Fish skin pigmentation in aquaculture: the influence of rearing conditions and its neuroendocrine regulation

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1 **Abstract**

2 Skin pigmentation pattern is a species-specific characteristic that depends on the
3 number and the spatial combination of several types of chromatophores. This feature
4 can change during life, for example in the metamorphosis or reproductive cycle, or as a
5 response to biotic and/or abiotic environmental cues (nutrition, UV incidence,
6 surrounding luminosity, and social interactions). Fish skin pigmentation is one of the
7 most important quality criteria dictating the market value of both aquaculture and
8 ornamental species because it serves as an external signal to infer its welfare and the
9 culture conditions used. For that reason, several studies have been conducted aiming to
10 understand the mechanisms underlying fish pigmentation as well as the influence
11 exerted by rearing conditions. In this context, the present review focuses on the current
12 knowledge on endocrine regulation of fish pigmentation as well as on the aquaculture
13 conditions affecting skin coloration. Available information on Iberoamerican fish
14 species cultured is presented.

15

16 **Keywords:** Fish pigmentation; Chromatophore; Hormones; Aquaculture

17

1 Introduction

Aquaculture contributes significantly to global seafood supply, accounting for 46% of the total production in 2018, and has had the fastest growth rate among major food production sectors for several decades (FAO, 2020a). Today, aquaculture plays an important role in income generation and food and nutrition security, particularly in developing countries (Belton et al., 2018), and promotes local biodiversity and the preservation of cultural traditions. Fish skin pigmentation is one of the most important quality criteria dictating the market value of fish for human consumption and ornamental use (Harpaz and Padowicz, 2007). For instance, colors in food are linked to anticipated quality and are cues that allow consumers to make judgements about desirability (Bjerkeng, 2008). However, aquaculture conditions can negatively affect the natural skin coloration of fish (Lim et al., 2018), thus hampering successful commercialization. Indeed, skin pigmentation in fish is regulated by both external (biotic and abiotic) and internal (genetic, cellular, nervous, and hormonal) factors (Pittman et al., 2013). For that reason, several studies have been conducted aiming to understand the mechanisms underlying fish pigmentation as well as the influence exerted by rearing conditions.

Aquaculture in Iberoamerica (IA), the Spanish- and Portuguese-speaking nations of the Americas and Europe, represents 3.05% of the world's global production with nearly 3.5 million tons produced in 2018 (FAO, 2020b), and several studies have addressed skin pigmentation in fish species cultivated in these countries. Reared flatfish species (Pleuronectiformes), which are known for their asymmetric pigmentation and their ability to adapt to background color changes by adjusting their ocular-side pigmentation

(Inui and Miwa, 2012), frequently present pigmentation anomalies, such as albinism and ambicoloration. Research on pigmentation has been conducted on flatfish species that either are cultivated or have been identified as candidate species for aquaculture diversification in IA, such as turbot, *Scophthalmus maximus* (also known as *Psetta maxima*; e.g., Reitan et al., 1994; Estévez and Kanazawa, 1995; Estévez et al., 1999), Senegalese sole, *Solea senegalensis* (e.g., Villalta et al., 2005; Darias et al., 2013a; Boglino et al., 2014), common sole, *Solea solea* (Lund et al., 2008, 2010), California halibut, *Paralichthys californicus* (Vizcaíno-Ochoa et al., 2010), *Paralichthys adspersus* (Orihuela et al., 2018), *Paralichthys orbignyanus* (López et al., 2009; Vieira Rodrigues et al., 2012) or *Paralichthys woolmani* (Benetti, 1997; Bohórquez-Cruz et al., 2018). Further studies have dealt with other fish species cultivated in IA, such as salmonids (Colihueque, 2010), red porgy, *Pagrus pagrus* (e.g., Kalinowski et al., 2007; Tejera et al., 2010), gilthead sea bream, *Sparus aurata* (e.g., Gouveia et al., 2002; Ribeiro et al., 2017), Nile tilapia, *Oreochromis niloticus* (Ponce-Palafox et al., 2004; Valente et al., 2016) or ornamental species like *Hyphessobrycon eques* (Berchielli-Morais et al., 2016), which require dietary carotenoid supplementation in order to maintain their natural skin coloration (Bjerkeng, 2008). Besides, the influence of rearing conditions such as tank color, light intensity or social interactions on skin pigmentation has been studied in other IA fish species, such as *Lophiosilurus alexandri* (Costa et al., 2017, Santos et al., 2019), *Paralichthys woolmani* (Benetti, 1997; Venizelos and Benetti, 1999; Han et al., 2005), Neon tetra, *Paracheirodo ninnesi* (Kasai and Oshima, 2006) or *Cichlasoma dimerus* (Alonso et al., 2011; Cánepa et al., 2006, 2012, Delgadin et al., 2020).

In this context, the present review focuses on the current knowledge on endocrine regulation of fish pigmentation as well as on the aquaculture conditions affecting skin coloration. Available information on species cultured in IA is presented.

2 An overview on fish skin pigmentation

Skin pigmentation pattern is a species-specific characteristic that depends on the number and spatial combination of several types of chromatophores included in the epidermis and in the dermis (Aspengren et al., 2012; Darias et al., 2013a). Compared to other vertebrates, it has been suggested that this great variety of pigmentation patterns in fish is due to the fish-specific genome duplication which gave rise to about 30% more pigmentation-related genes (Braasch et al. 2008; reviewed in Pittman et al., 2013). Furthermore, the skin pigmentation pattern can change during life time, for example, during metamorphosis or the reproductive cycle, or as a response to biotic and/or abiotic environmental cues (nutrition, UV incidence, surrounding luminosity, and social interactions) (Price et al., 2008; Leclercq et al., 2010; Darias et al., 2013a, b; Parichy and Spiewak, 2015). Studies performed in flatfish species have shown that there is a sensitive period during pre- and pro-metamorphosis, named pigmentation window, in which different external factors can disrupt the normal development of pigmentation (Darias et al., 2013a, b; Pittman et al., 2013).

In vertebrates, chromatophores cells derive from one of the most fascinating cells of vertebrate development biology: the neural crest cells (NCC). These cells arise from a region between the border of the neural plate and the non-neural ectoderm and, after undergoing an epithelial-to-mesenchymal transition, they migrate throughout the embryo, colonizing different tissues and organs where they settle and differentiate (Bronner and LeDouarin, 2012; Theveneau and Mayor, 2012). It has been proposed that

all chromatophores are generated from a common chromatoblast (Bagnara et al., 1979) through progressive fate-restriction processes (Le Douarin and Dupin, 2003; Dupin et al., 2007; Kimura et al., 2014). Different chromatophores have been described in fish, classified into light-absorbing chromatophores (melanophores, erythrophores, xanthophores, and cyanophores) and light-reflecting chromatophores (leucophores and iridophores) (Fujii, 2000; Sugimoto, 2002). While melanophores, iridophores, and xanthophores are widely distributed in teleosts (Schartl et al., 2016), leucophores are less abundant (Menter et al., 1979; Iga and Matsuno, 1992; Nagao et al., 2018). In addition, two cell types of melanophores and xanthophores, differing in size and sequentially appearing during development, have been described in Japanese flounder, *Paralichthys olivaceus*, and Senegalese sole (Seikai et al., 1987; Nakamura et al., 2010; Darias et al., 2013a). These two different cell types have been identified as larval and adult melanophores and xanthophores in Japanese flounder (Seikai et al., 1987; Nakamura et al., 2010), whereas in the case of Senegalese sole melanophores, the two cell types rather correspond to different morphological stages of newly differentiated and melanized melanophores at post-metamorphosis (Darias et al., 2013a).

Melanophores are the most common and studied chromatophores and are responsible for the dorsal pigmentation in vertebrates (Aspengren et al., 2012). Melanophores are dendritic shaped cells that extend their projections, containing the pigmented organelles (melanosomes), almost parallel to the plane of the skin (Fujii, 2000; Nüsslein-Volhard and Singh, 2017). In teleosts' skin, melanophores are mostly found in the dermis, although they can also be observed in the epidermis (Fujii, 2000).

3 How does skin color change in fish?

3.1 Cellular mechanisms

Skin color can vary through two different mechanisms. On the one hand, the physiological color changes, which are rapid and transient, are produced by the motility of pigment vesicles (chromatosomes) or by the movement of reflective structures within their cells. On the other hand, the morphological color changes, which occur within days and/or weeks, involve variations in skin pigment concentration or the density and distribution of chromatophores in the integument (Leclercq et al., 2010).

The translocation of chromatosomes, which are characteristic of physiological color changes, is coordinated by the microtubule and actin filament architecture of the cytoskeleton and the associated motor proteins. When light-absorbing chromatophores receive an input (such as hormones, neurotransmitters or environmental cues) that produces the aggregation or dispersion of chromatosomes, the specific molecular motor hauls pigment granules back toward the nucleus or to the cell periphery (Ligon and McCartney, 2016). In general, decreases in cAMP levels and/or increases in Ca^{2+} levels within chromatophores trigger aggregation responses, while the opposite changes in cAMP or Ca^{2+} levels induce dispersion responses (reviewed in Fujii, 2000). Regarding iridophores, which contain thin reflecting platelets in their cytoplasm, under certain inputs they simultaneously change the distance between adjoining platelets, leading to a shift in the spectral reflectance of the skin (Kasukawa et al., 1986).

Chromatophores density variation implies both differentiation and apoptosis processes. It is believed that the number of melanophores increases through precursor cell differentiation rather than the division of already differentiated melanophores (Sugimoto et al., 2002). There is evidence that these precursors are neural crest-derived stem cells that have been set aside in distinct niches, such as the ganglia of the

peripheral nervous system, the base of the fins, or in deep layers of the dermis, which migrate and differentiate into adult-type pigment cells under specific stimuli (reviewed in Sugimoto et al., 2002; Yamada et al., 2010; Darias et al., 2013a; Frohnhöfer et al., 2013). This differentiation implies the molecular action of the chromatophore-differentiating genes that are also implicated in the regulation of skin pigment concentration. In particular, microphthalmia-associated transcription factor (*mitf*) is considered the master regulator of melanophore development and controls expression of genes required for melanophore development, including dopachrome tautomerase (*dct*), tyrosinase (*tyr*), tyrosinase related peptides (*trp 1* and *2*) and the receptor tyrosine kinase (*c-kit*) (Steingrímsson et al., 2004, Darias et al., 2013a, Nagao et al, 2018). Furthermore, the sodium/potassium/calcium exchanger 5 (*slc24a5*) is crucial for proper melanin synthesis. The paired box protein 3 (*pax3*) can promote or inhibit melanogenesis through transcriptional regulation of *mitf* and *cKit*, the latter being necessary for melanophore differentiation and responsible for the activation of *tyr*. Besides, *pax3* can also modulate the expression of *trp1* and *trp2* (see model in Darias et al., 2013a). Although the molecular mechanisms of fish melanophore differentiation have been well characterized, those of the other chromatophores have remained largely unknown (Otsuki et al., 2020). It was demonstrated that Sry-box transcription factor 5 (Sox5) acts antagonistically against Sox10 in the specification of zebrafish chromatophores and in melanophore and iridophore lineages in medaka. However, in this last species, xanthophores and leucophores developed from a shared progenitor Pax7a positive. This progenitor differentiates in xanthophore or leucophore depending on Sox5/Sox10. While Sox5/10 promotes xanthophore specification, it represses leucophore formation (Kimura et al., 2014; Nagao et al., 2018).

The decrease in chromatophore number occurs by apoptosis stimulated by specific factors (Sugimoto et al., 2002; Sköld et al., 2016). Interestingly, xanthophores can eliminate the surrounding melanophores, and vice versa, in zebrafish (Nakamasu et al., 2009), and similarly, xanthophores in the skin of Senegalese sole pseudo-albinos seemed to be responsible for the degeneration of melanophores (Darias et al., 2013b). Besides, variation in melanophore morphology, which mainly implies variation in dendritic process elongation, has been described as another type of morphological color change (reviewed in Sugimoto et al., 2002).

Since morphological color changes are preceded by physiological color changes, similar control mechanisms have been proposed to function both in the motile responses and in the chromatophore densities (reviewed in Sugimoto, 2002).

3.2 Hormone regulators

Unlike other vertebrate taxa, it is generally accepted that teleost fish present a dual-hormonal mechanism for skin color regulation (reviewed in Bertolesi et al., 2019). Two hormones with opposite effects, skin lightening and darkening, have been proposed as the main morphological and physiological color change regulators: the melanin-concentrating hormone (Mch) and the melanophore-stimulating hormone (Msh), derived from precursor Proopiomelanocortin. However, skin color regulation is more complex, and other regulatory factors have been identified in studies performed on the regulation over other chromatophores cells. Table 1 summarizes this complex scenario with the old and new actors involved in skin color regulation in fish. In addition, figure 1 shows the endocrine and nervous effect over the different chromatophores. In this figure, the lack of studies on the regulation of some pigmentary cells is reflected. More

studies will help to improve the understanding of pigment disorders in aquaculture species.

3.3 Nervous control

Rapid chromatosome aggregation is mainly controlled by the sympathetic postganglionic system. Chromatic information is captured by the eyes, processed in the optic tectum and partly at the level of the motoneurons in the medulla, and sent to chromatophores via direct nervous connections (Grove, 1994; reviewed in Fujii, 2000). Since Fujii and Oshima (1994), Fujii (2000) and Sköld et al. (2016) have reviewed this issue in depth, we will only point out some aspects of this regulation that are relevant for the following sections. It has been proposed that there is a constant rate of firing of noradrenaline (NA) from nerve terminals that increases or decreases depending on different stimuli (Fujii and Oshima, 1994). Other studies have demonstrated that ATP is released as a co-transmitter together with NA (true-transmitter) and that, in the synaptic cleft, it is dephosphorylated to adenosine, which survives longer and reverses NA action, causing re-dispersion of pigment after the cessation of the stimulus (Fujii and Oshima, 1994).

Noradrenaline interacts with α - and β -adrenoreceptors, with α_2 -adrenoreceptor subtype being more effective than α_1 -adrenoreceptor in producing pigment aggregation, while β_2 -adrenoreceptor subtype induces pigment dispersion. Concerning NA effects over chromatosomes, its release induces aggregation of these vesicles in melanophores, xanthophores and erythrophores, but disperses the light-scattering organelles in leucophores, and also produces a change in the arrangement of reflecting platelets in iridophores (Fujii and Oshima, 1994; reviewed in Fujii 2000; Sköld et al., 2016).

Besides this action, Sugimoto (2000) observed that NA induces melanophore apoptosis in medaka skin culture, and that denervation decreases melanophore density in this species (Sugimoto, 1993) (Figure 1).

4 Influence of rearing conditions on skin pigmentation

Rearing conditions, such as environment and feeding, which are very different from those of natural habitats, influence fish physiology and behavior (Eslamloo et al., 2015). Especially in intensive farming, fish are exposed to grading, handling, transportation, stocking densities, diseases, vaccination, food withdrawal or aggression, among other, that affect welfare and can lead to acute or chronic stress (Sneddon et al., 2016). In this sense, besides nutrition—which is a source of pigments for several species and plays an essential role in morphogenesis during early development (Bjerkeng, 2008; Rønnestad et al., 2013)—, stress can trigger skin pigmentation changes. During an acute stress response, higher amounts of catecholamines (CA), i.e., adrenaline, noradrenaline, and dopamine, are released from the chromaffin cells of the head kidney and thus, increase in the bloodstream (reviewed in Wendelaar Bonga, 1997). As chromatophores express CA receptors, this increase directly impacts fish coloration, generally inducing skin paling (Figure 1). If the stressful stimulus continues, the chronic stress response begins with the activation of the hypothalamus-pituitary-interrenal axis. Thus, corticotropin-releasing hormone (Crh) and thyrotrophin-releasing hormone (Trh) produce an increase in adrenocorticotrophic hormone (Acth) and α -Msh secretion, which in turn stimulates cortisol release causing skin darkening or paling depending on the species. Cortisol can also exert a negative feedback on α -Msh and the interrenal cells, in addition to a downregulation of certain CA receptors, such as adrenergic receptors (Wendelaar

Bonga, 1997). Furthermore, stressor-induced cortisol production has been associated with disruption of the gut microbiome in fish (Uren Webster et al., 2020). Considering the major role of the gut microbiome in the regulation of the physiology of the organism, including the modulation of neuronal and endocrine pathways (Lerner et al., 2017), and the recent association found between the pseudo-albino phenotype and gut microbiome modification in Senegalese sole (Pinto et al., 2019), deeper research towards deciphering the molecular mechanisms and cellular processes of skin pigmentation regulated by the gut microbiome and their link with other biological processes will undoubtedly shed light into better understanding the intricate and interlocked processes of physiological regulation in fish.

Finally, as more than one stressor can be present at the same time, different effects on skin pigmentation can be observed depending on the hormonal response to each stimulus

4.1 Nutrition

The influence of nutrition in fish skin pigmentation has been widely reported; however, fewer studies have dealt with its endocrine regulation. The association between nutrition and pigmentation has been mostly studied in flatfish, which can present a high incidence of pigmentation anomalies under aquaculture conditions, and in fish species owing their skin coloration to dietary carotenoids.

In flatfish, larval nutrition has been proved to be essential for proper physiological and morphological transformations occurring during the complex process of metamorphosis, including pigmentation (Hamre et al., 2005; Boglino et al., 2013; Darias et al., 2013b). Several studies have shown higher survival rates and better pigmentation when fish are fed copepods than with any other live prey (Seikai, 1985; Shields et al., 1999; Wilcox et

al., 2006). Several differences in nutrient composition between copepods and live preys such as *Artemia* or rotifers have been suggested to account to the dissimilarities in the pigmentation process of fish, such as the amount of docosahexaenoic (DHA) and eicosapentaenoic acids (EPA) (and their ratios), polar lipids and amino acids, as well as vitamin A (VA) and carotenoid composition (Næss and Lie, 1998). Kanazawa (1993) suggested that albinism in flatfish resulted from the insufficiency of rhodopsin, the production of which depends on VA, DHA and phospholipids, necessary to the formation of melanin. According to this author, feeding Japanese flounder larvae fed a diet deficient in those nutrients during the formation of the retina (at around 10 days post hatching-dph) hampers the production of rhodopsin in the retina. The absence of rhodopsin prevents the visual transmission from the retina to the central nervous system, then the production of Msh is not triggered resulting in the interruption of black pigment formation (Kanazawa, 1993). Copepods contain 5 times higher DHA content than *Artemia* (Hamre et al., 2002), thus the involvement of DHA in vision development and its importance to stimulate melanin synthesis might be the reason behind the importance of DHA in pigmentation. Copepods also present higher levels of EPA. Adequate levels of DHA and EPA and their ratios have shown to be necessary for the correct development of skin pigmentation of turbot (Reitan et al., 1994; Estévez and Kanazawa, 1995), common sole, *Solea solea* (Heatch and Moore, 1997), Atlantic halibut, *Hipoglossus hipoglossus* (Hamre et al., 2005), and California halibut, *Paralichthys californicus* (Vizcaino-Ochoa et al., 2010). Besides, the lower iodine content in *Artemia* compared to copepods has been suggested to decrease the level of thyroid hormone (Th) in fish larvae (Hamre et al., 2005), which could in turn interfere in the metamorphosis process, including pigmentation (Inui and Miwa, 2012; Wang et al., 2019). VA also influences the fate of chromatophores in flatfish, high doses of

retinoic acid stimulating the development of chromatophores in the blind side of flatfish (Miwa and Yamano, 1999). It has been suggested that interactions between VA and fatty acids, as well as between VA and Th at the nuclear receptor level are key in the stimulation of normal pigmentation (Hamre et al., 2005).

Adequate dietary arachidonic acid (ARA) content has also been demonstrated to be important for proper skin pigmentation of several flatfish species such as Yellowtail flounder, *Limanda ferruginea* (Copeman and Parrish, 2002), common sole (Lund et al., 2008), turbot (Estévez et al., 1999), Japanese flounder (Estévez et al., 2001), Atlantic halibut (Hamre et al., 2007) and Senegalese sole (Villalta et al., 2005; Darias et al., 2013b; Boglino et al., 2014). Pre- and pro-metamorphosis are the sensitive periods during which nutrition exerts its greatest influence on pigmentation, coinciding with the time in which chromatoblast differentiation takes place towards the adult type chromatophores (Bolker et al., 2005; Darias et al., 2013b). Senegalese sole larvae fed with high levels of ARA becoming pseudo-albinos at later stages developed pigmentation in the same way as future normally pigmented specimens, but once metamorphosed, the future pseudo-albinos began to show different relative proportions, allocation patterns, shapes and sizes of skin chromatophores that progressively disappeared during post-metamorphosis (Darias et al., 2013b). This process was mainly attributed to the down-regulation of *trp1* and *slc24a5*, which prevented melanin production, and the involvement of *pax3*, *mitf* and *asip1* (agouti signaling protein) in the developmental disruption of the new post-metamorphic populations of melanophores, xanthophores and iridophores (Darias et al., 2013b). Melanophores in pseudo-albino specimens were less abundant and not so aggregated in patches as they were in normally pigmented ones, whereas their shape differed (round vs. dendrite-like shape) suggesting their inability to disperse melanin (Darias et al., 2013b). Besides, high amounts of

307 dietary ARA can produce imbalances in the relative content of EPA and DHA (Moren
308 et al., 2011), which in turn modify the relative concentrations of prostaglandin E of the
309 2 (ARA-derived) and 3 (EPA-derived) series (Boglino et al., 2014). In fact, EPA and
310 DHA compete as substrates for cyclo- and lipoxygenases, which are involved in
311 prostaglandin biosynthesis pathways. Prostaglandin E2 (PEG2) and PEG3 are potent
312 regulators of metabolism with opposing effects (Bell and Sargent, 2003); thus, the
313 balance in their synthesis from both series is dependent on a balanced dietary intake of
314 both ARA and EPA (Hamre et al., 2005). ARA-induced abnormally pigmented
315 individuals have shown to present higher levels of PGE2 than normally pigmented fish
316 fed with a control diet in both Senegalese sole (Villalta et al., 2005, Boglino et al.,
317 2014) and common sole (Lund et al., 2010). Further, pseudo-albino specimens fed a
318 high ARA content diet displayed higher PGE2 concentrations than normally pigmented
319 fish fed the same diet (Boglino et al., 2014). In Senegalese sole, high dietary ARA
320 levels and altered PGE2 concentrations not only affected the pigmentation success, but
321 also disrupted the process of head remodeling during metamorphosis (Boglino et al.,
322 2013).

323 Many fish species owe their bright coloration to carotenoids, which are the predominant
324 pigments in xanthophores and erythrophores. Fish are not able to biosynthesize
325 carotenoids *de novo*, and thus must obtain them from the diet (Bjerkeng, 2008). In
326 aquaculture, several cultured fish species require carotenoid supplementation in order to
327 avoid skin paleness (Bjerkeng, 2008). The effect of carotenoids on the endocrine system
328 as well as their mechanisms of action remain to be elucidated (De Carvalho and
329 Caramujo, 2017). However, it is known that carotenoid deposition in the skin is induced
330 during the breeding season in many fish species, and gonadal hormones such as 17 β -

estradiol and 11-ketotestosterone have shown to play a role in carotenoid-based nuptial coloration (reviewed in Leclercq et al., 2010; Lim et al., 2018).

Astaxanthin is the main carotenoid used in aquaculture feeds and is either obtained from chemical synthesis or from natural resources such as algae, fungi, yeast and bacteria, (Lim et al., 2018). Besides a source of pinkish-red pigments, astaxanthin is known to improve survival, growth performance, reproductive capacity, stress tolerance, disease resistance and immune related gene expression (Lim et al., 2018). Several studies have analyzed the effect of dietary astaxanthin on skin coloration of cultured fish species for human consumption, such as Atlantic salmon, *Salmo salar*, rainbow trout, *Oncorhynchus mykiss*, red porgy, gilthead sea bream, red sea bream, *Pagrus major*, Japanese flounder or Australasian snapper, *Pagrus auratus*, as well as in ornamental species, such as goldfish, *Carassius auratus*, kissing gourami, *Helostoma temminckii*, false clownfish, *Amphiprion ocellaris* or koi carp, *Cyprinus carpio*, among others (reviewed in Lim et al., 2018). Besides, other carotenoid sources have been also assessed to enhance fish skin coloration, as for example the fucoxanthin-rich microalga *Phaeodactylum tricornutum* (gilthead sea bream; Ribeiro et al., 2017), China rose petals, *Hibiscus rosa-sinensis* (goldfish; Sinha and Asimi, 2007), annatto, *Bixa orellana* (goldfish; Fries et al., 2014), sea lettuces *Ulva rigida* and *Ulva lactuca* (Nile tilapia; Valente et al., 2016) or *Spirulina* sp. (yellow tail cichlid, *Pseudotropheus acei*; Guroy et al., 2012), among others.

4.2 Tank color

The characteristics of rearing tanks are an important issue to consider in aquaculture, since it has been demonstrated that they can induce stress (Ishibashi et al., 2013), affect

growth and survival (Martinez-Cardenas and Purser, 2015; Wang et al., 2017), induce skeletal anomalies (Cobcroft and Battaglene, 2009), and alter fish behavior (Höglund et al., 2002; Cobcroft and Battaglene, 2009) and skin pigmentation (van der Salm et al., 2005; Doolan et al., 2008b; Eslamloo et al., 2015). Despite all the evidence, tank characteristics are often under-considered in aquaculture, and, for instance, the color of the rearing tanks is seldom described in the scientific literature.

Background adaptation is widely observed in fish and refers to the ability to modify body color in response to environmental luminosity, as in the case of dark or bright backgrounds. This ability is exploited in aquaculture to improve skin pigmentation. For example, skin darkening in sparids, which negatively affects market value (Matsui et al., 1992; Kolios et al., 1997; Lin et al., 1998; Rotllant et al., 2003; Booth et al. 2004; Van der Salm et al., 2004; Doolan et al., 2007), can be reversed by rearing these species in white tanks (Doolan et al, 2008a, b). However, a white environment has been shown to induce an increased stress response to overcrowding in *P. pagrus*, which may depend on the size of the fish (Rotllant et al., 2003; Van der Salm et al., 2004). In tilapia, *Oreochromis mossambicus*, white and grey backgrounds induce skin lightening, whereas a black background induces skin darkening and a more stressful response (Van der Salm et al., 2005). In goldfish, red and blue backgrounds are chronically stressful, whereas a white background improves fish growth, but generates a skin color loss (Eslamloo et al., 2015). In *Lophiosilurus alexandri* dark colored tanks promoted an increase in plasma cortisol levels and a reduction in brightness of the skin, while the use of light colors resulted in paler skin (Costa et al., 2017).

As previously mentioned, tank color not only affects fish pigmentation, but can also cause other physiological changes. In several fish species, it has been observed that fish

379 adapted to a white background present better growth performance than those adapted to
380 other background color (Amiya et al. 2005; Karakatsouli et al. 2007; Strand et al. 2007;
381 Takahashi et al., 2004; Yamanome et al. 2005; Pérez Sirkin et al., 2012; Eslamloo et al.,
382 2015). In part, this could be due to the high contrast between feed and background color
383 that improves the visibility of feed in the tanks (Jentoft et al., 2006; Strand et al. 2007;
384 Eslamloo et al., 2015). Besides, white background induces high levels of Mch and, as
385 Mch has been proposed to play an orexigenic role in some species (Takahashi et al.,
386 2014; Volkoff, 2016), the increase in somatic growth could be interpreted as an increase
387 of food intake. On the other hand, in *C. dimerus*, it was demonstrated that Mch
388 stimulates Gh release in pituitary cultures, so the increase in fish growth could also be
389 related to this regulation (Pérez Sirkin et al., 2012).

390 The adaptation to black background results in the dispersion of pigment in
391 melanophores within a few hours, concomitant with an increase in plasma α -Msh levels
392 (Mizusawa et al., 2013). However, the involvement of this hormone in long-term
393 background adaptation has no consensus in fish (Cal et al., 2017). Despite what would
394 be expected, gilthead sea bream adapted to a white background for 15 days presented an
395 increase in plasma α -Msh levels compared to specimens adapted to grey or black
396 backgrounds (Arends et al., 2000). Similar results were observed in red porgy adapted
397 for one month to white or black backgrounds (Rotllant et al., 2003). However, it has
398 been hypothesized that the regulation of α -Msh acetylation may be an important
399 mechanism for background adaptation, more than total amounts of α -Msh released into
400 the blood (Arends et al., 2000).

401 The pioneering works of Zhu and Thomas (1996, 1997, 1998) and Zhu et al. (1999)
402 introduced somatolactin (Sl) as a hormone involved in background color adaptation.

They suggested that SI plays a role in background adaptation and possibly regulates pigment movement in the chromatophores of sciaenid fishes. In *C. dimerus*, the long-term exposition to a black background produces an increase in the number and area of SL immunoreactive cells (Cánepa et al., 2006), even from early stages of development (Delgadin et al., 2020). Moreover, growth hormone receptor 1 (GhR1; probably the SL receptor) was detected in the epidermis and dermis from fish scales (Cánepa et al., 2012). This receptor showed changes in its transcript level concomitant with changes in melanophores, suggesting plausible evidence for the role of SI and its receptor in the regulation of chromatophores in *C. dimerus* (Cánepa et al., 2012). Furthermore, it was determined that medaka larvae with biallelic mutations of the GhR1 receptor failed to adapt to the background, unless at the beginning of development (Delgadin et al., 2020).

SL has been shown to be involved in different physiological processes, including reproduction, stress responses, Ca²⁺ homeostasis, acid–base balance, growth, metabolism, and immune responses (reviewed in Kawauchi et al., 2009); therefore, changes in tank color can influence the general physiology in different ways, thus affecting fish welfare.

4.3 Social interactions

In many social species, skin pigmentation reflects the social hierarchy; for example, in salmonids, social subordination is associated with skin darkening (Abbott et al., 1985; O'Connor et al., 1999; Höglund et al., 2000, 2002). Subordinate fish are subjected to chronic stress induced by aggressive acts from dominant fish (Winberg and Lepage, 1998; Øverli et al., 1999; Höglund et al., 2000, 2002). As it was previously mentioned, this leads to a chronic activation of the hypothalamic–pituitary–interrenal axis, and to an increase of α -Msh that induces interrenal cortisol release and skin darkening (Fujii and

Oshima, 1986, Höglund et al., 2000). In *Astatotilapia burtoni* it was demonstrated that yellow males are more aggressive than blue ones (Korzan and Fernald, 2007; Korzan et al., 2008). Later on, it was demonstrated that blue males have higher cortisol levels than yellow ones, indicated by an activation of the melanocortin system in the skin (Dijkstra et al., 2017).

In *C. dimerus*, body color pattern is associated with different social status. A relation between color and dominance was observed in territorial individuals, which had bright body color patterns, while non-territorial individuals were opaque grey (Alonso et al., 2011). Furthermore, a negative correlation was found between plasma cortisol levels and dominance; fish of lower social hierarchy rank had higher plasma cortisol levels than those in higher rank (Alonso et al., 2011, 2012).

It is important to point out that the color of the tank can increase social agonist encounters, besides inducing stress. In Nile tilapia, blue and brown tanks increased this kind of behavior (Merighe et al., 2004), whereas in Arctic char, *Salvelinus alpinus*, white tanks induced a more aggressive behavior than black ones (Höglund et al., 2002).

4.4 Light and other factors

It is known that chromatophores respond directly to incident light. This “primary color response” can be observed during embryonic and larval stages, when chromatophores are not innervated or under endocrine control, as well as in adulthood regardless of the presence of both regulatory systems (reviewed in Fujii, 2000; Oshima, 2001). In this sense, cone opsin expression has been detected in melanophores (Chen et al., 2013) and erythrophores (Ban et al., 2005; Chen et al., 2013) in Nile tilapia and in iridophores in

Neon tetra (Kasai and Oshima, 2006). Melanophores respond to wavelengths between 380-580 nm by dispersing melanosomes (Chen et al., 2013), and erythrophores aggregate or disperse pigment depending on exposure to short or middle/long wavelengths, respectively (Sato et al., 2004; Ban et al., 2005; Chen et al., 2013). The photo-response of iridophores depends on light intensity, with the wavelength of 500 nm being the most effective one (Kasai and Oshima, 2006). Besides, the photic environment affects fish pigmentation by modulating nervous and endocrine systems. Unfortunately, there are few studies conducted on the impact of different wavelengths on fish pigmentation. For example, adults of red porgy became paler when exposed to blue light compared to individuals exposed to the full spectrum, with no observed changes in melanin content or α -Msh and cortisol levels (Szisch et al., 2002). These authors proposed that these changes in fish coloration could be due to changes in melanosome aggregation produced by the control of the nervous system. In addition, Amano and Takahashi (2009) suggested that, since green light increased somatic growth in barfin flounder, *Verasper moseri* (Yamanome et al., 2009), *mch* expression and its secretion could be higher, so the skin color of those animals should be paler. Unfortunately, the effect of green light on skin color was not analyzed in that study.

Light intensity has been shown to affect growth, behavior, physiology, and coloration in some fish species, such as *Paralichthys woolmani* (Benetti, 1997; Venizelos and Benetti, 1999; Han et al., 2005). Santos et al. (2019) showed that light influences food consumption and conversion, behavior, and plasma cortisol levels of *Lophiosilurus alexandri* juveniles; however, no effect on skin pigmentation was observed.

Photoperiod can also induce alterations in skin color, given that melatonin not only acts directly over chromatophores but also modifies other endocrine pathways that affect

skin pigmentation. For example, in Neon tetra, the red and brown colors produced by erythrophores and melanophores were found to be markedly reduced at night, suggesting the regulation of coloration by an endogenous circadian rhythm (Lythgoe and Shand, 1983). Differences in skin pigmentation due to photoperiod were also observed in Japanese flounder after metamorphosis when comparing the effects of continuous 24 h illumination (LL) to natural light conditions (15 h light: 9 h dark, LD) during larval development. Itoh et al. (2012) found that larvae reared in LL presented paler skin color, and a higher ratio of abnormal pigmentation after metamorphosis. Moreover, LL conditions decreased tyrosine hydroxylase-1 (*th1*) in dopaminergic neurons, but increased *α -msh* levels in melanotrophs with no changes in *mch* expression levels in the lateral tuberal nucleus (NLT). Authors concluded that there could be an accumulation of α -Msh in the melanotrophs because of the inhibitory action of Mch over its protein secretion, causing a pale skin color. In another study, Ginés et al. (2004) found that the skin luminosity of gilthead sea bream was higher under the longer the photoperiod. Similar results were obtained by Lyon and Baker (1993) in rainbow trout, who also described that Mch secretion reached a peak during the light period and then, it gradually declined before night, when the lowest concentrations were observed. These hormone variations were directly related to animal skin paleness.

Other factors such as handling, crowding, transport, hydrostatic pressure, and variations in temperature, oxygen, and salinity, can affect either directly or indirectly chromatophores' physiology and thus modify fish pigment. The direct impact of some of these stimuli on chromatophores is poorly studied, although, for example, it is accepted that high temperatures aggregate chromatosomes, while lower temperatures disperse them (Fujii and Oshima, 1994). In any case, these factors are generally considered as

stressors, promoting an acute or chronic stress response depending on the duration of the stimuli (reviewed in Wendelaar Bonga, 1997).

5 Conclusions and perspectives

The skin pigmentation pattern in fish is species-specific and is given by the number and spatial combination of several types of chromatophores. Research efforts have been made to improve understanding of the underlying endocrine regulation of skin pigmentation. In particular, recent studies have identified other actors besides the classic color change regulators Mch and Msh, such as Sl, Asip, and Th, that seem to play an important role in the regulation of pigmentation. In this sense, more studies are needed to understand how these factors interact in a coordinated way to regulate skin color. Furthermore, considering that most studies on the physiology of pigment cells focus on melanophores and that some studies have demonstrated that cellular communication between different types of chromatophores is essential in the pigmentation patterning process, further research on the regulatory factors of all types of chromatophores and the interactions among them is essential to understand the intricate mechanisms of skin pigmentation as well as to identify the origin and the causes leading to pigmentation disorders. Furthermore, as chromatophores derive from NCC, pigmentation anomalies could be the visible sign of more complex physiological disruptions.

Skin pigmentation is one of the most important quality criteria dictating the market value of fish for both human consumption and ornamental use. Rearing conditions such as nutrition, tank coloration, UV incidence, surrounding luminosity, or social interactions can negatively affect the natural skin coloration. In this sense, further studies are needed to identify pigmentation-related endocrine factors that are being

modulated when fish are reared under suboptimal conditions. This knowledge will also be useful to better understand the impact of rearing conditions on other biological processes, as many endocrine signals affecting pigmentation are additionally regulating processes such as growth, reproduction, or nutrition, among others. In this sense, skin pigmentation could be considered an indicator of fish well-being.

New insights on the influence of stress in gut microbiome modulation and on the role of gut microbiome in the regulation of skin pigmentation reinforces the need for a better understanding of the influence of environmental conditions. Taken together, research on the endocrine factors affecting pigmentation, the communication among different types of chromatophores, the influence of nutrition and abiotic factor in the modulation of these endocrine signals, and the role of gut microbiome in the regulation of these physiological processes could contribute to identify the best rearing conditions for species presenting pigmentation disorders and hence to improve their commercial production.

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1153

Table 1. Summary of the hormonal skin color regulation in fish. In this table we only focus on their role in pigmentation; therefore, some general characteristics of each hormone are omitted.

Mch: Kawauchi and Baker, 2004¹; Amano and Takahashi, 2009²; Pandolfi et al., 2003³; Mizusawa et al., 2009⁴; Takahashi et al., 2004⁵; Yamanome et al., 2007⁶; Oshima et al., 1986⁷; Mizusawa et al., 2011⁸; Kasukawa et al., 1986⁹; Baker et al., 1986¹⁰; Yamanome et al., 2005¹¹. **Msh:** Cal et al., 2017¹²; Takahashi and Kawauchi, 2006¹³; Lamers et al., 1991¹⁴; Arends et al., 2000¹⁵; Kobayashi et al., 2012¹⁶; Sánchez et al., 2010¹⁷; Kobayashi et al., 2016¹⁸; Dijkstra et al., 2017¹⁹; Fujii and Miyashita, 1982²⁰; Kobayashi et al., 2011²¹; Ligon and McCartney, 2016²²; Sugimoto, 2002²³. **Sl:** Kaneko, 1996²⁴; Fukada et al., 2005²⁵; Chang and Wong, 2009²⁶; Cánepa et al., 2012²⁷; Fukamachi and Meyer, 2007²⁸; Zhu et al., 1999²⁹; Nguyen et al., 2006³⁰; Fukamachi et al., 2004³¹, 2009³². **Asip:** Cerdá-Reverter et al., 2005³³; Guillot et al., 2012³⁴; Ceinos et al., 2015³⁵; Cal et al., 2019³⁶; McNulty et al., 2005³⁷. **Cortisol:** Wendelaar Bonga, 1997³⁸; Khan et al., 2016³⁹; Ruane et al., 2005⁴⁰; Yamada et al., 2011⁴¹; Matsuda et al., 2018⁴². **Prl:** Kawauchi et al., 2009⁴³; Freeman et al., 2000⁴⁴; Kitta et al., 1993⁴⁵; Oshima and Goto, 2000⁴⁶; Oshima et al., 1996⁴⁷; Sage, 1970⁴⁸; Sköld et al., 2008⁴⁹. **Mt:** Falcon et al., 2011⁵⁰, 2010⁵¹; Fujii, 2000⁵²; Fujii and Oshima, 1994⁵³; Nagaishi and Oshima, 1989⁵⁴; Oshima et al., 1989⁵⁵. **Th:** Janz, 2000⁵⁶; Blanton et al., 2007⁵⁷; Bernier et al., 2009⁵⁸; Walpita et al., 2009⁵⁹, 2007⁶⁰; Saunders et al., 2019⁶¹; Guillot et al., 2016⁶²; Yoo et al., 2000⁶³; McMenamin et al., 2014⁶⁴.

Figure 1. Endocrine and nervous factors involved in physiological and morphological color changes. This figure summarized the physiological (left) and morphological (right) hormone effects over different chromatophores presented in Table 1. Besides, local synthesis (as it was described for Asip and Mch) and factors delivered through the bloodstream are shown. Note that most studies focus on the regulation of melanophores while there is scarce information about other pigmentary cell's regulation. Arrows indicate stimulation and T-lines indicate inhibition. Mch: melanin-concentrating hormone; Msh; melanophore-stimulating hormone; Sl: somatolactin; Prl: prolactin; Mt: melatonin; Th: thyroid hormone; Asip: agouti signaling protein; CA: catecholamines; NA: noradrenaline.

Hormone/ peptide	Synthesis (place and/or gene)	Mode of action	Receptors	Overall effect	Physiological changes in chromatophores	Morphological changes in chromatophores
Melanin- concentrating hormone (Mch)	-NLT, some neurons project to the hypophysis and bloodstream ^{1,2}	endocrine	Type 1 G-protein coupled receptors. Two subtypes: Mch- r1 and Mch-r2 ^{2,4}	Skin paling ^{5,6}	-Aggregation of melanosomes in several fish species ^{5,6} erythrosomes in swordtail ⁷ and xanthosomes in medaka ⁸ -Dispersion of light-scattering organelles of leucophores in medaka ⁷ - No effect over iridophores in blue damsel fish ^{7,9}	- Prevents melanin synthesis ^{10,11} -Prevent melanophore differentiation ¹¹
	-Skin neuromast ³	paracrine				
Melanophore- stimulating hormone (Msh)	-melanotropes of the <i>pars intermedia</i> ¹²	-endocrine	Seven transmembrane- domain-G-protein- coupled family/ rhodopsin class family A-13. Subtypes: Mc1R and Mc5R ^{12,16-18}	Skin darkening ¹² and/or promotes yellow coloration ¹⁹	- Dispersion of melanosomes (epidermis and dermis) ²⁰ and xanthosomes in <i>A. burtoni</i> ^{16,19,21} -Promotes platelet aggregation in motile iridophores ²²	- Stimulate melanin synthesis ²³ -Acts as a melanophore differentiation factor ²³
	-Skin ¹⁶ -In teleost: α -Msh and β -Msh isoforms ¹³	-paracrine - α -Msh: des-, mono- (dominant), and di- acetylated ^{14,15}				
Somatolactin (Sl)	-somatolactotropes of the <i>pars intermedia</i> ²⁴	-endocrine	Proposed: type I cytokine receptor: growth hormone (Gh) receptor type 1 (GhR1) ²⁵⁻²⁸	Skin darkening ^{27,29-30}	-Dispersion of melanosomes in red drum ²⁹ and zebrafish ³⁰	-Promotes proliferation of melanophores in <i>C. dimerus</i> ²⁷ , and it is involved in the proliferation and morphogenesis of certain chromatophores in medaka ³¹⁻³²
Agouti signaling protein (Asip)	-skin ^{12,33-36}	-paracrine	Antagonist of Mc1R ^{33,37}	Determines dorso-ventral pigment pattern ^{12,33-36} Involved in skin paling?	- Aggregation of melanosomes in medaka ³³	-Inhibits melanogenesis ³⁶ and modulates chromatoblast fate: decreasing melanophores n° in different species of flatfish ^{33,34} , and also decreasing xanthophores and increasing iridophores n° in zebrafish ³⁶
Cortisol	- Interrenal cells of the head kidneys ³⁸	-endocrine	Direct or indirect effect? Proposed to act through <i>asip</i> in	Skin darkening or paling depending on species ³⁹⁻⁴²		

Prolactin (Prl)	-lactotropes of the <i>rostral pars distalis</i> ⁴³	-endocrine	rainbow trout ³⁹ Cytokine/hemotopoietin superfamily. Long and Short isoforms of Prlr ⁴⁴	Promotes red and yellow skin coloration ⁴⁵⁻⁴⁸	-Weak aggregating effect on melanophores ^{45,46} . -Dispersion of xanthosomes in Nile tilapia and the rose bitterling ⁴⁶ , and of erythrosomes in Nile tilapia, swordtails and paradise gobies ⁴⁷ . Similar effects in two-spotted gobies and the mudsucker ^{48,49}	
Melatonin (Mt)	-Pineal gland ⁵⁰	-endocrine	Seven transmembrane-domain-G-protein-coupled family: Mt1 Mt2 and Mel1c ⁵¹	Skin paling and transparency ^{49,52}	-Aggregation of melanosomes ⁵² and erythrosomes ^{49,53} . -Dispersion of erythrosomes and xanthosomes ⁴⁹ . -Increase between platelets spacing in iridophores ^{54,55} .	
Thyroid hormones (Th)	-Thyroid follicles, local conversion to T3 ⁵⁶⁻⁵⁸	-endocrine	transcription factors from the family of type-2 nuclear receptors: α and β TR ⁵⁸	Skin paling ⁵⁹⁻⁶²		-Prevent melanin synthesis ^{59,60} -Change the balance of melanophore stem cell proliferation/ differentiation in zebrafish ^{61,62} and Japanese flounder ⁶³ - Decrease melanophore and increase xanthophore number <i>Danio albolineatus</i> ⁶⁴