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Review article

Dietary fatty acids applied to pig production and their relation to the biological processes: A review

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HIGHLIGHTS

- Lipids are diet source of fatty acids, which contributes to energy supply, cell structure, and gene expression level.
- Fatty acids are important functional components involved in several physiological processes and biological processes associated with health benefits.
- Molecular animal nutrition or nutrigenomics combines nutrition with molecular biology.

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ABSTRACT

Lipids are an important source of fatty acids (FA) and energy, which are essential for biological processes and influence the regulation of transcription. Pigs are an excellent model for the study of nutrigenomics, particularly lipid metabolism, because the deposition and composition of FA in their tissues reflects the composition of FA in their diet. Studies of the influence of dietary components and their effects are fundamental to nutrigenomics, or the study of how nutrients can act as cellular sensors to influence biological processes and gene expression in various tissues. Recent studies show that the use of FA in pig diets is important for production systems because it can improve the energy value of the diet, help reduce costs, improve animal welfare, and influence the nutritional value of the meat. Studies show that FA such as oleic acid (OA), linoleic acid (LA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) are important for animal and human health, associated with the regulation of transcription in tissues such as muscle, liver, adipose tissue, and brain. Because of the importance of FA to biological processes, pig health and production, and the health of pork consumers, this review focuses on dietary FA used in pig production and their relationship to biological processes in different tissues.

1. Introduction

According to the World Population Review (2021), about 219,000 people are added to the world population each day. Taken together with the limited natural resources on the planet, there is a real need to identify new production strategies in agriculture that increase the efficiency of food production (Daniel et al., 2011). The projected increase in food consumption will likely increase the demand for meat consumption

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from 200 million to 470 million tons per year, requiring a 70% increase in production efficiency by the year 2050 (OECD-FAO, 2021). Thus, in the animal production sector, in addition to the demand for greater efficiency and sustainability in production, nutritional quality has become a decisive factor for consumer choice (OECD-FAO, 2021).

In recent years, concern about centralized food production in some countries has increased, especially in the face of a pandemic crisis (Aday and Aday, 2020). A prolonged pandemic situation, it causes problems in the food supply chain, with the imposition of export restriction policies, triggering a domino effect (Aday and Aday, 2020). As an example, the serious direct and indirect economic losses caused by African swine fever (Nguyen-Thi et al., 2021), in addition to the impacts caused by COVID-19 (Aday and Aday, 2020). Perspectives for the adoption of strategies to reduce the negative impact on the global economy should be worked out, improving market linkages, developing mechanisms for risk sharing, assistance, organization and financing at national and local levels (Aday and Aday, 2020; Nguyen-Thi et al., 2021).

Ensuring the continuity of meat production and supply chain is possible by respecting practical recommendations and health-related precautions to minimize the impact caused by the pandemic situation. The distribution of food with the increase in global demand is a concern that must constantly be in discussion. Measures such as improved communication between ranchers, service providers and consumables suppliers help to guarantee the supply of inputs, agricultural services and consequently in the meat supply chain. As well as strategies regarding mandatory exemptions for transport of feed, animals and personnel; adoption of strict hygienic-sanitary measures to prevent the spread of diseases; guarantee of animal health and biosecurity on farms; measures to control food and meat prices in the market (Ijaz et al., 2021).

The economic potential and nutritional quality have placed pork as a global highlight. Pork is the second most consumed source of animal protein worldwide, accounting for 33% of production and 34% of global meat consumption (OECD-FAO, 2021). In addition, pork has a nutritional profile that can ensure a healthy, balanced and safe diet for the growing population (Dugan et al., 2015; Park et al., 2012). Lean pork has a composition high in protein, low in fat, being rich in saturated fatty acids (SFA) and is considered an important source of unsaturated fatty acids (UFA) (Dugan et al., 2015; Moghadasian and Shahidi, 2017).

Fatty acids (FA) are important for several physiological processes and mechanisms and when in proper proportions are associated with health benefits (Dugan et al., 2015; Moghadasian and Shahidi, 2017). Furthermore, pigs are monogastric (like humans) and have FA deposition as a reflection of the FA composition of their diet. Thus, in pig production, specific dietary nutrients, such as fats, are critical to the quality and nutritional profile of the meat (Doreau and Chilliard, 1997; Dugan et al., 2015; Moghadasian and Shahidi, 2017; Rosenvold and Andersen, 2003).

Supplementing the diet of pigs with different levels and sources of oils can modulate the FA composition of pork (Coates and Ayerza, 2009; Freeman, 1984). Lipid digestibility is affected by characteristics associated with molecular structures, such as the degree of saturation of FA, the length of the carbon chain, and the position of FA in the triglyceride molecule. With this the bioavailability of lipids in different sources can affect digestion, absorption, and metabolism (Lauridsen, 2020). According to Ravindran et al. (2016), due to the greater access and viability of lipase with triglycerides, unsaturated chain lipids from diets are considered more digestible in pigs, than SFA. Thus, the availability of these lipids can influence tissue composition and effects on metabolism (Coates and Ayerza, 2009; Freeman, 1984). Furthermore, according to Coates and Ayerza (2009), the fat depot interacts with diet, and can also determine the fatty acid composition of tissues of pigs. Allowing an improvement in relation to the nutritional profile of the meat (Doreau and Chilliard, 1997), besides bringing benefits related to animal and human health (Moghadasian and Shahidi, 2017). This supplementation or alteration of the diet of these animals is known as a feeding strategy and is the most widely used management factor in the meat, milk, and egg industry. This strategy is also used as a tool for quality control in animal production, as well as to improve the quality and nutritional value of the final product, animal welfare, and food safety and technology (Andersen et al., 2005; Nong et al., 2020; Xu et al., 2020).

Changes in feeding strategy are used to supplement the animal diet with specific components to obtain nutritional and health advantages, such as using dietary components that contribute to the content and composition of lipids in relation to the nutritional value of the meat (Andersen et al., 2005; Wood et al., 2008; Xu et al., 2020). An example of this is a study by Øverland et al. (1996), where different types and inclusion levels of soybean oil and fish oil were used in pig diet. The addition of fish oil was associated with an increase in the content of omega-3 (n-3) polyunsaturated fatty acids (PUFA) in muscle and adipose tissue and a decrease in the ratio of omega-6:omega-3 (n-6:n-3), which ideally should be 1:1. A lower proportion of n-6 and higher proportion of n-3 is important for modulating anti-inflammatory processes, since n-6 PUFA may act to increase the concentrations of pro-inflammatory mediators (Simopoulos, 2002).

Foods fortified with vegetable oils, especially sunflower, soybean, and canola, contain high levels of linoleic acid (LA, C18:2 n-6) and oleic acid (OA, C18:1 n-9). The alpha-linolenic acid (ALA, C18:3 n-3) can be found in addition to soybean and canola oil, in flaxseed oil and walnuts, and the FA eicosapentaenoic acid (EPA, C20:5 n-3) and docosahexaenoic acid (DHA, C22:6 n-3) are found in seafood (Moghadasian and Shahidi, 2017). For this reason, the demand for foods with higher PUFA and monounsaturated fatty acids (MUFA) content has increased among consumers, who demand healthier foods (Baker et al., 2016; Park et al., 2012).

Pork has a high n-6:n-3 ratio due to the diets used in pig production. These practices are based on the use of corn, sunflower, and soybean vegetable oils, which are rich in n-6 family PUFA, mainly LA (Dugan et al., 2015). The UK Department of Health (1994), obtained in a research that the n-6:n-3 ratio of 7.2:1 in pork, Juárez et al. (2011) obtained in his research the ratio of 4.5:1, and Romans et al. (1995), a ratio of 14.3:1. In addition, genetic selection of pigs designed for lean growth has increased the concentration of LA in pork (Wood et al., 2008).

In general, the inclusion of fish oil in the diet of pigs is characterized by a better deposition of FA of the n-3 family and does not affect the sensory quality in fresh meat. However, especially the addition of high percentages of fish oil (4% - 8%) can affect meat quality parameters and consumer acceptance in the long term (Hallenstvedt et al., 2010; Komprda et al., 2021, 2020). However, fat content has a direct effect on the flavor and juiciness, as well as the tenderness and firmness of pork. For example, OA is the predominant FA in pork tissue (about 40%), while LA content is highly correlated with fat firmness (Świątkiewicz et al., 2016). A high n-6:n-3 ratio may also bring negative impacts to animal and human health, due to the increase in AA-derived eicosanoid metabolites. These metabolites have been linked to a higher pro-inflammatory and pro-aggregative state than EPA-derived eicosanoids. In addition, a higher intake of LA or AA at the detriment of n-3 PUFA can stimulate allergic disorders, as well as the propensity for thrombus and atheroma formation (Simopoulos, 2003).

For pork, lower ratios of n-6:n-3, such as 5:1 and 3:1, were responsible for better meat quality, reduced triglyceride content and also showed a in the FA composition of the meat, bringing greater health benefits to animals and humans (Liu and Kim, 2018; Nong et al., 2020; Sun et al., 2020). Other benefits of including lipids in pig diets include reduced wear and tear on feed processing equipment. Furthermore, in warm climatic conditions, lipid-enriched diets reduced heat gain (fat digestion and metabolism) compared to carbohydrate- and protein-enriched diets, as well as increased feed intake and body weight gain (Kyriazakis and Whittemore, 2006).

With n-3 FA as important dietary components for health and found mainly in fatty fish, fortifying pork with n-3 PUFA-rich sources, is a viable strategy to increase n-3 FA intake, especially in populations that consume less fish or other marine products. It also helps to reduce the consumption of SFA, which consequently helps to reduce negative health effects and the risk of developing some diseases (Cesar et al., 2016; Dugan et al., 2015).

In addition, to presenting great economic and food importance, domestic pigs (*Sus scrofa*) are considered animal models for nutrigenomics research and for the investigation of metabolic diseases in humans (Doreau and Chilliard, 1997; Lunney, 2007; Pan et al., 2021). Since they share anatomical, morphological, physiological and metabolic similarities with humans (Bassols et al., 2014; Pan et al., 2021). Pigs also have high homology and chromosome structure with the human genome compared to other animal species (Pan et al., 2021; Schook et al., 2015). When the genomes of 48 individual pigs were sequenced, 32,548 non-synonymous single nucleotide polymorphisms (SNP) were observed, six of which were linked to human diseases and 11 of which were associated with human disease phenotypes (Schook et al., 2015). There is also evidence that processes revealed by the pig transcriptome are similar to that of humans (Szostak et al., 2016).

Several studies have been conducted to verify the effects of these FA on animal nutrition and relevant biological processes. The study of the fatty acids and cellular lipids is known as lipidomics, which is a new tool applied to understand the role of lipids in cellular and metabolic functions and, with that, how they can be related to the nutrition and diet of animals (Yang and Han, 2016). As an example, the influence of maternal nutrition on offspring phenotype has been widely studied in several species. Studies have shown that the inclusion of different levels and types of fat in the diet of pregnant sows has been shown to affect the number of piglets born, birth weight, neonatal piglet survival, body weight, FA composition of milk, plasma of lactating sows and their piglets. This inclusion has also been shown to affect oxidative stress, inflammatory response and cognitive development (Amusquivar et al., 2010; Clouard et al., 2016; Luo et al., 2019). Recent studies have also reported the important role of lipids in immune response and susceptibility to metabolic diseases (Duan et al., 2014; Ramayo-Caldas et al., 2012; Vodolazska and Lauridsen, 2020).

As technological advances, molecular animal nutrition stands out as a field of study that combines nutrition with molecular biology at its basic level (Hasan et al., 2019). This branch studies the biological processes involved at the level of gene expression and the interaction between genes and nutrients with the help of modern molecular biology techniques and technologies (Zempleni and Daniel, 2003). Following the advancement of molecular biology, omics sciences provide the tools to unravel the molecular mechanisms involved in the phenotypes of interest and metabolic diseases affecting humans such as obesity, type 2 diabetes, and atherosclerosis level (Hasan et al., 2019).

Currently, the most useful and applied molecular biology tool is next-generation sequencing (NGS), which include genomic DNA, mRNA, and miRNA. These approaches combine high-throughput sequencing and/or mass spectrometry technologies with food components and seek to understand how a nutrient may affect genetic, protein, and metabolic abundance. These types of studies can elucidate the basic molecular mechanisms in which nutrients may interact to regulate gene expression, physiological processes, cellular biochemical responses, as well as phenotype expression (Norheim et al., 2012). Because of the importance of FA to biological processes, pig health and production, and the health of pork consumers, this review focuses on dietary FA used in pig production and their relationship to biological processes in different tissues.

2. Lipids and fatty acid metabolism

Lipids are a class of molecules found in all cell types and play a fundamental role in cell membrane structure and biological function, from transcriptional regulation to physiological processes (Eshak et al., 2018; Moghadasian and Shahidi, 2017). They are molecules of hydrophobic nature, are an important source of metabolic energy, play a role in the membrane permeability barrier and act as structural matrix (Elmadfa and Kornsteiner, 2009; Moghadasian and Shahidi, 2017). As part of complex lipid molecules, FA are the basic structure of lipids such as fats and phospholipids, which are stored in adipose tissue as triacylglycerides, which is the predominant dietary source of FA (Moghadasian and Shahidi, 2017; Petrovic and Arsic, 2016). Due to the vast cellular functions, the ability to synthesize a variety of FA is essential. However, humans and animals cannot synthesize n-6 and n-3 FA *de novo* because they do not have a enzymatic machinery to do it (Surette, 2008), and must be acquired, for example LA and ALA, from the diet (Moghadasian and Shahidi, 2017; Shireman, 2003; Yehuda et al., 2002).

One way of classifying FA occurs according to the number of carbon-carbon double bonds (unsaturation). In this way FA are classified into SFA and UFA, and this second class being divided into MUFA and PUFA. SFA are part of components in cell membranes and they are categorized as non-essential FA since their synthesis can occur in all organisms (Moghadasian and Shahidi, 2017; Petrovic and Arsic, 2016). The most common SFA found in plant and animal tissues are those with a linear chain of 12 to 18 carbons, with palmitic acid (C16:0) being the most abundant and found in most plant oils, in fish oil, and in the body fat of some animals. As examples of SFA may be mentioned, stearic acid (C18:0), myristic acid (C14:0) and lauric acid (C12:0) (Eshak et al., 2018; Moghadasian and Shahidi, 2017). For the human body, the stearic acid is important and related to cholesterol levels, some studies have shown that this SFA can contribute to reduce the cholesterol levels in human blood (Monsma and Ney, 1993). The moderate inclusion of myristic acid in the human diet improves long-chain n-3 levels, improving the cardiovascular system (Dabadie et al., 2005). The ingestion of showed that ingested lauric acid disappears more quickly from the bloodstream of mice than palmitic acid. Suggesting that a small amount is metabolized by the liver in the form of triglycerides (Dayrit, 2015).

Unsaturated fatty acids contain at least one carbon-carbon double bond and may occur in cis- and trans-isomeric forms (Eshak et al., 2018; Moghadasian and Shahidi, 2017). The cis-form or Z-configuration is the one found in all biological FA and contains two adjacent carbons on the same side as the double bond carbons. On the other hand, the trans-form or E-configuration contains at least one double bond with the two adjacent carbons on opposite sides of the carbon bond (Moghadasian and Shahidi, 2017; Petrovic and Arsic, 2016).

The MUFA are defined as having only one double bond in the aliphatic chain. The MUFA are synthesized in the human body, and found in olive and canola oil, nuts, avocados, seeds, and peanuts. An important example is OA, which is produced from stearic acid by the enzyme stearoyl-CoA desaturase and is associated with increased membrane fluidity and transport and acts by stimulating enzyme activity (Moghadasian and Shahidi, 2017; Petrovic and Arsic, 2016; Wood et al., 2008).

The MUFA have been attributed to health benefits such as prevention of cardiovascular disease as they reduce low-density lipoprotein (LDL) and increase high-density lipoprotein (HDL) (Moghadasian and Shahidi, 2017; Nakamura and Nara, 2003; Petrovic and Arsic, 2016). They are also associated with a lower likelihood of cognitive decline in the elderly, reduced rates of breast and ovarian cancer, and are important for the cell membrane structure of the myelin sheath of nervous tissue (Eshak et al., 2018; Moghadasian and Shahidi, 2017). In addition to OA promoting a healthy lipid profile and acting in the mediation of blood pressure, it also positively modulates insulin sensitivity by reducing triacylglycerol (TG) levels, helps in glucose control, and acts by regulating the signal transduction and transcription of some genes and the activity of membrane receptors (Nakamura and Nara, 2003; Petrovic and Arsic, 2016).

The PUFA have two or more double bonds in their aliphatic chain and have two important families: n-3 PUFA and n-6 PUFA. The n-3 family can be divided into short-chain PUFA, such as ALA, and long-chain PUFA including EPA, DHA, and docosapentaenoic acid (DPA, C:22:5 n-3) (Baker et al., 2016; Bork et al., 2020; Caterina, 2011; Moghadasian and Shahidi, 2017). The most important PUFA are LA, ALA, arachidonic acid (AA, C20:3 n-6), DHA and EPA, among them LA and ALA are essential FA, and precursors of other FA, such as AA and EPA, through the action of enzymes such as Δ5 and Δ6 desaturase and elongase (Baker et al., 2016; Moghadasian and Shahidi, 2017; Wood et al., 2008). The ALA is found in canola, soybean and flaxseed oils, as well as in nuts and meats, while EPA and DHA are found in seafood, especially oily fish (Baker et al., 2016; Moghadasian and Shahidi, 2017; Yehuda, S.; Mostofsky, 1997). The AA is one of the most abundant FA and is present in all biological membranes, moreover, it can represent 5 to 15% of the total FA in most tissue phospholipids (Neuringer et al., 1988).

The AA, EPA, and DHA are the three most important PUFA in human physiology. In addition, intake of EPA and DHA may be related to reduced risk of stroke and coronary heart disease (Moghadasian and Shahidi, 2017; Ulbricht and Southgate, 1991; Yokoyama et al., 2007). The EPA and DHA can be ingested from the diet or synthesized by the body from ALA. On the other hand, AA, despite being very important for

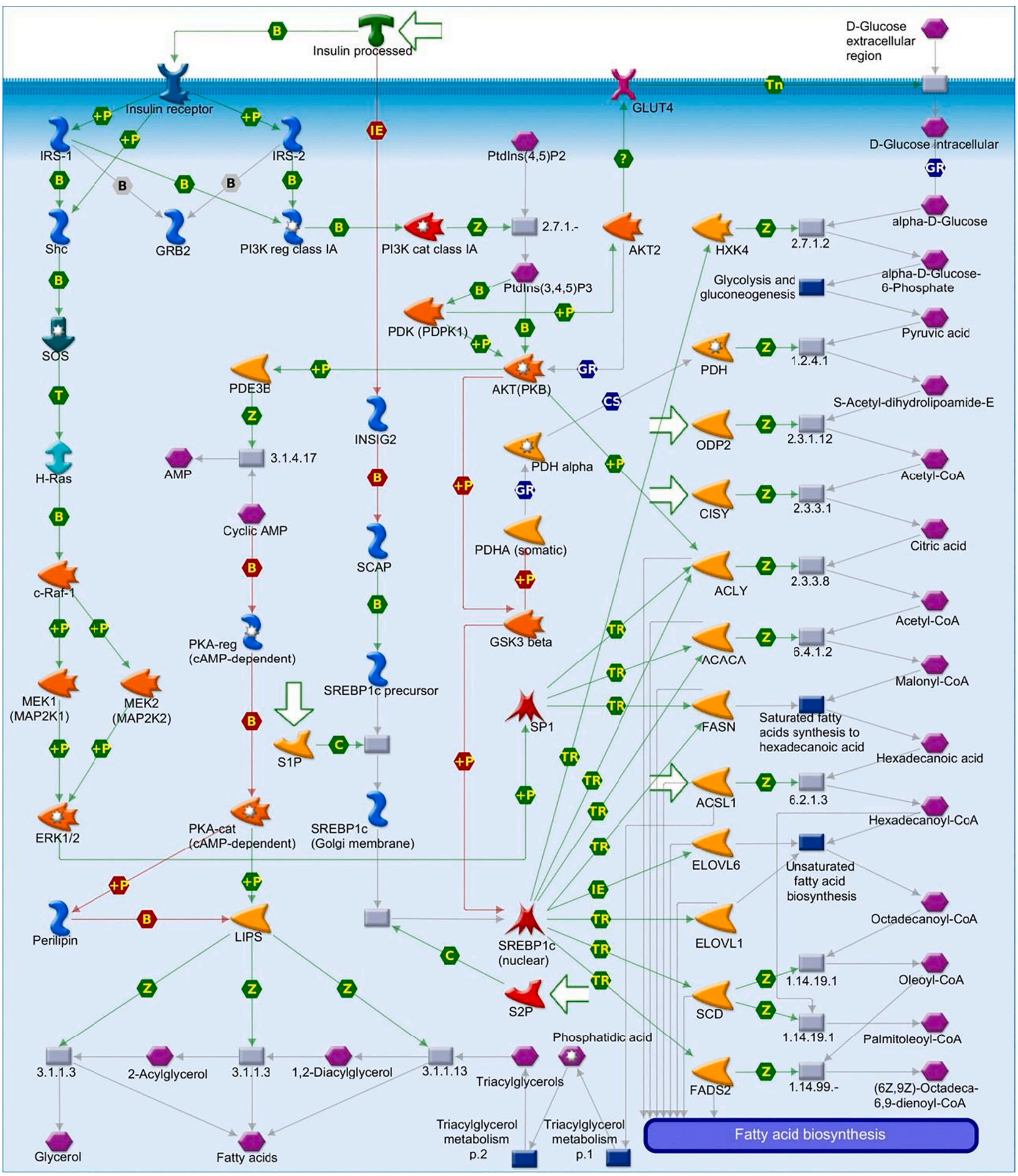

Fig. 1. Regulation of lipid metabolism and Insulin regulation of fatty acid metabolism Pathway. Image created by MetaCore (Clarivate Analytics) [https://portal.genego.com/]. Green arrows indicate positive/activation, red arrows indicate negative/inhibition. The nodes in the graph represent GeneGo Network objects that represent genes and/or gene complexes. For a detailed definition, see https://portal.genego.com/legends/MetaCoreQuickReferenceGuide.pdf.

physiology in general, is a potent precursor of pro-inflammatory mediators, and may play roles in the progression or suppression of inflammatory processes (Innes and Calder, 2018). Another important factor is that n-3 and n-6 PUFA are involved in regulating the synthesis of eicosanoids (molecules derived from C:20 FA of the n-3 and n-6 families), which control the activity of the immune system (Szostak et al., 2016).

Mammals generally do not have the fundamental enzymes to insert the double bond at the n-3 and n-6 positions. Therefore, LA and ALA and some derivatives, which are also considered essential, depend only on food, and their absence or intake in reduced amounts can cause general deficiency syndrome in the body or parts of it (Caterina, 2011). This deficiency can result in some symptoms such as fatigue, immune problems, problems related to the cardiovascular system, as well as growth retardation, and neurological diseases, including attention deficit hyperactivity disorder (ADHD), depression, and Alzheimer's disease (Yehuda and Mostofsky, 1997; Yehuda et al., 2002).

In insulin-dependent tissues, such as adipose tissue, skeletal muscle and the liver, insulin is considered to be the most important inhibitor of lipolysis (Holm et al., 2000; Østerlund, 2001) and also a potent regulator of lipogenesis. Insulin processing (Fig. 1) is responsible for insulin receptor activation and inhibits insulin induced gene 2 *(INSIG2),* a protein found in the endoplasmic reticulum that blocks sterol regulatory element-binding protein 1 *(SREBP-1)* processing by binding to *SREBP* cleavage-activating protein *(SCAP)* (Yabe et al., 2002). Furthermore, *SREBP-1* is a key transcriptional activator for the initiation of lipogenesis (Osborne, 2000), playing a fundamental role in the action of insulin on the activation of genes involved in FA metabolism and *de novo* lipogenesis (Song et al., 2018). *SREBP-1* is markedly increased rate of FA synthesis, owing to the activation of biosynthetic genes such as acetyl-CoA carboxylase (*ACACA*), ATP citrate lyase (*ACLY*),

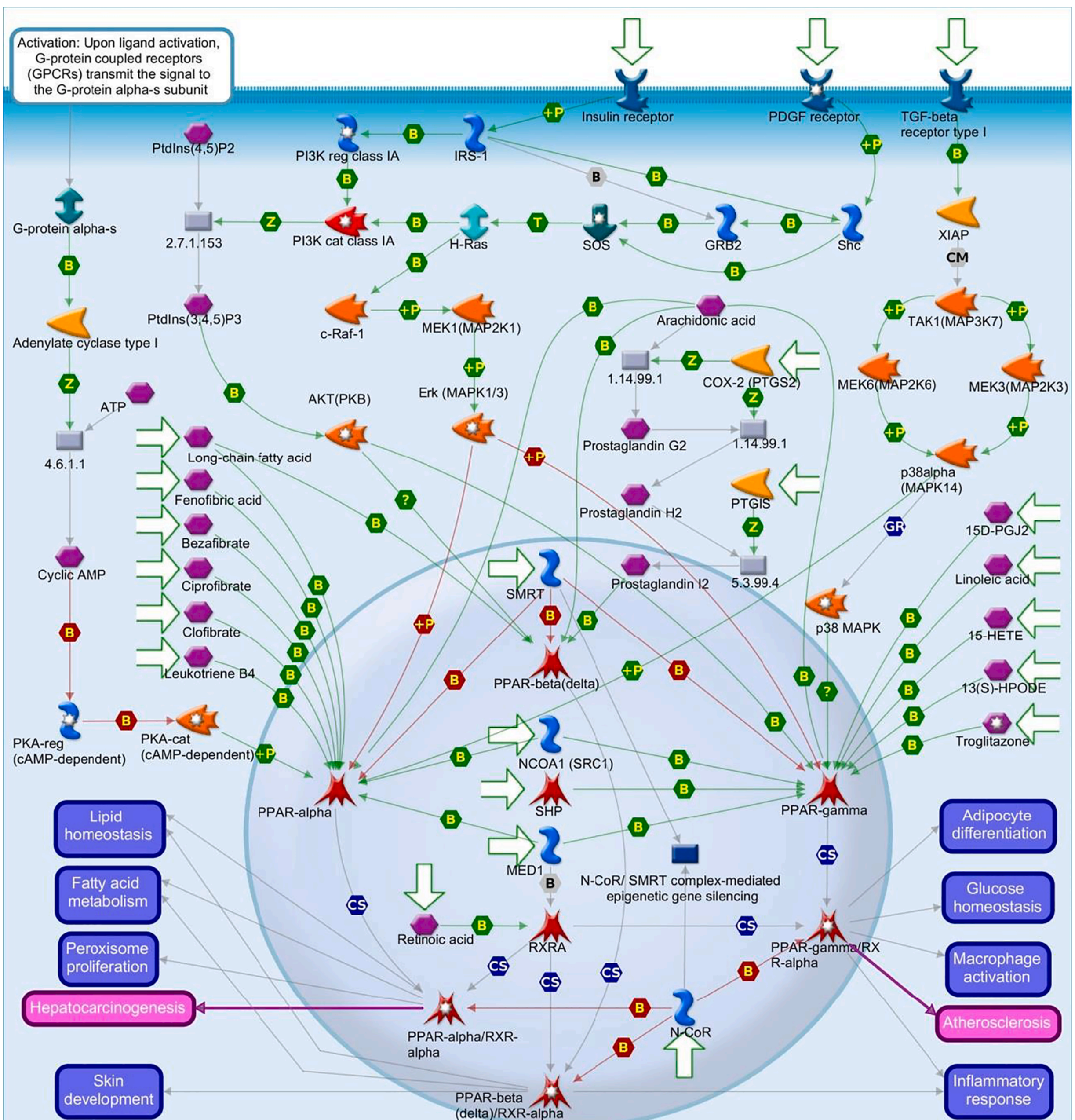

Fig. 2. Transcription PPAR Pathway. Image created by MetaCore (Clarivate Analytics) [https://portal.genego.com/]. Green arrows indicate positive/activation, red arrows indicate negative/inhibition. The nodes in the graph represent GeneGo Network objects that represent genes and/or gene complexes. For a detailed definition, see https://portal.genego.com/legends/MetaCoreQuickReferenceGuide.pdf.

stearoyl-CoA desaturase (*FADS2*) and fatty acid synthase (*FASN*) (MetaCore, 2022; Moon et al., 2001).

Fatty acid synthesis, or the initial phase of lipogenesis, is also regulated by the transcription factor *SP1*. In which its activation by the *ERK1/2* signaling pathway, which is induced by insulin, leads to the activation of enzymes such as *ACACA, ACLY* and *FASN* (Daniel and Kim, 1996; Moon et al., 1999; Xiong et al., 2000).

In general, the metabolism of FA and TG is regulated by transcriptional and post-transcriptional mechanisms (Georgiadi and Kersten, 2012). Digestion of dietary TG occurs in the intestine, where they are hydrolyzed to FA and monoglycerides and absorbed by enterocytes. After hydrolysis, FA are re-esterified to TG and secreted into the lymph as part of the chylomicrons (Georgiadi and Kersten, 2012). The chylomicrons present in the plasma undergo rapid lipolytic processing by the action of lipoprotein lipase (LPL), which results in the release of FA into the tissues. The rate of uptake into individual tissues varies independently of the specific delivery route and is influenced by factors such as tissue metabolic activity, food intake and nutritional status, fat intake and other nutrients such as carbohydrates (Georgiadi and Kersten, 2012; Wang et al., 2009). In addition, metabolic disturbances can affect the flow of free fatty acids (FFA) and TG derived FA. After absorption FA can have various metabolic fates such as esterification and storage and mitochondrial oxidation. FA also act as signaling molecules that can affect intra- and extracellular receptor sensor systems, which is in part due to regulation of gene transcription (Georgiadi and Kersten, 2012).

The peroxisome proliferator-activated receptors (*PPAR*) are the best-known transcription factors/sensing system for FA (Fig. 2). They are part of the nuclear hormone receptor family, which through a modular structure consisting of a DNA- and ligand-binding domain, bind to small lipophilic molecules and the *PPAR* group consists of three types: *PPAR-alpha, PPAR-beta (or delta)* and *PPAR-gamma* (MetaCore (Clarivate Analytics), 2021). Thus, *PPAR* play an important role in various biological processes. Fatty acids, derivatives or compounds that have a structure similar to acyl-CoA and oxidized FA, can activate *PPAR* (Georgiadi and Kersten, 2012; Hostetler et al., 2005; Kersten et al., 2000). In terms of beneficial effects, studies have shown evidence of PUFA interaction with nuclear receptors. The n-6 and n-3 affect gene expression and modulate transcription factors, such as *PPAR*, sterol regulatory element-binding protein (*SREBP*), liver X receptor *(LXR*) and retinoid X receptor (*RXR*) (Szostak et al., 2016).

The *PPAR* regulate gene expression by forming heterodimer with retinoid X receptor alpha (*RXRA*) at a DNA response element known as the Peroxisome Proliferator Response Element (*PPRE*) (Bishop-Bailey, 2000; Desvergne and Wahli, 1999). Thus, *PPARs* can bind both co-depressors and co-activators proteins (Desvergne and Wahli, 1999).

Regarding *PPAR-alpha*, its expression occurs preferentially in tissues with intense FA oxidation, such as in liver, muscle, heart, arterial wall, and kidney cells (Bishop-Bailey, 2000). Moreover, it is involved in the control of hepatic lipid content as well as the number of lipids for synthesis and secretion of very low density lipoproteins (VLDL) that induce FA oxidation, whereas *SREBP-1c* induces FA synthesis (Jump et al., 2005).

In the other hand, *PPAR*-beta *(or delta)* can be found in various tissues (Bishop-Bailey, 2000; MetaCore (Clarivate Analytics), 2021), and although its physiological function is unknown, it is shown to affect the expression of some genes involved in fatty acid metabolism, inflammation and lipid homeostasis (Bishop-Bailey, 2000; Smith, 2002).

3. Diet and gene interactions

The lipid sources available for the animal industry have a wide variety of composition, energy content, and quality, mainly due to the availability of lipid sources by geographic areas. In general, as a source of high levels of PUFA, corn, and soybeans are used globally in pig diets, varying locally in other grains and vegetables such as wheat, barley, canola, and sorghum used (Navarro et al., 2021). In addition, the demands of adding and enriching products with specific levels of healthier FA profiles are highly influenced by consumers. Examples of oils used in pig diets: are palm, fish, sunflower, linseed, canola (Souza et al., 2020) and soybean oil (Fanalli et al., 2022). Oil blends were tested to improve performance, composition, and deposition of FA and carcass characteristics, with positive results in relation to carcass yield, meat marbling, enrichment of bacon and loin with omega 9 and stearic acid, in contrast to the price of diet has been increased (Souza et al., 2020). The inclusion of 3% soybean oil or canola oil in pig diets reduced loin shear force and increased oleic acid content in the intramuscular fat (Almeida et al., 2021). Furthermore, the amount of oil used in the diet influences the differential expression of genes related to inflammation, immune processes, and pathways associated with oxidative stress, type 2 diabetes, and metabolic dysfunction as in the diet containing 1.5 or 3% soybean oil in animals in the growing and finishing phases (Fanalli et al., 2022).

Studies show that fish oil supplementation can alter the release of pro-inflammatory cytokines and consequently an improvement in performance flaxseed decreased gene expression of inflammatory cytokines, such as tumor necrosis factor α (TNF-α) (Zhan et al., 2009; Zhang et al., 2020). A significant increase was found in the concentration of C20:5 and C22:6 n −3 in the epithelium and intestinal mucosa of weaning pigs (28 days to 56 days of age) fed fish oil compared to tallow and sunflower with 5% of inclusion in the diet. Emphasizing the influence caused by the alteration of PUFA intake and the influence on the membrane structure with the incorporation of phospholipids from the cell membrane in many tissues, such as in the intestine of weaning pigs causing an effect on immune response cells (Lauridsen, 2020).

With the advancement in omics and its combined use with nutrition, information about the complex biology of important phenotypes is obtained (Núñez et al., 2021). The study of nutrient-gene interactions assists in studying the effect of nutrients on gene expression and consequently metabolic responses, canonical and disease-related pathways, and phenotypic changes impacted by dietary changes (Hasan et al., 2019).

The application of nutrigenomics uses omics techniques/tools both independently and with their integration, such as genomics, transcriptomics, proteomics, metabolomics, and lipidomics generating high data sets that improve the understanding of transcriptional regulation, biological role of molecules in metabolic pathways and networks, cell signaling, among others (Hasan et al., 2019; Song et al., 2022).

The advent of high-throughput technology, as NGS, has enabled the identification of transcriptome changes in nutrigenomic studies (Szostak et al., 2016). These technologies allow the measurement of the expression of each gene in each tissue of an individual using techniques such as RNA-seq (Tizioto et al., 2016). In addition, this tool is widely used to characterize and compare gene expression profiles for the identification of transcripts with different expression patterns between two or more biological conditions of interest in tissue samples (Pareek et al., 2019).

Through transcriptomics, information is obtained on RNA transcription alterations in response to dietary changes. With the use of RNA sequencing there is the massive generation of data that allow the identification of differential expression in response to diets or nutrients, or specific conditions through energy restrictions, vitamins or even related to diseases (Hasan et al., 2019; Núñez et al., 2021).

Transcriptomics provides a direct insight into the features involved in gene expression and has as the main objective the analysis of the presence or absence and quantification of a transcript (Manzoni et al., 2018). Also, with this kind of analysis, it is possible to verify the post-transcriptional modifications, such as pattern and assessment of alternative splicing, the quantitative assessment of the influence of genotype on gene expression - using eQTL or allele-specific expression analysis (ASE), the gene expression levels and changes under different conditions and, also, to determine the transcriptional structure of genes (Lehnen et al., 2015; Manzoni et al., 2018; Schena et al., 1998).

Several studies related to diet and gene interaction have been conducted, with the use of tannin supplementation (Núñez et al., 2021); with high-calorie diet supplemented with bioactive ingredients (Ballester et al., 2020); with different energy sources (Benítez et al., 2019). In addition to studies evaluating effect of different fat sources on the transcriptome, (Oczkowicz et al., 2019), and studies with diet enriched with n-6 and n-3 FA in *gluteus medius* muscle and liver samples with differential expression of 749 genes in muscle and pathways involved in lipid metabolism, immune response and more than 3000 differentially expressed genes (DEG) in liver with pathways related to energy metabolism, immune response and signal transduction (Ogłuszka et al., 2017; Szostak et al., 2016), among others.

The study by Ogłuszka et al. (2017) corroborates previous studies relating omega-3 fatty acid to the inflammatory response. The authors observed a decrease in the expression of the chemokines: *CCL2, CCL4, CCL5, CCL16, CCL19* and *CCL21*, with a diet supplemented with 1% rapeseed oil and 2% linseed oil (660 mg of LA and 64 mg of ALA/ 100) compared to a regular control diet (with 268 mg of LA and 25 mg of ALA/100 g). The chemokines found play an important role in the recruitment of macrophages and monocytes in inflammatory processes. Furthermore, apolipoprotein genes such as *APOA1, APOA2, APOA4, APOA5, APOC3, APOE* and *APON* were down-regulated with the supplemented diet. The biological processes most affected with the supplemented diet refer to "complement and coagulation cascades", "remodeling of very low density lipoprotein (VLDL) particles", "upregulation of cholesterol esterification" and "intestinal absorption of cholesterol" (Ogłuszka et al., 2017).

In a study of untargeted lipidomics and transcriptomics in pigs (18 gilts and 18 barrows), in the growing and finishing phases, evaluating the supplementation of two diets rich in n-3 of extruded flaxseed (5%) and extruded linseed and plant extracts obtained from grape-skin and oregano compared to a standard diet resulted in changes in several classes of lipids and DEG. The grape skin polyphenols and oregano extracts diet showed the up-regulated DEG, such as *APOE, CAVIN1, CCDC80, SCD* and *ELOVL5* that are related to glucose homeostasis and lipid metabolism. The authors identified correlations between the lipid profile and the modulation of gene expression (Rocchetti et al., 2022).

There are several benefits of adding FA to the diet/nutrition of pigs. Among them is the ability to increase the energy density of pig diets, mainly when feeding heat-stressed pigs and high-producing lactating sows. In addition, FA can improve digestibility of feeds, improve nutritional quality of feeds, and improve diet palatability (Apple et al., 2009; Benz et al., 2011; Gomes et al., 2021; Horodyska et al., 2018; Lauridsen et al., 2007).

In humans, the goals of nutrigenomics is the search for a better understanding of molecular mechanisms and the relationship diet and diseases such as obesity, cancer, cardiovascular disease and in production species is to elucidate how nutrients affect food quality and how they can aid in the human diet (Amills et al., 2020). Offering insights into gene networks and their pathways affected by dietary factors and the interventions in gene regulation in particular tissues. Gene networks are important with relevant information, not only with the identification of genes that are expressed differently according to interventions, but can identify candidate genes for traits of interest and that explain much of the changes (Amills et al., 2020).

4. Fatty acids and their effects on human health

Propositional studies have been carried out in recent years for manipulation to improve the nutritional quality of pork, enriching the FA composition to meet or improve the human health recommendation (Almeida et al., 2021; Czyż et al., 2021; Vodolazska and Lauridsen, 2020).

Some FA, such as ALA has been attributed to anti-inflammatory, anti-atherosclerotic and antithrombotic effects (Bork et al., 2020). The AA and EPA are precursors of important eicosanoids such as prostaglandins, leukotrienes and thromboxane (Szostak et al., 2016). Docosahexaenoic acid, on the other hand, affects cellular interactions and enzyme activity, influences some physical properties of brain membranes and the properties of their receptors. Docosahexaenoic acid, EPA and ALA are also associated with a decrease in the production and activity of pro-inflammatory cytokines such as *TNF-alpha, IL-6* and *IL-1* (Yehuda et al., 1999, 2002).

The AA presents great importance, since it is found in liver and brain tissues and ensures the normal functioning of these two tissues (Yehuda and Mostofsky, 1997). Thus, studies point out that AA is involved in several brain functions, including physiological membrane permeability and local blood flow (Yehuda et al., 1999, 2002). The AA is also a precursor to pro-inflammatory mediators such as prostaglandins, thromboxanes, and leukotrienes contributes significantly to FA present in membrane phospholipids, being associated when in higher concentrations with increased inflammatory processes (Innes and Calder, 2018; Simopoulos, 2011).

In general, an appropriate intake of PUFA is associated with reduced risk of cardiovascular disease, due to lower LDL, in the same way as MUFA. These FA also have the ability to modify food related properties such as nutritional value, composition and lipid content and oxidative stability. Thus, due to these benefits and the increasing interest of consumers for this type of food, several studies have been done to bring more safety and food quality to the population (Andersen et al., 2005; Yehuda et al., 1999).

To form EPA and DHA from ALA, numerous reactions occur in the biosynthetic pathway. These include desaturation and elongation reactions, which occur in the endoplasmic reticulum, and beta oxidation that occurs in the peroxisomes (Baker et al., 2016). The beta-oxidation of ALA that occurs in the mitochondria, has the enzyme Δ6-desaturase (D6D) as a rate-limiting factor in the conversion and carbon units of acetyl-CoA can be formed. These can be recycled and used to synthesize other compounds such as SFA, MUFA, ketone bodies, and cholesterol. In addition, EPA and DHA, are present in larger quantities in cells at the end of the ALA metabolic process (Baker et al., 2016).

Results from epidemiological studies show that there is a positive association between consumption of some FA and long-term health benefits (Yokoyama et al., 2007). Very long-chain EPA and DHA are involved in cell membrane viscosity and are associated with reduced mortality related to cardiovascular disease (Casula et al., 2013; Marik and Varon, 2009). They show positive results for visual and neurological development and are important for the prevention of diseases such as Alzheimer's disease (Calder, 2014). The EPA and DHA are also associated with changes in specific cell signaling pathways, gene expression, and biophysical properties of cell membranes (Georgiadi and Kersten, 2012; Turk and Chapkin, 2013).

The $n-3$ and $n-6$ PUFA, such as DHA and EPA, are reported to have atheroprotective roles, with the potential to improve cardiovascular health (Manual Kollareth et al., 2020). In addition, PUFA play a role in influencing membrane ion channels may be involved in regulating blood pressure by improving endothelial functions. The $n-6$ PUFA exhibit pro-atherogenic effects, but $n-3$ PUFA rich diets increase plasma concentrations of HDL cholesterol related to benefits the cardiovascular diseases, and one of the main sources found is with fish oil (Manual Kollareth et al., 2020). The EPA and DHA are involved in the regulation of the inflammatory response, associated with the inhibition of the expression of inflammatory genes, such as *COX-2, iNOS* and *IL-1* in macrophages (Rogero and Calder, 2018).

Although the intake and/or synthesis of FA n-6 and n-3 are essential for the body, studies point out, that excess FA, even when considered beneficial to health, can cause harmful effects (Martin et al., 2006; Moghadasian and Shahidi, 2017). Essential FA from the n-6 family, when consumed together with SFA and in high amounts, as in Western diets, can bring a number of health risks. They can increase the chances of developing diseases such as obesity, coronary heart disease, and neurodegenerative diseases (Caterina, 2011; Yehuda et al., 2002).

Studies indicate that an ideal n-6:n-3 ratio is important to maintain the healthy homeostasis of metabolism and biological processes. The availability of different types of FA, coming from the diet and biological synthesis, may affect this n-6:n-3 ratio, and it determines the availability of energy and FA available for biological processes (Martin et al., 2006; Moghadasian and Shahidi, 2017; Simopoulos, 2003). This reason may also be affected during the synthesis process as the reactions of the two families occur in the same metabolic pathway, thus generating competition for the desaturation and elongation enzymes during the conversion process (Baker et al., 2016; Martin et al., 2006; Szostak et al., 2016). This proportion was discussed and evaluated in each region and country according to the trend in nutrition and availability of food sources. These proposals have been reviewed and generally agreed on the range of 4:1 to 5:1, but some authors recommend a ratio of 2:1 to 3:1, stating that this range allows greater conversion of ALA in DHA (Martin et al., 2006; Moghadasian and Shahidi, 2017). With the high risk for cardiovascular disease (CVD) in Americans the recommendation ranges from 2 to 4: 1, in return in developed countries this ratio up to 15: 1 (Moghadasian and Shahidi, 2017).

According to Yehuda et al. (1999), diets based on a specific n-6:n-3 ratio may have several benefits, such as reducing total cholesterol and increasing PUFA content in the nerve membrane, thereby reducing the risk of coronary and neurodegenerative diseases. When this ratio is imbalanced, it can be associated with cardiovascular, inflammatory, autoimmune, and diabetic diseases (Simopoulos, 2011). Another important point is the need to understand that the effects of a given ratio may be related to several factors, such as changes in FA profile, cholesterol profile, in addition to the availability and dependence of metabolism of FA, which vary in the population (Simopoulos, 2011; Yehuda et al., 2002).

Studies have reported that the consumption of FA can positively or negatively alter a wide range of metabolic pathways associated with chronic diseases. Several studies have demonstrated that OA, LA, DHA and EPA may regulate gene transcription in some tissues and organs, including skeletal muscle, adipose tissue, liver, and brain (Cesar et al., 2016; Park et al., 2012). Furthermore, studies must demonstrate ways to quantify the impact of FA. In other words, present knowledge on how the property (signaling molecules) directly affects biological processes of interest (Georgiadi and Kersten, 2012). Table 1 provides further details on important fatty acids described in pork.

Table 1
Important fatty acids already described in pork.

Fatty Acids	Description	
Saturated fatty acids (SFA)		
Lauric Acid (LA)	It is used as a food additive and has antimicrobial and immunomodulatory activity (Jackman et al., 2020)	
	Palmitic Acid (PA)	The fatty acid coming mainly from the synthesis products in the animal (Wood et al., 2008)
Unsaturated fatty acids (UFA)		
Polyunsaturated fatty acids (PUFA)		
	Linolenic acid (LA)	Correlated with back fat thickness (Świątkiewicz et al., 2016)
Alpha-Linolenic acid (ALA)	It is fundamental to physiological processes. When it is absorbed in insufficient amounts, processes such as inflammation, healing, and blood clotting can be affected (Elmadfa and Kornsteiner, 2009; Eshak et al., 2018)	
	Arachidonic acid (AA)	Is the precursor of important eicosanoids (YEHUDA et al., 1999)
Docosahexaenoic acid (DHA)	DHA is associated with changes in specific cell signaling pathways, alteration of gene expression and changes in the biophysical properties of cell membranes (Georgiadi and Kersten, 2012; Turk and Chapkin, 2013)	
	Eicosapentaenoic acid (EPA)	Together with DHA they are involved in cell membrane viscosity and are associated with reduced mortality related to cardiovascular disease (Casula et al., 2013; Marik and Varon, 2009).
Monounsaturated fatty acids (MUFA)		
Oleic Acid (OA)	Corresponds to about 40% of the fatty acid composition in pigs (Świątkiewicz et al., 2016)	

5. The impact of dietary fatty acids on biological processes

Tissue fat content impacts the flavor and juiciness, as well as the tenderness and firmness of pork. Low saturated fatty acid contents are highly desirable, as this content is often associated with high blood cholesterol levels, such as low-density lipoprotein cholesterol (LDL-c) (Albuquerque et al., 2021). However, high levels of MUFA and PUFA are helpful in decreasing LDL-c levels and increasing high-density lipoprotein cholesterol, which is influential in reducing the risk of heart disease (Albuquerque et al., 2021).

The liver is a highly specialized organ, it is related to the regulation of several metabolic processes, together with skeletal muscle are essential for the regulation of lipid metabolism in pigs, the liver is the main site for the de novo synthesis of fatty acid oxidation and cholesterol (Ramayo-Caldas et al., 2012).

Ballester et al. (2020) evaluated the liver and adipose tissue (visceral and subcutaneous) transcriptome of 20 pigs submitted to four dietary treatments (conventional diet; a Western diet; and a Western diet containing *Bifidobacterium breve* and hydrolysate, either with or without the addition of n-3 for 10 weeks. Differentially expressed analysis concluded an increase in cholesterogenesis, lipogenesis, and inflammatory processes in animals on the western-type diet. In relation to supplementation with bioactive ingredients, there was an induction of FA oxidation, a decrease in adipogenesis and inflammation, and induction of cholesterol catabolism.

The balanced ratio of n-6:n-3 is fundamental in several biological processes, besides maintaining metabolic homeostasis (Szostak et al., 2016). A study analyzing pigs fed diets enriched with LA and ALA compared to a standard diet showed differences in FA profile with higher amounts of PUFA in the liver in pigs fed associated with unchanged or lower n-6 content and higher n-3 FA content, achieving reduction of the n-6:n-3 ratio (Szostak et al., 2016). From the differential expression analysis several pathways were enriched grouped around the biological themes, such as inflammatory response, signaling pathways, carbohydrate/lipid metabolism. On the other hand, the authors found specifically for dietary control inflammatory response pathways, chemokine biosynthetic process, as well as pathways such as potassium transport ATPase activity and cGMP biosynthetic processes (Szostak et al., 2016). Furthermore, FA has an important role in immune modulation due to their contribution as the main source of energy, their important components in cell membranes, being metabolic substrates in many biochemical pathways, and in cell signaling molecules. The FA still has effects on innate immune response, neutrophils, macrophages, dendritic cells, and adaptive immune responses as reviewed by (Radzikowska et al., 2019). The use of immunonutrients such as FA to modify inflammatory and immunologic responses has become of increasing interest both in animal and human health. It is because PUFA such as n-3 modulate immune system functions and thereby decrease the severity of inflammatory disorders (Yates et al., 2014). The PUFA have been used as added ingredients in animal feed and human food to improve health status and immune function (Al-Khalaifah, 2020). The type and amount of FA influence the immune response and immune status through mechanisms related to the production of anti-inflammatory mediators, inhibition of the metabolic process of AA, modification of intracellular lipids and activation of nuclear receptors (Al-Khalaifah, 2020).

Furthermore, the n-6:n-3 ratio in pork is related to human health, affecting the quality of the meat. A study conducted with 54 Heigai pigs were fed 3 diets with different n-6:n-3 ratios: 8:1, 5:1, and 3:1, and showed significant differences in subcutaneous adipose tissue and *longissimus dorsi* muscle (Nong et al., 2020). Low n-6:n-3 ratio (3:1) increased the deposition of n-3 PUFA and hormone-sensitive lipase (*HSL)* expression in the *longissimus dorsi* muscle. Hormone-sensitive lipase is an enzyme that regulatesnon-esterified fatty acid NEFA release from lipid stores. In the other hand, in subcutaneous adipose tissue *HSL* expression was not altered (Nong et al., 2020).

In the study by Almeida et al. (2021) in Large White pigs on diets with different proportions of oils they found that with the use of 3% fish oil the n-6:n-3 ratio PUFA in the fat of the *longissimus lumborum* muscle was decreased. The other diets were composed of 1.5% soybean oil or 3% soybean oil or 3% canola oil, the n-6:n-3 ratio was similar in either 1.5% or 3% soybean oil or 3% canola oil, with higher values compared to fish oil.

Longissimus lumborum muscle contains > 90% of total FA including OA, LA, palmitic acid, stearic acid, palmitoleic acid, and myristic acid. These FA are correlated with pig's nutrition and sensory qualities (Zhang et al., 2019). In addition, muscle contains significant amounts of long-chain PUFA, such as AA and EPA, which have various metabolic functions, for example the production of eicosanoids (Wood et al., 2008).

In mammals, skeletal muscle is one of the main sites for FA catabolism. Furthermore, PUFA can regulate hormonal, metabolic and immunological processes. The study by Ogłuszka et al. (2017) evaluating the impact of n-6 and n-3 supplementation on pig muscle, identified 759 DEG as well as processes related to wound response and inflammation. Furthermore, other results linking n-6 and n-3 as fundamental to postprandial metabolism, in addition to biological functions, signaling pathways and lipid metabolism.

In the study of evaluating the transcriptome profile of the *longissimus thoracis et lumborum* muscle of pigs divergent in feed efficiency by obtaining biological events related to immune response, lipid and carbohydrate metabolism and lipids and with the DEG of 276 genes annotated by the Ingenuity® database (Horodyska et al., 2018).

The brain is another important tissue that contributes to various biological processes. The brain is a tissue that requires FA with a high degree of unsaturation to maintain normal conditions, with AA, DHA and EPA as important long-chain FA for maintaining the function of the entire central nervous system. These long-chain FA play important regulatory roles in various systems such as nervous, immune and cardiovascular systems (Innis and Dyer, 1999; Martin et al., 2006; Petrovic and Arsic, 2016). Docosahexaenoic acid is the most important long-chain FA for the brain, moreover this FA is part of cell membranes and plays an important role in the formation and development of this tissue (Chang et al., 2009; Martin et al., 2006; Neuringer et al., 1988). In addition, DHA participates in modulating the activity of signaling pathways in the brain through its presence in neuronal membrane phospholipids, and is also found mainly in synaptosomes, mitochondria, and synaptic vesicles (Neuringer et al., 1988; Yehuda et al., 2002). The DHA is also critical for cognitive development and influences the physical properties of brain membranes, membrane receptor characteristics, enzyme activity, and cellular interactions (Chang et al., 2009; Martin et al., 2006).

Studies indicate that AA and DHA, are responsible for the development and maintenance of brain and retinal functions, from the gestational period until the first years of development (Martin et al., 2006; Petrovic and Arsic, 2016; Yehuda et al., 1999). The AA is associated with synaptic transmission, through its presence in the phospholipids associated with neurons, even though it is found in smaller proportions in the brain than DHA. Moreover, through the action of phospholipases that is stimulated by neurotransmitters, AA because it is obtained in the form of FFA, can alter the activity of protein kinases and ion channels, affecting several relevant biological processes (Innis and Dyer, 1999; Martin et al., 2006). Thus, maintaining adequate amounts of these FA is very important. Diets deficient in n-3 FA cause a decline in the concentration of DHA and its precursors in the retina and brain (Martin et al., 2006; Sinclair et al., 2003). Already during the aging process, increased oxidative stress in brain tissue results in a reduction of n-3 FA and an increase in cholesterol, which is associated with neurodegenerative diseases such as Parkinson's, Alzheimer's, and amyotrophic lateral sclerosis (Martin et al., 2006).

The structure of the neuronal membrane is the most important factor in maintaining proper brain function. In addition to membrane structure, lipid composition is also an important factor, because it can be affected by the availability of FA in the diet. This availability can affect the membrane fluidity index and impair important physiological processes (Chang et al., 2009; Yehuda et al., 2002). Some FA, such as LA and ALA, may help reduce cholesterol in the neuronal membrane, improving the fluidity index. However, some studies have suggested that large reductions in cholesterol, as well as high concentrations of cholesterol, may compromise the membrane fluidity index. This compromised index affects the performance of cellular functions and increases susceptibility to injury, and may also lead to cell death (Chang et al., 2009; Yehuda et al., 2002).

This fluidity can also be altered by the n-6:n-3 ratio and the absolute content of FA in cell membranes (Yehuda et al., 2002, 1999). Alpha-linolenic acid is responsible for the composition of FA in membranes and has an inverse relationship with cholesterol levels (Bourre et al., 1991; Yehuda et al., 1999). Salem and Niebyski (1995) reported that cholesterol levels and membrane composition are controlled by DHA. Other studies, have also indicated that an n-6:n-3 ratio of 1:4, promotes the reduction of cholesterol levels in membranes and helps optimize PUFA uptake, promoting better FA incorporation into neuronal membranes (Chang et al., 2009; Yehuda et al., 2002). The brain can obtain long-chain PUFA directly from the diet, or it can utilize supplemental essential FA such as LA and ALA and convert them into long-chain FA. Being that LA and ALA are necessary to maintain under normal conditions cell membranes, brain functions, and nerve impulse transmission (Martin et al., 2006; Yehuda et al., 2002).

6. Final considerations

The supply of food is a decisive factor for being able to feed the world population in the near future and sustainable production with greater efficiency and nutritional quality is essential. As future perspectives, nutrigenomics studies will increasingly help biological models with reliable information to achieve accurate nutritional strategies and knowledge of signaling pathways, putative genes and consequently the best oils for specific demands. There has been an increased interest in the use of different sources of lipid and their fatty acid profile in animal production, because of the important role of this macromolecule on animals' production efficiency and health, which is directly related to human health. Then, in this review, we highlighted the main role of dietary fatty acids on animal and human health. Our main goal was to lead the reader to reflect on the role of fatty acids as a functional component present in foods of animal and plant origin, which plays an important role in nutrigenomics studies. Further studies have to be performed to help understand the biological processes that the fatty acids can modulate and affect health, either positive or negative.

Data availability statement

Not applicable.

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Declaration of Competing Interest

The authors declare that there is no conflict of interests associated with this publication.

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