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Genetic and epigenetic regulation of growth, reproduction, disease resistance and stress responses in aquaculture

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Major progress has been made with genomic and genetic studies in aquaculture in the last decade. However, research on epigenetic regulation of aquaculture traits is still at an early stage. It is apparent that most, if not all, aquaculture traits are regulated at both genetic and epigenetic levels. This paper reviews recent progress in understanding of genetic and epigenetic regulation of important aquaculture traits such as growth, reproduction, disease resistance, and stress responses. Although it is challenging to make generalized statements, DNA methylation is mostly correlated with down-regulation of gene expression, especially when at promoters and enhancers. As such, methylation of growth factors and their receptors is negatively correlated with growth; hypomethylation of genes important for stress tolerance is correlated with increased stress tolerance; hypomethylation of genes important for male or female sex differentiation leads to sex differentiation into males or females, respectively. It is apparent that environmental regulation of aquaculture traits is mediated at the level of epigenetic regulation, and such environment-induced epigenetic changes appeared to be intergenerationally inherited, but evidences for transgenerational inheritance are still limited.

KEYWORDS

DNA methylation, epigenetic regulation, genome, QTL, fish, shellfish, aquaculture

1 Introduction

Important performance and production traits for aquaculture include growth rate, feed conversion efficiency, disease resistance, stress tolerance such as low oxygen tolerance, reproductive success, harvestability, and processing yields, among many others (Gjedrem, 2012; Boyd, 2015; Abdelrahman et al., 2017; Zhong et al., 2017; Li et al., 2019; Houston et al., 2020; Xu et al., 2022). Of these traits, disease resistance continues to be the top priority for aquaculture production because disease problems constitute the largest single cause of economic losses in aquaculture (Mzula et al., 2021; Naylor et al., 2021). Most, if not all, of these traits are regulated at both genetic and

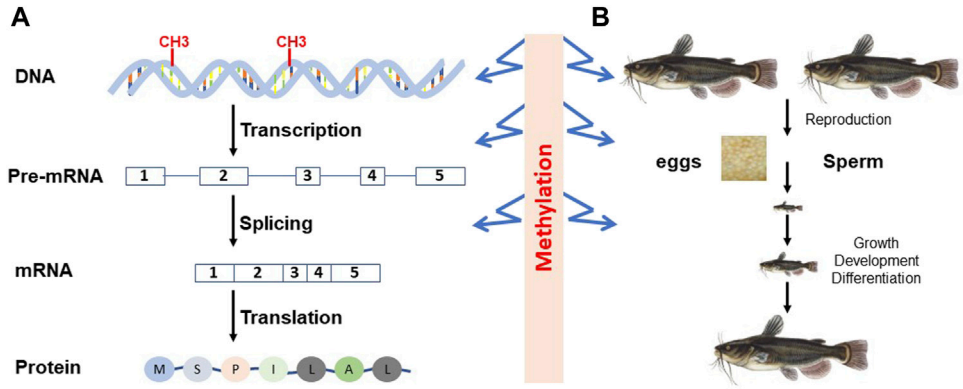

FIGURE 1
Epigenetic regulation of gene expression in the context of central dogma **(A)** and organismal development **(B)**. At the molecular level, DNA methylation can affect transcription and mRNA splicing, leading to different types or different amounts of transcripts. At the organismal level, DNA methylation is involved in gamete production, embryonic and later development, and differentiation.

epigenetic levels, and as such, understanding of genetic and epigenetic regulation of aquaculture traits is of high priority for aquaculture genomics and genetics research (Abdelrahman et al., 2017; Granada et al., 2018; Rexroad et al., 2019; Roy et al., 2021; Ren et al., 2022).

The central dogma has guided biological research for over half of a century. However, research advances in the last 20 years have provided information for the more complete interpretation of the central dogma. These included the huge regulatory functions of non-coding and small RNAs, epigenetic regulation through DNA methylation, and epigenetic regulation through histone modifications. This review will focus on DNA methylation and its regulation of genomic expression related to aquaculture traits. While research is very active with non-coding RNAs and histone modifications with aquaculture species, systematic knowledge of how such mechanisms are involved in the control of aquaculture traits is yet to be published, and as such, we will only briefly discuss epigenetic regulation through histone modifications.

In eukaryotic organisms, cytosine methylation is the primary form of DNA methylation, and 5 mC is the major methylated form of cytosine. As shown in Figure 1, DNA methylation can insert its roles in the regulation of genome expression at the level of transcription through activation or repression of transcription, thereby having an impact on the types of transcripts and their amounts, or at the level of posttranscription. At the organismal level, DNA methylation can affect development, growth, differentiation, reproduction, and most other processes throughout the life cycle of organisms (for reviews, see Moore et al., 2013; Zeng and Chen, 2019).

Although DNA methylation is stably maintained in somatic tissues, its patterns and levels show dynamic changes during development. In mammalian systems, the genome undergoes two waves of global demethylation and remethylation: One in the germline, initiated with the erasure of global methylation in primordial germ cells and completed with the establishment of sex-specific methylation patterns during later stages of germ cell development; and the second after fertilization, including the erasure of most methylation marks inherited from the gametes and the subsequent establishment of the embryonic methylation pattern (Cavalli and Heard, 2019; Zeng and Chen, 2019). Histone marks and 3D genome organization are also reprogrammed in the germline and after fertilization (Eckersley-Maslin et al., 2018). In zebrafish, the primordial germ cells (PGCs) undergo significant DNA methylation reprogramming during germ cell development (Jessop et al., 2018; Marchione et al., 2021); the methylome of PGCs is reset to an oocyte/ovary-like pattern at 9 days post fertilization (9 dpf), suggesting that methylation reprogramming is required for zebrafish sex transition (Wang et al., 2021). It was demonstrated that zebrafish achieve a totipotent chromatin state at zygotic genome activation (ZGA) through paternal genome competency and maternal genome DNA methylation reprogramming (Potok et al., 2013). Similar developmental regulation processes for epigenetic factors have been observed in a non-model teleost (Wang et al., 2022; Yang et al., 2022).

In the last decade, drastic progress has been made in aquaculture genomics and genetics research. Major milestones included the production of whole genome sequences for many aquaculture species. Many of these genome sequences are of high quality. The availability of high-quality genome sequence assemblies allowed mapping of QTLs controlling important performance and production traits to chromosomal locations, with information of tightly linked markers, especially sequence-tagged single nucleotide polymorphic (SNP) markers. Such high-quality genome sequence assemblies also allowed mapping of methylated bases to genome locations in relation to performance traits. At the same time, high throughput RNA-Seq has allowed

qualitative as well as quantitative assessment of genome-wide transcription in relation to genomic sequence variations and epigenomic regulation. This review will summarize recent studies of aquaculture traits at genetic and epigenetic levels, with a focus of DNA methylation.

2 DNA methylation and epigenetic regulation

DNA methylation is catalyzed by DNA methyltransferases, and its regulation of gene expression is materialized by the differential binding affinities of methylated DNA to various transcriptional factors and methylated DNA binding proteins, as compared to those of unmethylated DNA. Most often, methylation at the transcriptional regulatory sequences such as the promoters has a negative impact to the transcription of the involved gene(s). Therefore, significantly lower levels of CpG methylation have been observed around transcriptional start sites (TSS). This section reviews general information of DNA methylation and its regulation at various levels.

2.1 DNA methyltransferases and methylated DNA binding proteins

DNA methyltransferases (DNMTs) regulate the transfer of methyl groups from S-adenosylmethionine to cytosine residues on genomic DNA. In mammals there are four members of the DNMT family, including DNMT1, DNMT3A, DNMT3B, and DNMT3L, of which DNMT3L does not harbor any transferase activities (Jin and Robertson, 2013), but is essential for establishment of maternal genomic imprints in the growing oocyte and at dispersed repeated sequences. In addition, DNMT2 exists in most, if not all, eukaryotic organisms as a homologue of DNA methyltransferase. It has all the sequence characteristics of a cytosine methyltransferase but has not been demonstrated to carry any methyltransferase activities. DNMT1 has greater methyltransferase activity on hemimethylated substrates and therefore has been assigned into the category of maintenance methyltransferase although it also methylates unmethylated DNA. DNMT3A and DNMT3B are regarded as *de novo* methyltransferases because they do not require hemi-methylated DNA to function and transfer methyl groups to mainly non-methylated cytosine residues (for a review, see Goll and Bestor 2005). In zebrafish, there are eight DNMT enzyme orthologues to the mammalian counterparts (Takayama et al., 2014; Balasubramanian et al., 2019); its DNMT1 is related to mammalian DNMT1, maintaining the methylated DNA created during replication; its DNMT2 is homologous to the mammalian DNMT2; It has a unique function as tRNA transferases catalyzing the methylation at 38th position in $tRNA^{AspGUC}$. Zebrafish DNMT6 and DNMT8 are related to mammalian DNMT3a; its DNMT4 is related to mammalian DNMT3b; and DNMT3, DNMT5, and DNMT7 are unique in fishes (Balasubramanian et al., 2019). DNA methyltransferases have also been studied in other fishes such as Japanese rice fish (Dasmahapatra and Khan, 2015), mandarin fish (Zhou et al., 2021), fathead minnow (Wood et al., 2016), and goldfish (Zhang et al., 2014).

Several methylated DNA binding proteins have been identified, whose expression is involved in the epigenetic regulation through DNA methylation. These included methyl-CpG binding protein 2 (MeCP2), and methyl-CpG-binding domain proteins 1 (MBD1) and 2 (MBD2). MeCP2 is believed to be a global repressor of methylated promoters (Cross et al., 1997), and MDB1 and MDB2 have also been reported to bind with higher affinity to methylated CpG sites than to unmethylated sites (Goll and Bestor, 2005). To date, methylated DNA binding proteins have been studied with aquatic animals only in model species such as zebrafish (Gao et al., 2015; Nozawa et al., 2017).

2.2 DNA demethylation

The reverse of DNA methylation is DNA demethylation that can happen passively or actively. Functional deficiency in maintenance of methylation can lead to replication-dependent dilution of 5 mC, which is known as passive DNA methylation (for a review, see Zeng and Chen, 2019). Active DNA demethylation involves rapid loss of DNA methylation by removal of the methyl group from 5 mC. The first step of active demethylation involves oxidation of 5 mC by the ten-eleven translocation (TET) family of enzymes, TET1, TET2, and TET3, which oxidizes 5 mC into 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5 fC), and 5-carboxylcytosine (5caC) (Tahiliani et al., 2009; Ito et al., 2010, 2011; He et al., 2011). These oxidized products serve as intermediates of DNA demethylation. They are repaired into unmodified C, achieving demethylation (reviewed by Zeng and Chen, 2019).

2.3 Major methylation sites in the context of genomic DNA

Although methylation of adenine can also happen, we will focus this review on methylation of cytosine. Depending on the sequence context where base C is situated, the chances of being methylated vary greatly (Figure 2). The position of C in a sequence can be in three different situations: 1) CG motifs; 2) CHG motifs where H is A, C, or T; and 3) CHH, where H is A, C, or T. In many fish species studied to date, approximately 70%–80% CpG sites were found to be methylated. For

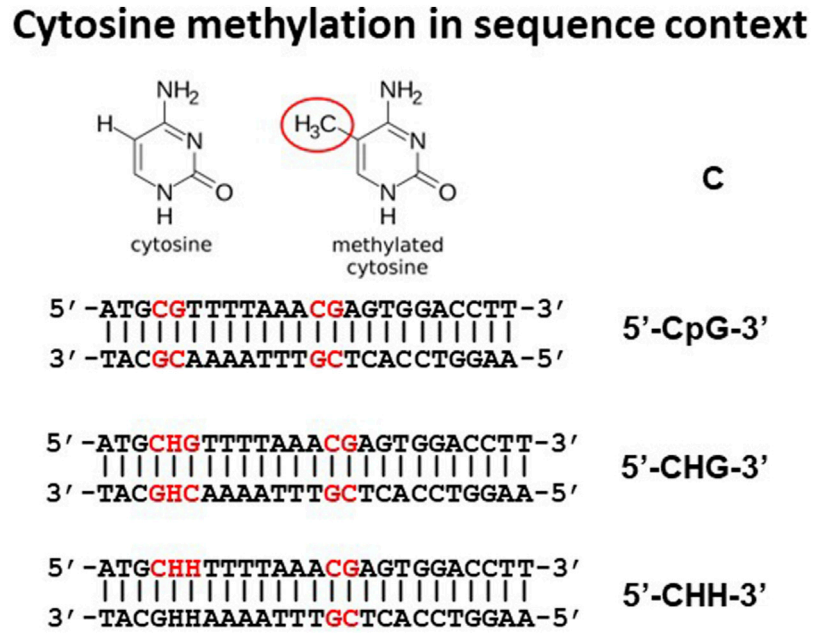

FIGURE 2
Cytosines within DNA can be within CpG, CHG, or CHH context where H is A, C, or T.

instance, 74.5%–78.4% of all C's at the CpG sites were methylated in channel catfish (Yang et al., 2022). This is similar to those observed in other vertebrate animal species, slightly higher than that seen in mice (74%) (Feng et al., 2010) and tilapia (69.60%) (Wan et al., 2016), but slightly lower than that in zebrafish (80.3%) (Feng et al., 2010). Methylation rate at CHG and CHH sites are much less frequent, at only miniscule scale as compared to methylation at CpG sites. For example, only 0.3%–0.4% of Cs within the CHG and CHH context were methylated in channel catfish (Yang et al., 2022). Similarly, only 1.22% and 0.91% of Cs within CHG and CHH context were methylated in zebrafish (Feng et al., 2010), 0.47% and 0.57% of Cs within CHG and CHH were methylated in tilapia (Wan et al., 2016). However, methylation rates at CHG and CHH sites is much higher in plants (Kenchanmane Raju et al., 2019).

In contrast to the situations with teleost fish, methylation in invertebrate aquaculture species such as mollusks and crustaceans appeared to be quite different in two aspects: 1) the levels of methylation in crustaceans and bivalves appear to be much lower than those in teleost fish; and 2) DNA methylation in these invertebrate species appears to be predominantly found in gene bodies (Gavery and Roberts, 2013; Gavery and Roberts, 2014). For example, about 15% of CG (1.8% total cytosines) in the Pacific oyster *Crassostrea gigas* genome are methylated (Gavery and Roberts, 2013), which is similar to those in gastropod (snails have ~2% of cytosines being methylated) (Fneich et al., 2013), but much lower than those observed with vertebrate animals. With marbled crayfsh, *Procambarus virginalis*, the global 5-methylcytosine level was 2.78% at mid-embryonic development and decreased slightly to 2.41% in 2-year-old adults (Vogt, 2022). Methylation levels are even lower with micro-crustaceans. Average percentage CpG methylation was below 1% (Kvist et al., 2018) or just slightly above 1% with *Daphnia magna* (Hearn et al., 2021). Using whole genome bisulfite sequencing, Kvist et al. (2018) demonstrated that DNA methylation in *Daphnia* is mainly enriched within the coding regions of genes, with the highest methylation levels observed at exons 2–4, in contrast to the situations of vertebrates whose genomes are globally methylated. Significant negative correlation between gene family size and the degree of methylation was observed with *Daphnia*, suggesting that gene body methylation may help regulate gene family expansion and functional diversification of gene families leading to phenotypic variations (Asselman et al., 2016).

2.4 Regulation of gene expression through DNA methylation

Epigenetics refers to heritable changes in gene expression and phenotype that arise "on top of" or "in addition to" primary DNA sequence. After almost half a century since the term was published, epigenetics has now become one of the

hottest research areas in biology because it is involved in essentially all biological processes and often serves as a mechanism of control and regulation. These processes span from life to death involving embryonic development, cell cycle control, growth and development, differentiation, responses to diseases and other environmental factors (Venney et al., 2021), and regulation of aging and cancer (for review, see Skvortsova et al., 2018; Zeng and Chen, 2019; Vidaurre and Chen, 2021; Fu et al., 2020).

A well-established concept of epigenetic regulation is that DNA methylation regulates gene expression by inhibiting the binding of transcription factor(s) to DNA or recruiting proteins involved in gene repression, thereby repressing transcription (Jones, 2012; Moore et al., 2013). Because this is well established and almost over-used concept, we will not further elaborate on this. However, regulation of gene expression by DNA methylation is more complex than this simple notion. In fact, DNA methylation can not only repress transcription, but also activate transcription. For example, transcriptional anti-silencing factors SUVH1 and SUVH3 bind to methylated DNA and recruit the DNAJ proteins to enhance proximal gene expression, thereby encountering the repressive effects of transposon insertion near genes (Harris et al., 2018).

How DNA methylation regulates transcription is complex depending on where and when DNA methylation occurs in relation to gene structure and development. The promoter-region hypermethylation events are especially critical and can frequently serve as alternative mechanisms for coding-region mutations for loss of key gene function (Herman and Baylin, 2000). CpG methylation in promoters are negatively correlated with transcription. As such, most CpG islands when located at transcription start sites are not methylated (Jones 2012). Hypermethylation of the promoter and coding region can inhibit gene expression, while demethylation of the promoter and coding region can activate gene expression (Han et al., 2021a). However, intragenic methylation of CpG sites can activate transcription (Jones, 2012), but such positive correlation of intragenic methylation and transcriptional activation may be tissue specific. Intragenic methylation at CH sites is positively correlated with gene expression in human embryonic cells but is negatively correlated with gene expression in the brain (Luo et al., 2018).

2.5 Regulation of recombination through DNA methylation

Genes are not distributed evenly in the genome. Instead, genomes are divided into gene-rich euchromatin regions and repeat-rich heterochromatin regions. Typically, chromosome regions such as centromeres, telomeres are composed almost purely of repetitive sequences. In addition, ribosomal (rRNA) and transfer RNA (tRNA) loci are composed of tandem repeats of these structural RNA genes. Transposable elements can be highly repetitive but in teleost fish, the most abundant types of transposable elements are Tc1/mariner type of transposons that are dispersed throughout the genomes. Repeat-containing regions undergo little or no meiotic crossover recombination.

DNA methylation is a widespread epigenetic mark of repeat sequences associated with heterochromatin in eukaryote genomes. DNA methylation repress meiotic recombination. Recombination rates in heterochromatin regions are generally very low. For instance, genomic regions surrounding the centromeres are generally enriched in DNA methylation and histone modifications such as H3K9me2 (Simon et al., 2015), and there is no recombination in centromeric regions (Termolino et al., 2016). However, the causal relationship of DNA methylation and recombination is not fully demonstrated. The repressive roles of methylation on meiotic recombination in euchromatic regions have been demonstrated, but additional factors may be involved in controlling the suppression of recombination in heterochromatin. For instance, in *Arabidopsis*, deficiency in DNA methylation increased meiotic crossover rates in euchromatic but not in heterochromatic regions (Melamed-Bessudo and Levy, 2012).

2.6 Regulation of alternative splicing through DNA methylation

Alternative splicing is an evolutionarily conserved mechanism that increases transcriptome diversity by producing multiple mRNA products from a single gene. In humans, >90% of genes have alternatively spliced transcripts (Wang et al., 2008). In fish species, the proportion of genes with alternative splicing is probably lower. In channel catfish, approximately 39% of genes were found with alternative splice transcripts after infection with *Edwardsiella ictaluri* (Tan et al., 2018a). Methylation levels in exons are higher than in introns, and alternative exons display lower levels of DNA methylation than constitutively spliced exons, suggesting methylation is involved in alternative splicing (Lev Maor et al., 2015). Such regulation of alternative splicing is believed to be mediated by CCCTC-binding factor (CTCF). Intragenic CTCF binding sites, particularly those proximal to splice junctions, influence pre-mRNA splicing decisions, and thus mediate alternative exon or intron inclusion (for a review, see Alharbi et al., 2021). DNA methylation at CpG sites within CTCF target sites can prevent CTCF binding, thereby regulating alternative splicing. Such regulatory processes also involve MeCP2 and TET1. DNA methylation mediates opposing effects on the role of CTCF and MeCP2 binding to DNA and subsequently regulation of pre-mRNA splicing, although the detailed mechanisms are not fully understood (Alharbi et al., 2021).

TABLE 1 Major aquaculture species of finfish, crustacean, and molluscs in the world and their whole genome sequence resources.

Species groups	Species involved	% Of world production	References of annotated genomes
Finfish			
Carps (Cypriniformes)	Grass carp, silver carp, **common carp**, catla, bighead carp, **goldfish**, rohu carp, **Wuchang bream**, black carp, and other cyprinids	51.1%	Xu et al. (2014); Chen et al. (2019); Liu H. et al. (2021)
Tilapias	**Nile tilapia**, **blue tilapia**, and other tilapia species	10.2%	Tao et al. (2021); Conte et al. (2017)
Catfishes	**Striped catfish**, Clarias spp., **yellow catfish**, **channel catfish**	7.5%	Liu P. et al. (2016) Gong et al. (2018) Gao et al. (2021)
Salmonids	**Atlantic salmon, rainbow trout, pink salmon, chum salmon, coho salmon, sockeye salmon, Chinook salmon**	6.1%	Lien et al. (2016); Berthelot et al. (2014)
Milkfish	**Milkfish**	2.4%	
All other finfishes	Flatfishes such as Atlantic halibut, Pacific halibut, **Japanese flounder, half-tongue smooth; Atlantic cod**	16.4%	Chen et al. (2014); Shao et al. (2017); Star et al. (2011)
Crustaceans			
Shrimps	***Penaeus vannamei, P. monodon, P. japonicus, P. chinensis***	60.9	Zhang et al. (2019), Uengwetwanit et al. (2021); Wang et al. (2022)
Red swamp crayfish	***Procambarus clarkii***	18.2	Xu et al. (2021)
Chinese mitten crab	*Eriocheir sinensis*	8.1	
Oriental river prawn	*Macrobrachium nipponense and Macrobrachium rosenbergii*	5.0	Jin et al. (2021)
Molluscs			
Oysters	***Crassostrea gigas*, *C. virginica***	33.2	Zhang et al. (2012); Gómez-Chiarri et al. (2015)
Japanese carpet shell	*Ruditapes philippinarum*	23.6	
Scallops	***Mizuhopecten yessoensis*** *and various species in Pectinidae*	11.0	Wang et al. (2017a)
Sea mussels	Various species in Mytilidae	6.9	Jin et al. (2017)
Constricted tagelus	*Sinonovacula constricta*	4.9	Ran et al. (2019)
Blood cockle	*Anadara granosa*	2.5	
Chilean mussel	*Mytilus chilensis*	2.1	

Source: Food and Agricultural Organization of the United Nations (https://www.fao.org/documents/card/en/c/ca9229en/).
Bold species are those whose genome sequences have been annotated at NCBI.

3 Review of recent progress of genetic and epigenetic studies of aquaculture traits

Most of the studies of epigenetic regulation were conducted in humans, rodents, and model organisms. Epigenetic research with aquaculture species, compared to those in model species, are relatively recent and limited, but more and more researchers are turning their attention to this hot research area (Metzger and Schulte, 2016; Gavery and Roberts, 2017). Understanding of epigenetic regulation of various traits will lead to practical applications in aquaculture with various approaches such as epigenomic editing (for a recent review, see Nakamura et al., 2021), environmental manipulation, and epigenetic selection (Metzger and Schulte, 2016).

3.1 Reference genome sequences as resources for genetic and epigenetic studies

According to FAO (https://www.fao.org/documents/card/en/c/ca9229en/), aquaculture produced an annual total of over 82 million metric tons of seafood, with finfish contributing over 54 million tons, crustacean contributing over 9.3 million tons, and molluscs contributing over 17.5 million tons. The major

finfish, crustaceans and molluscs species of the world aquaculture are summarized in Table 1. Genome sequences for many of the major aquaculture species have been produced. However, well-assembled genome sequences with annotations are still limited. Currently, there are almost 900 eukaryotic genomes that have been annotated at the National Center for Biotechnology Information (NCBI), and it is increasing at a speed of about 150 additional species per year (https://www.ncbi.nlm.nih.gov/genome/annotation_euk/). The annotated genomes to date included 142 fish species, 42 "other vertebrates", and 69 "other invertebrates" where many of the aquaculture species belong. Despite these impressive numbers, genome sequences for many of the major aquaculture species are yet to be annotated, as summarized in Table 1. Genome annotation is important because well annotated reference genome sequences facilitate genetic and epigenetic research allowing aquaculture traits to be studied more effectively and efficiently.

3.2 Genetic and epigenetic regulation of growth

Growth is among the most important traits for aquaculture production. However, because growth can be selected readily by phenotypes, genetic and genomic work on growth QTL was limited. Nonetheless, genomic work allowed identification of novel growth controlling genes (for review, see Abdelrahman et al., 2017). For example, significant growth QTL have been identified from tilapia (Liu et al., 2014), channel catfish (Li et al., 2018), and Asian seabass (Wang et al., 2019). Interestingly, in eastern oysters, Zeng and Guo (2022) identified a set of genes that are both important for biomineralization and growth. With triploid sea cucumber *Apostichopus japonicus*, the term ribosome production was enriched in fast growing sea cucumbers, and a set of 11 significant differential metabolites were found to be associated with growth advantage (Xie et al., 2022).

A few studies of epigenetic regulation of growth trait have been conducted with fish and shellfish species. Methylation differences were observed between slow and fast muscle in *Takifugu rubripes* (Wang et al., 2021). In allotriploid carps, heterosis and growth are regulated by DNA methylation (Ren et al., 2022). However, the detailed relationship between DNA methylation and gene expression can be complicated. With large yellow croaker, dynamic alterations of methylation of growth-related genes and their expression were observed after starvation treatment, but the correlation of methylation and expression was not consistently observed (Zhang et al., 2019). Increased growth in the interspecific hybrid of snakehead fish was found to be correlated with reduced methylation in the hybrid fry (Ou et al., 2019). In tilapia, increased methylation was observed at the promoter of growth hormone (GH) gene in females, but not in males, correlated with expression of the GH gene and growth performance (Zhong et al., 2014), suggesting epigenetic regulation of growth differences between males and females (Podgorniak et al., 2019). In triploid sea cucumber (*Apostichopus japonicus*), 23 genes (such as Guf1, SGT, Col5a1, HAL, HPS1, etc.) exhibited correlation between levels of promoter methylation and levels of expression, suggesting functional interactions of promoter methylation and growth in triploid sea cucumbers (Han et al., 2021a). DNA methylation is believed to regulate gene expression in polyploid organisms (for a review, see Osborn et al., 2003), and such regulation by DNA methylation was a part of the regulatory mechanism for allelic silencing in allopolyploid fish (Matos et al., 2016). In a study with tilapia, Konstantinidis et al. (2021) showed tissue-specific differential methylation of genes involved in somatic growth, such as growth factors and their receptors, with hypomethylation in the muscle tissues. All these studies demonstrated the involvement of DNA methylation in regulation of fish growth. With Giant freshwater prawn, *Macrobrachium rosenbergii*, increased levels of genomic methylation were observed with the "iron prawn", prawns with serious growth retardation (Jiang et al., 2020). This is similar to the situation in Japanese flounder, where increased methylation of MyoD and IGF genes are correlated with reduced growth (Huang et al., 2018).

3.3 Genetic and epigenetic regulation of disease resistance

Great efforts have been made to understand the molecular basis for disease resistance. Studies on genetic basis have focused on identification of QTL controlling disease resistance or susceptibility, and determination of causal genes (Table 2). A good example is the determination of resistance for the infectious pancreatic necrosis virus (IPNV) in Atlantic salmon (Houston et al., 2008; Houston et al., 2010; Moen et al., 2015; Pavelin et al., 2021). In a series of studies, these researchers identified a single QTL fully responsible for the disease resistance, and such information has been applied in the aquaculture industry to control IPVN. Interestingly, earlier studies seemed to indicate that a cellular receptor for the virus, cadherin 1, was the causal gene (Moen et al., 2015). However, further analysis of whole genome sequencing and functional annotation, knockout, and differential expression analysis of homozygous resistant and susceptible fish after infection allowed the identification of NEDD-8 activating enzyme 1 (nae1) as the causal gene (Pavelin et al., 2021). As summarized in a recent white paper (Abdelrahman et al., 2017), QTL studies have been conducted to identify genetic variants and genomic regions associated with disease resistance in various aquaculture species, including channel catfish, Atlantic salmon, rainbow trout, Asian seabass, and Japanese flounder, among many other aquaculture species (Table 2). Moreover, transcriptomic analyses after disease infection and stress challenges were conducted in aquaculture

TABLE 2 Some examples of genetic studies of disease resistance in several major aquaculture fish species.

Species	Diseases	QTL and candidate genes	References
Atlantic salmon	Infectious pancreatic necrosis (IPN), viral	A single QTL on chromosome 26 explains all the resistance, and NEDD-8 activating enzyme 1 was the candidate causal gene	Moen et al. (2009); Moen et al. (2015); Houston et al. (2010); Pavelin et al. (2021)
	Pancreas disease (PD), viral	QTL mapped to chromosome 3 and chromosome 7	Gonen et al. (2015); Hillestad et al. (2020a)
	Infectious salmon anemia (ISA), viral	QTL mapped to chromosome 15	Moen et al. (2007); Li et al. (2011); Gervais et al. (2021)
	Cardiomyopathy syndrome, viral	QTL mapped to chromosome 27	Hillestad and Moghadam, (2019); Hillestad et al. (2020b)
	Amoebic gill disease (AGD), parasitic	QTL mapped to various chromosomes 1, 2, 5, 4, 9, 13	Boison et al. (2019); Aslam et al. (2020)
	Sea lice, parasitic	QTL mapped to chromosomes 3, 18, 21	Robledo et al. (2019)
Rainbow trout	Bacterial coldwater disease	QTL for resistance was mapped to chromosome 19, 8 and 25	Wiens et al. (2013); Vallejo et al. (2014); Liu et al. (2015); Palti et al. (2015); Fraslin et al. (2019); Liu et al. (2022)
	Whirling disease	A single QTL was identified on chromosome 9 for resistance	Baerwald et al. (2011)
	Columnaris disease (CD), bacterial	Major QTL were mapped to chromosomes 3 and 5	Calboli et al. (2022); Fraslin et al. (2022)
		A major QTL was identified for resistance to rhabdovirus	Verrier et al. (2013)
	White spot disease (WSD), parasitic ciliate *Ichthyophthirius multifiliis*	Two QTL were identified on chromosome 16 and 17	Jaafar et al. (2020)
Common carp	RNA-Seq	DEGs related to CyHV-3 disease resistance were identified	Tadmor-Levi et al. (2019a)
Common carp	Cyprinid herpes virus disease	QTL mapped to chromosome 14, 30, 43, 44, and 46	Palaiokostas et al. (2018)
			Tadmor-Levi et al. (2019b)
Grass carp	Grass carp reovirus	Resistance against GCRV has high heritability	Huang et al. (2015)
Catfish	Enteric septicemia of catfish (ESC) disease, bacterial	QTL were mapped to chromosome 1, 12, and 16	Zhou et al. (2017); Shi et al. (2018); Tan et al. (2018b)
			Jin et al. (2022)
	Columnaris disease, bacterial	QTL mapped to linkage group 7, 12, and 14 in genomic hubs	Geng et al. (2015)
			Zhang et al. (2020)
	Aeromonas septicemia disease, bacterial	QTL mapped to linkage groups 2, 26, and 29	Wang et al. (2019)
Asian seabass	Viral nervous necrosis disease (VNN or NNV)	QTL and suggestive QTL were identified	Liu et al. (2016); Yang et al. (2020)
Gilthead sea bream	Pasteurellosis disease	Two significant QTL were identified	Massault et al. (2011)
Japanese flounder	Lymphocystis disease, viral	Marker-assisted selection	Fuji et al. (2007)
Turbot	Aeromonas disease, bacterial	QTLs were identified	Rodríguez-Ramilo et al. (2011)

species (Qian et al., 2014; Jin et al., 2022), providing insights into differentially expressed genes, and their involved gene pathways. Genes important for immune response were identified in Atlantic salmon using RNA-Seq (Fu et al., 2022). With catfish, Jin et al. (2022) applied the bulk segregant analysis and RNA-Seq (BSR-Seq) to determine genes involved in QTLs important for ESC resistance. Such analysis allowed identification of potential candidate genes for ESC resistance. As summarized in Table 2, one of the major characteristics of disease resistance in aquaculture species is that just one or few genes control disease resistance in aquatic species. This has been demonstrated with viral diseases, as well as bacterial diseases.

In contrast to extensive genetic studies, studies of epigenetic regulation of disease resistance are still limited. In grass carp, hypermethylation of GC island upstream of the RIG-I gene in the susceptible fish led to reduced expression of RIG-I gene, which in turn accounted for the observed susceptibility for the grass carp reovirus (Shang et al., 2016). With brine shrimp (*Artemia franciscana*), biological control treatment with a plant-based phenolic compound resulted in transgenerational inherited increased resistance against *Vibrio parahaemolyticus*, the pathogen for acute hepatopancreatic necrosis (Roy et al., 2019, 2022), and DNA methylation was involved in the elevated expression of innate immune genes.

3.4 Genetic and epigenetic regulation of heat stress

Heat stress is increasingly a problem for aquatic organisms with the trend of climate change. Heat stress tolerance is particularly important for cold- and cool-water species. As such, much work has been conducted with salmonids. QTL for upper temperature tolerance (UTT) have been identified (Jackson et al., 1998; Perry et al., 2001; Somorjai et al., 2003). Genes associated with UTT have been identified; small heat shock proteins, along with hsp90, were found to be associated with UTT (Quinn et al., 2011). Strains were developed to have enhanced upper temperature tolerance for rainbow trout (Chen et al., 2015; Tan et al., 2016). Similarly, QTL for UTT were identified in turbot (Ma A. et al., 2021).

Genetic research of heat stress tolerance with warmwater fish is rare. While temperature may not be a major factor for survival with warmwater fish, the adverse impacts of high temperature on growth, disease resistance and sex reversal (see below) make it important to study heat stress tolerance with warmwater fish as well. Jin et al. (2017) identified three significant loci associated with tolerance to heat stress in channel catfish, a warmwater species. Genes included in these QTL regions included those involved in protein folding, protein degradation and protein synthesis, as well as those for iron transport and cytoskeletal reorganization.

Temperature is probably a single most frequent and most important environmental factor for poikilothermic animals such as fish. With just a few degrees of temperature change, thousands of genes are differentially expressed (e.g., Liu et al., 2013). The question is how such expression is regulated. Although the detailed mechanisms await to be elucidated, it is apparent that DNA methylation is intensely involved. Several studies have been conducted with epigenetic regulation of heat stress resistance. These studies provided strong evidence for intergenerational inheritance of acquired traits that were epigenetically regulated. With an *Artemia* model, Norouzitallab et al. (2014) conducted common garden experiments, where the *Artemia* was exposed to nonlethal heat shocks. The parental population was observed with increased expression of heat shock protein 70, and they are more tolerant to lethal heat stress, and more resistant against pathogenic *Vibrio campbellii*. Most interestingly, they found that the acquired phenotypic traits were transmitted to three successive generations without any additional exposure to heat stress. However, in this study, the measurement was levels of global DNA methylation and acetylated histones H3 and H4, not specific epigenetic marks (Norouzitallab et al., 2014). In a separate study, Robinson et al. (2019) demonstrated that early developmental stress can affect subsequent gene expression response to an acute stress in Atlantic salmon. Using reduced representation bisulfite sequencing, they found differences in methylation in the genomic neighborhood of the response genes, but the patterns of methylation was complicated (Robinson et al., 2019). Similarly, a study using zebrafish demonstrated complex interactions of temperature, DNA methylation and other environmental factors (Pierron et al., 2021). In that work, they found strong correlation of heat and methylation level of cyp19a1a gene with population masculinization.

High temperature stress may be a real threat to many aquatic species in the face of global climate change. Adaptive phenotypic response through epigenetic regulation may be particularly important for K-strategy species, where the species population are maintained at its maximal capacity as allowed by the environment, as demonstrated with winter skate (*Leucoraja ocellata*) (Lighten et al., 2016). Such adaptive responses are believed to be regulated by epigenetic regulation. DNA methyltransferase 3a was shown to mediate developmental thermal plasticity in zebrafish (Loughland et al., 2021) as its knockout led to decrease survival and increased deformities under cold temperatures. High temperature stress caused a significant increase of *de novo* DNA methyltransferase genes although it did not cause global cytosine methylation levels during reprogramming of DNA methylation (Dorts et al., 2016). There is a clear gender-specific response to temperature stress, as demonstrated by the work with Chinese tongue sole (*Cynoglossus semilaevis*), where approximately a quarter of the differentially expressed genes were shared among males, females, and pseudo-males (Wang et al., 2020). Although the literature is still limited at present, it is apparent that high temperature stress may have a fundamental impact on fish and shellfish species, affecting their growth, development, and sex phenotypes, mostly through the mechanisms of epigenetic regulation, especially with global climate change scenarios. With European seabass, increases of even 2°C in larvae significantly changed global DNA methylation and the expression of ecologically-relevant genes related to DNA methylation, stress response, muscle and organ formations (Anastasiadi et al., 2017). Similarly, with marine stickleback (*Gasterosteus aculeatus*), parental acclimation to ocean warming led to dynamic and temperature-sensitive re-programming throughout offspring development (Fellous et al., 2022).

3.5 Genetic and epigenetic regulation of tolerance to low oxygen

Aquatic organisms face frequent variations in dissolved oxygen in water. Under aquaculture conditions, hypoxia can be caused by natural phenomena (e.g., weather, temperature, or water flow rate), water pollution and eutrophication, high stocking density, and improper use of aeration. Aquatic species often are encountered with hypoxia (low oxygen) or even anoxia (no oxygen) environments. During the normal production cycle, aquaculture species experience great levels of variation in dissolved oxygen; even during a 24-h day and night shift, oxygen in the water vary greatly. In aquaculture ponds,

oxygen levels are high during the sunny hours of the day and start to decline in the evening, related to the photosynthesis activities of algal species. As a result, aquaculture species must cope with such variations in dissolved oxygen concentrations. In the face of climate change and potential global warming, aquatic organisms are facing unprecedented challenges. While responses to high temperature can be different types of responses as compared to responses to hypoxia, temperature and oxygen conditions are much interwoven for aquatic organisms. Most often, high temperature could be related to reduced dissolved oxygen (Breitburg et al., 2018). In addition, exposure to hypoxia can also cause depression of the immune system in fish such as catfish, leading to increased susceptibility to diseases (Kvamme et al., 2013; Geng et al., 2014).

Much genetic and genomic research has been conducted to identify genes underlining low oxygen tolerance. With catfish, QTL analyses were conducted to localize low oxygen tolerance genes with both intra- and inter-specific systems (Wang et al., 2017c; Zhong et al., 2017). Selection signatures in the domestication processes that involved low oxygen conditions have been identified (Sun et al., 2014). Through RNA-Seq and gene expression studies, Yang et al. (2018) identified a large number of differentially expressed genes under hypoxic conditions in the swim bladder. Several gene pathways were involved in response to low oxygen including HIF signaling pathway, MAPK signaling pathway, PI3K/Akt/mTOR signaling pathway, Ras signaling pathway, and signaling by VEGF in the catfish swim bladder. A common set of genes important to both hypoxia and disease responses were identified, suggesting a common linkage of disease and hypoxia responses, such as claudin gene (Sun et al., 2015), CC chemokines (Fu et al., 2017a; 2017b), and their receptors (Fu et al., 2017c), Bcl-2 (Yuan et al., 2016), as well as hypoxia-specific responses such as hypoxia inducible factors 1 alpha (HIF-1) and hypoxia inducible factor inhibiting factor (FIH-1) (Geng et al., 2014). Similarly, hypoxia tolerance QTL have been identified from tilapia (Li et al., 2017), and in *Pelteobagrus vachelli* (Zhang et al., 2020). HIF-1 was found important for hypoxia in red swamp cray fish (Xu et al., 2022). With bighead catfish, Ma et al. (2021) identified 26 candidate genes involved in air-breathing development and function.

Good progress has been made in understanding of the involvement of DNA methylation in tolerance of hypoxia and anoxia. DNA methylation has regulatory functions in the Pacific oyster (*Crassostrea gigas*), particularly in gene families that have inducible expression, including those involved in the stress and environmental responses (Gavery and Roberts, 2010). Beemelmanns et al. (2021) used a set of biomarker genes for temperature stress (cirbp, serpinh1), oxidative stress (prdx6, ucp2), apoptosis (jund), and metabolism (pdk3), and uncovered distinct CpG methylation profiles under high temperature and low oxygen. With freshwater turtle, Wijenayake and Storey (2016) determined expression of four DNA methyltransferases, DNMT1, DNMT2, DNMT3A, and DNMT3B, and two methyl-binding domain proteins, MBD1 and MBD2, and found upregulated expression of these genes in the liver and white muscles under anoxic submergence of the organism, suggesting increased DNA methylation under hypoxic conditions. With rainbow trout, hypoxia treatment induced expression of BCL2 interacting protein 3 (bnip3) and its related genes. Such induced expression was found to be regulated by DNA methylation (Veron et al., 2018). Similarly, reduced levels of methylation in the promoter regions of STAT3 and VEGFA genes were found to be correlated with their increased expression under hypoxic conditions (Li et al., 2022a).

3.6 Genetic and epigenetic sex determination and regulation of sex differentiation

Teleost fish exhibit a tremendous level of diversity and plasticity in sex determination. Not only genotypes are important for sex determination, in many cases the environment, especially the temperature, can exert its effect on sex determination. Thus, genetic sex determination (GSD) and temperature-dependent sex determination (TSD) may be operating in the same or different species of lower vertebrates.

Extensive research has been conducted with sex determination and differentiation. The first sex determination gene in fish was identified from medaka, where DMY gene, a duplicate gene of DMRT1 on the Y chromosome, was identified as the sex determination gene in medaka fish *Oryzias latipes* (Matsuda et al., 2002). This gene was found as the sex determination gene in closely related medaka species of *O. curvinotus* (Table 3). However, in a different medaka species of *O. luzonensis*, GsdfY, the gonadal soma derived growth factor on the Y chromosome, was found to be the master sex determination gene, suggesting rapid evolution of master sex determination genes among teleost fish (Myosho et al., 2012).

However, new master sex determination genes are generally recruited from genes involved in the downstream of the sex determination regulatory genetic network. These included DMRT1, Gsdf, AMH, Amhr2, and Hsd17b1 (Table 3). The only exception is Sdy, the master sex determination gene in rainbow trout and Atlantic salmon (Yano et al., 2012, 2013). Sdy is a duplicated immune-related gene that became integrated in the classical vertebrate sex differentiation cascade by interacting with the Forkhead box domain of the female-determining transcription factor, Foxl2 (Bertho et al., 2018). In the presence of Foxl2, SdY is translocated to the nucleus where the SdY:Foxl2 complex prevents activation of the aromatase (cyp19a1a) promoter, thereby disrupting the female differentiation pathway, consequently allowing testicular differentiation to proceed (Bertho et al., 2018). In channel catfish, we have identified an epigenetically marked locus

TABLE 3 Sex determination genes in selected fish species.

Species	Sex determination gene	References
Medaka, *Oryzias latipes*, and *O. curvinotus*	DMY (duplicate of DMRT1 on Y chromosome)	Matsuda et al. (2002); Matsuda et al. (2003); Nanda et al. (2002); Zhang, (2004)
Medaka, *O. luzonensis*, Sablefish (*Anoplopoma fimbria*)	GsdfY (Gonadal soma derived growth factor on the Y chromosome)	Myosho et al. (2012) Herpin et al. (2021)
Rainbow trout, Atlantic salmon	Sdy (Sexually dimorphic on the Y-chromosome)	Yano et al. (2012); Yano et al. (2013)
Chinese tongue sole	DMRT1 (Doublesex and mab-3 related transcription factor 1)	Chen et al. (2014)
Nile tilapia	AMH (anti-Müllerian hormone)	Li et al. (2015); Cáceres et al. (2019)
Sebastes rockfish, Northern pike, *Odontesthes hatcheri*	AMH (Male-specific duplication of anti-Müllerian hormone)	Hattori et al. (2012); Pan et al. (2019); Song et al. (2021)
Fugu	Amhr2	Kamiya et al. (2012)
Seriola fishes	Hsd17b1 (17β-hydroxysteroid dehydrogenase 1)	Koyama et al. (2019)
Channel catfish	Epigenetically controlled allelic expression	Yang et al. (2022)

TABLE 4 Sexual dimorphism in patterns of DNA methylation.

Species	Major findings	References
Tilapia	Differential methylation patterns between males and females	Wan et al. (2016)
Threespine stickleback	Hypermethylation of X chromosome compared to Y chromosome	Metzger and Schulte, (2018)
Ussuri Catfish	Differential methylation patterns between males and females	Li et al. (2022b)
Channel catfish	Sex-specific epigenetically marked locus was identified in the sex determination region (SDR)	Yang et al. (2022)
Oyster	Methylomes are related to infertility of triploid oysters	Sun et al. (2022)

within the sex determination region (SDR), where hypermethylation was found on the X chromosomes but hypomethylation was found on the Y chromosome, leading to differential expression of the sex determination gene (Yang et al., 2022). Similarly, with the Siamese fighting fish (*Betta splendens*), genetic sex is determined by an X/Y system with dmrt1 gene as the master sex determination gene, but the expression of the dmrt1 gene on the X chromosome is down-regulated by changes in DNA methylation caused by transposon-induced epigenetic silencing, where a transposon, drbx1, inserted into the fourth intron of the X-linked dmrt1 allele (Wang et al., 2022).

Extensive studies have been conducted with epigenetic regulation of sex determination and/or differentiation. These studies have focused on the following aspects of epigenetic regulation: 1) Sexual dimorphism in DNA methylation patterns; 2) Epigenetic regulation through DNA methylation of key genes involved in the sex determination regulatory genetic network and/or sex differentiation; and 3) Involvement of epigenetic regulation in temperature (or other factors)-induced sex reversal. Sexual dimorphism of methylation patterns was observed with several fish species. Some examples are summarized in Table 4. Detailed examination of the sex differences in methylation patterns differentiates the sexual methylation pattern dimorphism into two categories: 1) The difference is concentrated on sex chromosome, and 2) the differences are general. In this regard, there are many similarities between the situations of three spine stickleback (Metzger and Schulte, 2018) and channel catfish (Wang et al., 2022; Yang et al., 2022), where sex dimorphism in DNA methylation is concentrated on the sex chromosome. In both cases, hypermethylation was observed on the X chromosome and hypomethylation was observed on the Y chromosome. In channel catfish, such differential methylation was observed within the SDR, suggesting the importance of DNA methylation in sex determination and differentiation.

Many studies have focused on the relationship between expression of key genes involved in sex determination regulatory genetic network and DNA methylation. Table 5 shows many examples of such research. In general, key genes for female gonadal differentiation such as cyp19a are differentially expressed and differentially methylated, with higher expression and lower levels of methylation in females than in males. In contrast, key genes for male gonadal differentiation such as dmart1 are differentially expressed and differentially methylated, with higher expression and lower levels of methylation in males than in females. However, in most cases,

TABLE 5 Differential DNA methylation of key genes involved in sex determination and/or differentiation.

Species	Major findings	References
European sea bass	Juvenile males have double the DNA methylation levels of females in the promoter of gonadal aromatase Cyp19a whose methylation is involved in temperature-dependent sex ratio shift	Navarro-Martín et al. (2011)
	Contrasting sex-specific methylation and temperature responses of cyp19a1a and dmrt1 genes	Anastasiadi et al. (2018)
Japanese flounder	High expression of dmrt1 and cyp19a in males and females, respectively, which are negatively correlated with methylation of their promoters	Wen et al. (2014)
Zebrafish	Differential CpG methylated in the brain	Chatterjee et al. (2016)
	Hypomethylation of esr1 promotor and overexpression in females; sex-specific patterns of transcription with dnmt1, dnmt3, and hdac1	Laing et al. (2018)
Nile tilapia	Cyp19a1a is important for high temperature-induced masculinization	Wang et al. (2017b)
	High expression and low methylation of cyp19a	Chen et al. (2018a)
Hermaphrodite barramundi	cyp19a1 and amh were more methylated in males, whereas dmrt1 and nr5a2 were more methylated in females	Domingos et al. (2018)
Chinese sea perch	Hypomethylated cyp19a1a promoter region in females	Chen et al. (2018b)
Culter alburnus	Dmrt1 gene hypomethylated and highly expressed in males	Jia et al. (2019)
Large yellow croaker	Key genes of sex determination are differentially methylated in males, females, and neomales	He et al. (2020a)
Schizothorax kozlovi	High expression and low methylation of dmrt1 in males	He et al. (2020b)
Pelvicachromis pulcher	Sex-specific hypomethylation and expression in females of copy A of cyp19a1 gene	Driscoll et al. (2020)
Orange-spotted grouper	Hypomethylated cyp19a1a promoter region in females	Guo et al. (2021)
Olive flounder	Global methylation was higher in testis than in ovary	Liu et al. (2021)

TABLE 6 Methylation/demethylation of specific genes and their involvement in sex reversal/sex ratio shift.

Species	Major findings	References
Tilapia	Upregulation of CYP11B2 and DMRT1 during high temperature-induced masculinization	Li et al. (2014)
	High temperature induced sex reversal to males is accompanied with higher methylation levels in the gonads	Sun et al. (2016)
Half-smooth tongue sole	Heat induced sex reversal into pseudomales are regulated by DNA methylation of key genes in sex determination pathway, and transgenerational inheritance after heat treatment was observed	Shao et al. (2014)
Zebrafish	Treatment of DNA methyltransferase inhibitor 5-Aza-dC feminizes zebrafish, with permanent alterations of gonadal transcriptome, with increased expression of key genes of female gonadal development	Ribas et al. (2017)
	High temperature induced sex shift toward males of parental families and F1 fish, but not F2 fish. Methylation was lower in F1, but not in P and F2 fish	Valdivieso et al. (2020)
	Sox9b and esr1 are down-regulated in high temperature-induced masculinization	Han et al. (2021b)
Channel catfish	Key genes for female gonadal development and male gonadal development were upregulated, and down-regulated, respectively, during hormone-induced feminization, but the methylation patterns were complex. These are independent from the sex determination region. High temperature induces sex reversal to females	Wang et al. (2022) Zhou et al., unpublished data

only the promoter regions were under investigation, and the definition of the promoter vary among studies. In addition, the correlation is generally not linear. The traditional notion that DNA methylation suppress gene expression may have its limitations (see Section 2.4). Whatever the detailed mechanisms are, the ultimate difference it makes is the difference in gene expression, which is the core of the central dogma of molecular biology, but the key modification here is at the level of DNA methylation, i.e., epigenetic regulation, rather than being coded in DNA sequences.

From the studies conducted to date (with some examples shown in Table 6), it is apparent that DNA methylation is involved in the temperature-dependent sex determination. However, high temperature apparently had opposite sex ratio shift with different species. In zebrafish, tilapia, and half-smooth tongue sole, high temperature induced masculinization, while

TABLE 7 Patterns of histone modification and regulation of gene expression.

Histone modification	Effect on gene expression	References
H3K4me3	Active promoters	Zhang et al. (2016)
H3K9me3	Gene repression and heterochromatin formation	Bannister et al. (2001)
H3K27me3	Gene repression	Zhang et al. (2015)
H3K36me3	Active genes	Oqani et al. (2019)
H3K79me3	Active transcription	Ooga et al. (2008)
H4K20 me1	Repressive hallmark	Sato et al. (2016)
H3K27ac	Active gene enhancers, often co-exist with H3K4me3	Kang et al. (2021)

high temperature induced feminization in channel catfish. These systems, therefore, provide a great comparative platform to determine the relationship of high temperature, DNA methylation, gene expression and phenotypic sex differentiation.

4 Histone modifications and their regulation of genome expression

There are numerous types of histone modifications, but several types of histone modifications are better understood as to how they are related to genome expression. These include histone methylation, acetylation and phosphorylation (Zhang et al., 2021). Histone methylation, usually at the lysine (K) residues of histone H3 and H4, are best understood in their roles for regulation of gene expression. The methylation is catalyzed by histone methyltransferase, which uses S-adenosyl methionine as the substrate to transfer methyl groups onto the lysine residues of histones. The lysine residues of histones can be mono-, di-, and tri-methylated to act as the active or repressive marks of gene expression. Gene activation has been correlated with H3K4, H3K36, and H3K79 methylation, while H3K9, H3K27, and H4K20 are known as repressive marks that are usually associated with the silenced gene expression and heterochromatin (Zhang et al., 2021). It is important to note that multiple histone modifications may occur, and they collectively affect genome expression. Table 7 summarizes the general pattern of histone modifications and their correlated gene expression.

Histone modifications can be most efficiently studied by chromatin immunoprecipitation with high-throughput sequencing (ChIP-Seq). ChIP-Seq is a powerful technology to locate regulatory elements, as indicated by association of histone modifications such as H3K4me3 with actively transcribed gene promoters, and H3K27ac with enhancers. It is also very useful to locate sites involved in gene silencing, as indicated by association of some histone modifications with repression of gene expression such as H3K9me3 and H3K27me3 (Table 7). ChIP-Seq has been well demonstrated with human and mouse research with over a dozen different histone modifications being assayed, but less so with agricultural animals. However, as histone proteins are so highly conserved, the antibodies for mammalian species should, for the most part, work for various fish species.

Among teleost fish, ChIP-Seq has been primarily conducted in model systems. For example, Zhu et al. (2019) studied histone modification patterns with H3K4m3 and H3K27me3 early during development. In zebrafish, ChIP-Seq after infection of spring viremia of carp virus (SVCV) allowed identification of key immune genes of interferon signalling pathway and c-reactive protein genes, and demonstrated the importance of epigenetic modifications in response to viral infections (Medina-Gali et al., 2018). As a proof of concept, ChIP-Seq was conducted with tilapia (Kratochwil and Meyer, 2015). With common carp, increased H4K12ac was found to be associated with aging oocytes (Waghmare et al., 2021).

5 Intergenerational and transgenerational epigenetic inheritance

One of the most interesting questions is if the environmentally induced epigenetic changes and their regulated gene expression are inherited. For this discussion, we would like to differentiate intergenerational and transgenerational epigenetic inheritance. Intergenerational epigenetic inheritance refers to inheritance of epigenetic marks and/or their related phenotypes from one generation (F_0) to the next (F_1), while transgenerational epigenetic inheritance refers to the passage of information from grandparents to grandchild (F_2) or later generations if paternal grandparent was exposed or F_3 if maternal grandparent was exposed (Skinner and Guerrero-Bosagna, 2009; Lacal and Ventura, 2018).

Like the situation with mammalian species, where intergenerational epigenetic inheritance is not uncommon, but transgenerational epigenetic inheritance has not been fully demonstrated (For a review, see Cavalli and Heard, 2019), most studies with aquatic species have clearly supported

TABLE 8 Examples of studies of intergenerational and transgenerational epigenetic inheritance.

Species	Treatment	Epigenetic marks or phenotypic analysis		References
Half-smooth tongue sole	High temperature induced sex reversal to pseudomales	Pseudomales produced F_1 pseudomales without temperature treatment	Intergenerational	Shao et al. (2014)
Zebrafish	Crude oil containing diet	Global methylation of F_1 was decreased as exposed parents	Intergenerational	Bautista et al. (2020)
Atlantic salmon	Captivity	Differential methylation in F1 with exposed parents	Intergenerational	Wellband et al. (2021)
Pipefish	Heat-killed bacteria	Expression of genes involved in DNA methylation	Intergenerational and transgenerational	Beemelmanns and Roth, (2017)
Zebrafish	benzo[a]pyrene exposure of F0 fish	F2 fish exhibited altered phenotypes	Transgenerational	Knecht et al. (2017)
Zebrafish	Mercury exposure of F_0	F_2 fish exhibited altered phenotypes	Transgenerational	Carvan et al. (2017)
Zebrafish	Permethrin exposure of F_0	F_2 fish exhibited altered phenotypes	Transgenerational	
Zebrafish	F_0 exposure to mono(2-ethylhexyl) phthalate and 5-azacytidine	Differential methylation in F_1 and F_2	Intergenerational and transgenerational	Kamstra et al. (2017)
Medaka	F_0 exposure to bisphenol A and 17α-ethinylestradiol	Changed gene expression in F_2	Transgenerational	Thayil et al. (2020)
Atlantic molly	Exposure of F_0 fish to hydrogen sulfide	80% overlap of epigenetic profiles of F_2 of treated F_0 fish	Transgenerational	Kelley et al. (2021)
Artemia franciscana	Phloroglucinol Treatment	Elevated methylation was observed in F_1, and in cysts in F_2 but not in F_2 nor F_3 of juveniles	Intergenerational and perhaps Transgenerational	Roy et al. (2019)
	Vibrio challenge or injection	Treated progenies had transgenerational immune memory		Roy et al. (2022)
Daphnia magna	Zinc exposure	Significant reduction of cytosine methylation in F_1 but not in F_2	Intergenerational	Vandegehuchte et al. (2009); Vandegehuchte et al. (2010a)
Daphnia magna	Exposure to 5-azacytidine		Transgenerational	Vandegehuchte et al. (2010b)
Daphnia magna	Chronic external γ-irradiation	Changes of DNA methylation were observed in F_2 and F_3 animals, but not very specific	Transgenerational	Trijau et al. (2018)
Daphnia magna	High salinity	Differential methylation of a set of specific genes were observed in exposed F0 and unexposed F_1, F_2, and F_3 animals	Transgenerational	Jeremias et al. (2018)

intergenerational epigenetic inheritance. For example, with Atlantic salmon, captive rearing of adult caused intergenerational differential methylation in F1 (Wellband et al., 2021). However, it is not concretely solid with transgenerational epigenetic inheritance. Some examples of intergenerational and transgenerational epigenetic studies are provided in Table 8. Most of these studies were conducted with model species zebrafish, or microcrustacean *Daphnia* or *Artemia* species.

As shown in Table 8, most of these studies were conducted for just two generations, and in some cases for three generations. In addition, in many of these cases, the measurements were general performance traits, rather than specific molecular patterns. Even when DNA methylation was determined, demonstration of transgenerational epigenetic inheritance with specific patterns of DNA methylation is very limited. Perhaps a best example is from a recent study with Atlantic molly (*Poecilia mexicana*), where the epigenetic alterations under hydrogen sulfide are inherited to laboratory-reared, non-exposed F2 fish (Kelley et al., 2021). When epigenetic changes in response to hydrogen sulfide were examined in red blood cells, there was over 80% overlap in differentially methylated regions (DMRs) across generations, suggesting that DMRs have stable generational inheritance in the absence of the sulfidic environment.

With *D. magna*, treatment with 5-azacytidine reduced the level of DNA methylation, and such reduced level of methylation was stably transferred to two subsequent non-exposed generations (Vandegehuchte et al., 2010a). A reduced level of methylation was observed after exposure to zinc, and such patterns of reduced methylation and correlated gene expression was observed in F_1 animals, but not in F_2 animals (Vandegehuchte et al., 2010b), suggesting intergenerational epigenetic inheritance. γ-irradiation-induced DNA methylation patterns were found to be inheritable, as common methylation patterns were observed from unexposed F_2 and F_3 individuals, but specific patterns of methylation were not reported (Trijau et al., 2018). High levels of salinity led to hypomethylation of treated F_0 animals, and such

hypomethylation was transgenerationally inherited to three consequent nonexposed generations (F_1, F_2, and F_3) (Jeremias et al., 2018).

With brine shrimp (*Artemia franciscana*), phloroglucinol treatment significantly enhanced the expression of a core set of innate immune genes and resistance against bacterial infections of *Vibrio parahaemolyticus* and *V. harveyi*. Such enhanced resistance was observed in their progeny in three subsequent generations (Roy et al., 2019, 2022). In a separate study, Norouzitallab et al. (2014) exposed *Artemia* to nonlethal heat shocks, which increased the expression of Hsp70. The treated *Artemia* exhibited increased levels of tolerance for lethal heat stress, and resistance against pathogenic *Vibrio campbellii*. These acquired phenotypic traits were transmitted to three successive generations, none of which were exposed to the parental stressor. This transgenerational inheritance of the acquired traits was associated with altered levels of global DNA methylation and acetylated histones H3 and H4 in the heat-shocked group compared to the control group, where both the parental and successive generations were reared at standard temperature. These results indicated that epigenetic mechanisms, such as global DNA methylation and histones H3 and H4 acetylation, have particular dynamics that are crucial in the heritability of the acquired adaptive phenotypic traits across generations.

6 Future perspectives

Although the current literature of epigenetic regulation of aquaculture traits is limited, it is apparent that epigenetic regulation is involved in most, if not all, traits important for aquaculture. This is because ultimately what is important is the qualitative and quantitative expression of genes; and DNA methylation regulates both. This importance is reflected in normal processes of the life cycle, and in response to the ever-changing environment. Under normal conditions, aquaculture organisms are composed of various tissues, with nearly all of them having identical genomic sequences, and yet they can maintain their respective functions over the lifetime of the organism. This challenge is met mostly through epigenetic regulation including chromatin accessibility, DNA and histone modifications, activity of RNA, and protein factors interacting with the genome (Nakamura et al., 2021). In terms of development and differentiation, much needs to be learned from aquaculture species because finfish and reptiles are lower vertebrates where many of the developmental processes are conserved with those reported from higher vertebrates, but they show greater levels of plasticity that can well be epigenetically regulated. Therefore, much can be learned from studies with aquaculture species.

Although DNA methylation is perhaps the most studied of epigenetic regulation of aquaculture performance and production traits, the exact mechanisms of epigenetic regulation requires great attention. The studies of histone modifications and their relations with aquaculture performance and production traits are so limited to date, but this apparently demands research efforts, especially in understanding of transcriptional activation and inactivation. Finally, the regulation by ncRNAs is extremely important and likely is involved in expression of aquaculture performance and production traits; although this review intentionally left this out because systematic knowledge of epigenetic regulation of aquaculture traits is very limited at this time, but the importance of research in these areas cannot be overstated.

In addition to understanding epigenetic regulation, precise epigenome editing technologies have become available (for reviews, see Laufer and Singh, 2015; Goell and Hilton, 2021; Nakamura et al., 2021). Applications of epigenome editing technologies will deepen our understanding of epigenetic regulation from the level of correlation to the level of establishing causal effect relationships between epigenome modifications and performance traits. More directly, epigenome editing will also allow "engineering" of desired traits, based on information of epigenetic regulation.

Author contributions

ZL wrote the manuscript, DG and TZ reviewed and revised the manuscript, prepared the tables and references.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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