include histone extraction with immunodetection, chromatin immunoprecipitation (ChIP) sequencing, and assay for transposase-accessible chromatin (ATAC) sequencing. While histone extraction and immunodetection quantify total changes in modification levels, ChIP-seq and ATAC-seq provide single-nucleotide resolution and site-specific data (Eirin-Lopez and Putnam, 2019). Among the ten studies included here, only two did not report any changes in gene expression, though one still observed significant variation in histone modifications over the course of the experiment (Signorini et al., 2023). Two studies identified broad changes in both histone methylation and acetylation: one reported differential expression of genes involved in histone regulation and changes in histone methylation levels (Fellous et al., 2015), while the other found no correlation between changes in histone marks and transcription levels of immune genes or acquired resistance traits (Norouzitalab et al., 2016). In another study, a ChIP-PCR assay targeting genes involved in DNA double-strand break repair showed increased acetylation and upregulation of one key gene at a specific timepoint under pH stress. Although two additional genes showed similar trends, these were not statistically significant (Lee et al., 2020).

A comprehensive analysis using ATAC-Seq and RNA-Seq in two oyster species under heat stress identified numerous significantly up- and down-regulated accessible chromatin peaks and a correlation analysis showed a broad positive relationship between ATAC-seq signal and gene expression (Wang C. et al., 2024). Interestingly, one species displayed a higher number of downregulated genes with open chromatin. Four heat stress-related genes exhibited differential chromatin opening in promoter regions. Of these, two showed

increased chromatin accessibility and gene expression in both species, while one exhibited decreased chromatin opening and downregulation in both species. The last gene was downregulated in one species but upregulated in the other, both in terms of chromatin opening and expression, showing species-specific responses (Wang C. et al., 2024). Overall, these findings support the idea that chromatin remodeling plays a role in transcriptional regulation during thermal stress, with both general correlations and gene-specific responses. Finally, in a study examining heat-stressed sea cucumbers, acetylation of lysine 9 on the H3 histone (H3K9) in the promoter regions of 13 genes were found to be dysregulated (Xu et al., 2022). Of these, five genes were upregulated and hyperacetylated, while two genes were downregulated and hypoacetylated. One gene, *NECAP1*, displayed a negative correlation between increased gene expression and decreased acetylation, while the remaining genes showed no significant changes in expression despite alterations in acetylation. This underscores the complexity and sometimes unpredictable nature of the relationship between histone modifications and gene regulation (Xu et al., 2022).

Taken together, these studies suggest that while histone modifications are clearly responsive to environmental stress and can correlate generally with changes in gene expression, the relationship is not always direct or consistent. Gene- and context-specific factors likely play a role in mediating transcriptional outcomes, and further work is needed to clarify the regulatory role of histone modifications in stress responses, as it is inadvisable to generalize across aquatic invertebrates based on such a small number of studies.

4.4 RNA methylation and its impact on gene expression

Five recent studies have investigated the role of m6A RNA methylation in mediating organismal responses to environmental stress. RNA methylation requires advanced quantitative methods, such as epitranscriptome profiling, to detect transcriptome-wide methylation patterns (Eirin-Lopez and Putnam, 2019). RNA methylation, along with other post-transcriptional RNA modifications, collectively known as epitranscriptomics, play a critical role in regulating diverse biological processes (Saletore et al., 2012). While primarily studied in model vertebrate species (i.e., mouse, human), the METTL proteins responsible for writing RNA methylation are present across the animal kingdom, exhibiting low sequence-level variation and slow rates of evolution, emphasizing their biological necessity (Wong and Eirin-Lopez, 2021). In mammals, m6A methylation has been shown to promote translation initiation of heat shock response genes under temperature stress, demonstrating its influence on regulating gene expression during environmental challenges (Zhou et al., 2015). The conservation of RNA methylation machinery across metazoans, together with its role in stress-related gene regulation, supports the idea that RNA methylation functions as a mechanism for responding to environmental stress. However, within the surveyed literature, only five of the 223 studies

examined solely epitranscriptomic mechanisms in aquatic invertebrates, reflecting the novel state of this field.

All studies reported mediation of gene expression during environmental stress, although the direct influence of RNA methylation was less directly apparent. In one publication examining responses to temperature and hypoxia, genes with m6A modifications were found to exhibit variable, and in some cases elevated, expression levels, with enrichment analyses revealing pathways related to oxidative stress, energy metabolism, and protein homeostasis (Wang Q. et al., 2025). Similarly, infection-induced upregulation of RNA methylation writers, erasers, and readers was associated with increased m6A levels and corresponded with immune-related gene upregulation, as well as enrichment of pathways with known sites of m6A methylation, including splicing, lysosomal function, and ciliary movement (Li H. et al., 2025). Although no phenotypic measurements were conducted, together these studies highlight an important and understudied dimension of gene expression modulation through epitranscriptomics.

4.5 Multiple epigenetic modifications and their impacts on gene expression

To further complicate the molecular understanding of stress responses, it has been increasingly suggested that no single epigenetic modification alone can provide the full picture, as these mechanisms are often interconnected (reviewed in Eirin-Lopez and Putnam, 2019). Nine studies explored this integrative approach, with three examining ncRNA and RNA methylation and six focusing on the relationship between DNA methylation and chromatin organization, though of the latter group, only one directly investigated how multiple epigenetic modifications jointly influence gene expression (Bogan et al., 2023). In the publications examining ncRNA and RNA methylation, they observed RNA methylation altering circRNA function (Liu J. et al., 2024) and lncRNA abundance (Zhang et al., 2022; Zhang S. et al., 2025) in sea cucumbers exposed to infection events. In the publications examining DNA methylation and histone modifications, one study reported no significant changes in either DNA methylation or histone acetylation in brine shrimp following heat shock and exposure to cadmium or zinc (Pestana et al., 2016). Two other studies documented increased Histone H2A variant (H2A.X) phosphorylation, associated with DNA damage and repair, following harmful algal bloom exposure in oysters (Gonzalez-Romero et al., 2017) and temperature and nutrient enrichment in corals (Rodriguez-Casariago et al., 2018). The first study observed a concurrent decrease in global DNA methylation, while the second reported no change. Additional studies reported varied impacts on histone acetylation and methylation as well as global DNA methylation in response to environmental stress, while still not examining how these changes may influence gene expression (Norouzitallab et al., 2014; Thaulow et al., 2020).

One of the most comprehensive studies to date utilized publicly available ATAC-seq data to investigate how baseline chromatin accessibility and gene architecture interact with DNA methylation to influence gene expression and splicing under upwelling conditions (Bogan et al., 2023). Gene body methylation was

found to have a strong, positive effect on gene expression, whereas promoter methylation had a weaker, negative association. However, once chromatin accessibility was accounted for, the influence of DNA methylation on both gene expression and splicing became more pattern-dependent. For example, gene body methylation was more strongly associated with increased expression in genes with inaccessible transcription start sites, while exon methylation affected exon inclusion primarily in genes characterized by low exon accessibility and longer introns. Differential exon use was also linked to gene body methylation, but only within particular chromatin and architectural contexts, underscoring the complexity and interdependence of these molecular mechanisms. These findings provide a more nuanced understanding of how epigenetic regulation mediates transcriptional and splicing responses to environmental change and highlight the importance of considering multiple layers of epigenomic information. While ATAC-seq datasets are currently limited for many non-model aquatic organisms, their availability represents an important and cost-effective opportunity to deepen investigations into the relationship between epigenetic modifications and gene expression in aquatic invertebrates exposed to environmental stress.

4.6 Association between phenotype, gene expression, and epigenetics during stress exposure

Phenotypic plasticity refers to an organism's ability to alter its morphology, behavior, or physiology in response to environmental conditions (Pfennig et al., 2010). These changes are often adaptive, aiming to enhance survival and fitness, although short-term exposure to stressors can initially lead to detrimental phenotypic outcomes. Commonly measured traits and fitness metrics in the reviewed studies included survivorship, growth rates, and fecundity, as well as developmental abnormalities, altered swimming behavior, shifts in metabolomic or hormonal profiles, and markers of DNA damage. Interestingly, several studies documented partial or full recovery of these phenotypes over time, particularly under chronic or multigenerational exposure to stressors, as seen in the restoration of growth rates and fecundity in later generations (Shen et al., 2022; Lee et al., 2022).

Despite frequent measurements of gene expression and epigenetic modifications, few studies found clear, direct correlations between molecular changes and phenotypic traits. However, studies employing epigenetic inhibition offer compelling evidence that these modifications play a functional role in phenotypic outcomes. For example, chemical inhibition of DNA methylation prevented copepods from recovering fecundity by the F3 generation under ocean acidification, a recovery that was observed in uninhibited treatment groups exposed to the same stressor (Lee et al., 2022). Similarly, DNA methylation inhibition significantly reduced survival in annelids under sulfide stress (Zhang et al., 2024). In another example, inhibition of a specific lncRNA implicated in shell repair led to malformed shell crystals in oysters, with rough, hollow structures replacing the smooth, organized crystals seen in controls (Cai et al., 2022). These results

suggest that epigenetic mechanisms are not merely correlational but may actively shape phenotypic traits, although the precise molecular pathways remain unclear.

Among the studies reviewed, one demonstrated a strong association between phenotypic plasticity, gene expression, and DNA methylation. After two years of exposure to low pH, corals developed larger cells and calyxes as well as more porous skeletons, interpreted as a compensatory mechanism to maintain linear skeletal extension despite reduced calcification under ocean acidification stress (Liew et al., 2018). This phenotype was accompanied by differential methylation in growth- and stress-related genes, as well as differential expression in cell growth pathways, suggesting a coordinated molecular and phenotypic response. Notably, this experiment featured the longest duration of any study included in this review (2 years), indicating that extended exposure times may be necessary to detect meaningful links between epigenetic regulation and phenotypic plasticity. While such long-term studies may not always be feasible, incorporating phenotypic measurements, regardless of whether they yield statistically significant results, remains essential. Doing so provides a crucial layer of biological context, helping to connect molecular patterns with real-world organismal outcomes.

4.7 Temporal variation in epigenetic modifications

A prominent trend observed across studies in this review is the highly dynamic and temporally sensitive nature of epigenetic modifications. Epigenetic changes were found to occur rapidly after environmental stress exposure, often within hours, and to fluctuate over time even when the stressor remained constant. This temporal plasticity raises important questions about the stability, function, and role of epigenetic mechanisms in sustained stress responses and acclimation.

In terms of DNA methylation, several studies documented significant changes within very short time frames. For example, changes in DNA methylation were observed in oysters exposed to heat and salinity stress within one to three hours, with differences persisting for 48 hours before reverting to control levels despite remaining in experimental stress treatments (Huang et al., 2017). A similar pattern was seen in pteropods exposed to ocean acidification, where hypomethylation occurred after one day but returned to baseline levels by day seven despite continued exposure (Bogan et al., 2020). Crustaceans exposed to chemical stress showed significant hypomethylation at 14 days, followed by non-significant hypermethylation after one month, indicating dynamic shifts over time, with many examples of reverting to control levels after an initial shift (Cribiu et al., 2018). Histone modifications have also demonstrated rapid and reversible responses. In sea cucumbers, hyper- and hypoacetylation of histone H3 lysine 9 acetylation (H3K9ac) peaks were observed within 48 hours of heat stress (Xu et al., 2022). A study on two oyster species found thousands of histone peaks to be differentially regulated after just 12 hours of heat exposure, with notable differences between species (Wang C. et al., 2024). Additionally, histone methylation states in oysters varied across early developmental stages (6- and 24-hours post-

fertilization) under temperature stress, although developmental stages may also have contributed to these differences (Fellous et al., 2015). Non-coding RNAs showed similarly rapid and transient responses. Differentially expressed miRNAs were observed within eight hours of exposure to low salinity stress in oysters and within eight hours of immune challenge in mussels (Pereiro et al., 2021; Zhao et al., 2016). In crabs exposed to hypoxia, 39 differentially expressed miRNAs were detected after just one hour, with expression profiles shifting further by 24 hours; however, not all miRNAs were conserved across timepoints, highlighting the transience of the response (Ning et al., 2023). In a longer-duration example, prawn tissues collected at 7, 14, and 21 days of starvation had largely distinct miRNA profiles, with only four shared across all timepoints (Li et al., 2021).

Taken together, these findings underscore that epigenetic modifications are not static imprints but constitute a highly dynamic regulatory layer. They can be rapidly induced and reversed, even under continuous stress, suggesting a role more nuanced than serving as fixed molecular signatures of exposure. However, when evaluating their relationship with gene expression, it is important to recognize that most studies measure epigenetic marks and transcriptional activity at a single timepoint, even though these processes likely operate on different timescales. For example, gene expression can shift within minutes of environmental change, whereas DNA methylation typically responds more gradually and remains relatively stable over longer periods (Strader et al., 2020). This temporal mismatch implies that transient transcriptomic responses may precede, or occur independently of, DNA methylation changes, complicating causal interpretation. Collectively, these dynamics challenge simplistic models of epigenetic regulation and highlight the need to understand how such modifications integrate over time to shape acclimation, gene regulation, and phenotypic plasticity.

4.8 Transgenerational heritability of epigenetic modifications

The potential for epigenetic modifications to be inherited across generations has long been a subject of debate, carrying important implications for rapid, non-genetic adaptation through selection on epigenotypes and environmentally induced phenotypes (Bird, 2024). Traditionally, epigenetic reprogramming during development was assumed to erase parental epimarks, resetting the offspring's epigenome each generation (Jablonka and Raz, 2009; Reik et al., 2001; Skvortsova et al., 2018). However, increasing evidence challenges this view, particularly from studies that track molecular and phenotypic changes across multiple generations following parental or continuous environmental exposure. Experimental designs in this field often distinguish between parental (F0), embryonic (F1), and germline (F2) exposure within a single generation, with F3 typically representing the first unexposed generation (diagram in Jeremias et al., 2018). To capture true transgenerational inheritance, many studies followed organisms through at least three generations. Due to logistical constraints, these experiments have predominantly used short-lived species such as copepods, water fleas, rotifers, and brine

shrimp, while studies on longer-lived species such as corals and sea urchins have generally focused on parental effects to one generation.

Within the DNA methylation literature, parental exposure alone has been shown to induce DNA methylation changes in offspring. For example, offspring from pollution-exposed oysters exhibited global hypermethylation and reduced survival (Bachère et al., 2017). In corals, transmitted DNA methylation patterns in stress-related genes correlated with enhanced offspring survival under thermal stress, indicating environmentally responsive epigenetic priming (Liew et al., 2020). Several studies have extended observations to F3, revealing stress-induced DNA methylation signatures, in this case hypomethylation in regulatory genes, that persist across generations without apparent fitness costs (Jeremias et al., 2018; Trijau et al., 2018). Interestingly, in copepods exposed to ocean acidification, an initial reduction in fecundity was resolved by the third generation, but only in the presence of active DNA methylation, as inhibition of methylation prevented full recovery (Lee et al., 2022). Alternatively, some multigenerational exposure studies suggest that global DNA methylation changes may be reversible during or after acclimation to novel stressors. For instance, in water fleas the F0 generation was initially hypermethylated after exposure to pollution but showed a return to baseline DNA methylation and physiology in subsequent exposed generations (Chatterjee et al., 2019). Findings from longer-lived species (i.e., sea urchins) reinforce the importance of maternal conditioning. Two-generation studies under simulated upwelling conditions revealed DNA methylation and transcriptional changes in offspring from exposed mothers, despite minimal intragenerational methylation shifts between offspring exposed to control and upwelling conditions. However, phenotypic responses to maternal exposure were inconsistent between experiments, suggesting context-dependent outcomes (Strader et al., 2019, 2020).

In contrast to DNA methylation, evidence for transgenerational roles of ncRNAs and histone modifications remain limited. Only two studies examined miRNA dynamics beyond a single generation. In *Daphnia* with F0 exposed to dietary restrictions, differential miRNA expression in eggs and adult F1 was not sustained through F3, suggesting limited stability of miRNA-mediated inheritance (Hearn et al., 2018). Similarly, rotifers chronically exposed to ocean acidification displayed enhanced resistance to nanoplastic exposure compared to short-term exposure, with distinct miRNA profiles associated with both exposure times, though this was not tracked across generations, preventing knowledge of heritability (Kim et al., 2024b). While these findings implicate ncRNAs in environmental responsiveness, they provide little evidence for long-term inheritance. Similarly, histone modifications have few studies in the context of transgenerational inheritance. In rotifers, shifts in histone acetylation coincided with recovery of life-history traits over successive generations, implying a potential epigenetic mechanism for phenotypic restoration (Lee et al., 2020). In *Artemia*, exposure to *Vibrio* pathogens or sublethal heat stress conferred resistance through F3, but changes in histone acetylation and DNA methylation were inconsistent across generations, and outcomes varied depending on whether the stressor matched that of the parental generation (Norouzitalab et al., 2014, 2016).

Taken together, these studies demonstrate that epigenetic modifications, particularly DNA methylation, can persist across generations and influence offspring phenotype in the absence of continued exposure. However, mechanisms and consistency of inheritance vary widely by epigenetic marker, stressor, and taxon. While DNA methylation shows the strongest evidence for heritability, data on histone modifications, ncRNAs, and RNA methylation remain scarce and inconclusive, highlighting the need for more comprehensive, multigenerational studies. With only six studies addressing histone and ncRNA inheritance, substantial knowledge gaps remain regarding the stability, function, and adaptive significance of these epigenetic mechanisms in transgenerational plasticity.

4.9 Source-specific epigenetic modifications during stress

The differences between the source of the sample material are well-established features of epigenetic regulation, with differential responses between tissue, cell, or fluid types assumed to influence both gene expression and phenotype. In the current synthesis, source-specific patterns were observed in studies of DNA methylation and non-coding RNAs but were notably absent in studies on histone modifications and chromatin organization, and RNA methylation. Conceptually, regions most directly impacted by environmental stressors are expected to exhibit the most pronounced epigenetic and transcriptional changes (Feil and Fraga, 2012). Accordingly, many studies targeted tissue types relevant to the stressor's biological effects. For example, mantle edge tissue was selected in ocean acidification studies due to its role in biomineralization, while hepatopancreas tissue was prioritized during immune challenge experiments for its role in host defense (Downey-Wall et al., 2020; Li et al., 2021). However, some studies noted limitations associated with single-tissue sampling. A study on ocean acidification suggested that restricted sampling may have underestimated the full organismal response due to overlooking systemic effects or responses in other tissues (Downey-Wall et al., 2020). In small-bodied taxa, such as copepods and *Artemia*, and in colonial organisms like corals, whole-organism or holobiont samples were commonly used, both to maximize DNA and RNA yield and to sidestep tissue isolation challenges, effectively eliminating tissue specificity. In at least one study, RNA was intentionally pooled from four tissues in equal proportions, masking inter-tissue differences (Sun et al., 2016).

Several studies directly examined inter-tissue variation. In oysters exposed to pollution, DNA methylation and gene expression were measured in whole tissue and separately in the digestive gland, gill, and gonad. DNA methylation changes were only significant in the digestive gland, highlighting the potential for misrepresentative results when relying on whole or non-targeted tissue samples (Akcha et al., 2021). Similar trends were observed in salinity-stressed arthropods, in which DNA methylation ratios decreased in gill and muscle but increased in hepatopancreas tissue (Lu et al., 2019). This tissue-specificity extended to ncRNA responses. Hypoxia and anoxia-responsive miRNAs were more numerous in the hepatopancreas than in muscle tissue in one

study (English et al., 2018), while another found that regenerating mantle tissue expressed distinct sets of miRNAs following injury, suggesting a shift during stress (Cerveau and Jackson, 2021). Likewise, lncRNA expression was also tissue-specific in mussels, with 24% of variation attributable to tissue type alone (Yévenes et al., 2024).

While histone modifications, chromatin organization, and RNA methylation specificity were not measured in the reviewed studies, it is reasonable to expect similar trends based on findings from other epigenetic mechanisms. These observations highlight an important methodological question for future work: should researchers prioritize sampling whole organisms or pooled tissues to capture broad stress responses, or focus on discrete, functionally relevant tissues to uncover more precise but potentially incomplete patterns? Balancing resolution and generalizability while remaining cost-effective is a central challenge in epigenetic research on environmental stress in aquatic invertebrates.

4.10 Outstanding questions and future recommendations

The field of environmental epigenetics in aquatic invertebrates has grown remarkably in scope and sophistication over the past decade, but many critical questions remain unresolved. Despite abundant descriptive evidence linking epigenetic variation to stress exposure, mechanistic clarity regarding how such modifications regulate gene expression and shape phenotypic plasticity remains limited. Moving forward, progress will depend on the deliberate pairing of methodological rigor with ecological realism, improved data integration across regulatory layers, and greater investment in experimental and genomic infrastructure for non-model taxa.

Methodological choice must be closely aligned with the research question. For instance, base pair-resolution techniques are essential when the goal is to infer causal links between DNA methylation and gene regulation. Global methylation assays remain valuable for screening taxa lacking genomic resources, but they cannot identify regulatory regions or provide functional insight. Researchers should also report the genomic context of all epigenetic modifications (i.e., promoters, gene bodies, or transposable elements) to clarify potential mechanisms of transcriptional control. Epigenetic profiling should, whenever feasible, be paired with transcriptomic analysis from the same tissues, as molecular patterns without gene expression data cannot distinguish functional from incidental changes. Beyond transcriptomics, integrating additional omics approaches, such as proteomics to assess protein abundance and metabolomics to characterize metabolic states, can further strengthen inferences by capturing regulatory processes that occur downstream of transcription and more directly linking epigenetic variation to phenotypic outcomes. Likewise, assessing the activity or expression of enzymes involved in epigenetic regulation (e.g., DNA methyltransferases, histone acetyltransferases) warrants greater attention, as such measurements can provide cost-effective and mechanistically informative insights into epigenetic change.

Sample selection (i.e., cell, tissue, fluid type) is another key consideration. Studies should explicitly justify this choice relative to

the stressor, recognizing that parts of the organism that are directly engaged in stress response are likely to show the most relevant changes. If whole-organism samples are used for practical reasons, the tradeoff between greater yield and loss of tissue specificity should be acknowledged. Beyond the molecular level, measurement of phenotype and fitness (or a reasonable proxy of fitness) remains essential. Simple metrics such as survival, growth, fecundity, or behavior are often inexpensive to collect yet provide critical biological context linking molecular patterns to organismal function. Temporal design is equally important: because many epigenetic and transcriptomic modulations are dynamic and transient, time-series sampling is necessary to distinguish short-term responses from long-term acclimatization and inheritance. However, further research does need to be conducted in the temporal relationship between epigenetic modifications and gene expression, as the two likely operate on separate time scales but most of the sample collection for sequencing occurs at the same time.

Interpretations of gene-body methylation (GBM) warrant refinement. The long-held view that GBM promotes transcription while promoter methylation represses it should be reconsidered, as this dichotomy often breaks down at the level of individual genes and emerging evidence points to additional regulatory roles. Future work should adopt an integrated epigenomic perspective, combining DNA methylation with measures of chromatin accessibility, histone modification, and RNA-mediated regulation to better resolve their interactions. Incorporating chromatin context, for example, can substantially alter inferred relationships between DNA methylation, gene expression, and splicing. Broadening the focus beyond DNA methylation to include histone marks, non-coding RNAs (miRNAs, lncRNAs, circRNAs), and RNA methylation (e.g., m6A) will help reveal greater regulatory flexibility within the epigenome. Moreover, post-transcriptional mechanisms such as alternative splicing and isoform expression merit increased attention, as they may represent a crucial axis of rapid physiological acclimatization.

Causal inference will further benefit from deliberate experimental manipulations. Use of methyltransferase inhibitors, RNA interference (RNAi), and genome-editing tools can help establish whether specific modifications directly drive changes in gene expression and phenotype. Likewise, studies designed to track multiple generations, ideally to F3 or beyond, are crucial for distinguishing parental effects from true transgenerational inheritance. At the scientific community level, expanding high-quality genome assemblies and annotations, particularly for understudied phyla, will provide the foundation needed for integrative analyses. Equally important is the adoption of ecologically realistic stress regimes, emphasizing gradual or chronic exposures rather than acute, lethal shocks, to capture biologically meaningful acclimation responses. Data transparency will also strengthen reproducibility; raw sequencing reads, processed tracks, and analysis pipelines should be deposited in open repositories. Finally, the field would benefit from closer engagement with methodologies and theoretical frameworks developed in model systems where the causal architecture of molecular regulation is far better characterized.

The following priorities may guide future research:

1. Pair epigenetic assays with complementary omics technologies (i.e., transcriptomics, proteomics, metabolomics) as well as phenotypic and fitness measurements when feasible.
2. Integrate multiple layers of epigenetic mechanisms rather than focusing solely on singular modifications.
3. Incorporate time-series and multigenerational designs to capture transient and heritable responses.
4. Employ realistic, sublethal stress regimes over longer durations.
5. Increase genomic resources for non-model taxa and utilize pre-existing datasets when plausible.
6. Incorporate advanced molecular techniques and pull information from established model organisms.

5 Conclusion

In summary, advancing our understanding of how epigenetic mechanisms mediate acclimatization in aquatic invertebrates will require careful experimental design, multilayered data integration, and realistic ecological framing. A tremendous body of research has already laid the foundation for this work, and adopting these next steps will help transform environmental epigenetics in aquatic invertebrates from an emerging, descriptive field into a predictive and mechanistic discipline capable of informing species resilience under environmental change.

Data availability statement

The scripts and initial string search results that can be found here: https://github.com/emc-johnson/EmGePt_LitReview. Further inquiries can be directed to the corresponding author/s.

Author contributions

EJ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. JW: Conceptualization, Methodology, Supervision, Writing – review & editing, Funding acquisition, Project administration.

Funding

The author(s) declared that financial support was received for this work and/or its publication. This material is based upon work

supported by the National Science Foundation Graduate Research Fellowship under Grant No. (2139754) to EJ. This work was also financially supported by faculty start-up funds to JW (Duke University).

Acknowledgments

The authors thank Kathleen Donohue for her feedback and Jessica Johnson for her graphic design assistance.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. Generative AI (ChatGPT 5.0) was used in the development of the Search String used in the Web of Science (WoS) Core Collection (Science Citation Index Expanded, 2000–present) publication search. Exact search string is in the [Supplementary Materials](#).

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmars.2026.1767697/full#supplementary-material>

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