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Epigenetics in teleost fish: From molecular mechanisms to physiological phenotypes

Carol Best[a], Heather Ikert[b], Daniel J. Kostyniuk[a], Paul M. Craig[b], Laia Navarro-Martin[c], Lucie Marandel[d], Jan A. Mennigen[a,*]

[a] Department of Biology, University of Ottawa, 20 Marie Curie Private, Ottawa, Ontario K1N 6N5, Canada
[b] Department of Biology, University of Waterloo, 200 University Avenue W, Waterloo, Ontario N2L 3G1, Canada
[c] Department of Environmental Chemistry, IDAEA-CSIC, Jordi Girona 18-26, 08034 Barcelona, Spain
[d] INRA, Université de Pau et des pays de l'Adour, UMR1419 Nutrition Metabolism and Aquaculture, Aquapôle, F-64310 Saint-Pée-sur-Nivelle, France

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ABSTRACT

While the field of epigenetics is increasingly recognized to contribute to the emergence of phenotypes in mammalian research models across different developmental and generational timescales, the comparative biology of epigenetics in the large and physiologically diverse vertebrate infraclass of teleost fish remains comparatively understudied. The cypriniform zebrafish and the salmoniform rainbow trout and Atlantic salmon represent two especially important teleost orders, because they offer the unique possibility to comparatively investigate the role of epigenetic regulation in 3R and 4R duplicated genomes. In addition to their sequenced genomes, these teleost species are well-characterized model species for development and physiology, and therefore allow for an investigation of the role of epigenetic modifications in the emergence of physiological phenotypes during an organism's lifespan and in subsequent generations. This review aims firstly to describe the evolution of the repertoire of genes involved in key molecular epigenetic pathways including histone modifications, DNA methylation and microRNAs in zebrafish, rainbow trout, and Atlantic salmon, and secondly, to discuss recent advances in research highlighting a role for molecular epigenetics in shaping physiological phenotypes in these and other teleost models. Finally, by discussing themes and current limitations of the emerging field of teleost epigenetics from both theoretical and technical points of view, we will highlight future research needs and discuss how epigenetics will not only help address basic research questions in comparative teleost physiology, but also inform translational research including aquaculture, aquatic toxicology, and human disease.

1. Epigenetics and teleost research models

In recent years, the field of epigenetics has received increasing attention, which has resulted in a series of papers aiming to provide historical context for its development (Haig, 2004; Deans and Maggert, 2015) in an effort to define clear working definitions for this dynamic research field (Bird, 2007; Berger et al., 2009; Dupont et al., 2009). Because of the historical utilization of the term epigenetics in different research contexts on the one hand, and the rapid development of molecular epigenetics on the other, agreement on a synthetic, clear-cut definition has proven challenging. While we acknowledge different viewpoints, we will, for the scope of this review, employ an integrative working definition of epigenetics, which firstly emphasizes the link between genes, their products and the temporal emergence of the phenotype. This directly reflects the initial definition of epigenetics by Waddington (1968) as 'the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being'. Since the initial focus on development and phenotype, the investigation of epigenetics has increasingly shifted to molecular mechanisms, which entail factors regulating 'heritable changes in gene expression without changes in the DNA sequence' (Riggs et al., 1996), which we include as a second definition.

Together, we therefore define epigenetics as the study of factors that heritably regulate the spatio-temporal genome expression that underlies the emergence of physiological phenotypes. Under this definition, epigenetic regulation at the molecular level is mediated by three principal mechanisms, all of which can heritably alter gene expression without a change in the DNA sequence. Two of these mechanisms, histone modifications and DNA methylation, regulate gene expression at the levels of chromatin structure and DNA, while microRNAs

* Corresponding author.
E-mail address: jan.mennigen@uottawa.ca (J.A. Mennigen).

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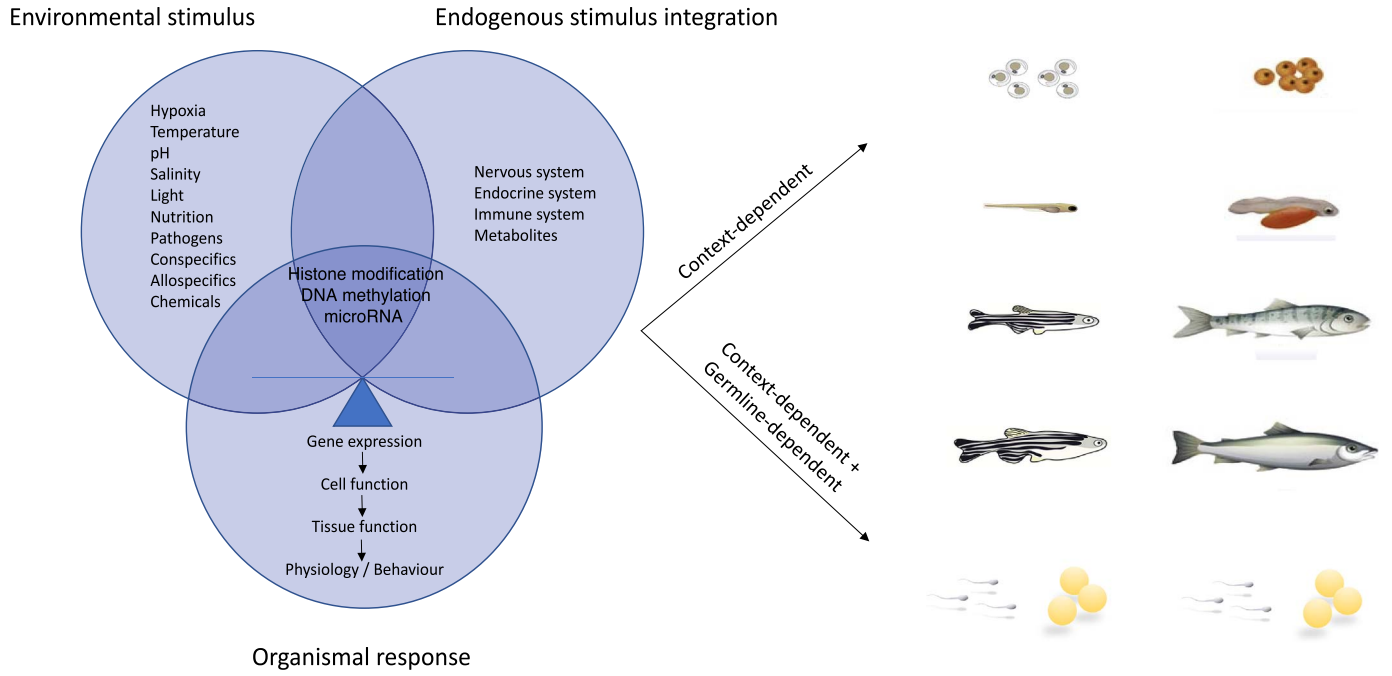

Fig. 1. Conceptual framework of the epigenetic regulation in teleost fish. Environmental (exogenous) and endogenous stimuli are integrated by molecular epigenetic mechanisms to regulate genomic gene expression, which shapes physiological phenotypes at higher levels of biological organization. Such regulation can occur across ontogenesis and result in the emergence of physiological phenotypes within a teleost's lifespan (context-dependent epigenetics) and be transmitted between generations (germline-dependent epigenetics).

(miRNAs), a type of small non-coding RNA, constitute a post-transcriptional mechanism regulating abundance and translation of specific mRNAs. Together, these epigenetic mechanisms can be affected by environmental and/or endogenous signals to regulate genome-wide gene expression, leading to the emergence of physiological phenotypes at higher levels of biological organization (Fig. 1). These processes can be spatially restricted to specific tissues or cell types and can occur across different temporal scales, which encompass both ontogenesis and the lifespan of an individual organism (termed context-dependent or intragenerational epigenetics) as well as generations (termed germline-dependent or transgenerational epigenetics), as distinguished by Burggren and Crews (2014). Briefly, intragenerational epigenetics encompass the emergence of physiological phenotypes in response to environmental and/or endogenous stimuli directly experienced by an organism during its life. These stimuli can introduce specific epigenetic marks in somatic cells, which may be mitotically transmitted and lead to temporal and spatial changes in expression of the organism's genome, which in turn can introduce physiological plasticity (Burggren, 2014). As the organism is directly exposed to the stimulus during its life cycle, this is also termed context-dependent epigenetics. Conversely, transgenerational epigenetics are based on epigenetic changes in the germline ('germline-dependent epigenetics'), which are meiotically stable and hereditary. Such changes may overtly manifest themselves phenotypically in subsequent generations never directly exposed to the initial stimulus or may be masked and emerge only in response to additional context-dependent stimuli experienced by the offspring. Indeed, recent publications reconsidered this phenomenon in the context of the Lamarckian theory of inheritance, which had historically long been neglected in favor of a genocentric view (Burggren, 2014). In this context, it is important to distinguish intergenerational from transgenerational inheritance, which differs conceptually between teleost fish and currently more widely studied mammalian models (Fig. 2). In pregnant female mammals, subsequent generations are still directly exposed to exogenous or endogenous stimuli as embryo (future F_1 generation) or embryonic germ-cells (contributor to future F_2 generation) within the founder generation (F_0). Therefore, transgenerational effects in female mammals will be evident only from the F_3 onwards,

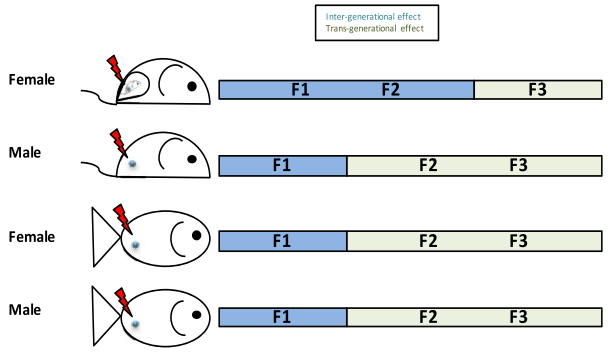

Fig. 2. Comparative definition of inter- and transgenerational epigenetics between traditional mammalian model systems and oviparous teleost fish. In therian mammals, sex differences exist with regard to transgenerational effects mediated by germ-line dependent epigenetics, since in pregnant females, stimuli act *via* context-dependent epigenetics on the dam (F_0), as well as on the fetus (F_1) and its primordial germ cells (F_3). Conversely, stimuli acting on sires affect F_0 and the gamete, which will give rise to F_1 offspring. In oviparous teleost fish, fertilization of the egg occurs externally, which limits context-dependent epigenetic regulation to the F_1 generation, while the F_2 generation of either sex is considered transgenerational or affected by germ-line dependent epigenetic regulation.

after which they may persist or 'wash-out' gradually over subsequent generations. With regard to male mammals, only direct offspring (F_1) are considered intergenerational because of context-dependent exposure of sperm in F_0 founders. In oviparous teleost fish, irrespective of sex, only the F_1 generation is considered intergenerational, while both F_2 and F_3 generations are considered transgenerational (Fig. 2). Semantics aside, oviparous teleosts will likely prove advantageous for transgenerational epigenetics, compared to mammals, as the study of maternal effects is much more feasible especially when investigating oocyte contributions. This is because unfertilized viable eggs are easily obtained to study molecular mechanisms, can be externally fertilized, and are amenable to genetic and pharmacological manipulation *via* microinjection, providing an avenue for mechanistic studies investigating maternal-lineage specific epigenetic effects.