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Review

Tumor necrosis factor alpha is a potent regulator in fish adipose tissue

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ABSTRACT

Adipose tissue acts as an endocrine organ releasing a variety of adipokines, which participate in the regulation of energy homeostasis. One of the most important adipokines secreted from adipose tissue is tumor necrosis factor alpha (TNFα). TNFα has been identified and characterized as a limiting factor of lipid deposition in several fish species. TNFα affects adipocyte function and inhibits the differentiation of preadipocytes, and may be a good regulator in lipid metabolism of fish. Nevertheless, the regulation and molecular mechanism of TNFα on adipocyte lipolysis, differentiation and lipid droplet remain mostly unexplored in cultured fish. In this review, the effects of TNFα on fish adipose tissue are summarized, and the molecular mechanisms underlying these effects are further discussed.

Contents

1. Introduction

Adipose tissue, which is the primary storage site for excess energy, plays a significant role in the regulation of whole-body fatty acid homeostasis. Adipose tissue stores free fatty acids in the form of triglycerides during periods of calorie abundance, and releases fatty acids back into the circulation in times of energy shortage. In addition, adipose tissue acts as an endocrine organ releasing a variety of adipokines (Ahima and Flier, 2000). In mammals, adipokines participate in the regulation of energy homeostasis, which is related to insulin resistance, obesity, and the regulation of fatty acid and glucose metabolism.

One of the most important adipokines secreted from adipose tissue is tumor necrosis factor alpha (TNFα), which is synthesized as a 26 kDa transmembrane protein and cleaved by a metalloproteinase to be released as a 17 kDa soluble molecule (Kriegler et al., 1988). In mammals, it has been confirmed that both adipose tissue and macrophages from activated adipose tissue secret TNFα, and TNFα is a negative regulator of insulin signal transduction (Hotamisligil et al., 1993, 1994; Weisberg et al., 2003). Moreover, the expression and production of TNFα increases with the augmented adipocyte size (Morin et al., 1995). In recent years, the functions and mechanisms of TNFα on adipose tissue have been fully elucidated in mammals (Cawthorn and

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Sethi, 2008; Chen et al., 2009; Langin and Arner, 2006; Sethi and Hotamisligil, 1999; Warne, 2003).

There is now increasing interest in investigating the effect of TNFα on the regulation of fish lipid metabolism. TNFα has been identified in several fish species and characterized as a limiting factor of lipid deposition in gilthead sea bream (Cruz-Garcia et al., 2009b; Saera-Vila et al., 2007). TNFα affects adipocyte function in rainbow trout and gilthead sea bream, and inhibits the differentiation of rainbow trout preadipocytes (Albalat et al., 2005b; Bouraoui et al., 2008; Saera-Vila et al., 2007). Thus TNFα may be a potent regulator in reducing the adipose tissue mass. Nevertheless, the regulation and molecular mechanism of TNFα on adipose tissue remain mostly unexplored in cultured fish.

Accumulated data reveal that TNFα plays a significant role in regulating lipid metabolism. Several critical reviews concerning the role of TNFα on adipocytes, chronic inflammation and adipocytes biology have been published (Cawthorn and Sethi, 2008; Chen et al., 2009; Langin and Arner, 2006; Popa et al., 2007; Sethi and Hotamisligil, 1999; Warne, 2003). However, these reviews were confined to the regulatory effect of TNFα on mammalian cells or tissues. Compared to the mammals, there are fewer reports about the effect of TNFα on lipid metabolism in fish. In this review, the effects of TNFα on fish adipose tissue are summarized and the molecular mechanisms underlying these effects are further discussed.

2. TNFα and TNFα receptor in fish

The mRNA of TNFα has been found in the Japanese flounder (*Paralychthys olivaceus*) (Hirono et al., 2000), rainbow trout (*Oncorhynchus mykiss*) (Laing et al., 2001), brook trout (*Salvelinus fontinalis*) (Bobe and Goetz, 2001), carp (*Cyprinus carpio*) (Saeji et al., 2003), tilapia (*Oreochromis niloticus*) (Praveen et al., 2006), and sea bream (*Sparus aurata*) (Garcia-Castillo et al., 2002). Two different TNF genes, including TNF1 and TNF2, have been characterized in rainbow trout (*O. mykiss*) (Bobe and Goetz, 2001; Zou et al., 2002). It is confirmed that the recombinant trout TNF1 and TNF2 proteins could induce various of proinflammatory factors in freshly isolated head kidney leucocytes and the macrophage cell line RST11 (Zou et al., 2003). In addition, an important TNF-α isoform type-II TNFα3 is present in rainbow trout, which is the most responsive gene at early time points of post-lipopolysaccharides stimulation (Hong et al., 2013).

TNFα participates in the regulation of biological effects via binding to two receptors on cell membrane, including TNFα receptor 1 (TNFR1) and TNFα receptor 2 (TNFR2), and both receptors can be nutritionally regulated. Homologues of TNFR1 and TNFR2 have been identified in the kidney, spleen, brain, heart, muscle, intestine, and immune cells of goldfish (*Carassius aurutus L.*), as well as in the leukocytes, kidney, gill, and spleen of Japanese flounder (*P. olivaceus*) (Grayfer and Belosevic, 2009; Park et al., 2003). The TNFR2 expression is substantially higher than that of TNFR1 in kidney, spleen, brain, heart, muscle, and intestine of goldfish (*C. aurutus L.*) (Grayfer and Belosevic, 2009). Furthermore, a death domain-containing TNF receptor has been found in zebrafish, which is highly expressed in the ovaries (Bobe and Goetz, 2001). However, there are few reports related to the effect of TNFα on the adipose tissue via binding to TNFR1 or TNFR2.

3. The effect of TNFα on lipolysis

3.1. Adipocyte lipolysis process

Adipocyte lipolysis is regulated by diverse hormonal and biochemical signals. The lipolysis process in mammal adipocytes has been well reviewed in previous reports (Jaworski et al., 2007; Lafontan and Langin, 2009). The lipolysis process is mainly catalyzed by three lipases, including adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL) and monoacylglycerol lipase (MGL). ATGL and HSL are the most important lipases in adipose tissue (Schweiger et al., 2006). ATGL catalyzes predominantly the hydrolysis of the first ester bond in triacylglycerol (TAG) to generate diacylglycerol (DAG). Then HSL hydrolyzes DAG to monoacylglycerol (MAG), which is further catalyzed by MGL (Fig. 1). Furthermore, some lipid droplet proteins, such as perilipin, which are important for protecting or exposing the TAG core of the droplets to lipases, are also potent regulators of lipolysis (Lafontan and Langin, 2009).

In lipolysis process, the intracellular cAMP is induced by the stimulation of adenylate cyclase. Then proteins kinase A (PKA) is activated by cAMP and further phosphorylates HSL (Langin, 2006) (Fig. 1). As a barrier to lipases, perilipin A also participates in the hydrolytic action of HSL. Under hormonal stimulation, perilipin A will be phosphorylated by PKA and further regulate PKA-stimulated lipolysis in adipocytes (Miyoshi et al., 2007; Zhang et al., 2003) (Fig. 1). HSL is more active against DAG and cholesteryl esters (CEs) than TAG and MAG (Kraemer and Shen, 2002). However, ATGL is a TAG hydrolase and cannot hydrolyze cholesteryl or retinyl ester bonds (Zimmermann et al., 2004). The lipolysis process is shown in Fig. 1.

3.2. The effect of TNFα on lipolysis

Adipose tissue stores lipids and provides energy from lipid stores. Triglycerides from diets are hydrolyzed by lipoprotein lipase (LPL), which is a glycoprotein enzyme binding to heparan sulfate and located in the capillary endothelium (Rader and Jaye, 2000). LPL is considered as a key enzyme in the lipid deposition. LPL hydrolyzes triglycerides from circulating chylomicrons and very low density lipoproteins (VLDL), and further provides free fatty acids for storage in adipose tissue or oxidation in other tissues (Albalat et al., 2006; Enerbäck and Gimble, 1993; Nilsson-Ehle et al., 1980). Moreover, the free fatty acids hydrolysed from triglycerides can be re-esterified and stored, or used as an energy source by peripheral tissues, such as muscle and heart (Nilsson-Ehle et al., 1980).

In fish, the gene of LPL has been detected in red sea bream (*Pagrus major*), rainbow trout (*O. mykiss*), and grass carp (*Ctenopharyngodon idella*) (Cheng et al., 2009; Lindberg and Olivecrona, 2002; Oku et al., 2002). It is found that LPL mRNA was present in the liver, head kidney, mesenteric adipose tissue, heart, and white muscle of adult grass carp (Cheng et al., 2009). Activity of LPL was detected in the liver, adipose tissue, muscle, heart, brain, and vitellogenic ovaries of rainbow trout (Black and Skinner, 1987; Black et al., 1983). Two LPL isoforms, which are confirmed as key enzymes of lipid metabolism, are present in gilthead sea bream with a differential and tissue-specific gene expression pattern in adipogenic and muscle tissues (Benedito-Palos et al., 2014). Moreover, LPL gene expression is regulated differentially according to the nutritional states and hormonal levels based on the needs of fatty acids in different tissues (Fielding and Frayn, 1998), and the effect of dietary fatty acids on LPL gene expression is tissue specific and related to the feeding conditions in red sea bream (Liang et al., 2002).

TNFα directly alters lipid metabolism through inhibition of fatty acid uptake and lipogenesis as well as stimulation of fatty acid release via lipolysis. TNFα plays an important role in the control of lipid metabolism in rainbow trout (*O. mykiss*) (Albalat et al., 2005a,b). TNFα inhibits LPL activity of adipose tissue in vivo, and stimulates lipolysis in trout adipocytes in a time- and dose-dependent manner (Fig. 1). Further studies indicate that TNFα stimulates lipolysis in isolated rainbow trout adipocytes through the activation of extracellular-signal-regulated kinase 1/2 (ERK1/2) and p38 kinase (Albalat et al., 2005b) (Fig. 1). TNFα inhibits LPL activity and increases the release of glycerol in the culture medium of freshly isolated adipocytes, which in turns limits the tissue uptake of fatty acids and the ultimate increase of tissue lipid reservoirs (Saera-Vila et al., 2007) (Fig. 1). Analysis of the 5′-flanking region showed the conservation through vertebrate evolution of a functional OCT-1/NF-Y site, which mediated the negative effect of TNFα on LPL expression (Saera-Vila et al., 2007). In another study, the preadipocytes were isolated from large yellow croaker (*Pseudosciaena crocea R.*) (Wang et al.,

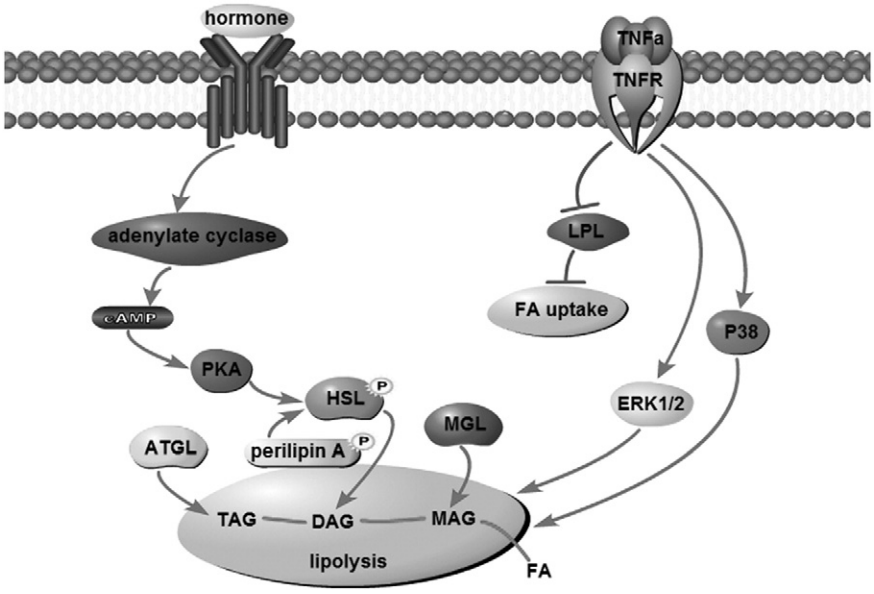

Fig. 1. The process of lipolysis and the effect of TNFα on lipolysis in fish. Adipocyte lipolysis is regulated by hormonal signals and TNFα. In the process of lipolysis, the intracellular cAMP is increased by the stimulation of adenylate cyclase and PKA is activated, which further phosphorylates HSL and perilipin A. The hydrolytic action of HSL is also regulated by perilipin A, which controls the magnitude of lipolysis and acts as a barrier to lipases. The lipolysis process is mainly catalyzed by ATGL, HSL and MGL. ATGL catalyzes TAG to generate DAG. Then HSL hydrolyzes DAG to MAG, which is catalyzed by MGL to release fatty acids (FA). In addition, TNFα inhibits LPL activity and the uptake of FA. TNFα stimulates lipolysis through the activation of ERK1/2 and p38 kinase signal pathway.

2012). TNFα inhibited cell proliferation and differentiation, but stimulated mature adipocyte lipolysis in the preadipocytes (Wang et al., 2012). Furthermore, Saera-Vila et al. (2007) found that TNFα transcripts were upregulated in summer with the increase of feeding and adiposity, while TNFα expression was reduced by fasting in liver and mesenteric adipose tissue of gilthead sea bream. This gene expression profile, in combination with a lipolytic effect, supports a key role of TNFα as a limiting factor of tissue adipose mass in fish. Thus, TNFα may regulate in an adaptive manner for the re-allocation of lipid depots and changing metabolic homeostasis (Martí-Palanca et al., 1996; Saera-Vila et al., 2007). Though some preliminary studies on the regulatory effect of TNFα on lipolysis have been made in the past years, the detailed mechanisms need to be further researched.

4. Effect of TNFα on adipocyte differentiation

The alternative and mutually exclusive pathways for cells are proliferation and differentiation, and growth arrest plays a key role in adipocyte differentiation (Smyth et al., 1993). The adipocyte differentiation and gene expression have been reviewed in detail, which focuses on those genetic events that link effectors to induction of adipocyte gene expression (Ntambi and Young-Cheul, 2000). In mammals, CCAAT/enhancer-binding protein β (C/EBPβ) and C/EBPδ are the first transcription factors involved in directing the differentiation process, which mediate the expression of peroxisome proliferator–activator receptor γ (PPARγ) and C/EBPα (Christy et al., 1991; Clarke et al., 1997; Lin and Lane, 1994; Wu et al., 1995). Then PPARγ and C/EBPα could cross-regulate each other to induce the expression of numerous adipocyte genes encoding proteins and enzymes involved in adipocyte differentiation (Gregoire et al., 1998; Shao and Lazar, 1997).

As in mammals, the development of adipose tissue in fish is a continuous process, which includes the hypertrophy of existing adipocytes and the proliferation of new ones. The transcriptional factors C/EBP and PPAR are necessary for the transition of pre-adipocytes into adipocytes (MacDougald and Lane, 1995). Three PPAR isotypes (α, β and γ) have been found in the Atlantic salmon (*Salmo salar*) (Ruyter et al., 1997), European sea bass (*Dicentrarchus labrax*) (Boukouvala et al., 2004), and gilthead sea bream (*S. aurata L*) (Diez et al., 2007; Leaver et al., 2005).

It has been found that C/EBPα and PPARγ are involved in adipocyte differentiation in rainbow trout (*O. mykiss*) (Bouraoui et al., 2008). Moreover, TNFα decreases glycerol-3-phosphate dehydrogenase activity and inhibits adipocyte differentiation (Bouraoui et al., 2008). The cDNA sequences of liver X receptor (LXR) were reported in zebrafish and salmonids (Archer et al., 2008; Cruz-Garcia et al., 2009a). Cruz-Garcia et al. (2009a) analyzed adiposity heterogeneity and the role of LXRα and peroxisome proliferator-activated receptors (PPARs) as targets of TNFα in gilthead sea bream (*S. aurata L.*). In adipocytes from fat fish, TNFα-induced lipolysis was transcriptionally mediated by the inhibition of PPARβ, but PPARγ and LXRα signaling pathways orchestrated the TNFα-mediated effects on lipolysis or adipogenesis in lean fish (Cruz-Garcia et al., 2009a). However, the detailed mechanisms of TNFα on adipocyte differentiation need to be researched in future.

5. The effect of TNFα on adiponectin

Adiponectin, one of the most abundant adipokines in mammalian plasma, is a seven transmembrane domain protein. Adiponectin participates in regulating infection and inflammation in adipose tissue by binding to adiponectin receptor 1 (adipoR1) and adiponectin receptor 2 (adipoR2) (Ajuwon et al., 2009; Fasshauer et al., 2004; Yamauchi et al., 2003). Moreover, adiponectin modulates insulin sensitivity, glucose homeostasis, and lipid metabolism, which further promotes the uptake or oxidation of glucose and fatty acid in rat muscle cells (Ceddia et al., 2005; Mullen et al., 2009). Adiponectin could activate the ERK1/2 mitogen-activated protein kinase pathway in primary vascular smooth muscle, vascular endothelial cells, and hepatocytes (Lee et al., 2008).

Adiponectin and adiponectin receptors (adipoR1 and adipoR2) have been identified in zebra fish and rainbow trout (*O. mykiss*) (Kondo et al., 2011; Nishio et al., 2008; Sánchez-Gurmaches et al., 2012a). Adiponectin activates Akt in rainbow trout myotubes, promotes the uptake and oxidation of fatty acid, and further modulates insulin sensitivity, glucose homeostasis and lipid metabolism (Fig. 2). The adiponectin system responds differently to various physiological

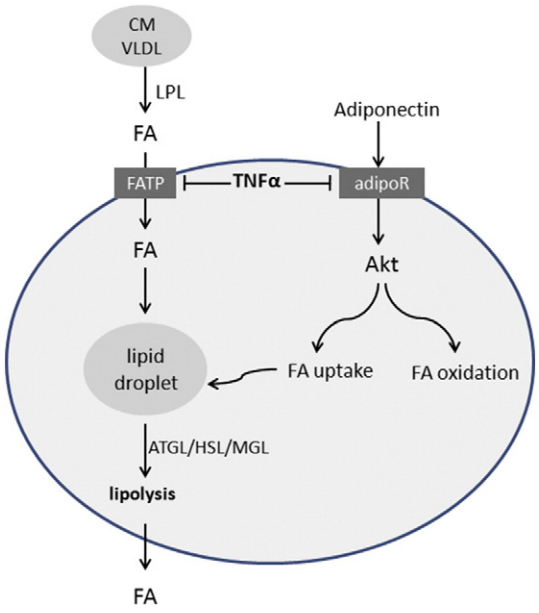

Fig. 2. The effect of TNFα on adiponectin and FATP. TNFα inhibits FATP expression and lipid accumulation in adipocytes. In addition, TNFα inhibits the expression of adipoR, activates Akt, and promotes the uptake and oxidation of fatty acid.

challenges. Since both the muscle and adipose tissue are organs of adiponectin expression and target tissues, there may be a regulatory feedback loop that adiponectin acts in an autocrine or paracrine fashion to regulate the function of its receptors (Sánchez-Gurmaches et al., 2012a). TNFα decreases adipoR2 expression in adipocytes and adipoR1 expression in myotubes of rainbow trout (Fig. 2). In addition, lipopolysaccharide inhibits the gene expression of adiponectin, but induces adipoR1 expression in the adipose tissue of rainbow trout (Sánchez-Gurmaches et al., 2012a).

6. The effect of TNFα on FATP

To maintain lipid fuel homeostasis, it is necessary to regulate the transport of fatty acid across cell membrane. One of the most studied fatty acid transporters is fatty acid transport protein 1 (FATP1) (Schaffer and Lodish, 1994), which has been studied during Atlantic salmon pre-adipocyte cell culture differentiation and in tissues from Atlantic salmon (Huang et al., 2010; Sánchez-Gurmaches et al., 2011; Todorčević et al., 2008; Torstensen et al., 2009). TNFα could decrease FATP1 expression in isolated adipocytes (Sánchez-Gurmaches et al., 2012b) (Fig. 2). However, there is not any report about the regulatory mechanism of FATP1 inhibition by TNFα. The effect of TNFα on adiponectin, FATP, and lipid accumulation is shown on Fig. 2.

7. Discussion and perspectives

Due to the continuous expansion of aquaculture and limitation of fish oil supply, the partial or total replacement of fish oil by vegetable oils is increasingly widespread in fish feed production. Though the use of vegetable oils to replace the majority of dietary fish oil is feasible without loss of growth performance (Bell et al., 2003; Bransden et al., 2003; Torstensen et al., 2004), it should be noted that the vegetable ingredients and high level of lipids in diets of fish easily induce high lipid deposition in the hepatic adipose tissue (Caballero et al., 2002, 2004). The accumulation of lipid will further lead to the production losses, alteration of flesh quality, and lipoid liver disease on the health of Atlantic salmon and gilthead sea bream (Benedito-Palos et al., 2008; Saera-Vila et al., 2009; Seierstad et al., 2005, 2009). In recent years, the regulation of lipid metabolism has become a notable point of interest in aquaculture research.

The excessive fatty deposition diseases related to fish diets are widely present in fish. High lipid intake elicits adverse effects on fish, including the induction of fatty liver syndrome and abnormal oxidative status (Dos Santos et al., 1993; Du et al., 2006; Gao et al., 2011). It is known that liver steatosis is associated with nutritional imbalances in cultured fish (Tacon, 1996). When dietary lipid exceeds the capacity of the hepatic cells to oxidize fatty acids, the excessive triacylglycerols will be deposited in liver vacuoles and lead to liver steatosis. In sea bream, steatosis has been observed due to an increase in the dietary lipid content and the inclusion of vegetable oils (Caballero et al., 1999, 2004). Lipoid liver disease and intense accumulation of intestinal lipid droplets are also documented as metabolic disorders arising from defective supplies of phospholipids and n-3 highly unsaturated fatty acids (Caballero et al., 2003; Fontagné et al., 1998; Olsen et al., 2003). In addition, altering the dietary ratios of n-3 to n-6 polyunsaturated fatty acids (PUFAs) could cause a marked cardiac muscle depletion of both the spongy and compact layers in salmonids (Bell et al., 1991). The fatty acid composition of fish feed may influence the development of arteriosclerotic changes in Atlantic salmon (Seierstad et al., 2005). In grass carp, excess lipid intake causes fat accumulation, affects lipoprotein synthesis, and induces lipid peroxidation (Du et al., 2008; Ji et al., 2011). Thus, understanding the signaling pathways in target tissues (such as the muscle, liver and adipose tissue), by which TNFα controls lipid metabolism, may also reveal novel mechanisms for excessive fatty deposition diseases in fish.

In mammalian adipocytes, TNFα inhibits the expression of PPARγ and C/EBPα, which play an important role on adipocyte differentiation. There are several signal pathways linked to suppression of PPARγ and C/EBPα, including extracellular signal-regulated protein kinase (ERK), c-Jun N-terminal kinase (JNK), and IKK (inhibitor of NFκB (IκB) kinase) (Adams et al., 1997; Chae and Kwak, 2003; Suzawa et al., 2003; Tominaga et al., 2005). In addition, TNF-α inhibits adipocyte differentiation and prevents the early induction of PPARγ and C/EBPα via canonical Wnt signaling pathway in 3 T3-L1 cells (Cawthorn et al., 2007). TNF-α augments the expression of low density lipoprotein receptor-related protein (LRD), Dishevelled, Wnt10b, and β-catenin, and further prevents the normal development of preadipocytes to fully differentiated adipose cells (Gustafson and Smith, 2006). Adipocyte lipolysis is a complex process that is tightly controlled by diverse hormonal and biochemical signals. In some fish species, it has been confirmed that TNFα affects adipocyte function, inhibits the differentiation of preadipocytes, and affects some genes related with adipocyte lipolysis and differentiation. Previous studies indicate that TNFα may be a good regulator in reducing the adipose tissue mass. However, there are very few studies about the regulatory signaling pathway of adipocyte differentiation induced by TNFα in fish, and the regulation and molecular mechanism of TNFα on adipose tissue remain mostly unexplored in cultured fish (Fig. 3). In the future, it is need to investigate whether the regulation

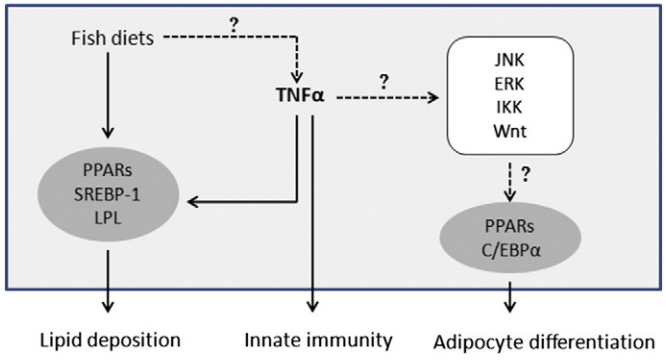

Fig. 3. The effect of TNFα on lipid deposition, innate immunity and adipocyte differentiation. TNFα may mediate the effect of fish diets on lipid deposition by regulating the expression of PPARs, SREBP-1 and LPL. In addition, TNFα induces innate immune response. TNFα may regulate adipocyte differentiation via PPARs, C/EBPα, and the signal pathways JNK, ERK, IKK, and Wnt.

of lipolysis and lipogenesis is completely conserved between mammals and fish, and whether it is markedly different between different fish species.

In some fish species, lipids are primarily stored in the liver. However, lipids are stored between muscles, in the mesentery, along the lateral line, or at the base of fins in other species (Henderson and Tocher, 1987). Except as a lipid storage depot, the liver is also the major site of lipid biosynthesis, and liver exhibits more dynamic lipid content than muscle tissue (Henderson and Tocher, 1987). Lipid accumulation is related to the balance between the lipid absorbed from the diet, de novo synthesis of fatty acids, transport of lipoprotein, and lipid catabolism via β-oxidation as well as the transcription factors PPARα, PPARγ, and sterol regulatory element binding protein-1 (SREBP-1) (Fig. 3). A significant reduction in the lipid contents is obtained in the liver of hybrid striped bass and yellow perch fed with 1% conjugated linoleic acid (CLA) (Twibell et al., 2000, 2001). The lipid-lowering effects of CLA are related to the expressions of fatty acid synthetase (FAS), acetyl-CoA carboxylase (ACC), LPL, HSL, PPARα, PPARγ, and SREBP-1c (Dong et al., 2014). Moreover, the expression of LPL, PPARα, FAS, and microsomal triacylglycerol transfer protein (MTP) was significantly increased, while the expression of LXR and carnitine palmitoyltransferase I (CPT I) significantly decreased with increasing level of dietary soybean oil in the liver of juvenile turbot (Peng et al., 2014). Whether TNFα participates in regulating lipid-lowering effects of vegetable oils needs to be elucidated.

The lipid droplets comprise a variety of proteins and lipid metabolizing enzymes, which participate in the lipolysis process in response to the hormonal or other stimulations. A conserved gene family important for lipid droplet formation named fat-inducing transcript (FIT) has been characterized in zebrafish, and FIT proteins are evolutionarily conserved and exclusively located in the endoplasmic reticulum. FIT proteins could enhance the partitioning of triglyceride into lipid droplets, and FIT2 induces the accumulation of lipid droplets in the intestine and liver (Kadereit et al., 2008). It has been found that the plant meal induced the expression of genes involved in lipid absorption and lipoprotein synthesis, cholesterol synthesis, and associated transcription factors in Atlantic salmon (Gu et al., 2014). The dietary fatty acids affected LPL mRNA levels not only in the visceral adipose tissue, but also in the liver of fed or starved fish. Oleate supplemented alone, or in combination with linoleate or n-3 PUFAs, increased the LPL mRNA level in the liver, but decreased it in the visceral adipose tissue under the fed condition (Liang et al., 2002). The results of Ryu et al. (2013) indicate that VLDL is metabolized by LPL in the granulosa cell layer to generate free fatty acids for uptake and biosynthesis of neutral lipids by growing oocytes. Whether TNFα affects the lipid droplet formation and the effect of TNFα on lipid droplet in fish also needs to be elucidated in future.

In addition, the innate response is considered an important component in combating pathogens due to the limitation of adaptive immune system in fish. TNFα has the ability to enhance the activation of macrophages, respiratory activity, and production of phagocytosis, and nitric oxide in rainbow trout, turbot, sea bream, goldfish, and catfish (Mulero and Meseguer, 1998; Tafalla et al., 2001; Yin et al., 1997). In recent years, marine fish are farmed intensively under conditions of high population density, and infectious diseases pose a constant and highly cost threat to aquaculture in most developed countries. Immunostimulants as diet supplement, especially those of non-nutritional origin, play a key role in inducing a brief disease resistance enhancement in marine fish (Galindo-Villegas and Hosokawa, 2004). Since TNFα also has the ability to inhibit the differentiation of preadipocytes and affect some genes related with adipocyte lipolysis and differentiation in fish, it may be supplemented as an immunostimulant and lipid regulator in fish diets (Fig. 3). However, concerted efforts are still needed to undertake an in-depth assessment of the consequences of feeding this diet supplement.

In summary, TNFα may mediate the effect of fish diets on lipid deposition by regulating the expression of PPARs, SREBP-1 and LPL (Fig. 3). TNFα could induce the innate immune response and regulate adipocyte differentiation via PPARs, C/EBPα, and the possible signal pathways, including JNK, ERK, and IKK (Fig. 3). In addition, besides of TNFα, there are lots of adipokines that participate in the regulation of energy homeostasis and fatty acid metabolism. Until recently, there are very few reports about the effect of some other adipokines on lipid metabolism in fish. Many questions, such as the regulation of lipolytic enzymes and their coordinate interaction, as well as the cooperation between adipokines and hormonal signals regulating lipolysis in adipocytes, remain to be answered. With the development of proteomics and genomics technology, it is likely that our understanding on the adipocyte lipolysis, differentiation and lipid droplet in fish will be achieved in the near future.

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