Rev Fish Biol Fisheries (2020) 30:67–92
https://doi.org/10.1007/s11160-019-09590-y

REVIEWS

Nutritional programming in fishes: insights from mammalian studies

Zhenxin Hou · Lee A. Fuiman

Received: 31 July 2019 / Accepted: 29 November 2019 / Published online: 11 December 2019

Abstract Epidemiological evidence and subsequent studies using mammalian models have established a strong correlation between suboptimal nutritional status during early life and predisposition to metabolic diseases later, such as permanent growth retardation and impairment of neural development and key metabolic pathways. This phenomenon, termed nutritional programming or metabolic programming, is beginning to be studied in fishes. Despite important differences in maternal nutrient delivery and developmental processes between mammals and fishes, early nutrition of fishes from both endogenous (maternally derived) and exogenous (larval feeding) sources, could induce similar programming effects on development and metabolism. Documented programming effects in fishes include: growth, survival, brain development, and nutrient metabolism. These programming effects could be mediated through altered metabolic pathways and/or epigenetic regulation of gene expression during a critical window when organisms exhibit high plasticity in development. As a result, nutritional programming could be employed as a strategy in aquaculture to promote sustainable feeding strategies. In addition, this critical window overlaps with high mortality during the early life stages. This means programming effects could potentially translate into measurable consequences for the dynamics of wild populations. Given the wide variety of metabolic consequences of programming and the diversity of fishes, many important questions remain unanswered. This report summarizes research from mammalian and fish models and identifies knowledge gaps and priority areas for research into nutritional programming in fishes.

Keywords Early priority hypothesis · Metabolic programming · Thrifty phenotype hypothesis · Metabolic syndrome · Early life stage · Plasticity

Z. Hou (✉) · L. A. Fuiman
Marine Science Institute, University of Texas at Austin, 750 Channel View Drive, Port Aransas, TX 78373, USA
e-mail: zhenxin.hou@utexas.edu

Introduction

Programming is a general phenomenon in which exposure to a particular stimulus during a critical window of development leads to long-term changes in structures or functions. Various stimuli or cues can act as programming agents and these can derive from endogenous and exogenous sources. That is, programming can be a genetically predetermined developmental event induced by internal triggers (e.g., release of hormone), or by exogenous programming agents such as sensory stimuli, antigens, and drugs (Lucas 1991). Among those exogenous stimuli, nutrition is especially important and has a well-established role in programming (Lucas 1998).

To date, nutritional programming has been reported in birds (reviewed by Morisson et al. 2017), farm animals (reviewed by Sinclair et al. 2016), and primates (including humans) but the greatest effort has been in laboratory experiments on rodents due to its important clinical and biomedical implications. Research on fishes has begun recently but it lags behind the research on mammals. This review summarizes the experimental studies on nutritional programming in mammals and in fishes (Tables 1, 2), and proposes key areas for exploration in order to facilitate the burgeoning field of nutritional programming within fish biology.

The concept of nutritional programming

Nutritional programming is usually referred to as "metabolic programming" in mammalian systems, referencing the outcome of programming, rather than the cause. Other common terms include "fetal programming", emphasizing the maternal–fetal interaction, or "developmental programming", associating programming with developmental processes. Regardless, it is usually linked to several human health conditions (e.g., obesity, insulin resistance, reduced glucose tolerance, hypertension and hypertriglyceridaemia) that are collectively known as metabolic syndrome (Petry et al. 2001; Symonds et al. 2009). In pioneering studies on mammalian metabolic programming, postnatal nutrition was commonly altered by manipulating litter size of rats. Later on, different levels of nutrient intake during early life stages were attained by a cross-fostering technique. Two maternal diets (e.g., a low protein and a control diet) were used during gestation and lactation and litters were cross-fostered at parturition, which produced four nutritional treatment groups for the offspring: control, low protein throughout gestation and lactation, postnatal low protein (low protein only during lactation) and recuperated (prenatal low protein) (Fig. 1). By cross-fostering, one can investigate whether programming occurs during the prenatal or postnatal period or both, and whether the programming effect is reversible.

A challenge experiment was conducted at the end of some cross-fostering studies, to test whether nutritional programming confers greater adaptability to nutritionally suboptimal conditions. Commonly, an animal that has been exposed to an experimental diet is transferred to a "normal" diet for several weeks to months (which implies an optimal diet, high quality food, or a replete diet with respect to the nutrients that have been insufficient in the experimental diet, referred to as "common feeding" thereafter). Then the experimental or a similar diet is given (referred to as the "challenge diet") and the response is measured at the end of this "challenge phase" (Fig. 1). In this review, a common feeding period after removal of an early nutritional stimulus was used as a criterion for determining whether a study measured the effects of nutritional programming. Studies that measured a response immediately after an early nutritional stimulus (without a common feeding period) were not deemed "programming". A crossover feeding paradigm (equivalent of cross-fostering) is not required.

Consequences of nutritional programming

Mammalian studies

In mammals, a variety of altered metabolic phenotypes induced by early nutrition are well-documented (Table 1). This section will briefly summarize the consequences of nutritional programming reported in mammalian studies to lay the groundwork for considering the knowledge gaps and priority areas for new research on fishes.

Growth/obesity

The association between early life nutrition and growth was described as early as the 1960s (Winick and Noble 1966) and supporting evidence has accumulated ever since. Maternal protein and caloric restriction resulted in stunting of postnatal growth in rats after common feeding (Winick and Noble 1966; Desai et al. 1996; Bieswal et al. 2006). Early malnutrition during late gestation and lactation caused consistently lower body weight, delayed time of onset of puberty, and reduced weight at the onset of puberty in rats (Engelbregt et al. 2000). A higher caloric intake during infancy resulted in obesity as well as greater fat depot triglyceride mass and adipocyte hypertrophy in female adult baboons (Lewis et al. 1986).

Altered growth trajectory, in turn, has long-term consequences for health. Studies on the Dutch Hunger Winter and subsequent studies have demonstrated the

Table 1 Summary of nutritional programming studies using mammalian models

Nutritional stimulus	Programming window	Effects	Species	References
Caloric restriction	Prenatal/postnatal	Growth	Rodents	Engelbregt et al. (2000)
	Postnatal/post-weaning	Growth (organogenesis)	Rodents	Winick and Noble (1966)
Iron deficiency	Infancy	Neural development	Human	Lozoff et al. (1991); Corapci et al. (2006)
	Postnatal	Neural development	Rodents	Yehuda et al. (1986)
IUGR	Prenatal	Homeostasis; muscle metabolism	Rodents	Lane et al. (2001)
	Prenatal/postnatal	Growth	Rodents	Engelbregt et al. (2000)
Maternal caloric restriction	Prenatal	Growth; metabolic syndrome[a]	Rodents	Vickers et al. (2000)
Maternal high fat	Prenatal + postnatal	Metabolic syndrome	Rodents	Coates et al. (1983)
	Prenatal/ prenatal + postnatal	Lipid metabolism; ingestion	Rodents	Chang et al. (2008)
Maternal high/low fat	Prenatal + postnatal	Lipid metabolism	Rodents	Hoile et al. (2013)
Maternal hypercaloric nutrition	Postnatal	Metabolic syndrome	Primate	Lewis et al. (1986)
	Prenatal	Homeostasis/lipid metabolism	Rodents	Borengasser et al. (2011)
	Postnatal	Metabolic syndrome	Rodents	Lemonnier et al. (1973); Hahn (1984)
Maternal hyperglucidic	Prenatal + postnatal	Metabolic syndrome	Rodents	D'Alessandro et al. (2014)
Maternal n-3 PUFA deficiency	Prenatal + postnatal	Neural development	Rodents	Li et al. (2006)
Maternal protein restriction	Prenatal	Carbohydrate metabolism	Rodents	Lillycrop et al. (2005, 2007)
	Postnatal	Growth	Rodents	Desai et al. (1996)
	Prenatal/postnatal	Lipid metabolism	Rodents	Lucas et al. (1996)
	Prenatal + postnatal	Growth	Rodents	Desai et al. (1996); Ozanne et al. (1998); Plagemann et al. (2000); Bieswal et al. (2006)
	Prenatal + postnatal	Metabolic syndrome; ingestion	Rodents	Plagemann et al. (2000)
	Prenatal + postnatal	Carbohydrate metabolism/ homeostasis: glycolysis; glucose tolerance	Rodents	Hales et al. (1996)
	Prenatal + postnatal	Lipid metabolism	Rodents	Lucas et al. (1996); Ozanne et al. (1998)
	Prenatal + postnatal	Digestion	Rodents	Timofeeva et al. (2000)
	Prenatal + postnatal/ prenatal	Homeostasis/carbohydrate metabolism	Rodents	Desai et al. (1995)
Maternal vitamin (methyl donor) deprivation	Prenatal + postnatal	Metabolic syndrome; homeostasis	Rodents	Pooya et al. (2012)
n-3 HUFA deficiency	Juvenile	Neural development	Primate	Connor et al. (1992)
Unfavorable flavor	Prenatal	Ingestion	Rodents	Youngentob and Glendinning (2009)
	Postnatal + postweaning	Ingestion	Rodents	London et al. (1979)

Programming window refers to the period of life when the nutritional stimulus was applied to produce consequences for one or more physiological processes (Effects)

[a]Metabolic syndrome includes a collection of a number of health conditions for which a detailed description can be found in the text

strong associations between poor fetal and early postnatal growth and the susceptibility to development of adult metabolic disorders (Roseboom et al. 2001; Fernandez-Twinn and Ozanne 2010).

Neural development

A review of experimental studies on non-human mammals revealed that 87% of studies (80 of 92) found that despite prolonged common feeding, early

Table 2 Summary of the nutritional programming studies using fish models

Nutritional stimulus	Programming window	Effects	Species	References
Copepod (vs rotifer)	Larval feeding	Stress tolerance	Atlantic cod	Øie et al. (2015)
	Larval feeding	Growth	Atlantic cod, Ballan wrasse	Imsland et al. (2006); Koedijk et al. (2010); Øie et al. (2015)
High fat	Larval feeding	Growth; muscle growth	Rainbow trout	Alami-Durante et al. (2014)
HUFA deficiency	Larval feeding	Lipid metabolism	European seabass	Vagner et al. (2007, 2009)
	Larval feeding	Neural development; stress tolerance	Pikeperch	Lund et al. (2012)
Hyperglucidic	Embryonic stage	Carbohydrate metabolism	zebrafish	Rocha et al. (2014, 2015)
	Larval feeding	Growth	European seabass	Zambonino-Infante et al. (2019)
	Larval feeding	Stress tolerance	European seabass	Zambonino-Infante et al. (2019)
	Larval feeding	Hypoxia tolerance	European seabass	Zambonino-Infante et al. (2019)
	Larval feeding	Carbohydrate metabolism	Rainbow trout; Siberian sturgeon; gilthead seabream; zebrafish; European seabass	Geurden et al. (2007, 2014); Fang et al. (2014); Gong et al. (2015); Rocha et al. (2016a, b); Zambonino-Infante et al. (2019)
Hyperglucidic + hypoxia	Larval feeding	Carbohydrate metabolism	Rainbow trout	Liu et al. (2017); Hu et al. (2018)
Intact protein (vs hydrolysate with polypeptides)	Larval feeding	Growth	Senegalese sole	Canada et al. (2018)
Maternal HUFA supplementation	Spawning	Growth, survival, routine swimming, escape response; lipid metabolism	Red drum	Fuiman and Perez (2015)
Methyl group donor	Prior to spawning	Growth, survival; ingestion	Rainbow trout	Fontagné-Dicharry et al. (2017)
	Prior to spawning	Lipid metabolism; carbohydrate metabolism	Rainbow trout	Seiliez et al. (2017)
Maternal one-carbon micronutrient deficiency	Adult life cycle	Lipid metabolism	Zebrafish	Skjærven et al. (2016, 2018)
Maternal high ARA	Adult life cycle	Lipid metabolism	Zebrafish	Adam et al. (2018, 2019)
Maternal PUFA and vitamin supplementation	Spawning	Growth, development(deformity); lipid metabolism	Senegalese sole	Morais et al. (2014)

Table 2 continued

Nutritional stimulus	Programming window	Effects	Species	References
Plant-based diet	Adult life cycle	Lipid metabolism; carbohydrate metabolism; muscle growth	Rainbow trout	Lazzarotto et al. (2016)
	Spawning	Growth; lipid metabolism	Gilthead seabream	Izquierdo et al. (2015); Turkmen et al. (2017)
	Larval feeding	Growth; digestion	Gilthead seabream	Perera and Yufera (2016a)
	Larval feeding	Ingestion	Rainbow trout	Geurden et al. (2013)
	Larval feeding	Growth	Rainbow trout; Atlantic salmon	Geurden et al. (2013); Clarkson et al. (2017)
	Larval feeding	Inflammation	Zebrafish, gilthead seabream	Perera and Yufera (2016a, b)
	Juvenile	Growth; lipid metabolism	Gilthead seabream	Turkmen et al. (2017)
Vitamin supplementation	Larval feeding	Lipid metabolism; muscle metabolism	Rainbow trout	Panserat et al. (2017)

Programming window refers to the period of life when the nutritional stimulus was applied to produce consequences for one or more physiological processes (Effects)

life stage (gestation to early post-weaning period) malnutrition gave rise to impaired learning ability, such as impaired ability to run complex mazes, visual discrimination, and extinction of learned responses (Smart 1986). Iron deficiency is recognized as one of the causes of cognitive deficit in mammals. In one study, learning deficit manifested in young rats after they had been on an iron-free diet for only 1 week and persisted until after 3 weeks of common feeding (Yehuda et al. 1986). Formerly iron-deficient children, recovered from iron-deficiency anemia after a full course of iron treatment administered during infancy, still showed poor mental, motor, social/emotional performance at 5 years of age (Lozoff et al. 1991; Corapci et al. 2006).

Lipid metabolism

Plasma cholesterol and insulin concentrations were elevated in rat offspring raised in small litters (high nutrient intake per individual) (Lemonnier et al. 1973; Hahn 1984). They also exhibited increased body weight, predominantly driven by an increase in body fat (Lemonnier et al. 1973). In another study, a high fat, low sucrose (HF) diet and a low fat, high sucrose (HS) diet were provided to two groups of rats from late gestation to weaning. When young rats were treated with a 3-day HF diet after 6 months of common feeding which began at weaning, rats from mothers that were fed the HF diet showed a significantly higher level of serum cholesterol (Coates et al. 1983). These results suggest that maternal HF diet facilitates diet-induced hypercholesterolemia in offspring. Protein deficiency at one point during early development (either prenatal, postnatal, or both) also induced a programmed reduction in plasma triacylglycerol (TAG), high-density lipoprotein (HDL), and cholesterol concentration in adult offspring (Lucas et al. 1996).

Effects of micronutrients (vitamins and minerals) on offspring lipid metabolism have been well demonstrated in mammals. Maternal dietary restrictions of vitamins and minerals (including vitamin A, B_{12}, folic acid, Mg, Mn, Cr and Zn) could alter cholesterol and TAG levels, expression and/or activities of enzymes such as fatty acid synthase (FAS), acetyl CoA carboxylase (ACC), and fatty acid transport proteins (FATPs). Maternal deficiency of micronutrients have also been associated with increased body fat percentage in offspring (reviewed by Rao et al. 2012).

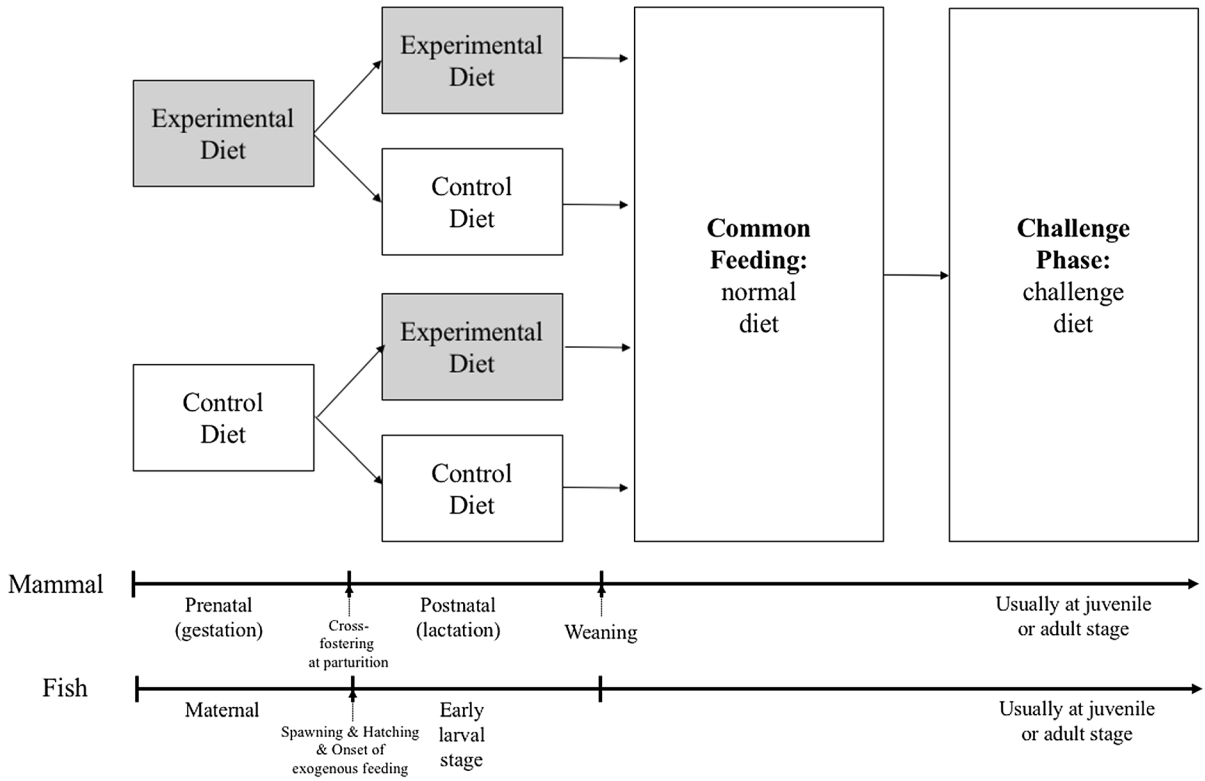

Fig. 1 Schematic figure of a classical crossover experimental design used in nutritional programming studies. In mammalian studies, two maternal diets are used during gestation and lactation, and litters are cross-fostered at parturition, which produces four nutritional treatment groups for the offspring. In fish studies, adult fish are provided different maternal diets, followed by different larval diets during larval feeding stages. Afterwards, an animal is fed a "normal" diet for several weeks to months (referred to as "common feeding"), after which the effects of nutritional programming are measured. In some studies, a challenge experiment is employed in which the experimental or a similar diet is given (referred to as the "challenge diet") after the common feeding period and the response is measured at the end of this "challenge phase."

Carbohydrate metabolism

Prenatal protein restriction was associated with reduced glucokinase (GK) and increased phosphoenolpyruvate carboxykinase (PEPCK)[1] activities in the liver of rat offspring at weaning and in adulthood (Desai et al. 1995). GK and PEPCK are expressed in different regions of the liver. Therefore, a possible explanation for the opposite changes in activity is that poor prenatal nutrition permanently alters physical structure (expanded/contracted) and function of the liver (Desai et al. 1995). The fact that GK and PEPCK do not express until after birth, but are regulated by prenatal nutrition, also suggests programming occurs before transcription (Desai et al. 1995). This speculation is supported by findings related to epigenetics (discussed in "Epigenetic mechanisms" section). Hales et al. (1996) also reported reduced pancreatic GK activity in 3-month-old rat offspring whose mother received a low protein diet during pregnancy and lactation. These rats were also less glucose tolerant as adults, exhibiting higher blood glucose levels after intraperitoneal injection of glucose.

Fish studies: exogenous nutritional stimuli

While the concepts of nutritional programming may be the same in mammals and fishes, there are important differences which must be considered when comparing findings. In mammals, the fetus developing in utero receives a blood-borne supply of nutrients through the placenta. Postnatally, maternally derived

[1] PEPCK is involved in gluconeogenesis. Glucokinase (GK) is a key enzyme in glycolysis.

nutrition continues via lactation. During both periods, offspring not only receive nutrition from their mother but they also receive other exposures (e.g., hormones, toxins, disease agents) from the maternal circulation. In contrast, most fishes are oviparous and produce eggs with a fixed amount of yolk, which provides nutrients for embryos and larvae during early development. The maternal connection for most fishes ends before the egg is fertilized. However, fishes may remain susceptible to programming afterwards via nutritional stimuli received through the maternally-derived nutrients in the yolk (see in "Fish studies—Maternally-derived nutritional stimuli" section) or through the larval diet because a considerable amount of anatomical and physiological development continues in fish larvae after the yolk supply has been exhausted. Therefore, despite significant differences between the development of mammals and fishes, a similar experimental design can be applied (Fig. 1) and the results from mammals may be useful for guiding studies of fishes (Table 2), which may, in turn, contribute to biomedical research.

Growth

Several studies have shown that the first feeding diet can have long-term effects on growth of fishes. Atlantic cod (*Gadus morhua*) and ballan wrasse (*Labrus bergylta*) larvae grew faster when fed zooplankton (primarily copepods) at first feeding, compared to rotifers (*Brachionus plicatilis*) or *Artemia* sp., and this positive effect persisted in juveniles even after an extended common feeding period (Imsland et al. 2006; Koedijk et al. 2010; Øie et al. 2015). In a study of Senegalese sole (*Solea senegalensis*), diets containing protein with different degrees of hydrolysis were given at first feeding followed by a 1-month common feeding. Fish that were fed intact protein (vs. protein hydrolysates composed of peptides) showed greater dry weight as juveniles (Canada et al. 2018). However, in several of these studies, there were no significant differences in growth rates, despite the larger body sizes in the experimental group (Imsland et al. 2006; Øie et al. 2015; Canada et al. 2018). It is not clear whether the growth-promoting effect of zooplankton and intact protein diets is a programming effect or merely a carry-over effect that could be removed by a longer period of common feeding.

Muscle growth and metabolism

A diet that contained a higher lipid:protein ratio given at first feeding produced long-term effects on muscle growth of rainbow trout (*Oncorhynchus mykiss*) (Alami-Durante et al. 2014). Juveniles that were fed the high fat (HF) diet for 75 days beginning at first feeding achieved greater body weight after 3 months of common feeding, compared to juveniles fed the low fat (LF) diet at first feeding. To account for the body size difference after the 75-day feeding period, a third group was maintained on the LF diet for an additional 15 days until they had reached the same weight as HF-fed fish after the 75-day feeding period. When compared to this group, the HF-fed juveniles had consistently smaller diameter white muscle fibers, fewer large white muscle fibers, and reduced expression of genes involved in proliferation and differentiation of muscle precursor cells, demonstrating the potential of early nutrition to program myogenesis (Alami-Durante et al. 2014). In another study, while no short-term changes were observed after 4 weeks on a vitamin-supplemented diet, the first feeding diet modified muscle gene expression in juveniles after a 4-month common feeding period. Specifically, metabolic genes involved in nutrient (lipid, glucose, and amino acid) catabolism (*hoad*, *pk-m*, *gdh3*[2]) and mitochondrial energy metabolism (*qcr2*, *cox4*[3]) were upregulated in the juveniles that were given the vitamin supplementation at first feeding (Panserat et al. 2017).

Brain development

Neural development of fishes in the context of nutritional programming is poorly investigated, but one study indicates that nutrition during the larval stage can have long lasting effects. Larval pikeperch (*Sander lucioperca*) were reared on either a DHA-deficient diet or a DHA-supplemented diet, followed by a prolonged common feeding period. Juveniles grown from the DHA-deficient larval diet had a lower cephalic index

[2] 3-hydroxyacyl-CoA dehydrogenase (*hoad*) is involved in lipid catabolism. Pyruvate kinase muscle isoform (*pkm*) is a glycolytic enzyme that catalyzes the last step in glycolysis. Glutamate dehydrogenase (*gdh*) is involved in amino acid catabolism.

[3] Ubiquitinol cytochrome c reductase core protein 2 (qcr2) and cytochrome oxidase 4 (cox4) are involved in oxidative phosphorylation processes in mitochondria.

(brain mass/body mass × 100) than those fed the DHA-supplemented diet, as well as lower brain DHA content (mg g^{-1} wet weight; Lund et al. 2012).

Stress tolerance/sensitivity

Differences in stress tolerance caused by early nutrition have been reported. When juvenile pikeperch were exposed to a salinity and confinement stress challenge, > 50% mortality occurred among fish reared on a DHA-deficient larval diet prior to a 4-month common feeding period, whereas almost no mortality occurred in groups fed HUFA-supplemented larval diets (Lund et al. 2012). Lund et al. (2012) suggested that the lack of DHA to fuel metabolism rendered the fish more sensitive to energetic deficiencies under stress conditions. Atlantic cod larvae that were fed copepods at first feeding followed by common feeding experienced significantly less mortality 24 h after handling stress (air exposure by netting) than those fed enriched rotifers, which, in turn, had significantly less mortality than cod fed unenriched rotifers (Øie et al. 2015). Lack of DHA was, again, hypothesized to be related to the differences in stress resistance (Øie et al. 2015). European seabass (*Dicentrarchus labrax*) juveniles were fed a high-carbohydrate diet at first feeding, followed by common feeding, during which they exhibited a better tolerance to hypoxia compared to those fed a control diet, but they showed no significant difference in hypoxia tolerance during the challenge phase (Zambonino-Infante et al. 2019).

Inflammation

Ingestion of soybean meal (SBM) is known to cause intestinal inflammation in some fishes. Inclusion of SBM in the first feeding diet protected zebrafish (*Danio rerio*) from inflammation when they ingested SBM again as juveniles. These individuals showed enhanced expression of anti-inflammatory *il10* and reduced expression of the extracellular matrix–remodeling enzymes—*mmp9* and *mmp13*[4]—indicating a low inflammatory and remodeling status. In contrast, soy protein concentrate (SPC) as an early nutritional stimulus induced a greater probability of intestinal inflammation in juveniles that had an SPC nutritional history, which was indicated by greater expression of *il1b, mmp9* and trypsin (*try*) (Perera and Yúfera 2016a). Similar results were found for gilthead seabream (*Sparus aurata*) when they had ingested SBM at first feeding. Expression of *il1b*, *mmp13* were upregulated immediately after the 2-week exposure to SBM, but after removal of SBM they showed significantly reduced expression of these genes (Perera and Yúfera 2016b).

Lipid metabolism

European seabass larvae were given either a high or a low HUFA[5] diet [expressed as eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) at 2.2% or 0.8% on dry matter basis, respectively] from first feeding, followed by a HUFA-rich common diet (2.7%) for 3 months. When juveniles were challenged with a HUFA-depleted diet (0.5%) for about 2 months, those that had been fed the low HUFA diet as larvae had higher DHA content in polar lipids (Vagner et al. 2007). This finding suggests that fish subjected to low HUFA at early stages could counterbalance low dietary intake of HUFA later in life, which was further supported by higher relative expression of the Δ6 desaturase (Δ6D) gene during the first month of the challenge phase (Vagner et al. 2007, 2009).

Carbohydrate metabolism

Excess dietary carbohydrate induces glucose intolerance and becomes a metabolic burden in teleosts, especially carnivorous fishes, which generally have a poor capacity to use carbohydrate as an energy source (Hemre et al. 2002). Several studies have provided evidence of enhanced utilization of dietary carbohydrates in fishes by means of programming. Adult zebrafish that were briefly exposed to a high carbohydrate diet at first feeding showed decreased plasma

[4] Proinflammatory cytokines interleukin 1 β (*il1b*), anti-inflammatory cytokine interleukin 10 (*il10*), matrix remodeling enzyme matrix metalloproteases 9 and 13 (*mmp9* and *mmp13*) are all involved in inflammation in fish. Elevated trypsin levels are associated with intestinal inflammation in fishes.

[5] Highly unsaturated fatty acid (HUFA) usually refers to 22 carbon atoms and at least 3 ethylenic bonds (Tocher 2003) or at least 20 carbon atoms and at least 4 ethylenic bonds (Morais et al. 2004).

glucose levels when challenged with a similar diet, contrary to the expectation for glucose intolerant teleost fishes (Fang et al. 2014). This result, along with altered expression and activity levels of enzymes involved in glycolysis and gluconeogenesis (GK, G6Pase,[6] PEPCK), indicates a greater capability for control of glucose homeostasis induced by early exposure to a high carbohydrate dietary stimulus (Fang et al. 2014). Gilthead seabream that had received a hyperglucidic stimulus during the larval stage showed higher catabolism and lower retention of glucose, and higher bio-conversion of glucose into lipids in tissues when challenged by a high glucose diet (Rocha et al. 2016a, b). In contrast, similar studies conducted on rainbow trout, Siberian sturgeon (*Acipenser baerii*) and European seabass revealed a different response to a high carbohydrate dietary challenge, including absence of, or opposite changes in glucose homeostasis (unaltered or higher postprandial plasma glucose) and/or expression of some genes related to carbohydrate metabolism (Geurden et al. 2007, 2014; Gong et al. 2015; Zambonino-Infante et al. 2019).

In two studies, the combination of a hypoxic stimulus (before/at hatching) and a high carbohydrate dietary stimulus at first feeding programmed glucose metabolism in juvenile rainbow trout. Despite the similar experimental design, effects on genes involved in hepatic and muscular glycolysis and glucose transport were in opposite directions. Juveniles that were exposed to a high-carbohydrate diet for 5 days at first feeding showed a lower level of mRNA for *pfkmbb*[7] in muscle during the challenge phase (Liu et al. 2017), whereas juveniles that were exposed to the same dietary stimulus for 8 days at first feeding showed a higher level of mRNA for *pfkmaa* (both were compared to a control group that was fed a carbohydrate-free diet) (Hu et al. 2018). *Glut*[8] was upregulated as the result of the hypoxic history in one study (Liu et al. 2017), but was downregulated in the other (Hu et al. 2018). The authors suggested that these disparate responses may derive from the differences in the application of the stimuli (duration of exposures, oxygen level) and duration of the common feeding period (Liu et al. 2017; Hu et al. 2018).

Overall, inconsistent results have been reported regarding the programming effect of an early glucidic dietary stimulus on glucose metabolism in fishes. The lack of constant responses across studies certainly invites further investigation.

Fish studies—maternally-derived nutritional stimuli

Contrary to the ever-increasing efforts into investigating programming via nutritional intervention during the larval stage, only a handful of studies have looked at programming via maternal nutrition. Maternally-derived nutrients have direct impacts on offspring during embryogenesis and the endogenous feeding period, and some effects could go beyond yolk exhaustion.

Senegalese sole eggs from broodstock that were fed a diet fortified with polyunsaturated fatty acids (PUFAs) and vitamins during spawning had significantly higher levels of EPA and DHA than eggs produced by adults on the control diet. Larvae reared from those eggs were significantly smaller at hatching but grew faster, resulting in significantly larger juveniles (Morais et al. 2014). In addition, larvae from the supplemented maternal diet had a lower incidence of caudal fin deformity (Morais et al. 2014).

Red drum (*Sciaenops ocellatus*) larvae from eggs that differed in fatty acid composition (achieved by manipulating maternal diets) were fed a DHA-replete diet. DHA content of larvae from eggs with higher levels of DHA was approximately twice that of larvae from eggs with low levels of DHA at approximately 21 days old (Fuiman and Perez 2015). Furthermore, larval traits, such as growth, survival, routine swimming, and escape response performance, were significantly correlated with levels of several HUFAs (including DHA) in larvae. This work identifies the importance of maternal nutrition to lipid metabolism in late stage larvae and a potential link between maternal nutrition and larval performances that are critical to survival, mediated through nutritional programming (Fuiman and Perez 2015).

Deficiency of one-carbon (1-C) micronutrients (vitamin B and methionine) in the parental diet resulted in alterations in the zebrafish embryo

[6] Glucose-6-phosphatase (G6Pase) is involved in glucose production (gluconeogenesis and glycogenolysis).

[7] Phosphofructokinase (*pfkmbb, pfkmaa*) is involved in glycolysis.

[8] Glucose transporter (*Glut*) transports glucose across the plasma membrane.

transcriptome that were associated with offspring health, such as changes in expression of genes related to 1-C cycle and lipid transportation (apolipoproteins) (Skjærven et al. 2016). Offspring from both control and 1-C deficient parental-diet groups were raised on a control diet until maturation, and those from parents fed the 1-C deficient diet exhibited an increased lipid content in the liver and downregulation of genes in the sterol, steroid and lipid biosynthesis and mitochondrial protein translation pathways, compared to controls (Skjærven et al. 2018). Parental 1-C deficiency also caused differential methylation (Skjærven et al. 2018) (discussed in "Epigenetic mechanisms" section).

Replacement of $\geq$ 60% fish oil in the broodstock diet with vegetable oils caused reduced growth in 45-day-old gilthead seabream larvae (compared to controls) when they were given a common diet, although the significant difference disappeared when fish reached 4 months of age (Izquierdo et al. 2015). In addition, total replacement of fish oil in the broodstock diet with linseed oil improved utilization of the diet by offspring, as evidenced by significantly higher specific growth rate (SGR) and lower feed conversion ratio in juveniles after they were challenged with a plant-based diet for 1 month. Turkmen et al. (2017) extended the study by keeping the offspring on the common diet for 18 months, by which time they had begun gonadal development. When they were challenged for the second time with the plant-based diet for 2 months, parental feeding with vegetable oil had significant effects on growth and expression of hepatic enzymes involved in lipid metabolism (*lpl, elovl6, cpt1*[9]). In addition, the type of first challenge diet provided at 4 months of age (either a marine-based or plant-based) influenced growth, feed conversion, and liver fatty acid composition during the second challenge phase, suggesting a programming effect resulting from a dietary stimulus applied at 4 months old. These results highlight an extended programming window that spans from the embryonic to the juvenile period.

[9] *Lpl*, lipoprotein lipase, facilitates the tissue uptake of circulating fatty acids from lipoproteins. *Elovl6*, elongation of very long-chain fatty acids protein 6, is a key lipogenic enzyme that elongates saturated and monounsaturated fatty acids of 12, 14 and 16 carbon atoms and 18:0 is a terminal product of lipogenesis. *Cpt1*, carnitine palmitoyltransferase I, is responsible for the formation of fatty acyl-carnitine esters from fatty acid that allows for the transport into mitochondria for β-oxidation.

Rainbow trout broodstock were fed either a commercial diet (COM, high in fish oils) or a plant-based substitution diet (VEG) for 3 years. At first feeding, alevins produced by these females were given either a diet lacking (n-3) HUFA (V) or diets containing fish oil (C or M). Alevins from COM-fed females had significantly greater body weights and higher levels of (n-3) PUFAs before first feeding, whereas alevins from VEG-fed adults had lower body weights and higher levels of (n-6) PUFA, arachidonic acid (ARA) and α-linolenic acid (ALA). These differences persisted until 3 weeks after first feeding, irrespective of larval diet. Whole-body lipid content after 3 weeks of exogenous feeding revealed effects of both maternal nutritional history and first feeding diet. Alevins that came from COM-fed females and grown on the V diet had significantly lower body lipid content, whereas those from VEG-fed adults and grown on C or M diet showed significantly greater body lipid content. Whole-body transcriptomic analysis, combined with real time quantitative PCR (RT-qPCR), revealed effects of maternal nutritional history on carbohydrate metabolism and energy pathways, and muscle growth and contraction (Lazzarotto et al. 2016).

In summary, the importance of maternal nutrition to larvae beyond endogenous feeding should not be overlooked. To understand how maternal nutrition mediates programming by altering egg composition, it is important to take into consideration the metabolism of adults (especially during oocyte maturation) and the process of nutrient incorporation into developing oocytes. For batch spawning fishes that feed continuously during spawning season, the nutritional composition of food they ingest is reflected in their eggs relatively quickly (Fuiman and Faulk 2013). Some other fishes that decrease or stop feeding during sexual maturation and spawning mobilize body reserves, such as carcass and viscera, abdominal fat, muscle and liver, to supply nutrients needed during yolk formation (Fernández-Palacios et al. 2011). Therefore, egg composition may be relatively stable and, if nutritional programming studies were to use such species, a relatively long feeding period may be required before spawning begins.

Mechanisms

Discussions on mechanisms of programming have been ongoing since the 1990s, yet they remain largely

unknown. One proposed mechanism is by physically altering or impairing somatic structures during a critical period. Alternatively, the nutritional stimulus could "set" or irreversibly switch on or off certain metabolic pathways, resulting in prolonged effects on system functionality (Lucas 1991; Pittman et al. 2013).

In general, nutritional programming induces metabolic changes that can manifest at the tissue, cellular and molecular levels, leading to altered physiological phenotypes. Disruption of either differentiation or proliferation processes under adverse conditions during organ development could yield tissue remodeling. For example, protein restriction during gestation and lactation induced changes in the size of the hypothalamic center (proliferation) as well as density of neurons that express appetite-regulatory neuropeptides (differentiation) (Langley-Evans 2009). Development of diabetes was associated with a reduced number of pancreatic Beta cells (tissue level) and differences in mitochondrial numbers (cellular level) and expression of genes regulating the insulin signaling pathway (molecular level) as a result of poor nutrition in fetal and early infant life (Hales and Barker 1992; Fall 2012). Another common consequence of early nutritional intervention is alteration of energy homeostasis, mediated by several mechanisms including remodeling of the hypothalamic center (tissue level), altered mitochondrial function (production of ATP), reduced oxidative capacity (cellular level), or interference with hormonal secretion and sensitivity (molecular level) (Lucas 1991; Patel et al. 2008; Symonds et al. 2009). The particular mechanism involved is likely to vary based on the nature, timing and duration of the nutritional stimulus (Symonds et al. 2009).

Using fishes as a model to study mechanisms of nutritional programming offers several advantages over mammalian models: (1) their high batch fecundity makes it easy to obtain a large sample size with the same genotype; (2) embryonic development and organogenesis occur externally, allowing easier access to the developing animal and control of environmental conditions; and (3) lecithotrophy provides an opportunity to examine the effects of maternally derived nutrients on embryos and larvae without fluctuations in maternal nutrients, hormones and metabolites during gestation and lactation (Fuiman and Perez 2015) and nutrients contained in fish eggs are fixed and quantifiable compared to the nutrient supply via placenta and lactation in mammals, which are difficult to assess.

Metabolic pathways (Physiological mechanisms)

A useful step toward understanding how early nutrition alters nutrient utilization and programs changes in metabolic pathways is to construct a budget for metabolic compounds of interest. For example, the differential accumulation of DHA in the body of red drum larvae, which is associated with variations in embryonic nutrition, could be the result of differences in DHA inputs (ingestion, digestion, absorption, or biosynthesis) by larvae or differences in the fate of DHA (egestion, excretion, or oxidation) (Fuiman and Perez 2015).

Ingestion

The hypothalamus regulates appetite and influences energy homeostasis (Suzuki et al. 2010). Structural and functional modifications of the hypothalamus as a result of early nutritional stimuli have been reported extensively in the biomedical literature. Rats that were raised in a small litter (postnatal over-nourishment) expressed increased body weight gain, a strong predisposition for hyperinsulinemia, obesity, and other metabolic disorders. They also demonstrated altered activity of neurons in the hypothalamus in response to several neuropeptides, which suggests activation of the orexigenic drive and inhibition of anorexigenic signaling in the hypothalamus (reviewed by Patel et al. 2008). Post-weaning rats that experienced a prenatal high fat diet had greater daily caloric intake and a stronger preference for fat, in addition to elevated body weight, body fat, serum levels of TAG, free fatty acid (FFA), leptin and insulin, as well as elevated orexigenic neuropeptide galanin (GAL) mRNA and peptide levels and elevated cell proliferation and neurogenesis in the hypothalamus (Chang et al. 2008).

There are conflicting results on the development of hyperphagia in response to malnutrition. Caloric restriction (30% of ad libitum intake) during gestation has been shown to lead to permanent growth retardation and increased food intake in rat offspring. This hyperphagia might be attributed to the reduced insulin action, as evidenced by elevated fasting plasma insulin

(Vickers et al. 2000). In contrast, weanling rats had lower numbers of neurons expressing the orexigenic neuropeptides, neuropeptide Y (NPY) and GAL in the arcuate hypothalamic nuclei (ARC) and paraventricular nucleus (PVN), respectively, as a result of maternal protein deficiency during gestation and lactation. These changes were accompanied by modifications in the organization of the PVN and ventromedial nucleus (VMN) of the hypothalamus, all of which may have resulted in the observed reduction in body weight, hypoglycemia, and hypoinsulinemia in these under-nourished rats (Plagemann et al. 2000).

Few studies have examined feed intake of fishes in the context of programming. Different levels of methionine in the diet of rainbow trout broodstock influenced offspring survival and growth, which may be associated with the altered expression of an anorexigenic peptide (proopiomelanocortin A, POMCa) and an orexigenic peptide (NPY) in offspring after hatching, and the effect on POMCa expression remained three weeks after initiation of exogenous feeding (Fontagné-Dicharry et al. 2017). In contrast, Geurden et al. (2007) and Gong et al. (2015) reported no effects on feed intake of juvenile rainbow trout or Siberian sturgeon after early hyperglucidic stimuli.

Appetite regulation in fishes is incompletely understood. It is still not clear when during development the internal appetite regulating mechanisms become functional in larval fishes (Bonacic et al. 2016). Fish larvae generally feed constantly if prey are available, which suggests that the satiety signals (anorexigenic factors) generated by the gastrointestinal tract (GIT) are not yet functional (Rønnestad et al. 2013). In addition, there is great variability among species in the roles of appetite-regulating factors (Volkoff 2016). Therefore, caution is required when using data from mammals or other fish species to infer that a programming effect might be mediated by ingestion rates (appetite). For instance, it has been shown that chemical stimuli applied during perinatal periods can modify innate flavor preferences in mammals. For example, rat offspring exposed to innately aversive odors/flavors through maternal diet or during early post-weaning showed increased acceptability and voluntary ingestion of these substances (London et al. 1979; Youngentob and Glendinning 2009). Similarly, the greater intake of a plant-based diet during the challenge phase in rainbow trout was suggested to be due to either a change in flavor preference or an alleviated food flavor neophobia by exposure to the plant materials at first feeding (Geurden et al. 2013). A follow-up study that used microarray analysis showed that the plant-based diet altered the pathway related to flavor acquisition and feed preferences (Balasubramanian et al. 2016).

Digestion

To date, little is known about the programming effect on the GIT or digestive function (except for the endocrine pancreas). Decreased activities of the digestive enzymes maltase, aminopeptidase M, and glycyl-leucine dipeptidase in the intestine of rat offspring at the adult stage was associated with protein deficiency during pregnancy and lactation (Timofeeva et al. 2000). However, Guilloteau et al. (2010) suggested that rodents are not a suitable model for studying programming of GIT because their GIT development and digestive function are different from those in man.

For most fish species, measurable activities of digestive enzymes are present as early as the onset of exogenous feeding (Izquierdo et al. 2000) or at hatching (Oozeki and Bailey 1995; Lazo et al. 2011), despite the incomplete development of the digestive system. Specific digestive enzymes become active at different stages (Govoni et al. 1986; Kolkovski 2001; Thompson et al. 2019) and this process is nutrient sensitive (Lazo et al. 2011). After receiving a hyperglucidic diet during the larval stage, juvenile rainbow trout upregulated expression of pancreatic α-amylase and intestinal maltase when challenged with a high carbohydrate diet (Geurden et al. 2007). Adult zebrafish that had been exposed to a high glucose stimulus at first feeding exhibited enhanced expression and activity of α-amylase when challenged (Fang et al. 2014). Gilthead seabream larvae that were fed SBM for 2 weeks since first feeding showed decreased pancreatic enzyme activities (trypsin, chymotrypsin, amylase) and reduced growth. After the SBM was removed from the diet, these larvae resumed chymotrypsin and amylase activities, but trypsin activity and growth did not recover (Perera and Yúfera 2016b).

Absorption and transport

After 3 weeks of common feeding, juvenile zebrafish that were fed the SBM diet at first feeding showed enhanced fatty acid transport and suppressed peptide

absorption, marked by upregulation of intestinal *fabp2* and downregulation of *slc15a1*.[10] The authors suggested that the intestine is very likely to be susceptible to programming of the early diet (Perera and Yúfera 2016a).

Oxidation

Oxidation of fatty acids is an important source of energy and a key process in energy homeostasis. Studies have shown that modified mitochondrial oxidation is associated with development of metabolic syndrome. Intrauterine growth retardation (IUGR) is associated with metabolic syndrome during adulthood (Valsamakis et al. 2006). Preweaning rats with IUGR showed increased mitochondrial lipid oxidation machinery (increased mRNA levels of *cpt*I, UCP3, and HADHA, and increased HADH activity[11]), which is associated with increased energy expenditure and oxygen consumption and elevated TAG levels in skeletal muscle, indicating dysregulation of skeletal muscle mitochondrial metabolism (Lane et al. 2001). In another study, offspring of rats that had received a high sucrose diet during pregnancy and lactation experienced a variety of metabolic responses, including increased adipose tissue weight (but not body weight), elevated levels of TAG in the plasma and liver, enhanced de novo lipogenesis activity in the liver, secretion of very-low density lipoprotein-TAG (VLDL-TAG), and reduced mitochondrial fatty acid oxidation (CPTI activity) (D'Alessandro et al. 2014).

In marine fishes, β-oxidation capacity may be programmed by the maternal or first feeding diet. Feeding a diet based on linseed oil to gilthead seabream broodstock caused downregulation of *cpt*Ib expression in the liver of offspring (Turkmen et al. 2017). The same response was reported in the liver of juvenile rainbow trout that were given vitamin supplementation at first feeding (Panserat et al. 2017).

It has been suggested that the altered oxidation associated with dietary manipulations was primarily the result of changes in the availability of dietary fatty acids, rather than direct stimulation of the β-oxidation system (Turchini and Francis 2009; Eroldoğan et al. 2013). The significant, positive correlation between the relative expression of *cpt*Ib and the fatty acid, 18:1(n-9), in the gilthead seabream seems to support this argument (monounsaturated fatty acids, such as 18:1(n-9), generally are regarded as energy substrates). However, opposing evidence is accumulating. Impaired mitochondrial function was suggested as the molecular mechanism of reduced hepatic fatty acid oxidation in rat offspring from obese parents (fed a high caloric diet), as evidenced by several hepatic mitochondrial function markers (Borengasser et al. 2011). In another study, offspring of rats subjected to methyl donor deficiency during gestation and lactation suffered from impaired mitochondrial fatty acid oxidation, as shown by downregulation of key enzymes involved in mitochondrial fatty acid oxidation (HADHA, SCAD[12]) and decreased activity of complexes I and II (Pooya et al. 2012). Related Epigenetic mechanisms are discussed below.

Biosynthesis

The biomedical literature provides evidence for associations between metabolic disorders and biosynthesis of PUFAs. Growth retarded rat offspring showed reduced Δ5 desaturase (Δ5D)[13] activity in hepatic microsomes as a result of maternal protein restriction (Ozanne et al. 1998). Susceptibility to obesity is correlated with Δ5D, Δ6D, Δ9 desaturase activities in humans (estimated by product: precursor fatty acid ratios) (Warensjö et al. 2006).

Marine fishes were traditionally thought to lack the ability to synthesize HUFAs in sufficient amounts to meet their nutritional requirements (Sargent et al. 1995). However, a number of studies revealed that HUFA synthesis may not be completely absent in marine fishes (Seiliez et al. 2003; Zheng et al.

[10] Fatty acid binding protein 2 gene (*fabp*) is related to fatty acid transport and uptake. Solute carrier family 15 oligopeptide transporter member 1b (*slc15a1*) is related dipeptide and tripeptide absorption and growth in fishes (Perera and Yúfera 2016a).

[11] CPTI (carnitine palmitoyltransferase I) and UCP3 (uncoupling protein 3) regulates skeletal muscle fatty acid oxidation and their expression is positively associated with increased substrate flux for mitochondrial β-oxidation. HADH (trifunctional protein of β-oxidation, also referred to as TFE, MTPA) is an inner mitochondrial membrane protein and its function causes a decline in NAD + /NADH ratio in skeletal muscle mitochondria, which subsequently leads to a reduced Krebs cycle flux. HADHA is the HADH α subunit (Lane et al. 2001).

[12] SCAD (short chain acyl-CoA dehydrogenase).

[13] Δ5D mediates synthesis of ARA and EPA from their respective precursors, 20:3(n-6) and 20:4(n-3).

2004, 2009; Tocher et al. 2006) and is regulated by dietary HUFA levels (reviewed by Monroig et al. 2011). However, the extent to which the synthesis pathway is activated in marine fishes remains to be clarified.

Several studies have shown altered fatty acid synthesis activities in fishes as a result of programming, although most of them focused on the gene expression level. Increased levels of replacement of fish oil with linseed oil [higher levels of ALA and linoleic acid (LA)] in broodstock diets resulted in progressively increased expression of the Δ6D gene in gilthead seabream larvae, except that Δ6D expression was significantly repressed in offspring from adults fed a pure vegetable oil diet (Izquierdo et al. 2015; Turkmen et al. 2019). The elevated biosynthetic activity persisted until the juvenile stage (4 months old), as evidenced by an increase in ARA, EPA and DHA levels and a reduction in their precursors in the liver with an increased maternal dietary level of linseed oil (Turkmen et al. 2019). When the larvae from partial replacement groups reached adulthood, they showed downregulation of hepatic elongase (*Elovl6*) (Turkmen et al. 2017). Elevated transcript levels of the genes involved in the fatty acid biosynthesis were observed in Senegalese sole embryos (elongase 5 (*Elovl5*)) and newly hatched larvae (*Elovl5* and Δ4 desaturase (*Δ4fad*)) when broodstock were fed a regular diet (compared with a HUFA-supplemented diet), suggesting an ability to regulate lipid metabolism that becomes effective as early as the embryonic period (Morais et al. 2014). The differences, however, were later reversed, with enhanced expression of *Δ4fad* at 2 dph (days post-hatching) and both *Δ4fad* and *Elovl5* at 7 dph in larvae from the HUFA-supplemented broodstock diet. Juvenile European seabass given a HUFA-deficient diet during the larval period showed enhanced expression of Δ6D, higher DHA content in polar lipids, when challenged with a HUFA-deficient diet, concomitant with upregulation of three forms of PPAR (peroxisome proliferator-activated receptors, α, β, and γ) (Vagner et al. 2007, 2009). Interestingly, when given a larval diet high in ALA and low in DHA, 21-day-old red drum larvae reared from eggs that contained lower DHA levels had elevated levels of fatty acids in the initial steps of the n-3 HUFA biosynthetic pathway (i.e., stearidonic acid, 18:4n-3; eicosatrienoic acid 20:3n-3; eicosatetraenoic acid 20:4n-3) compared to larvae from eggs that contained higher DHA levels, suggesting a compensatory response stimulated by deficiency of DHA during the embryonic period (Faulk and Fuiman, *submitted*).

Epigenetic mechanisms

Epigenetics refers to heritable modifications that are independent of changes in the DNA sequence which ultimately result in changes in gene expression (Villeneuve and Natarajan 2011). Diet, among other environmental stimuli, can trigger epigenetic modifications. Methylation of CpG islands (CpG-rich clusters), which are typically located at the promoter regions of genes and are free of methylation, is associated with transcription repression. Histone lysine acetylation, in contrast, promotes transcription. Histone lysine methylation can either promote or repress transcription depending on the lysine residue modified (Villeneuve and Natarajan 2011).

It has been proposed that adaptive changes in gene expression associated with nutritional programming remain silent until the same or opposite environmental stimuli arise again (Symonds et al. 2009). Epigenetics bridges the time gap by giving cells "metabolic memory" of a previous nutritional state (Villeneuve and Natarajan 2011). It also links the prenatal nutritional environment with metabolic disease in later life because epigenetic patterns are heritable (Fall 2012).

There is growing evidence of epigenetic regulation of metabolism-related genes associated with early nutrition. A maternal high-fat diet induced hyperacetylation in fetal hepatic tissue at H3K14 in Japanese macaques, as well as the expression and function of several key components of epigenetic machinery, including upregulation of DNA methyltransferase 1 (*Dnmt1*) and downregulation of histone deacetylase 1 (HDAC1[14]) (Aagaard-Tillery et al. 2008). Such site-specific alteration in H3 acetylation rather than a potentially disastrous global histone modification may provide important insights into the regulatory mechanism of the expression of genes integral to glucose and lipid homeostasis (Aagaard-

[14] *Dnmt 1* is responsible for methylation maintenance during cell replication. HDAC1-Dnmt1 complexes initiate the recruitment of methyl-CpG-binding domain proteins that mediate CpG island methylation.

Tillery et al. 2008). Increased maternal intake of fish oil during gestation and lactation in rats induced higher methylation levels in several CpG dinucleotides in the promoter of the Δ6D gene (*fads2*), which led to lower expression of *fads2* (Hoile et al. 2013). Since the offspring were maintained on a post-weaning soybean-oil-based diet, in which LA and ALA (precursors for (n-3) and (n-6) HUFAs, respectively) were the only PUFAs, levels of ARA and DHA in liver and plasma phospholipids were lower in offspring when they reached adulthood (Hoile et al. 2013). This study strongly suggests an epigenetic mechanism that effectively alters the metabolic phenotypes in the offspring by maternal nutrition (Hoile et al. 2013).

In a mouse population having a genetic tendency for obesity, a methyl-supplemented diet provided during development prevented the cumulative and amplified effect of maternal obesity (demonstrated in the control group) in successive generations, suggesting the possible role of epigenetics in mediating metabolic syndrome (Waterland et al. 2008). Maternal protein restriction during pregnancy in rats induced hypomethylation in PPARα and glucocorticoid receptor (GR) promoter regions in the liver of offspring, which led to higher mRNA levels in these genes, concomitant with increased expression levels of PEPCK, and acyl-CoA oxidase (AOX), and decreased expression level of *Dnmt1* (Lillycrop et al. 2005, 2007). PPAR are nuclear receptors that play a crucial role in lipid-metabolism regulation in addition to their role in regulating growth and differentiation. AOX is an enzyme in the peroxisomal β-oxidation pathway and a target gene of PPAR, and PEPCK is a target gene of GR. These findings suggest a relation between epigenetic regulation of nuclear receptors induced by early nutrition and the subsequent effect on expression of important metabolic genes (Lillycrop et al. 2007). In addition, they corroborate the speculation of Desai et al. (1995) that programming of PEPCK expression occurs before transcription (see in "Mammalian studies—Carbohydrate metabolism" section).

While the epigenetic mechanisms provide a compelling explanation for nutritionally programmed metabolic syndrome in mammals, evidence of epigenetic mechanisms being associated with nutritional programming in fishes is still scarce. Early feeding of SBM to gilthead seabream larvae produced a reversible increase in global histone H3 acetylation and a persistent global DNA hypomethylation after removal of the SBM diet (Perera and Yúfera 2016b). These epigenetic modifications could be responsible for the altered transcription of genes related to digestion and inflammation that was observed in the SBM-fed larvae. The sulfur-containing essential amino acid methionine emerges as a potential epigenetic modulator of nutritional programming in fishes. In rainbow trout, broodstock dietary methionine levels mediated expression of several genes involved in the metabolism of sulfur-containing amino acids (Fontagné-Dicharry et al. 2017), cholesterol, and glucose (gluconeogenesis) (Seiliez et al. 2017) in larvae after 21 days of feeding. Whether an epigenetic mechanism is involved was not clarified, but it certainly is plausible.

The mechanisms by which various types of nutritional intervention induce epigenetic modifications are largely unknown, but it may be related to some nutrient components or metabolites that act as regulators or substrates of enzymes that catalyze DNA methylation/histone modifications or affect methyl donor availability (Choi and Friso 2010; Feil and Fraga 2012). In the aforementioned studies by Lillycrop et al. (2005, 2007), hypomethylation of hepatic GR and PPARα in offspring and subsequent changes in gene expression induced by maternal protein restriction were prevented by supplementation of folic acid, suggesting its role as the mediator of epigenetic modifications. Dietary vitamins are known to interact with the epigenome of mammals, either as cofactors or substrates of enzymes involved in DNA methylation or histone modifications (Chango and Pogribny 2015; Young et al. 2015). A maternal diet free of methyl donors (vitamin B12 and folate) induced hypomethylation of PPARγ co-activator-1 (PGC1-α), as well as reduced expression levels of nuclear receptors, which led to a dramatic decrease in the interaction of PGC1-α with PPAR-α, ERR-α and HNF-4α[15] in the liver of young rats (Pooya et al. 2012). These epigenetic and subsequent modifications were believed to be responsible for the impairment of mitochondrial fatty acid oxidation and liver steatosis. In rainbow trout, differences in dietary intake of vitamins at first feeding induced different patterns of global DNA methylation

[15] ER-α, estrogen receptor α; ERR-α, estrogen-related receptor α; HNF-4α, hepatic nuclear factor 4α.

and H3 acetylation in the liver, whereas the majority of the programming effects on gene transcription involved in nutrient catabolism and mitochondrial metabolism occurred in muscle, instead of liver (Panserat et al. 2017). This study provides evidence that vitamins could also program a fish's epigenome, although the link between epigenetic and phenotypic modifications as a result of this nutritional stimulus needs clarification. Maternal 1-C (vitamin B and methionine) deficiency increased lipid inclusion, altered expression of genes involved in the lipid biosynthetic pathway and DNA methylation at more than 2800 CpG sites in the liver of zebrafish offspring (Skjærven et al. 2018). These included hypermethylation and downregulation of genes encoding proteins in the mitochondrial respiratory chain (e.g., succinate dehydrogenase complex), and demethylation of genes important for cell growth and proliferation during brain development (e.g., *ppp2r2ba*[16]) in the promoter region. Clarifying the developmental stage at which DNA methylation differences were established will be helpful for understanding how parental nutrition influences gene expression during brain development via epigenetic regulation (Skjærven et al. 2018). High levels of ARA in the maternal diet altered gene expression related to the methionine cycle, lipid and retinoid metabolism (Adam et al. 2018), and DNA methylation patterns in the liver of zebrafish offspring, although whether these methylation modifications functionally regulate gene expression remains to be clarified (Adam et al. 2019).

Important aspects of nutritional programming

Reversibility

There is considerable evidence in support of protracted or permanent effects of nutritional programming on growth, metabolism and critical organ functions, even after a period of common feeding following an early nutritional stimulus. For example, a (n-3) PUFA-deficient diet provided from gestation until 6 weeks post-weaning caused reduction in DHA in phospholipids in the hypothalamus of rat offspring, and it was not recovered after 24 weeks of feeding on a high-PUFA diet (Li et al. 2006). Dietary DHA deficiency during the larval stage resulted in an irreversible reduction in cephalic index of juvenile pikeperch. A subsequent 4-month common feeding period mostly restored the fatty acid composition of the brain, although the DHA level failed to reach control levels (Lund et al. 2012). However, restoration of DHA in the brain through dietary recuperation does not necessarily mean recovery of brain functions. For example, in 10- to 24-month-old rhesus monkeys that had received a (n-3) HUFA-depleted diet, a diet rich in (n-3) HUFA restored normal brain levels of DHA in phosphatidylethanolamine (PE) within 12 weeks (Connor et al. 1990), but a normal electroretinogram, which measured the retina-evoked response to flashes of light, was not restored (Connor et al. 1992).

Whether animals are able to recover from an early nutritional stimulus seems to depend on the timing of the onset of the stimulus. Winick and Noble (1966) proposed that the earlier an animal is exposed to nutrient deficiency, the greater the likelihood that the stunting effect will be long-lasting, based on work with a rat model, which we will refer to as the "early priority hypothesis." The concept was based on a study on rats in which a 21-day calorie-restricted diet was initiated at birth, at weaning (day 21), and at day 65, followed by a normal diet until adulthood. All three groups showed reduced growth in organs but with progressively better recovery. The first group (diet restricted at birth) did not recover normal body or organ weight. In the second group (diet restricted at weaning), only the brain and lungs attained normal weight at maturity. All organs in the third group (diet restricted at day 65) recovered except the thymus. Since growth results from hyperplasia (during early development) and hypertrophy (later), Winick and Noble (1966) proposed that early malnutrition impedes cell division, which produces an irreversible stunting effect, and that malnutrition at a later period leads to reduction of cell size, from which the animal could recover. This work established the concept of a critical window of developmental plasticity and a link with persistence of nutritional programming. It laid the foundation for subsequent work aimed at specifying the critical window for nutritional programming.

[16] *ppp2r2ba*, encodes protein phosphatase 2, regulatory subunit B, β a.

Critical window

The early priority hypothesis is supported by several studies that used the classical cross-fostering experimental paradigm. Hepatic metabolism was permanently altered in groups that received low protein nutrition throughout the prenatal and postnatal periods or during only the prenatal period, while not in the postnatal low protein group (Desai et al. 1995). Interestingly, a follow-up study revealed the critical role of postnatal nutrition during lactation in determining subsequent growth (Desai et al. 1996). In this study, the postnatal low protein group started with birth weight comparable to that of the control group, but their growth rate decreased continuously, resulting in significantly lower body weight at weaning and thereafter. Conversely, the recuperate group (prenatal low protein, postnatal normal protein) exhibited lower initial weight, but caught up quickly even though weight was still significantly lower than controls at weaning, but was indistinguishable from controls at adulthood. This result seemed to contradict the early priority hypothesis in that postnatal (instead of prenatal) protein restriction had a major effect on growth. But the authors pointed out that the timing of nutritional rehabilitation was equally important as the timing of nutrition deprivation because nutritional compensation immediately after birth corrected the body weight deficit, but rehabilitation after weaning did not (Desai et al. 1996).

For fishes, the embryonic and larval periods are characterized by organogenesis, establishment of metabolic pathways, and high metabolic plasticity. Therefore, they are "vulnerable" to nutritional stimuli encountered during this period. In general, studies on fishes agree with the early priority hypothesis. While rainbow trout juveniles that received a hyperglucidic diet at first feeding showed upregulation of the carbohydrate digestive enzymes α-amylase and maltase, those fed the same diet after yolk absorption (3 weeks after first feeding) failed to show upregulation of maltase (Geurden et al. 2007). A study which took into consideration the complex genome (due to a whole-genome duplication event) of rainbow trout suggests that first feeding might be too late to program glucose metabolism because glucose metabolism-related genes exhibited patterns similar to those of juveniles without any alterations in response to a high-carbohydrate diet (compared to control) soon after first feeding (Marandel et al. 2016). In contrast, the critical window for programming glucose metabolism (transport, glycolysis, and gluconeogenesis) in zebrafish extends from the first-feeding stage until a brief period after yolk exhaustion (Fang et al. 2014). Soybean meal diets given to yellow perch (*Perca flavescens*) during juvenile stage (followed by common feeding and challenge phase) revealed no significant differences in growth or reproductive performances compared to fish fed the fish meal diet (Kemski et al. 2018). Among many plausible explanations, it is likely that the juvenile stage is too late to program development of fishes.

An experimental approach—microinjection of nutrients into eggs—is especially useful for elucidating the critical window. Microinjection of zebrafish eggs with an overdose of glucose (a 43-fold increase in egg glucose concentration) at 0.2 days postfertilization (dpf) downregulated expression of genes involved in a range of metabolic pathways, including glycolysis, glycogenolysis, glucose transport, lipogenesis, and carbohydrate digestion at 4 dpf (endogenous feeding period), but such effects disappeared after the onset of exogenous feeding and were only observed in few genes of juveniles (41 dpf) challenged with a hyperglucidic diet (Rocha et al. 2014). In contrast, a sixfold ^{14}C-labled glucose increase at 1 dpf (before hatching) induced significantly lower visceral retention of glucose in juvenile zebrafish (35 dpf) after they were challenged with a hyperglucidic diet (Rocha et al. 2015). Such differences might be explained by cellular damage or compromised key metabolic regulators caused by microinjection at a very early stage (0.2 dpf), whereas 1 dpf is a period of organogenesis when there is a high degree of plasticity for establishment and activation of important metabolic pathways (Rocha et al. 2015).

These studies collectively suggest that plasticity is greater during rapidly developing stages and it decreases as development proceeds. Programming can be viewed as a consequence of the plasticity during early life (Langley-Evans 2009). During this critical window, animals experience rapid cell differentiation and proliferation, making them sensitive to nutritional environments (Symonds et al. 2009). Similarly, Hales and Barker (1992) suggested that the timing and precise nature of the nutritional stimuli have a determinative role in the pattern of metabolic and functional abnormalities later in life as a result of

the specific timing of cell division in different tissues. This explains the varying critical windows for programming different physiological processes. That is, different physiological processes correspond to different time frames of a critical window, which depends upon the timeline of functional development of the specific pathway/organ. In addition to the time of a nutritional stimulus, its duration can be an important factor. Gilthead seabream larvae showed reduced growth when they were given a SBM diet for 14 days from first feeding, whereas larvae that were given the same diet for 10 days showed normal growth (Perera and Yúfera 2016b).

Adaptiveness

A key notion concerning nutritional programming is that it is adaptive—that it confers fitness advantages under certain nutritional conditions by modulating metabolic phenotypes and altering growth trajectories accordingly (Lucas 1991). Hales and Barker (1992) put forth a "thrifty phenotype hypothesis" that proposed poor early nutrition as the cause of a reduced number of pancreatic Beta cells and reduced insulin secretion in humans in anticipation of continued under-nutrition but ultimately predisposes to Type 2 diabetes in times of adequate nutrition. This hypothesis is valuable in connecting early nutrition with metabolic diseases at a later stage, but more importantly, in shaping our view of the adaptive meaning of nutritional programming. Being "nutritionally thrifty" under the circumstances of nutritional deprivation, programming could permanently alter adult metabolism in a way that ensures short-term survival, and is beneficial when such a nutritional condition continues, but detrimental when there is a mismatch between early and future nutritional environments (Hales et al. 1996). A prominent example is catch-up growth, which refers to the accelerated growth induced by increased nutrition in formerly growth-retarded offspring (due to malnutrition). It is well-documented that catch-up growth is associated with the development of obesity in adulthood (Bieswal et al. 2006; West-Eberhard 2019). According to West-Eberhard (2019), the global epidemic of obesity is a result of nutritional status mismatch on a massive scale: populations that underwent transition from poverty and poor nutrition to improvement of nutrition or migration are prone to development of obesity and other metabolic diseases, and this situation is exacerbated by high-caloric diets.

Challenge experiments have shown that early exposure could successfully adapt fishes to nutritionally suboptimal but economically superior substitution diets, such as hyperglucidic, low HUFA, or plant-based diets (Geurden et al. 2007, 2013; Vagner et al. 2007, 2009; Rocha et al. 2015, 2016a; Perera and Yúfera 2016a; Clarkson et al. 2017). That is, these diets improve utilization of suboptimal nutrients by increasing acceptance or modifying metabolic pathways without compromising growth when the animal is challenged. For example, when rainbow trout were challenged with the same plant-based diet for 25 days after a 7-month common feeding period, those that were fed a plant-based diet for 3 weeks at first feeding showed better growth, concomitant with higher feed intake and feed utilization efficiency, in comparison to fish that were fed the control diet (containing fishmeal and fish oil) (Geurden et al. 2013). Conditioning at first feeding with a vegetable-based diet produced faster growth, better feed efficiency, and greater retention of EPA and DHA in Atlantic salmon (*Salmo salar*) when challenged (Clarkson et al. 2017).

Confounding factors

Identifying the particular nutritional components that cause programming in fishes poses numerous challenges. First, the studies that have been published to date employed a variety of experimental conditions—dietary treatments, onset and duration of nutritional stimulus, etc.—which makes it difficult to identify commonalities. For example, although vegetable oils generally contain low amounts of long chain HUFAs and (n-3) fatty acids but greater amounts of shorter chain and (n-6) fatty acids, the specific composition and essential fatty acid ratios vary among different vegetable oils. This variability is increased by the different dietary inclusion levels used. Second, while most studies have focused on the programming effect of a single class of nutrients, there could be concurrent changes in the dietary availability of non-target macronutrients or micronutrients as a result of dietary manipulation, so it might be as important to consider the balance of nutrients (Symonds et al. 2009; Collins et al. 2013). One study has shown that high blood pressure in people with low birth weights is associated

with a low protein/carbohydrate ratio of the average ration during pregnancy instead of any other absolute measures of intake (Roseboom et al. 2001). Third, it is difficult to control the actual nutrient consumption by broodstock or larvae. With regard to applying interventions to the larval diet, nutritional profiles of live prey vary greatly depending on the culture method, enrichment products applied, and the metabolism of the live prey. For example, a liposome technique (which encapsulates water-soluble nutrients in microparticles such as liposomes) has shown efficacy for enrichment of live prey, but nutrient concentration in the live prey may vary based on the liposome membrane composition (Tonheim et al. 2000; Hawkyard et al. 2016). The metabolism of the live prey (e.g., rotifers, copepods, *Artemia*) could also alter their intended nutritional profile, introducing additional variation to the nutrition received by larvae [although lowering the temperature has been suggested to decrease the rate of metabolism of rotifers and extend the storage of nutrients (Hawkyard et al. 2016)]. For example, *Artemia* tend to retroconvert DHA to EPA, and rotifers tend to digest phospholipids and store the digestive products as TAG (Hamre et al. 2013). These factors make the process of identifying nutritional components responsible for nutritional programming more complicated.

Early nutrition may act together with other environmental factors, such as oxygen, temperature and pH, and cause differential metabolic responses in organisms (Panserat et al. 2019). For example, it has been demonstrated that a high-carbohydrate dietary stimulus during embryonic and early larval stages can induce changes in carbohydrate metabolism in juvenile rainbow trout, but when combined with hypoxic conditions, the effects differed and there was an interaction between dietary history and oxygen level (Liu et al. 2017; Hu et al. 2018). These complicated responses remain largely unexplored but are becoming more relevant with the ever-increasing number and variety of environmental disturbances.

Future prospects and significance

Langley-Evans (2009) pointed out that the focus of current studies—characterizing the processes that mediate the metabolic consequences of programming—may be the secondary phenomenon of programming rather than the fundamental basis of programming. The "gatekeeper" hypothesis proposes that changes in a few "gatekeeper" genes or gene pathways whose expression has a major impact on cell type and number, tissue function, and homeostasis may represent the core responses that are common to nutritionally programmed metabolic disorders, irrespective of the nutritional stimuli experienced. Therefore, a systematic and unbiased search for the "gatekeeper" genes should be a priority for identifying underlying mechanisms of nutritional programming (Langley-Evans 2009; McMullen et al. 2012).

The emerging field of nutrigenomics could spearhead this effort. Nutrigenomics uses a collection of powerful tools, including transcriptomics, proteomics, metabolomics and high-throughput genotyping, to understand observed phenotypes and recognize pathways that are altered by nutrition on a genome scale (reviewed by Trujillo et al. 2006; Kersten, 2011). The exploratory nature of nutrigenomic techniques makes it very promising for becoming a valuable tool in studies of nutritional programming. Microarray analysis was employed as a tool to identify the molecular mechanisms involved in nutritional programming in rainbow trout and Atlantic salmon, where a plant-based diet given at first feeding improved feed acceptance of the same diet in juveniles (Geurden et al. 2013; Clarkson et al. 2017). Several pathways were differentially expressed in juvenile rainbow trout challenged with the plant-based diet, including flavor and feed preferences, intermediary metabolism, proteolysis, and cytoskeletal regulation of the cell cycle (Balasubramanian et al. 2016). In Atlantic salmon liver, key pathways of intermediary metabolism, including oxidative phosphorylation, pyruvate metabolism, TCA cycle, glycolysis and fatty acid metabolism, were upregulated in response to the plant-based diet, all of which are involved in the conversion of dietary nutrients to cellular components (Vera et al. 2017).

Nutrients such as fatty acids could act as the building blocks of tissues that interfere with somatic growth and organogenesis, or as the energy substrates that influence energy homeostasis. Additional roles that are less understood are their functions in regulation of transcription via interactions with transcription factors and nuclear receptors [e.g., PPAR, HNF, retinoid X receptor (RXR)] (Jump 2004). Nutrigenomics could be used as a tool to identify the nutrient

components that act as dietary signals, transcription factors that act as nutrient sensors, and the signaling pathways (Müller and Kersten 2003).

Many current research efforts on fishes report responses in gene expression without confirmation of protein changes or functional significance. Changes in gene expression alone may not necessarily translate into a significant physiological impact, so the programming effects may be exaggerated or misleading if interpretation is based solely on gene expression results. On the other hand, epigenetic modifications may be functionally significant, since as little as a two-fold difference in methylation could have a measurable physiological impact (Langley-Evans 2009). Technologies such as methylated DNA immunoprecipitation-sequencing (MeDIP-seq) and bisulfite pyrosequencing greatly facilitate genome-wide analysis of epigenetic modification (Li et al. 2010). Integrating data from different "omics" approaches, would provide an accurate and robust representation of the actual condition (Samuelsson and Larsson 2008; Mathers 2017).

Early life mortality rates of fishes are exceedingly high compared to other vertebrates, estimated to be $> 88\%$ between fertilization and hatching (Fuiman et al. 2015) and as high as 99% over the larval period (Houde 1997). Nutritional programming may operate in nature through altered maternal and larval diets (caused by food-web changes; Fuiman 2018) and influence offspring performance (growth, sensory/brain function, locomotor performance, and stress response) that is crucial to survival. These effects could extend to recruitment and adult populations, given that small variations in early life mortality rates can have order-of-magnitude consequences for year-class strength and population size (Houde 2006).

Sustainable aquaculture requires reduction in the use of fisheries products in feeds and at least partial replacement with more sustainable ingredients (Izquierdo et al. 2015). Nutritional programming is a promising strategy to improve aquaculture production at a lower cost and with fewer environmental impacts (Engrola et al. 2018; Panserat et al. 2019), which could be achieved by manipulating broodstock diet or through nutritional intervention during the larval period. Some current finfish aquaculture research is motivated by the physiological adaptability demonstrated by fishes through nutritional programming (see in "Adaptiveness" section) and has successfully applied this strategy to several economically important fish species. Further work is needed to determine how long the programming effects created in this manner persist and whether they have detrimental side effects.

Research into nutritional programming in fishes has just begun and questions remain unanswered about every aspect: causes, outcomes, duration (persistence), critical window, and the underlying mechanisms. To date, research has been conducted on only a small number of fish species. Results are expected to vary among species that differ in natural habitats, nutritional requirements, developmental programs, and life histories. In the future, expanding the number of species in which programming is investigated might provide important insights into the question. In addition, it has been pointed out that many studies report programming effects without following the whole life-course of the animals (Langley-Evans 2009), and this is especially true for studies on fishes, most of which were terminated during the juvenile stage or earlier. Extending the duration of experiments, perhaps to multiple generations (Panserat et al. 2019) could lead to important benefits to the biomedical, ecological, and aquacultural communities.

Acknowledgement The authors would like to thank Cynthia Faulk for her critical reading and insightful comments on the manuscript.

References

Aagaard-Tillery KM, Grove K, Bishop J, Ke X, Fu Q, McKnight R, Lane RH (2008) Developmental origins of disease and determinants of chromatin structure: maternal diet modifies the primate fetal epigenome. J Mol Endocrinol 41:91–102. https://doi.org/10.1677/JME-08-0025

Adam A-C, Skjærven KH, Whatmore P, Moren M, Lie KK (2018) Parental high dietary arachidonic acid levels modulated the hepatic transcriptome of adult zebrafish (*Danio rerio*) progeny. PLoS ONE 13:e0201278. https://doi.org/10.1371/journal.pone.0201278

Adam A-C, Lie KK, Whatmore P, Jakt LM, Moren M, Skjærven KH (2019) Profiling DNA methylation patterns of zebrafish liver associated with parental high dietary arachidonic acid. PLoS ONE 14:e0220934. https://doi.org/10.1371/journal.pone.0220934

Alami-Durante H, Cluzeaud M, Duval C, Maunas P, Girod-David V, Médale F (2014) Early decrease in dietary protein:energy ratio by fat addition and ontogenetic changes in muscle growth mechanisms of rainbow trout: short- and

long-term effects. Br J Nutr 112:674–687. https://doi.org/10.1017/S0007114514001391

Balasubramanian MN, Panserat S, Dupont-Nivet M, Quillet E, Montfort J, Cam AL, Medale F, Kaushik SJ, Geurden I (2016) Molecular pathways associated with the nutritional programming of plant-based diet acceptance in rainbow trout following an early feeding exposure. BMC Genomics 17:1–20. https://doi.org/10.1186/s12864-016-2804-1

Bieswal F, Ahn M-T, Reusens B, Holvoet P, Raes M, Rees WD, Remacle C (2006) The importance of catch-up growth after early malnutrition for the programming of obesity in male rat. Obesity 14:1330–1343. https://doi.org/10.1038/oby.2006.151

Bonacic K, Campoverde C, Gómez-Arbonés J, Gisbert E, Estevez A, Morais S (2016) Dietary fatty acid composition affects food intake and gut–brain satiety signaling in Senegalese sole (*Solea senegalensis*, Kaup 1858) larvae and post-larvae. Gen Comp Endocrinol 228:79–94. https://doi.org/10.1016/j.ygcen.2016.02.002

Borengasser SJ, Lau F, Kang P, Blackburn ML, Ronis MJJ, Badger TM, Shankar K (2011) Maternal obesity during gestation impairs fatty acid oxidation and mitochondrial SIRT3 expression in rat offspring at weaning. PLoS ONE 6:e24068. https://doi.org/10.1371/journal.pone.0024068

Canada P, Engrola S, Mira S, Teodósio R, del Yust M, Sousa V, Pedroche J, Fernandes JMO, Conceição LEC, Valente LMP (2018) Larval dietary protein complexity affects the regulation of muscle growth and the expression of DNA methyltransferases in Senegalese sole. Aquaculture 491:28–38. https://doi.org/10.1016/j.aquaculture.2018.02.044

Chang G-Q, Gaysinskaya V, Karatayev O, Leibowitz SF (2008) Maternal high-fat diet and fetal programming: increased proliferation of hypothalamic peptide-producing neurons that increase risk for overeating and obesity. J Neurosci 28:12107–12119. https://doi.org/10.1523/JNEUROSCI.2642-08.2008

Chango A, Pogribny I (2015) Considering maternal dietary modulators for epigenetic regulation and programming of the fetal epigenome. Nutrients 7:2748–2770. https://doi.org/10.3390/nu7042748

Choi S-W, Friso S (2010) Epigenetics: a new bridge between nutrition and health. Adv Nutr 1:8–16. https://doi.org/10.3945/an.110.1004

Clarkson M, Migaud H, Metochis C, Vera LM, Leeming D, Tocher DR, Taylor JF (2017) Early nutritional intervention can improve utilisation of vegetable-based diets in diploid and triploid Atlantic salmon *Salmo salar*. Br J Nutr 118:17–29. https://doi.org/10.1017/S0007114517001842

Coates PM, Brown SA, Sonawane BR, Koldovsky O (1983) Effect of early nutrition on serum cholesterol levels in adult rats challenged with high fat diet. J Nutr 113:1046–1050

Collins SA, Øverland M, Skrede A, Drew MD (2013) Effect of plant protein sources on growth rate in salmonids: meta-analysis of dietary inclusion of soybean, pea and canola/rapeseed meals and protein concentrates. Aquaculture 400:85–100. https://doi.org/10.1016/j.aquaculture.2013.03.006

Connor WE, Neuringer M, Lin DS (1990) Dietary effects on brain fatty acid composition: the reversibility of n-3 fatty acid deficiency and turnover of docosahexaenoic acid in the brain, erythrocytes, and plasma of rhesus monkeys. J Lipid Res 31:237–247

Connor WE, Neuringer M, Reisbick S (1992) Essential fatty acids: the importance of n-3 fatty acids in the retina and brain. Nutr Rev 50:21–29. https://doi.org/10.1111/j.1753-4887.1992.tb01286.x

Corapci F, Radan AE, Lozoff B (2006) Iron deficiency in infancy and mother-child interaction at 5 years. J Dev Behav Pediatr 27:371

D'Alessandro M, Eugenia Oliva M, Alejandra Fortino M, Chicco A (2014) Maternal sucrose-rich diet and fetal programming: changes in hepatic lipogenic and oxidative enzymes and glucose homeostasis in adult offspring. Food Funct 5:446–453. https://doi.org/10.1039/C3FO60436E

Desai M, Crowther NJ, Ozanne SE, Lucas A, Hales CN (1995) Adult glucose and lipid metabolism may be programmed during fetal life. Biochem Soc Trans 23:331–335

Desai M, Crowther NJ, Lucas A, Hales CN (1996) Organ-selective growth in the offspring of protein-restricted mothers. Br J Nutr 76:591–603

Engelbregt MJT, Houdijk MECAM, Popp-Snijders C, Delemarre-van de Waal HA (2000) The effects of intra-uterine growth retardation and postnatal undernutrition on onset of puberty in male and female rats. Pediatr Res 48:803–807. https://doi.org/10.1203/00006450-200012000-00017

Engrola S, Aragão C, Valente LMP, Conceição LEC (2018) Nutritional modulation of marine fish larvae performance. In: Yúfera M (ed) Emerging issues in fish larvae research. Springer, Cham, pp 209–228

Eroldoğan TO, Yilmaz AH, Turchini GM, Arslan M, Sirkecioğlu NA, Engin K, Özşahinoğlu I, Mumoğullarında P (2013) Fatty acid metabolism in European sea bass (*Dicentrarchus labrax*): effects of n-6 PUFA and MUFA in fish oil replaced diets. Fish Physiol Biochem Dordr 39:941–955. https://doi.org/10.1007/s10695-012-9753-7

Fall CHD (2012) Fetal programming and the risk of noncommunicable disease. Indian J Pediatr 80:13–20. https://doi.org/10.1007/s12098-012-0834-5

Fang L, Liang X-F, Zhou Y, Guo X-Z, He Y, Yi T-L, Liu L-W, Yuan X-C, Tao Y-X (2014) Programming effects of high-carbohydrate feeding of larvae on adult glucose metabolism in zebrafish, *Danio rerio*. Br J Nutr 111:808–818. https://doi.org/10.1017/S0007114513003243

Faulk CK and Fuiman LA. Nutritional programming of n-3 highly unsaturated fatty acid metabolism in larvae of the marine fish *Sciaenops ocellatus*. Fish Physiol Biochem (Submitted).

Feil R, Fraga MF (2012) Epigenetics and the environment: emerging patterns and implications. Nat Rev Genet 13:97–109. https://doi.org/10.1038/nrg3142

Fernández-Palacios H, Norberg B, Izquierdo M, Hamre K (2011) Effects of broodstock diet on eggs and larvae. Larval Fish Nutrition. John Wiley and Sons Publisher, Oxford, UK, Wiley-Blackwell, pp 151–181

Fernandez-Twinn DS, Ozanne SE (2010) Early life nutrition and metabolic programming. Ann N Y Acad Sci 1212:78–96. https://doi.org/10.1111/j.1749-6632.2010.05798.x

Fontagné-Dicharry S, Alami-Durante H, Aragão C, Kaushik SJ, Geurden I (2017) Parental and early-feeding effects of dietary methionine in rainbow trout (*Oncorhynchus*

mykiss). Aquaculture 469:16–27. https://doi.org/10.1016/j.aquaculture.2016.11.039

Fuiman LA (2018) Egg boon fatty acids reveal effects of a climatic event on a marine food web. Ecol Monogr 88:585–599. https://doi.org/10.1002/ecm.1324

Fuiman LA, Faulk CK (2013) Batch spawning facilitates transfer of an essential nutrient from diet to eggs in a marine fish. Biology Letters 9(5):20130593

Fuiman LA, Perez KO (2015) Metabolic programming mediated by an essential fatty acid alters body composition and survival skills of a marine fish. Proc R Soc B Biol Sci 282:20151414. https://doi.org/10.1098/rspb.2015.1414

Fuiman LA, Connelly TL, Lowerre-Barbieri SK, McClelland JW (2015) Egg boons: central components of marine fatty acid food webs. Ecology 96:362–372. https://doi.org/10.1890/14-0571.1

Geurden I, Aramendi M, Zambonino-Infante J, Panserat S (2007) Early feeding of carnivorous rainbow trout (*Oncorhynchus mykiss*) with a hyperglucidic diet during a short period: effect on dietary glucose utilization in juveniles. Am J Physiol Regul Integr Comp Physiol 292:R2275–R2283. https://doi.org/10.1152/ajpregu.00444.2006

Geurden I, Borchert P, Balasubramanian MN, Schrama JW, Dupont-Nivet M, Quillet E, Kaushik SJ, Panserat S, Médale F (2013) The positive impact of the early-feeding of a plant-based diet on its future acceptance and utilisation in rainbow trout. PLoS ONE 8:e83162. https://doi.org/10.1371/journal.pone.0083162

Geurden I, Mennigen J, Plagnes-Juan E, Veron V, Cerezo T, Mazurais D, Zambonino-Infante J, Gatesoupe J, Skiba-Cassy S, Panserat S (2014) High or low dietary carbohydrate:protein ratios during first-feeding affect glucose metabolism and intestinal microbiota in juvenile rainbow trout. J Exp Biol 217:3396–3406. https://doi.org/10.1242/jeb.106062

Gong G, Xue M, Wang J, Wu X, Zheng Y, Han F, Liang X, Su X (2015) The regulation of gluconeogenesis in the Siberian sturgeon (*Acipenser baerii*) affected later in life by a short-term high-glucose programming during early life. Aquaculture 436:127–136. https://doi.org/10.1016/j.aquaculture.2014.10.044

Govoni JJ, Boehlert GW, Watanabe Y (1986) The physiology of digestion in fish larvae. Environ Biol Fishes 16:59–77. https://doi.org/10.1007/BF00005160

Guilloteau P, Zabielski R, Hammon HM, Metges CC (2010) Nutritional programming of gastrointestinal tract development. Is the pig a good model for man? Nutr Res Rev 23:4–22. https://doi.org/10.1017/S0954422410000077

Hahn P (1984) Effect of litter size on plasma cholesterol and insulin and some liver and adipose tissue enzymes in adult rodents. J Nutr 114:1231–1234

Hales CN, Barker DJP (1992) Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 35:595–601. https://doi.org/10.1007/BF00400248

Hales CN, Desai M, Ozanne SE, Crowther NJ (1996) Fishing in the stream of diabetes: from measuring insulin to the control of fetal organogenesis. Biochem Soc Trans 24:341–350

Hamre K, Yúfera M, Rønnestad I, Boglione C, Conceição LEC, Izquierdo M (2013) Fish larval nutrition and feed formulation: knowledge gaps and bottlenecks for advances in larval rearing. Rev Aquac 5:S26–S58. https://doi.org/10.1111/j.1753-5131.2012.01086.x

Hawkyard M, Stuart K, Langdon C, Drawbridge M (2016) The enrichment of rotifers (*Brachionus plicatilis*) and *Artemia franciscana* with taurine liposomes and their subsequent effects on the larval development of California yellowtail (*Seriola lalandi*). Aquac Nutr 22:911–922. https://doi.org/10.1111/anu.12317

Hemre G-I, Mommsen TP, Krogdahl Å (2002) Carbohydrates in fish nutrition: effects on growth, glucose metabolism and hepatic enzymes. Aquac Nutr 8:175–194. https://doi.org/10.1046/j.1365-2095.2002.00200.x

Hoile SP, Irvine NA, Kelsall CJ, Sibbons C, Feunteun A, Collister A, Torrens C, Calder PC, Hanson MA, Lillycrop KA, Burdge GC (2013) Maternal fat intake in rats alters 20:4n-6 and 22:6n-3 status and the epigenetic regulation of *Fads2* in offspring liver. J Nutr Biochem 24:1213–1220. https://doi.org/10.1016/j.jnutbio.2012.09.005

Houde ED (1997) Patterns and trends in larval-stage growth and mortality of teleost fish. J Fish Biol 51:52–83. https://doi.org/10.1111/j.1095-8649.1997.tb06093.x

Houde ED (2006) Subtleties and episodes in the early life of fishes. J Fish Biol 35:29–38. https://doi.org/10.1111/j.1095-8649.1989.tb03043.x

Hu H, Liu J, Plagnes-Juan E, Herman A, Leguen I, Goardon L, Geurden I, Panserat S, Marandel L (2018) Programming of the glucose metabolism in rainbow trout juveniles after chronic hypoxia at hatching stage combined with a high dietary carbohydrate: protein ratios intake at first-feeding. Aquaculture 488:1–8. https://doi.org/10.1016/j.aquaculture.2018.01.015

Imsland AK, Foss A, Koedijk R, Folkvord A, Stefansson SO, Jonassen TM (2006) Short- and long-term differences in growth, feed conversion efficiency and deformities in juvenile Atlantic cod (*Gadus morhua*) startfed on rotifers or zooplankton. Aquac Res 37:1015–1027. https://doi.org/10.1111/j.1365-2109.2006.01523.x

Izquierdo MS, Socorro J, Arantzamendi L, Hernández-Cruz CM (2000) Recent advances in lipid nutrition in fish larvae. Fish Physiol Biochem 22:97–107. https://doi.org/10.1023/A:1007810506259

Izquierdo MS, Turkmen S, Montero D, Zamorano MJ, Afonso JM, Karalazos V, Fernández-Palacios H (2015) Nutritional programming through broodstock diets to improve utilization of very low fishmeal and fish oil diets in gilthead sea bream. Aquaculture 449:18–26. https://doi.org/10.1016/j.aquaculture.2015.03.032

Jump DB (2004) Fatty acid regulation of gene transcription. Crit Rev Clin Lab Sci 41:41–78. https://doi.org/10.1080/10408360490278341

Kemski M, Wick M, Dabrowski K (2018) Nutritional programming effects on growth and reproduction of broodstock and embryonic development of progeny in yellow perch (*Perca flavescens*) fed soybean meal-based diets. Aquaculture 497:452–461. https://doi.org/10.1016/j.aquaculture.2018.07.001

Kersten AH (2011) Nutrigenomics of fatty acid sensing. In: Rodriguez RL, Bidlack WR (eds) Nutritional genomics: the impact of dietary regulation of gene function on human disease. CRC Press, Boca Raton, pp 173–184

Koedijk RM, Folkvord A, Foss A, Pittman K, Stefansson SO, Handeland S, Imsland AK (2010) The influence of first-feeding diet on the Atlantic cod *Gadus morhua* phenotype: survival, development and long-term consequences for growth. J Fish Biol 77:1–19. https://doi.org/10.1111/j.1095-8649.2010.02652.x

Kolkovski S (2001) Digestive enzymes in fish larvae and juveniles—implications and applications to formulated diets. Aquaculture 200:181–201. https://doi.org/10.1016/S0044-8486(01)00700-1

Lane RH, Kelley DE, Ritov VH, Tsirka AE, Gruetzmacher EM (2001) Altered expression and function of mitochondrial β-oxidation enzymes in juvenile intrauterine-growth-retarded rat skeletal muscle. Pediatr Res 50:83–90. https://doi.org/10.1203/00006450-200107000-00016

Langley-Evans SC (2009) Nutritional programming of disease: unravelling the mechanism. J Anat 215:36–51. https://doi.org/10.1111/j.1469-7580.2008.00977.x

Lazo JP, Darias MJ, Gisbert E (2011) Ontogeny of the digestive tract. In: Holt GJ (ed) Larval fish nutrition. John Wiley and Sons Publisher, Oxford, UK, Wiley-Blackwell, pp 5–46

Lazzarotto V, Corraze G, Larroquet L, Mazurais D, Médale F (2016) Does broodstock nutritional history affect the response of progeny to different first-feeding diets? A whole-body transcriptomic study of rainbow trout alevins. Br J Nutr 115:2079–2092. https://doi.org/10.1017/S0007114516001252

Lemonnier D, Suquet JP, Aubert R, Rosselin G (1973) Long term effect of mouse neonate food intake on adult body composition, insulin and glucose serum levels. Horm Metab Res 5:223–224. https://doi.org/10.1055/s-0028-1096731

Lewis DS, Bertrand HA, McMahan CA, McGill HC, Carey KD, Masoro EJ (1986) Preweaning food intake influences the adiposity of young adult baboons. J Clin Invest 78:899–905. https://doi.org/10.1172/JCI112678

Li D, Weisinger HS, Weisinger RS, Mathai M, Armitage JA, Vingrys AJ, Sinclair AJ (2006) Omega 6 to omega 3 fatty acid imbalance early in life leads to persistent reductions in DHA levels in glycerophospholipids in rat hypothalamus even after long-term omega 3 fatty acid repletion. Prostaglandins Leukot Essent Fatty Acids 74:391–399. https://doi.org/10.1016/j.plefa.2006.03.010

Li N, Ye M, Li Y, Yan Z, Butcher LM, Sun J, Han X, Chen Q, Zhang X, Wang J (2010) Whole genome DNA methylation analysis based on high throughput sequencing technology. Methods 52:203–212. https://doi.org/10.1016/j.ymeth.2010.04.009

Lillycrop KA, Phillips ES, Jackson AA, Hanson MA, Burdge GC (2005) Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. J Nutr 135:1382–1386

Lillycrop KA, Slater-Jefferies JL, Hanson MA, Godfrey KM, Jackson AA, Burdge GC (2007) Induction of altered epigenetic regulation of the hepatic glucocorticoid receptor in the offspring of rats fed a protein-restricted diet during pregnancy suggests that reduced DNA methyltransferase-1 expression is involved in impaired DNA methylation and changes in histone modifications. Br J Nutr 97:1064–1073. https://doi.org/10.1017/S000711450769196X

Liu J, Dias K, Plagnes-Juan E, Veron V, Panserat S, Marandel L (2017) Long-term programming effect of embryonic hypoxia exposure and high-carbohydrate diet at first feeding on glucose metabolism in juvenile rainbow trout. J Exp Biol 220:3686–3694. https://doi.org/10.1242/jeb.161406

London RM, Snowdon CT, Smithana JM (1979) Early experience with sour and bitter solutions increases subsequent ingestion. Physiol Behav 22:1149–1155. https://doi.org/10.1016/0031-9384(79)90270-1

Lozoff B, Jimenez E, Wolf AW (1991) Long-term developmental outcome of infants with iron deficiency. N Engl J Med 325:687–694. https://doi.org/10.1056/NEJM199109053251004

Lucas A (1991) Programming by early nutrition in man. In: Bock GR, Whelan J (eds) The childhood environment and adult disease. CIBA Foundation Symposium 156. Wiley, Chichester, UK, pp 38–55

Lucas A (1998) Programming by early nutrition: an experimental approach. J Nutr 128:401S–406S

Lucas A, Baker BA, Desai M, Hales CN (1996) Nutrition in pregnant or lactating rats programs lipid metabolism in the offspring. Br J Nutr 76:605–612

Lund I, Skov PV, Hansen BW (2012) Dietary supplementation of essential fatty acids in larval pikeperch (*Sander lucioperca*); short and long term effects on stress tolerance and metabolic physiology. Comp Biochem Physiol A Mol Integr Physiol 162:340–348. https://doi.org/10.1016/j.cbpa.2012.04.004

Marandel L, Véron V, Surget A, Plagnes-Juan É, Panserat S (2016) Glucose metabolism ontogenesis in rainbow trout (*Oncorhynchus mykiss*) in the light of the recently sequenced genome: new tools for intermediary metabolism programming. J Exp Biol 219:734–743. https://doi.org/10.1242/jeb.134304

Mathers JC (2017) Nutrigenomics in the modern era. Proc Nutr Soc 76:265–275. https://doi.org/10.1017/S002966511600080X

McMullen S, Langley-Evans SC, Gambling L, Lang C, Swali A, McArdle HJ (2012) A common cause for a common phenotype: the gatekeeper hypothesis in fetal programming. Med Hypotheses 78:88–94. https://doi.org/10.1016/j.mehy.2011.09.047

Monroig Ó, Navarro JC, Tocher DR (2011) Long-chain polyunsaturated fatty acids in fish: recent advances on desaturases and elongases involved in their biosynthesis. In: Cruz-Suárez LE, Ricque-Marie D, Tapia-Salazar M, Nieto-López MG, Villarreal-Cavazos DA, Gamboa-Delgado J, Hernández-Hernández L (eds) Avances en Nutrición Acuícola XI—Memorias del Décimo Primer Simposio Internacional de Nutrición Acuícola, 23–25 de Noviembre, San Nicolás de los Garza, N. L., México. Universidad Autónoma de Nuevo León, Monterrey, México, pp 257–283

Morais S, Cahu C, Zambonino-Infante JL, Robin J, Rønnestad I, Dinis MT, Conceição LEC (2004) Dietary TAG source and level affect performance and lipase expression in larval sea bass (*Dicentrarchus labrax*). Lipids 39:449. https://doi.org/10.1007/s11745-004-1250-2

Morais S, Mendes AC, Castanheira MF, Coutinho J, Bandarra N, Dias J, Conceição LEC, Pousão-Ferreira P (2014) New

formulated diets for *Solea senegalensis* broodstock: Effects of parental nutrition on biosynthesis of long-chain polyunsaturated fatty acids and performance of early larval stages and juvenile fish. Aquaculture 432:374–382. https://doi.org/10.1016/j.aquaculture.2014.04.033

Morisson M, Coustham V, Frésard L, Collin A, Zerjal T, Métayer-Coustard S, Bodin L, Minvielle F, Brun J-M, Pitel F (2017) Nutritional programming and effect of ancestor diet in birds. In: Patel V, Preedy V (eds) Handbook of nutrition, diet, and epigenetics. Springer International Publishing, Cham, pp 1–18

Müller M, Kersten S (2003) Nutrigenomics: goals and strategies. Nat Rev Genet 4:315–322. https://doi.org/10.1038/nrg1047

Øie G, Galloway T, Sørøy M, Holmvaag Hansen M, Norheim IA, Halseth CK, Almli M, Berg M, Gagnat MR, Wold P-A, Attramadal K, Hagemann A, Evjemo JO, Kjørsvik E (2015) Effect of cultivated copepods (*Acartia tonsa*) in first-feeding of Atlantic cod (*Gadus morhua*) and ballan wrasse (*Labrus bergylta*) larvae. Aquac Nutr. https://doi.org/10.1111/anu.12352

Oozeki Y, Bailey KM (1995) Ontogenetic development of digestive enzyme activities in larval walleye pollock, *Theragra chalcogramma*. Mar Biol 122:177–186. https://doi.org/10.1007/BF00348930

Ozanne SE, Martensz ND, Petry CJ, Loizou CL, Hales CN (1998) Maternal low protein diet in rats programmes fatty acid desaturase activities in the offspring. Diabetologia 41:1337–1342. https://doi.org/10.1007/s001250051074

Panserat S, Marandel L, Geurden I, Veron V, Dias K, Plagnes-Juan E, Pegourié G, Arbenoits E, Santigosa E, Weber G, Verlhac Trichet V (2017) Muscle catabolic capacities and global hepatic epigenome are modified in juvenile rainbow trout fed different vitamin levels at first feeding. Aquaculture 468:515–523. https://doi.org/10.1016/j.aquaculture.2016.11.021

Panserat S, Marandel L, Seiliez I, Skiba-Cassy S (2019) New insights on intermediary metabolism for a better understanding of nutrition in teleosts. Annu Rev Anim Biosci 7:195–220. https://doi.org/10.1146/annurev-animal-020518-115250

Patel MS, Srinivasan M, Laychock SG (2008) Metabolic programming: role of nutrition in the immediate postnatal life. J Inherit Metab Dis 32:218–228. https://doi.org/10.1007/s10545-008-1033-4

Perera E, Yúfera M (2016a) Soybean meal and soy protein concentrate in early diet elicit different nutritional programming effects on juvenile zebrafish. Zebrafish 13:61–69. https://doi.org/10.1089/zeb.2015.1131

Perera E, Yúfera M (2016b) Effects of soybean meal on digestive enzymes activity, expression of inflammation-related genes, and chromatin modifications in marine fish (*Sparus aurata* L.) larvae. Fish Physiol Biochem. https://doi.org/10.1007/s10695-016-0310-7

Petry CJ, Ozanne SE, Hales CN (2001) Programming of intermediary metabolism. Mol Cell Endocrinol 185:81–91. https://doi.org/10.1016/S0303-7207(01)00627-X

Pittman K, Yúfera M, Pavlidis M, Geffen AJ, Koven W, Ribeiro L, Zambonino-Infante JL, Tandler A (2013) Fantastically plastic: fish larvae equipped for a new world. Rev Aquac 5:S224–S267. https://doi.org/10.1111/raq.12034

Plagemann A, Harder T, Rake A, Melchior K, Rohde W, Dörner G (2000) Hypothalamic nuclei are malformed in weanling offspring of low protein malnourished rat dams. J Nutr 130:2582–2589. https://doi.org/10.1093/jn/130.10.2582

Pooya S, Blaise S, Moreno Garcia M, Giudicelli J, Alberto J-M, Guéant-Rodriguez R-M, Jeannesson E, Gueguen N, Bressenot A, Nicolas B, Malthiery Y, Daval J-L, Peyrin-Biroulet L, Bronowicki J-P, Guéant J-L (2012) Methyl donor deficiency impairs fatty acid oxidation through PGC-1α hypomethylation and decreased ER-α, ERR-α, and HNF-4α in the rat liver. J Hepatol 57:344–351. https://doi.org/10.1016/j.jhep.2012.03.028

Rao KR, Padmavathi IJN, Raghunath M (2012) Maternal micronutrient restriction programs the body adiposity, adipocyte function and lipid metabolism in offspring: a review. Rev Endocr Metab Disord 13:103–108. https://doi.org/10.1007/s11154-012-9211-y

Rocha F, Dias J, Engrola S, Gavaia P, Geurden I, Dinis MT, Panserat S (2014) Glucose overload in yolk has little effect on the long-term modulation of carbohydrate metabolic genes in zebrafish (*Danio rerio*). J Exp Biol 217:1139–1149. https://doi.org/10.1242/jeb.095463

Rocha F, Dias J, Engrola S, Gavaia P, Geurden I, Dinis MT, Panserat S (2015) Glucose metabolism and gene expression in juvenile zebrafish (*Danio rerio*) challenged with a high carbohydrate diet: effects of an acute glucose stimulus during late embryonic life. Br J Nutr 113:403–413. https://doi.org/10.1017/S0007114514003869

Rocha F, Dias J, Geurden I, Dinis MT, Panserat S, Engrola S (2016a) High-glucose feeding of gilthead seabream (*Sparus aurata*) larvae: effects on molecular and metabolic pathways. Aquaculture 451:241–253. https://doi.org/10.1016/j.aquaculture.2015.09.015

Rocha F, Dias J, Geurden I, Dinis MT, Panserat S, Engrola S (2016b) Dietary glucose stimulus at larval stage modifies the carbohydrate metabolic pathway in gilthead seabream (*Sparus aurata*) juveniles: an in vivo approach using ^{14}C-starch. Comp Biochem Physiol A Mol Integr Physiol 201:189–199. https://doi.org/10.1016/j.cbpa.2016.07.016

Rønnestad I, Yúfera M, Ueberschär B, Ribeiro L, Sæle Ø, Boglione C (2013) Feeding behaviour and digestive physiology in larval fish: current knowledge, and gaps and bottlenecks in research. Rev Aquac 5:S59–S98. https://doi.org/10.1111/raq.12010

Roseboom TJ, van der Meulen JHP, Ravelli ACJ, Osmond C, Barker DJP, Bleker OP (2001) Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview. Twin Res Hum Genet 4:293–298. https://doi.org/10.1375/twin.4.5.293

Samuelsson LM, Larsson DGJ (2008) Contributions from metabolomics to fish research. Mol Biosyst 4:974–979. https://doi.org/10.1039/B804196B

Sargent JR, Bell JG, Bell MV, Henderson RJ, Tocher DR (1995) Requirement criteria for essential fatty acids. J Appl Ichthyol 11:183–198. https://doi.org/10.1111/j.1439-0426.1995.tb00018.x

Seiliez I, Panserat S, Corraze G, Kaushik S, Bergot P (2003) Cloning and nutritional regulation of a Δ6-desaturase-like enzyme in the marine teleost gilthead seabream (*Sparus aurata*). Comp Biochem Physiol B Biochem Mol Biol

135:449–460. https://doi.org/10.1016/S1096-4959(03)00111-8

Seiliez I, Vélez EJ, Lutfi E, Dias K, Plagnes-Juan E, Marandel L, Panserat S, Geurden I, Skiba-Cassy S (2017) Eating for two: Consequences of parental methionine nutrition on offspring metabolism in rainbow trout (*Oncorhynchus mykiss*). Aquaculture 471:80–91. https://doi.org/10.1016/j.aquaculture.2017.01.010

Sinclair KD, Rutherford KMD, Wallace JM, Brameld JM, Stöger R, Alberio R, Sweetman D, Gardner DS, Perry VEA, Adam CL, Ashworth CJ, Robinson JE, Dwyer CM (2016) Epigenetics and developmental programming of welfare and production traits in farm animals. Reprod Fertil Dev 28:1443–1478. https://doi.org/10.1071/RD16102

Skjærven KH, Jakt LM, Dahl JA, Espe M, Aanes H, Hamre K, Fernandes JMO (2016) Parental vitamin deficiency affects the embryonic gene expression of immune-, lipid transport- and apolipoprotein genes. Sci Rep 6:34535. https://doi.org/10.1038/srep34535

Skjærven KH, Jakt LM, Fernandes JMO, Dahl JA, Adam A-C, Klughammer J, Bock C, Espe M (2018) Parental micronutrient deficiency distorts liver DNA methylation and expression of lipid genes associated with a fatty-liver-like phenotype in offspring. Sci Rep 8:1–16. https://doi.org/10.1038/s41598-018-21211-5

Smart JL (1986) Undernutrition, learning and memory: review of experimental studies. In: Taylor TG, Jenkins NK (eds) Proceedings of XIII International Congress of Nutrition. John Libbey, London, pp 74–78

Suzuki K, Simpson KA, Minnion JS, Shillito JC, Bloom SR (2010) The role of gut hormones and the hypothalamus in appetite regulation. Endocr J 57:359–372. https://doi.org/10.1507/endocrj.K10E-077

Symonds ME, Sebert SP, Hyatt MA, Budge H (2009) Nutritional programming of the metabolic syndrome. Nat Rev Endocrinol 5:604–610. https://doi.org/10.1038/nrendo.2009.195

Thompson KL, Faulk CK, Fuiman LA (2019) Applying the ontogeny of digestive enzyme activity to guide early weaning of pigfish, *Orthopristis chrysoptera* (L.). Aquac Res 50:1404–1410. https://doi.org/10.1111/are.14015

Timofeeva NM, Egorova VV, Nikitina AA (2000) Metabolic/food programming of enzyme systems in digestive and nondigestive organs of rats. Dokl Biol Sci 375:587–589

Tocher DR (2003) Metabolism and functions of lipids and fatty acids in teleost fish. Rev Fish Sci 11:107–184. https://doi.org/10.1080/713610925

Tocher DR, Zheng X, Schlechtriem C, Hastings N, Dick JR, Teale AJ (2006) Highly unsaturated fatty acid synthesis in marine fish: cloning, functional characterization, and nutritional regulation of fatty acyl Δ6 desaturase of Atlantic cod (*Gadus morhua* L.). Lipids 41:1003–1016. https://doi.org/10.1007/s11745-006-5051-4

Tonheim SK, Koven W, Rønnestad I (2000) Enrichment of *Artemia* with free methionine. Aquaculture 190:223–235. https://doi.org/10.1016/S0044-8486(00)00402-6

Trujillo E, Davis C, Milner J (2006) Nutrigenomics, proteomics, metabolomics, and the practice of dietetics. J Am Diet Assoc 106:403–413. https://doi.org/10.1016/j.jada.2005.12.002

Turchini GM, Francis DS (2009) Fatty acid metabolism (desaturation, elongation and β-oxidation) in rainbow trout fed fish oil- or linseed oil-based diets. Br J Nutr 102:69–81. https://doi.org/10.1017/S0007114508137874

Turkmen S, Zamorano MJ, Fernández-Palacios H, Hernández-Cruz CM, Montero D, Robaina L, Izquierdo M (2017) Parental nutritional programming and a reminder during juvenile stage affect growth, lipid metabolism and utilisation in later developmental stages of a marine teleost, the gilthead sea bream (*Sparus aurata*). Br J Nutr 118:500–512. https://doi.org/10.1017/S0007114517002434

Turkmen S, Hernández-Cruz CM, Zamorano MJ, Fernández-Palacios H, Montero D, Afonso JM, Izquierdo M (2019) Long-chain PUFA profiles in parental diets induce long-term effects on growth, fatty acid profiles, expression of fatty acid desaturase 2 and selected immune system-related genes in the offspring of gilthead seabream. Br J Nutr 122:25–38. https://doi.org/10.1017/S0007114519000977

Vagner M, Zambonino Infante JL, Robin JH, Person-Le Ruyet J (2007) Is it possible to influence European sea bass (*Dicentrarchus labrax*) juvenile metabolism by a nutritional conditioning during larval stage? Aquaculture 267:165–174. https://doi.org/10.1016/j.aquaculture.2007.01.031

Vagner M, Robin JH, Zambonino-Infante JL, Tocher DR, Person-Le Ruyet J (2009) Ontogenic effects of early feeding of sea bass (*Dicentrarchus labrax*) larvae with a range of dietary n-3 highly unsaturated fatty acid levels on the functioning of polyunsaturated fatty acid desaturation pathways. Br J Nutr 101:1452–1462. https://doi.org/10.1017/S0007114508088053

Valsamakis G, Kanaka-Gantenbein C, Malamitsi-Puchner A, Mastorakos G (2006) Causes of intrauterine growth restriction and the postnatal development of the metabolic syndrome. Ann N Y Acad Sci 1092:138–147. https://doi.org/10.1196/annals.1365.012

Vera LM, Metochis C, Taylor JF, Clarkson M, Skjærven KH, Migaud H, Tocher DR (2017) Early nutritional programming affects liver transcriptome in diploid and triploid Atlantic salmon *Salmo salar*. BMC Genomics. https://doi.org/10.1186/s12864-017-4264-7

Vickers MH, Breier BH, Cutfield WS, Hofman PL, Gluckman PD (2000) Fetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition. Am J Physiol-Endocrinol Metab 279:E83–E87. https://doi.org/10.1152/ajpendo.2000.279.1.E83

Villeneuve L, Natarajan R (2011) Role of epigenetics in the complications associated with diabetes and related metabolic disorders. Nutritional genomics: the impact of dietary regulation of gene function on human disease. CRC Press, Boca Raton, pp 41–60

Volkoff H (2016) The neuroendocrine regulation of food intake in fish: a review of current knowledge. Front Neurosci. https://doi.org/10.3389/fnins.2016.00540

Warensjö E, Öhrvall M, Vessby B (2006) Fatty acid composition and estimated desaturase activities are associated with obesity and lifestyle variables in men and women. Nutr Metab Cardiovasc Dis 16:128–136. https://doi.org/10.1016/j.numecd.2005.06.001

Waterland RA, Travisano M, Tahiliani KG, Rached MT, Mirza S (2008) Methyl donor supplementation prevents transgenerational amplification of obesity. Int J Obes 32:1373–1379. https://doi.org/10.1038/ijo.2008.100

West-Eberhard MJ (2019) Nutrition, the visceral immune system, and the evolutionary origins of pathogenic obesity. Proc Natl Acad Sci 116:723–731. https://doi.org/10.1073/pnas.1809046116

Winick M, Noble A (1966) Cellular response in rats during malnutrition at various ages. J Nutr 89:300–306

Yehuda S, Youdim MEH, Mostofsky DI (1986) Brain iron-deficiency causes reduced learning capacity in rats. Pharmacol Biochem Behav 25:141–144. https://doi.org/10.1016/0091-3057(86)90244-3

Young JI, Züchner S, Wang G (2015) Regulation of the epigenome by vitamin C. Annu Rev Nutr 35:545–564. https://doi.org/10.1146/annurev-nutr-071714-034228

Youngentob SL, Glendinning JI (2009) Fetal ethanol exposure increases ethanol intake by making it smell and taste better. Proc Natl Acad Sci 106:5359–5364. https://doi.org/10.1073/pnas.0809804106

Zambonino-Infante JL, Panserat S, Servili A, Mouchel O, Madec L, Mazurais D (2019) Nutritional programming by dietary carbohydrates in European sea bass larvae: not always what expected at juvenile stage. Aquaculture 501:441–447. https://doi.org/10.1016/j.aquaculture.2018.11.056

Zheng X, Seiliez I, Hastings N, Tocher DR, Panserat S, Dickson CA, Bergot P, Teale AJ (2004) Characterization and comparison of fatty acyl Δ6 desaturase cDNAs from freshwater and marine teleost fish species. Comp Biochem Physiol B Biochem Mol Biol 139:269–279. https://doi.org/10.1016/j.cbpc.2004.08.003

Zheng X, Ding Z, Xu Y, Monroig O, Morais S, Tocher DR (2009) Physiological roles of fatty acyl desaturases and elongases in marine fish: characterisation of cDNAs of fatty acyl Δ6 desaturase and elovl5 elongase of cobia (*Rachycentron canadum*). Aquaculture 290:122–131. https://doi.org/10.1016/j.aquaculture.2009.02.010