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Review: Nutrigenomics of marbling and fatty acid profile in ruminant meat

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The present review will present the recent published results and discuss the main effects of nutrients, mainly fatty acids, on the expression of genes involved in lipid metabolism. In this sense, the review focuses in two phases: prenatal life and finishing phase, showing how nutrients can modulate gene expression affecting marbling and fatty acid profile in meat from ruminants. Adiposity in ruminants starts to be affected by nutrients during prenatal life when maternal nutrition affects the differentiation and proliferation of adipose cells enhancing the marbling potential. Therefore, several fetal programming studies were carried out in the last two decades in order to better understand how nutrients affect long-term expression of genes involved in adipogenesis and lipogenesis. In addition, during the finishing phase, marbling becomes largely dependent on starch digestion and glucose metabolism, being important to create alternatives to increase these metabolic processes, and modulates gene expression. Different lipid sources and their fatty acids may also influence the expression of genes responsible to encode enzymes involved in fat tissue deposition, influencing meat quality. In conclusion, the knowledge shows that gene expression is a metabolic factor affecting marbling and fatty acid profile in ruminant meat and diets and their nutrients have direct effect on how these genes are expressed.

Keywords: fatty acid, gene expression, lipids, lipogenesis, membrane transporters

Implications

Marbling is a very important characteristic of meat quality in ruminants due to its effect on flavor and juiciness. In addition, fatty acid composition of lipids in meat is also important for human health and, therefore, this subject has been extensively studied in recent decades. In this sense, nutrigenomic has been used to better understand the cellular mechanisms influencing marbling and fatty acid profile in meat. This knowledge may affect livestock sector, creating possibilities for the industry to produce substances or chemical compounds that can modulate gene expression and, therefore, improving meat quality. In addition, this knowledge will permit nutritionists to use feedstuffs and additives in order to modulate the expression of target genes and increase meat quality.

Introduction

Since the 1980s, consumers have become more concerned about the quality of food and how it could directly influence health. This concern became more pronounced during the 2000s, influencing consumption (Van Wezemael *et al*., 2010) and, consequently, directing research for healthier food production. In this sense, research around the world has been conducted with the goal to improve fatty acid profile in ruminant meat, aiming to increase concentrations of beneficial fatty acids to improve human health and reduce fatty acids that could have some detrimental effect (Scollan *et al*., 2014).

However, when analyzing research published in the last 10 years on this subject (Supplementary Table S1) in the main journals of Animal Science and Meat Science, it has been found that results showing that manipulating beef fatty acid profile in a way that is beneficial for human health are limited. It was considered as beneficial for human health concentrations of CLA, oleic and hypercholesterolemic fatty acids and *n*-6/*n*-3 ratio. Of the 28 articles selected, almost half (13) reported no improvement on fatty acid profile through dietary changes (Figure 1). In addition, specifically for CLA, a fatty acid linked with cancer prevention, reduction of atherosclerosis, improvement of the immune response, as well as changes in protein and energy metabolism (Whigham; Cook & Atkinson, 2000),

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only eight studies reported increased concentrations in muscle. Therefore, despite efforts to alter fatty acid profile in ruminant meat through dietary changes (i.e. use of high polyunsaturated fatty acids (PUFA) ingredients, grass-fed or feedlot in finishing phase), it has been found that this objective is hard to achieve. For this reason, the following questions arise: is it not possible to reduce/alter significantly ruminal biohydrogenation? Or, although fatty acid profile in the rumen is altered, does the muscle tend to maintain a pattern of their concentrations? To help answer these questions, research on how different fatty acids modulate expression of genes involved in muscle lipid metabolism have become important (Ladeira *et al.*, 2016), of which the main results are shown in this review.

Another important issue is marbling, a key factor for the production of high quality meat in some markets, such as the United States, Japan, Korea, Australia, Canada and Brazil. In this case, the knowledge about the metabolic mechanisms influencing lipogenesis and intramuscular fat deposition is fundamental to produce high marbling meat. According to Smith and Crouse (1984), glucose incorporation into fatty acids was significantly greater in intramuscular adipose than in subcutaneous adipose, and glucose was quantitatively the primary lipid precursor (51% to 76%) in intramuscular adipose tissue compared with acetate (10% to 26%). Therefore, it is necessary to understand the regulation of genes involved in starch digestion and glucose absorption in the small intestine, liver gluconeogenesis and glucose uptake by the muscle when the goal is to produce high marbling meat.

The marbling content in adult animals is dependent on the number and size of adipose intramuscular cells, and the potential amount of these cells is greatly affected during prenatal and early postnatal life (Zhu *et al.*, 2008). Environmental factors such as nutrition can affect gene expression in the animal through epigenetic effects varying the differentiation and proliferation of adipose cells. Therefore, the regulation of marbling and fatty acid profile starts with the maternal influences on fetal gene expression to modulate the differentiation and proliferation.

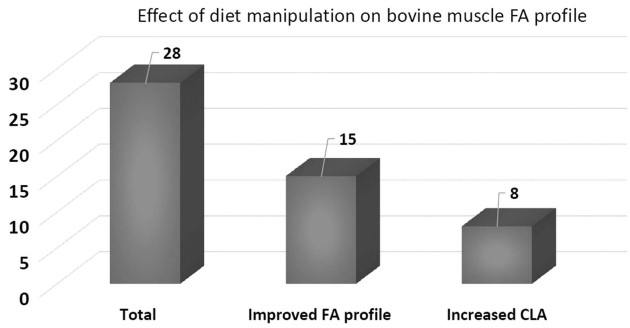

Figure 1 Effect of diets on ruminant muscle fatty acid profile. Improving fatty acid profile considered increase concentrations of conjugated linoleic acid (CLA) *c*9,*t*11-C18:2 and oleic acid; and decrease hypercholesterolemic fatty acids and *n*-6/*n*-3 ratio. Data were obtained in researches published in the last 10 years on this subject in the main journals of Animal Science and Meat Science (Supplementary Table S1). FA = fatty acid.

Therefore, this review has the objective to present a critical analysis of published results and new concepts on how nutrition affects expression of genes involved in adipogenesis, lipogenesis and fatty acid profile of ruminant meat.

Fetal programming of adipogenesis and marbling

Adipogenesis begins during the prenatal phase, which may have long-term influence on fat deposition and meat quality. Therefore, before discussing the direct effect of nutrients on genes during the finishing phase, it is necessary to examine the effect of nutrition of the dam on adipogenesis of the offspring through nutrients affecting the expression of genes in the fetus. This effect is part of the concept known as 'fetal programming'. How nutrition of the dam affects offspring is complex. The dam can influence progeny phenotype by providing half of the fetal genes and, besides that, epigenetic markings, through somatic epigenetic reprogramming, via the ooplasmic contribution to the fetus and via the provision of the intrauterine environment (Aiken and Ozanne, 2014).

Fetal programming may have a direct effect on progeny development and have transgenerational effects, transmitting a genetic inheritance to generations that were not exposed to the initial signal (Heard and Martienssen Robert, 2014). These epigenetic changes may affect adiposity and meat quality because several organoleptic characteristics are dependent on metabolic processes in the live animal and *postmortem*.

Epigenetics effects

Epigenetics is a concept of changes in gene functions related to parental inheritance without altering the base sequences of the DNA and can act as a key mechanism that allows phenotypic plasticity regarding a fixed genotype (Heard and Martienssen Robert, 2014). Alterations in chromatin structure by DNA methylation, histone modification and non-coding microRNAs are the most common mechanisms in epigenetics and regulate timing and intensity of gene expression allowing those changes to pass through generations (Link *et al.*, 2010). The combination of these three epigenetic mechanisms are responsible for controlling genetic expression, maintaining a robust combination that allows this regulation to be passed from one generation to another. The way that epigenetics is influenced by a nutritional stimuli was simplified and described by Mathers (2008), and is called the 4Rs of nutritional epigenomes. First the animal RECEIVED a nutritional stimuli and it is RECORDED by the genome. Then this exposure is REMEMBERED by following cell generations, and finally is REVEALED in changed gene expression, cell function and overall health.

Maternal nutrition and offspring adipogenesis and marbling

In utero development of muscle and adipose tissue are important events that impact the ultimate quantity and quality of meat produced. Nutrient restriction or excess during fetal and neonatal development can have long-term

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consequences on offspring adiposity (Figure 2), particularly if they occur during critical periods of adipose development. The development of adipocytes, which will generate brown adipose tissue, starts in early gestation, and ~ 80% of fetal adipogenesis occurs in the final few weeks of gestation (Symonds *et al*., 2007). Adipocyte hyperplasia occurs primarily during late fetal development and early postnatal life in cattle (Zhu *et al*., 2008). Although preadipocytes can proliferate and differentiate in adults, their capacity appears to be limited to the developmental stage in early life (Martin *et al*., 1998).

Fetal programming may occur during cell division in response to a recent stimulus and transferred to other cells (Bonasio and Reinberg, 2010). For example, maternal undernutrition may cause adaptation in the offspring, leading to metabolic changes to 'save' energy, resulting in greater fat deposition and lesser muscle mass in the progeny (Blair *et al*., 2013). The reason why nutrition of the dam can change cell tissues proliferation is that mesenchymal stem cells (MSC) originate muscle and adipose tissues by the action of transcription factors, regulating the involvement and differentiation of these cells and muscle composition (Du *et al*., 2010). Transcription factors can act in many ways, as influenced by concentrations, cell-to-cell interactions and the extra-cellular matrix (Ladeira *et al*., 2016).

The main transcription factor for MSC differentiation is Wingless and Int (Wnt) signaling. According to Du *et al*. (2010), the Wnt signaling pathway increases myogenesis and reduces adipogenesis in skeletal muscle, regulating body fat and reducing obesity susceptibility. Therefore, it is possible that adequate maternal nutrition during gestation will increase Wnt signaling, promoting more myogenesis in early- and mid-gestation. Then, during late-gestation, after a satisfactory myogenesis, Wnt signaling could be inhibited to increase adipogenesis.

Maternal nutrition may affect *Wnt* expression in an epigenetic manner. Maternal over-nutrition during pregnancy impairs myogenesis and elevates adipogenesis, which is partially explained by down-regulation of the Wnt signaling pathway (Yan *et al*., 2012). Dietary supplementation with methyl donor groups, such as folic acid, vitamin B_{12}, choline and betaine, increases *Wnt* expression and reduces adipogenic differentiation (Funston and Summers, 2013). Likewise, maternal nutrient restriction may increase visceral adipogenesis (Wang *et al*., 2016). In addition, overnourishment of beef cows during gestation enhanced the messenger RNA (mRNA) expression of adipogenic markers and collagen deposition without affecting myogenesis in skeletal muscle of beef cattle fetuses (Duarte *et al*., 2013).

The Zinc finger protein 423 (ZFP423) is another transcriptional factor involved in the regulation of adipogenesis. The ZFP423 stimulates expression of another transcription factor, known as *peroxisome proliferator-activated receptor-gamma* (*PPARG*), increasing adipogenic differentiation (Gupta *et al*., 2010). Peroxisome proliferator-activated receptor isoforms function as heterodimers with a retinoid X receptor (RXR), and both bind to a specific DNA sequence, inducing or repressing its expression (Ladeira *et al*., 2016). Because PPARα and PPARγ use fatty acids as endogenous ligands, it is suggested that they can be regulated by diet (Bispham *et al*., 2003). However, the bovine fetus has low

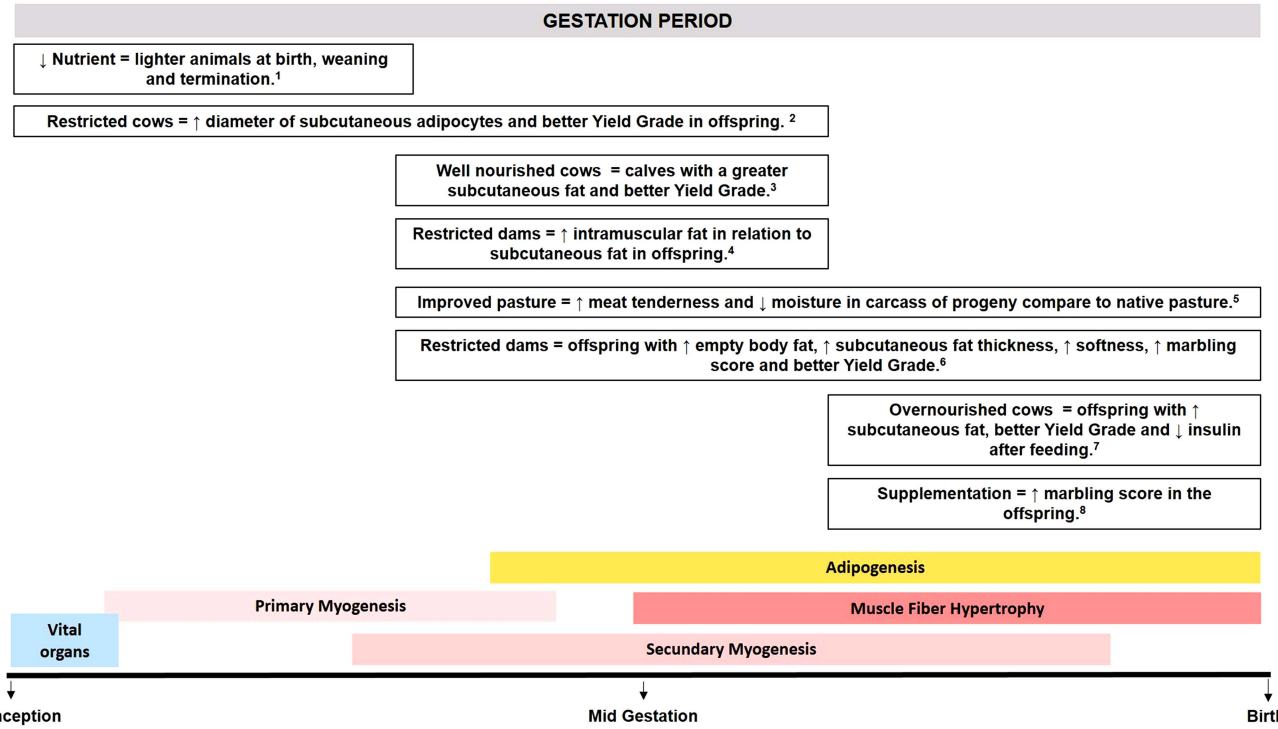

Figure 2 Long-term effects of maternal nutrition according to gestation period in ruminant offspring development and performance. [1]Greenwood *et al*. (2005); [2]Long et al. (2012); [3]Blair et al. (2013); [4]Mohrhauser *et al*. (2015); [5]Underwood et al. (2010); [6]Summers *et al*. (2015); [7]Wilson *et al*. (2016); and [8]Larson *et al*. (2009).

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concentrations of free fatty acids and this mechanism may be limited. Bispham *et al.* (2003) observed that maternal dietary restriction increased *PPARG* expression in fetus inducing greater amounts of adipose tissue. Similar results were observed by Paradis *et al.* (2017), who explain this effect as a consequence of an epigenetic effect, where mobilization of fatty acids from maternal adipose tissue increases expression of *PPARA* in the dam and fetus. Yang *et al.* (2013) observed that maternal obesity reduces DNA methylation in the promoter region of *ZFP423* and adipogenic progenitors in mice fetuses. In addition, Gionbelli *et al.* (2018) has shown that *ZFP423* and *PPARG* were more expressed at 139 days of gestation in fetuses of cattle whose dams were overnourished during gestation.

Non-myogenic progenitors as fibro-adipogenic precursors (FAP) are also involved in adipocyte formation. Fibro-adipogenic precursors has an adipogenic and fibrogenic capacity, act in the recovery of muscle damage (Uezumi *et al.*, 2014) and are responsible for the development of intramuscular fat. Late gestation is the period of greater production of intramuscular adipocytes, consequently, manipulation of maternal diet for greater expression of FAP could lead to greater marbling and meat quality, but more research is necessary to further examine these responses.

Although there is evidence that an increase in intramuscular adipocyte number may occur in the late stages of development (Cianzio *et al.*, 1985), late gestation and neonate phases are considered the best time for manipulation of the diet in order to increase marbling of progeny because of the large abundance of multipotent cells (Du *et al.*, 2010). In this case, after birth and until 250 days of life, there is still formation of adipose cells, but after this period the effects of dietary manipulation are conditioned to the hypertrophy of the existing adipocytes.

Deoxyribonucleic acid methylation also changes during the lifetime of the animal and can be manipulated by nutrition (Gueant *et al.*, 2014). Vitamin A supplementation to the dam promotes adipogenic commitment through the increase of cellular retinoic acid binding protein 2 (CRABP-II) delivering retinoic acid for binding to retinoic acid receptor (RAR). Therefore, vitamin A supplementation during early development is expected to increase adipogenesis, which is supported by studies in mice (Wang *et al.*, 2017). In Wang *et al.* (2017) study, authors identified that vitamin A affects fetal and offspring adipogenesis through promoting angiogenesis. In this case, retinoic acid up-regulated *Vegfa* and *Vegfr2* expression, which consequently increased the population of platelet derived growth factor receptor $\alpha+$ adipose progenitor cells in adipose tissue. Therefore, this finding shows that the increase of adipocytes in early life may increase intramuscular fat deposition in the finishing phase of ruminant animals. On the other hand, vitamin A supplementation in finishing cattle increases fatty acid binding protein (FABP)5 and stimulates PPAR activation leading to an increase of lipid oxidation and reducing adipocyte hypertrophy and marbling (Wang *et al.*, 2016).

Although the way maternal nutrition affects gene expression and fetal development is not totally clear, it is well known that maternal nutrition and metabolism affect nutrient supply in the fetus and it may alter metabolism by reducing availability of methyl donors and specific amino acids involved in DNA methylation and histone modification (Paradis *et al.*, 2017).

Nutrigenomic and glucose metabolism

Starch digestion

Ruminants evolved with cellulose supplying the majority of metabolizable energy for the rumen microbial fermentation. Cereal grains, which are primarily composed of starch, are a major feedstuff for ruminant production systems, especially in feedlots and dairies. Ruminants do not produce salivary α-amylase, so the first site of starch digestion is the rumen in which starch is fermented to volatile fatty acids (Kotarski *et al.*, 1992). Harmon *et al.* (2004) also reported a linear relationship between starch intake and starch digested in the rumen, suggesting that there are no limits to ruminal starch digestion. However, rapid and excessive fermentation of readily fermentable carbohydrate can result in ruminal and systemic acidosis (Owens *et al.*, 1998). Therefore, factors regulating the rate of fermentation, such as grain source and processing method, must be considered in relation to forage source and inclusion level.

From 4% to 60% of dietary starch intake passes to the small intestine in cattle fed high-concentrate diets, depending on grain source and processing (Theurer, 1986). The starch that passes to the small intestine is first hydrolyzed by pancreatic α-amylase. The mucosal disaccharidases of the small intestine then hydrolyze the starch breakdown products. Once free glucose is formed, it is absorbed by mucosa primarily via sodium-dependent glucose transporter 1 (SGLT1; Bauer *et al.*, 2001). Harmon *et al.* (2004) summarized several studies and reported that only 55% and 53%, respectively, of starch entering the small intestine disappears in the small intestine of cattle fed high-concentrate diets. Kreikemeier *et al.* (1991) simultaneously evaluated small intestinal carbohydrate disappearance and portal appearance of glucose in steers infused abomasally with increasing amounts of glucose, corn dextrin or cornstarch. Only the glucose infusion resulted in a linear proportional increase in net portal glucose absorption, suggesting a possible limit in carbohydrase activity. This is further supported by the fact that 15 times as much starch as glucose flows past the ileum when starch is infused post-ruminally at a rate of 60 g/h. This suggests that inadequate α-amylase activity may be responsible for the limited capacity for starch digestion in the small intestine of ruminants.

The regulation of pancreatic digestive enzyme production and secretion in ruminants is complex and differs from that of non-ruminants (Swanson and Harmon, 2002). Generally, the complexity of pre-gastric fermentation in ruminants makes the relationship between diet composition and nutrient regulation of enzymes difficult to discern. Dietary energy and post-ruminal flow of starch and protein and their breakdown

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products are thought to be the major factors influencing pancreatic exocrine function. Dietary energy typically has resulted in increased pancreatic content or secretion of α-amylase (Swanson and Harmon, 2002). Generally, increasing duodenal flow of starch, partially hydrolyzed starch, or glucose decreases pancreatic content and secretion of α-amylase in ruminants (Swanson *et al*., 2002). Interestingly, increase in post-ruminal flow of protein has resulted in increased starch digestion and secretion of α-amylase (Richards *et al*., 2003).

Less research has been conducted quantifying α-amylase mRNA and protein abundance than content or secretion of enzyme activity. Pancreatic α-amylase mRNA tended to be lower, and protein abundance and activity (U/g pancreas and U/g protein) were lower in calves receiving abomasal partially hydrolyzed starch. α-amylase protein and activity seems to have a similar magnitude of response to diet or abomasal infusion treatment in calves (Swanson *et al*., 2002), suggesting that regulation by post-translational modification of α-amylase is not responsible for dietary or small intestinal adaptation of α-amylase expression in ruminants. This, along with the observation that α-amylase mRNA and protein do not respond to post-ruminal nutrients in a directly proportional manner, suggests that dietary/small intestinal adaptation of α-amylase expression is regulated at least in part by translational events in ruminants. This differs from non-ruminants, in that changes in mRNA mediate the observed alterations in protein synthesis of pancreatic α-amylase and proteases in response to dietary changes in carbohydrate and protein (Scheele, 1994). Cao *et al*. (2018), investigating the effect of a duodenal infusion of leucine and phenylalanine on pancreatic development and enzyme gene expression in dairy goats, found that diet with 9 g/day of leucine and 2 g/day of phenylalanine increased amylase mRNA levels, and 2 g/day of phenylalanine increased lipase mRNA levels.

Intestinal regulation of *solute carrier family 5 member 1 (SLC5A1)* expression, which encodes the SGLT1, also seems to be complex in ruminants with inconsistent responses in mRNA and protein expression in response to luminal carbohydrates (Rodriguez *et al*., 2004). In a study, using *Bos taurus* and *Bos indicus* bulls, Carvalho (2015) did not find the effects of diet or breed on the abundance of *SLC5A* mRNA in the duodenum and jejunum. In this research, diets had different starch concentrations and degrees of corn processing. According to Liao *et al*. (2010), the SGLT1 transporter has high affinity for monosaccharides, and they observed that *SLC5A* expression was greater in the duodenum when there was infusion of hydrolyzed starch in the rumen, and only the ileal epithelium responded to the infusion of hydrolyzed starch in the abomasum.

Up to now, what is signaling the changes in pancreatic α-amylase and intestinal *SLC5A1* expression are not well understood in ruminants and likely includes substrate, endocrine and neuroendocrine factors. Because of the differences in digestive physiology resulting in differences in the flow and composition of digesta flowing through the digestive tract between ruminants and non-ruminants, differences likely exist in the regulation of digestive enzyme and nutrient transporter gene expression.

Liver gluconeogenesis

Glucose supply is one of the main factors affecting lipogenesis, marbling and beef quality in ruminants. Ruminants differ from non-ruminants in that they often absorb very little glucose from the diet as discussed above. Therefore, gluconeogenesis is critical to provide glucose, which is a universal fuel for cellular, tissue and whole-animal functions. Ruminants also differ in that propionate, a byproduct of ruminal fermentation, is the major precursor for gluconeogenesis. In addition, Harmon *et al*. (1985) demonstrated that high-grain diets increase L-lactate absorption, which also contribute significantly to gluconeogenesis. Therefore, the importance of pathways involved in precursor entry into gluconeogenesis differ between ruminants and non-ruminants. For example, Zhang *et al*. (2016) has suggested that the induction of cytosolic phosphoenolpyruvate carboxykinase transcription in response to propionate is much greater than in response to cyclic adenosine monophosphate and dexamethasone and this effect is not repressed by insulin as it is in non-ruminants. It is less well understood how glucose sensing influences metabolism in the liver in ruminants. Glucose sensing in the liver of non-ruminants is thought to have impacts on energy metabolism and maintenance of blood glucose concentrations (Oosterveer and Schoonjans, 2014).

According to Koser *et al*. (2008), bovine phosphoenolpyruvate carboxykinase 1 (PCK1) expression, the gene responsible to encode PEPCK, is positively regulated by propionate, constituting a feed-forward mechanism of substrate control for hepatic gluconeogenesis that is linked to the final products of rumen fermentation. However, despite the positive effect of propionate in *PCK1* expression, Ladeira *et al*. (2016) reported that glycerol seemed to exert a negative feedback in *glycerol kinase-1* expression. Still, according to these authors, researches evaluating transcription factors and mechanisms regulating the expression of genes involved in liver gluconeogenesis in ruminants are necessary. Some important transcription factors in which it is necessary to study are PPARG coactivator 1α and PPARG, due to their effects on PCK1 regulation in mice.

Muscle uptake and insulin sensitive

The transport of monosaccharides, including glucose, across cellular membranes is mediated by members of the glucose transporter (GLUT) family that are encoded by the *solute carrier family 2 (SLC2)* genes (Mueckler and Thorens, 2013). Skeletal muscle makes up a large proportion of the overall mass of mammals and thus is a large contributor to overall nutrient and energy needs. In addition, it is thought that because of the differences in carbohydrate digestion between ruminants and non-ruminants (described above) that ruminants are more insulin-resistant than non-ruminants. This may be supported by data suggesting that insulin has a lesser effect on GLUT4 translocation in bovine than in porcine skeletal muscle (Duhlmeier *et al*., 2005). However, other research (Duehlmeier *et al*., 2007) has

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suggested that GLUT1 may be of greater importance than GLUT4 for glucose uptake in skeletal muscle in ruminants. This is interesting as GLUT1 is thought to account for the basal glucose uptake and GLUT4 is thought to account for insulin-stimulated glucose uptake (De Koster and Opsomer, 2013), reinforcing the hypothesis that ruminants have greater insulin resistance. In addition, Hocquette *et al*. (1995) found that, in ruminants, glucose is the main energy-yielding substrate for glycolytic but not for oxidative muscles, and that insulin responsiveness may be lower in oxidative than in other skeletal muscles. Therefore, more insulin resistance or lesser glucose uptake by GLUT4 action in adipose cells would lead to a lower glucose available to fatty acid synthesis, based on the hypothesis proposed by Smith and Crouse (1984) in which glucose is the main substrate for lipogenesis in intramuscular fat tissue. According to Hocquette *et al*. (2010), a variety of genes may be used as markers of adipocyte development (such as *GLUT4*, lipoprotein lipase (*LPL*) and lipogenic enzymes), and adipogenesis (*PPARG* and sterol regulatory element binding transcription factor 1 (*SREBF1*)) and they would be of great potential for predicting subsequent intramuscular fat (IMF) development. Higher level of *GLUT4* expression and higher activities of metabolic enzymes involved in the conversion of glucose into long-chain fatty acids were detected in intramuscular adipose tissue compared with subcutaneous in cattle (Hocquette *et al*., 2005).

It is less clear how diet or management influences insulin sensitivity. Dietary chromium supplementation has been shown to increase insulin sensitivity (Spears *et al*., 2012), whereas increasing dietary energy intake (Sternbauer and Luthman, 2002) did not influence insulin sensitivity. Interestingly, early weaning has been shown to enhance insulin sensitivity (Zezeski *et al*., 2017) and temperamental cattle have been shown to respond to glucose and insulin differently than calm cattle (Burdick Sanchez *et al*., 2016). The mechanisms mediating differences in insulin sensitivity in ruminants have not been extensively studied but differences are likely because of changes in expression of the insulin receptor, which mediates the trafficking of the glucose transporter, GLUT4, to the cell membrane (Smith, 2017).

Nutrigenomic and lipogenesis

Marbling

Beef marbling is dependent of the energy content in the diet (Smith and Crouse, 1984) and therefore, for more intramuscular fat deposition, it is necessary for the diet to have high dietary energy. In addition, the hypertrophy or filling of adipocytes with lipids is an important component of intramuscular fat development. Robelin (1986) reported that fat deposition from birth to maturity in Friesian or Charolais bulls was primarily (70%) due to increases in cell volume or adipocyte hypertrophy. As mentioned before, early studies demonstrated that acetate and glucose are the major precursors used for biosynthesis of fatty acids in ruminants, where intramuscular adipocytes prefer glucose, and subcutaneous adipocytes prefer acetate as lipogenic substrates (Smith and Crouse, 1984, May *et al*., 1995). On the other hand, Nayananjalie *et al*. (2015) detected that acetate is the main precursor for lipid synthesis across fat depots. In addition, according to Choi *et al*. (2014), as cattle become heavier, the contribution of glucose to fat synthesis decreases whereas the use of acetate for fat synthesis increases in intramuscular adipose tissue (Figure 3). In this study, acetate was the main substrate for intramuscular fat and not glucose. Regardless of which substrate is used, the carbon sources or fatty acids must get transported through the circulation and into the cell for hypertrophy to proceed.

Fatty acid transport and lipolysis in muscle tissue also influences intramuscular fat deposition. Historically, uptake of fatty acids into the cell was believed to be by passive diffusion; however, current research shows that various membrane-associated proteins or fatty acid transporters facilitate the entry of fatty acids into the cell (Glatz *et al*., 2010). These transporters may also play a role in coordinating lipid metabolism and have been implicated in the development of metabolic diseases (Glatz *et al*., 2010; Kitessa and Abeywardena, 2016). In addition, as well as enzymes involved in fatty acid uptake (i.e. lipoprotein lipase), membrane transporters are regulated by transcriptional and translational mechanisms, which will affect fatty acid uptake and adipocyte filling.

Fatty acids are transported into the cell by three groups of fatty acid transporters: fatty acid translocase (CD36), fatty acid transport protein (FATP) or FABP in association with acyl-CoA synthase (Figure 4a). There are six subgroups of FATP and FATP1 is located in white adipose tissues and skeletal muscle (Kitessa and Abeywardena, 2016). There are 12 different FABPs with FABP3 and FABP4 (also known as AP2) expressed in skeletal muscle and adipose tissues, respectively. Moore *et al*. (1991) was the first study that reported FABP in bovine skeletal muscle. In addition, current research shows that there are also G-protein coupled receptors (GPR), also known as free fatty acid receptors (FFARs), that are on the cell membrane of bovine adipose tissues and transport fatty acids into the cell (Smith *et al*., 2012). There are four known FFARs and they have specificity for certain types of fatty acids. FFAR2 (GPR43) and FFAR3

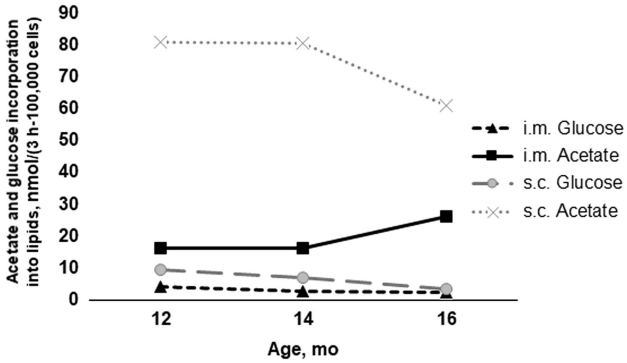

Figure 3 Fatty acid biosynthesis from acetate and glucose in intramuscular (i.m.) and subcutaneous (s.c) adipose tissues of Angus steers at 12, 14 and 16 months of age. Adapted from Choi *et al*. (2014).

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(GPR41) have high affinity for short-chain saturated fatty acids like acetate and propionate; whereas FFAR1 (GPR40) has high affinity for medium-chain fatty acids and long-chain fatty acids, and FFAR4 (GPR120) has high affinity for long-chain fatty acids and is activated by various PUFA (Miyamoto *et al.*, 2016).

Considering lipogenesis, the *de novo* fatty acid synthesis occurs by the action of the acetyl-CoA carboxylase (which is encode by the gene *ACACA*) and fatty acid synthase (FASN) (Ladeira *et al.*, 2016). Following their synthesis or uptake by adipocytes, fatty acids might be exposed to the action of the enzyme stearoyl-CoA desaturase (*SCD1*) (Figure 4b), inserting double bounds in the chain. During lipolysis, fatty acids needs to be oxidized into the mitochondrial via carnitine palmitoyl transferase enzyme (*CPT1*) (Bionaz *et al.*, 2012). Inside mitochondria, *CPT2* converts the long-chain acylcarnitine back to long-chain acyl-CoA, and then long-chain acyl-CoA enters β-oxidation pathway (Figure 4c).

Therefore, increasing lipogenesis, fatty acid uptake and decreasing lipolysis are associated with greater IMF deposition. In other words, changes in the balance between synthesis and degradation can cause an increase or decrease in IMF. Corroborating this assertion, Teixeira *et al.* (2017) reported that Nellore bulls fed ground corn had greater expression of genes related to synthesis (*ACACA* and *SCD1*), absorption (*FABP4* and *LPL*) and degradation (*CPT2*) (Table 1), characterizing greater lipid turnover in these animals, which could be responsible for less IMF. According to Knutson *et al.* (2017), intramuscular fat deposition is more complex than subcutaneous fat in beef cattle; it is affected by the genetic propensity to marble, nutritional plane throughout life, animal weight, age and environmental factors.

Duarte *et al.* (2013), studying Wagyu and Angus cattle, found that Wagyu had more IMF, and more expression of *ZFP423*, which induced adipogenesis and the upregulation of *PPARG*. Bong *et al.* (2012), comparing gene expression in bulls and steers, found that steers have greater expression of lipogenic genes (*ACACA* and *FASN*), lipid uptake (*LPL*, *CD36* and *FATP1*) and less lipolytic (*adipose triglyceride lipase* or official name: *patatin like phospholipase domain containing 2 – PNPLA2*). Therefore, steers had less lipid turnover, resulting in high marbling muscles (11.0% and 3.0%). These results are supported by positive correlations between IMF and *ACACA*, *FASN*, *LPL*, *CD36*, *FATP1* and negative correlation with *PNPLA2* (Jeong *et al.*, 2012).

In research carried out by Duckett *et al.* (Supplementary Material S1), changes in the gene expression of fatty acid transporters in the *longissimus* muscle of lambs supplemented with linolenic acid or palmitoleic acid compared with a control that received no supplemental oil were examined. Authors found that supplementation with C18:3 increased mRNA expression of *CD36*, *FFAR2*, *FFAR4* and *FFAR1* over the control (Figure 5). On the other hand, supplementation with C16:1 increased mRNA expression of *FFAR1* and reduced mRNA expression of *FFAR4* compared with control. Glucose transporter 4 expression was also down regulated in both C18:3 and C16:1 supplemented lambs. Chorner *et al.* (2016) also reported that α-linolenic acid supplementation may result in increased intramuscular lipid content and whole body fat due to the greater rate of lipid transport (FATP and FAT/CD36). In a study of Oliveira *et al.* (2014), the greater C18 fatty acid content in a soybean diet was responsible for greater expression of *LPL* and *FABP4*.

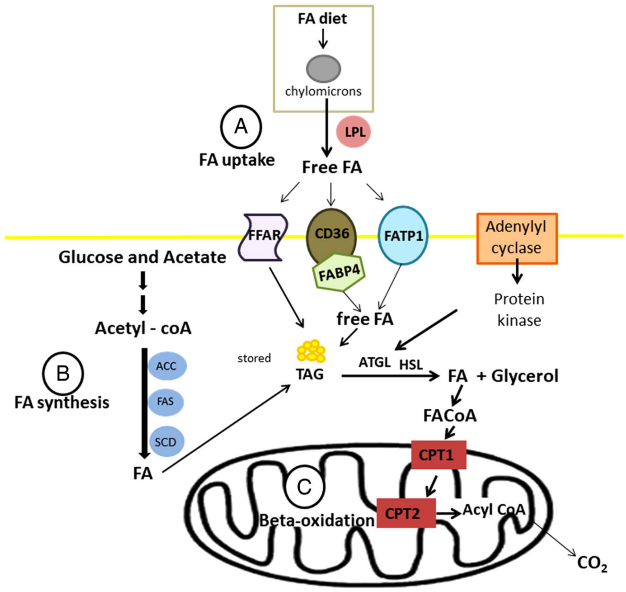

Figure 4 Synthesis (a), uptake (b) and oxidation (c) of fatty acid (FA) on ruminant adipose tissue. LPL = lipoprotein lipase; ACC = acetyl-CoA carboxylase; FAS = fatty acid synthase, SCD = stearoyl-CoA desaturase; FFAR = free fatty acid receptors; CD36 = fatty acid translocase; FATP = fatty acid transport protein; FABP4 = fatty acid-binding protein 4; TAG = triacylglyceride; ATGL = adipose triglyceride lipase; HSL = hormone sensitive lipase; CPT = carnitine palmitoyltransferase.

Table 1 *Average pH, t10,c12-C18:2 content and relative gene expression of lipogenic and transcription factors in longissimus muscle of Angus or Nellore young bulls fed ground corn (GC) diet or whole shelled corn (WSC) diet*

	Angus		Nellore			*P*-value		
	GC[1]	WSC[2]	GC	WSC	SEM	Breed	Diet	B × D[3]
Average pH	5.92	5.76	6.52	5.73	0.25	0.19	0.03	0.14
t10,c12-C18:2	0.14	0.18	0.14	0.17	0.012	0.96	0.01	0.68
ACACA	3.37	1.84	7.16	1.0	0.45	1.00	< 0.01	< 0.01
CPT2	2.02	2.87	7.20	1.0	0.27	0.91	< 0.01	< 0.01
FABP4	8.93	10.16	13.47	1.0	0.86	0.34	< 0.01	< 0.01
SCD1	1.95	1.67	3.18	1.0	0.21	0.91	< 0.01	0.02
SREBF1	5.71	2.61	5.25	1.0	0.28	0.03	< 0.01	0.1

ACACA = acetyl-CoA carboxylase α; *CPT2* = carnitine palmitoyltransferase 2; *FABP4* = fatty acid binding protein 4; *SCD1* = stearoyl-CoA desaturase 1; *SREBF1* = sterol regulatory element binding transcription factor 1.
Source: Teixeira *et al.* (2017).
[1]Diet contained 58% GC, 30% corn silage, 10% soybean and 2% mineral supplement.
[2]Diet contained 85% WSC with 15% of a pelleted protein, mineral and vitamin supplement.
[3]Breed and diet interaction.

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Therefore, fatty acid profile of the diet may change the expression of membrane transporters, increasing fatty acid uptake. According to Jurie *et al.* (2007), *FABP4* may be used as a marker of intramuscular adipocytes.

These results indicate that the expression of *CD36*, *GLUT4* and *FFARs* in skeletal muscle is altered with dietary fatty acid supplementation. CD36 and GLUT4 are both located within the cytosol of cells and move to the plasma membrane when activated to allow the entry of fatty acids or glucose, respectively, into the cell. During insulin resistance states, CD36 is believed to permanently move to the plasma membrane for greater uptake of fatty acids into the cell; whereas, GLUT4 becomes internalized resulting in lower glucose uptake by the cell (Kitessa and Abeywardena, 2016). These changes in CD36 and GLUT4 with insulin resistance can result in the intramyocellular uptake of fatty acids and deposition of lipid within the muscle. In Figure 5, Duckett *et al.*'s (Supplementary Material S1) results indicate that C18:3 supplementation up-regulated *CD36* and down-regulated *GLUT4* expression in skeletal muscle. Kitessa and Abeywardena (2016) suggest that ceramide and/or diacylglycerol species may regulate these changes in the skeletal muscle and further research is underway to characterize these species in our samples.

In Duckett *et al.*'s study, expression of *FASN* and *SCD1* also tended to be down regulated with C18:3 supplementation (Table 2), which would suggest that *de novo* lipogenesis was not stimulated. In this regard, Choi *et al.* (2015) reported that oleic acid and linoleic acid down-regulated *SCD1* expression in bovine subcutaneous and intramuscular preadipocytes. Also, feeding palm oil (high in oleic acid) or soybean oil (high in PUFA), to growing cattle, down-regulated *SCD1* expression in subcutaneous adipose tissue (Choi *et al.*, 2016). Therefore, the down-regulation of *SCD1* expression by fatty acids appears to be related to monounsaturated fatty acids (MUFA) and PUFA in general. In addition, *SREBF1* and *SCAP* expression, the genes responsible to encode the sterol regulatory element binding protein-1c (SREBP-1c) and SREBP cleavage-activating protein which are regulators of lipid synthesis in animal cells (Matsuda *et al.*, 2001), were not altered with oil supplementation (Table 2).

Overall, these results indicate that fatty acid transporters may play an important role in the uptake of fatty acids into the cell for intramuscular fat deposition. When we supplement oils rich in certain types of fatty acids, these fatty acids are increased in the skeletal muscle and may alter metabolism depending on fatty acid type. In Duckett study, C18:3 supplementation increased linolenic acid accumulation and intramuscular fat deposition; whereas, C16:1 supplementation increased palmitoleic acid accumulation in the muscle but did not alter intramuscular fat content. These results are consistent with previous research examining exogenous palmitoleic acid and intramuscular fat reduction in obese sheep (Duckett *et al.*, 2014). Further exploration into other lipid intermediates through lipidomics will be useful in investigating the potential mechanism of action of specific fatty acids that are supplied in the diet and how they alter overall lipid accumulation and metabolism.

It is well established that diets with high energy are also responsible for the production of meat with greater marbling. However, Teixeira *et al.* (2017) reported that bulls fed a diet with whole shelled corn and no forage did not increase intramuscular fat because this diet reduced rumen pH and increased *t*10,*c*12-C18:2, which reduced *SREBF1* expression (Figure 6). In this sense, SREBP-1c is an important transcription factor regulating lipogenesis, having positive correlation with expression of *ACACA* (Oliveira *et al.*, 2014) and *SCD1* (Waters *et al.*, 2009).

In other studies, Cooke *et al.* (2011) and Mangrum *et al.* (2016) reported that animals receiving rumen undegradable unsaturated fatty acid, that contained a high percentage of oleic and linoleic acid, had greater intramuscular fat and marbling scores. On the other hand, Schoonmaker *et al.* (2010) showed that animals fed wet distillers grains (rich in PUFA) had decreased marbling score. Therefore, more studies are necessary to understand the effects of specific fatty acids and their isomers on lipogenesis, fatty acid uptake and lipolysis which will affect meat intramuscular fat.

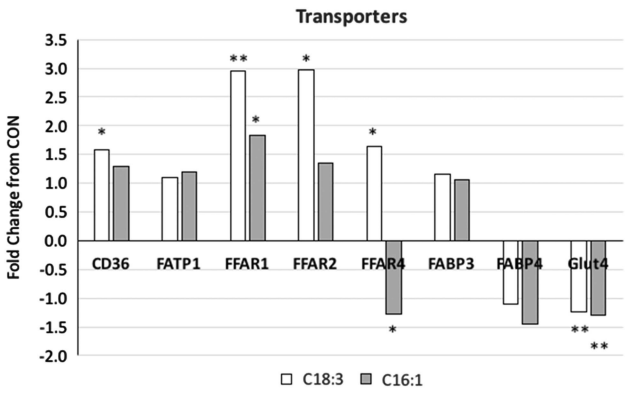

Figure 5 Gene expression of fatty acid and glucose membrane transporters in longissimus muscle of lambs supplemented with linolenic acid (C18:3; 56%) or palmitoleic acid (C16:1; 56%); * $P < 0.05$; ** $P < 0.01$. CD36 = fatty acid translocase; FATP = fatty acid transport protein; FFAR = free fatty acid receptors; FABP = fatty acid-binding protein; GLUT4 = glucose transporter type 4.

Table 2 *Fold-changes in relative gene expression of lipogenic and transcription factors or activators in longissimus muscle of lambs supplemented with α-linolenic acid or palmitoleic acid*

Genes	Fold-change compared with control	
ACACA	1.30	−1.20
FASN	−1.40*	−1.09
SCD1	−1.37*	−1.08
SCAP	1.17	1.16
SREBF1	−1.22	−1.28
PGC1A	2.07	2.11

ACACA = acetyl-CoA carboxylase α; *FASN* = fatty acid synthase; *SCD1* = stearoyl-CoA desaturase 1; *SCAP* = SREBF Chaperone; *SREBF1* = sterol regulatory element binding transcription factor 1; *PGC1A* = PPARG coactivator 1α.
*$P < 0.10$.

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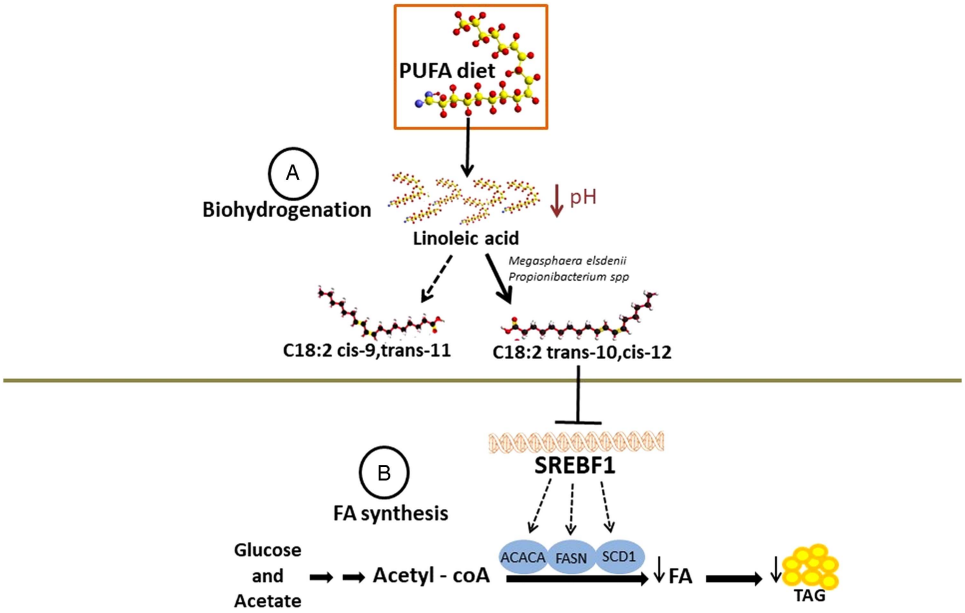

Figure 6 Effect of rumen pH on *t*10,*c*12-C18:2, sterol regulatory element binding transcription factor 1 (*SREBF1*) expression and lipogenesis in bovine muscle. PUFA = polyunsaturated fatty acids; FA = fatty acids; ACACA = acetyl-CoA carboxylase A; FASN = fatty acid synthase; SCD1 = stearoyl-CoA desaturase 1; TAG = triacyl-glyceride.

Table 3 *Fatty acids effects on expression of genes in ruminants associated with lipid metabolism*

Fatty acids	Effects	References
PUFA	Upregulate *PPARA* and *PPARG*	Wolfrum *et al.* (2001), Rodríguez-Cruz and Serna (2017)
PUFA	Downregulate *SREBF1*	Obsen *et al.* (2012)
PUFA	Downregulate *SCD1*	Waters *et al.* (2009)
n-3 PUFA	Downregulate *SREBF1*, *ACACA*, *FASN* and *SCD1*	Herdmann *et al.* (2010), Hiller *et al.* (2011), Rodríguez-Cruz and Serna (2017)
C18:0	Upregulate *LPL*, *FABP4* and *SCD1*	Choi *et al.* (2014)
C16:0 and C18:0	Upregulate *PPARA* and *PPARG*	Bionaz *et al.* (2012)
C17:0, C17:1 and C18:0	Upregulate *LPL* and *FABP4*	Oliveira *et al.* (2014)
MUFA, *t*11-C18:1 and *c*9,*t*11-C18:2	Upregulate *SCD1*	da Costa *et al.* (2013), Choi *et al.* (2014)
*t*10,*c*12-C18:2	Downregulate *SREBF1* and *SCD1*	Obsen *et al.* (2012), Teixeira *et al.* (2017)
C18:0 and α-C18:3	Downregulate *PPARA and SCD1*	Oliveira *et al.* (2014)
n-3 and *n*-6	Downregulate *FABP4*	Berton *et al.* (2016)

PUFA = polyunsaturated fatty acids; *PPARA* = peroxisome proliferator-activated receptor α; *PPARG* = peroxisome proliferator-activated receptor gamma; *SREBF1* = *sterol regulatory element-binding protein-1c*; SCD1 = stearoyl-CoA desaturase; *ACACA* = acetyl-CoA carboxylase α; *FASN* = fatty acid synthase; *LPL* = lipoprotein lipase; *FABP4* = fatty acid-binding protein 4; MUFA = monounsaturated fatty acids.

Gene expression and fatty acid profile

As mentioned before, there is interest in the manipulation of meat fatty acid profile, due to their possible beneficial and or detrimental action on human health. Conjugated linoleic acid *c*9,*t*11-C18:2 has been suggested to be an anticarcinogenic and hypolipidemic and reduces the risk of diabetes (Vahmani *et al.*, 2015) and some saturated fatty acids (SFA) also increase high-density lipoprotein (HDL)-cholesterol (Kris-Etherton *et al.*,1995). Furthermore, PUFA participates in several biological processes relevant to human health (Berton *et al.*, 2016). On the contrary, lauric, myristic and palmitic fatty acids are hypercholesterolemic because of the observed rise in low-density lipoprotein content in the blood (Wood *et al.*, 2003).

Meat fatty acid profile also plays an important role in the oxidative stability during the cooking process, which affects beef tenderness, flavor and juiciness. Age of animal, breed type and diet are the major factors influencing fatty acid composition of meat (Smith *et al.*, 2009a). In ruminant species, meat has a greater variety of fatty acids compared with meat from non-ruminant species due to microbial biohydrogenation in the rumen (Vahmani *et al.*, 2015).

Associated with the factors above, muscle fatty acid composition may control or be controlled by transcription factors which will affect expression of genes involved in the lipid metabolism (Table 3). According to Jump (2008), fatty acids act on the nucleus by binding to and regulating the

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activity of specific nuclear receptors or transcription factors, thus playing a central role regulating expression of genes involved in fatty acid uptake by muscle cells.

Interactions between nutrients from the diet and expression of genes involved in lipid metabolism have many possibilities regarding the deposition of fatty acids in the tissue. Diets rich in PUFA are important for the regulation of *SCD1* expression in the muscle of beef cattle, altering fatty acid profile in the beef (Waters *et al*., 2009). Furthermore, Herdmann *et al*. (2010) reported that animals fed greater *n*-3 PUFA content on the diet have less *SCD1* expression and thus, less CLA *c*9,*t*11-C18:2 and oleic acid on muscle. Ladeira *et al*. (2014) also demonstrated an increase of CLA concentration in the muscle of animals fed soybean compared with those fed rumen-protected fat, and this result may be due to the greater gene expression of *SCD1* in the muscle (Oliveira *et al*., 2014).

Other researchers reported that feeding of diets high in saturated fatty acids to pigs (Smith *et al*., 1999), high stearic acids diets in mice (Sampath *et al*., 2007) or high energy grain diets to finishing cattle (Duckett *et al*., 2009) significantly up-regulates *SCD1* expression in adipose tissues and increases adipose deposition.

Diets that increase *t*10,*c*12-C18:2 may be responsible for reducing *SREBF1* expression, which consequently reduces fat biosynthesis by reducing the gene expression and activity of key enzymes (Obsen *et al*., 2012). Furthermore, *t*10,*c*12-C18:2 either reduces directly *SCD1* expression, which consequently reduces MUFA synthesis (Smith *et al*., 2009b). Usually, high-concentrate or high ether extract diets result in changes in rumen biohydrogenation increasing production of *t*10,*c*12-C18:2 and decreasing *c*9,*t*11-C18:2. Therefore, it is necessary to control the rumen environment in order to avoid the excessive production of *t*10,*c*12-C18:2, which will reduce intramuscular adipocyte differentiation.

Previous reports showed that high levels of PUFA suppress *SREBF1* content by inhibiting proteolytic activation and decreasing mRNA stability (Nakamura *et al*., 2014). For example, long-chain *n*-3 PUFA such as docosahexaenoic and EPAs are nuclear suppressors of *SREBF1* via inhibition of transcription and by increasing mRNA turnover (Rodríguez-Cruz and Serna, 2017). This result is responsible for decreased lipogenesis, because of decreasing expression of *ACACA* and *FASN* in muscle, thus reducing concentration of products from *de novo* fatty acid synthesis (Hiller *et al*., 2011). Other nutrients may be responsible to affect the expression of transcription factors. For example, González-Calvo *et al*. (2014) reported that vitamin E supplementation upregulated *SREBF1* expression in the *longissimus thoracis* of lambs.

Beyond SREBP-1c, another transcription factor stands out in lipid metabolism, the PPARs (Ladeira *et al*., 2016). The PPARs are a family of nuclear receptors that bind to fatty acids and perform significant functions in the regulation of nutrient metabolism and energy homeostasis (Lemay and Hwang, 2006). Peroxisome proliferator-activated receptor isoforms act as heterodimers with RXR, and both bind to a specific DNA sequence in the promoter region of the gene, inducing or repressing its expression (Poulsen *et al*., 2012). Peroxisome proliferator-activated receptors are activated by a large variety of fatty acids that are binding the ligand dependent activation function present in PPAR structure, and they thereby serve as major transcriptional sensors of fatty acids (Poulsen *et al*., 2012).

In general, depending on the fatty acid, PUFA can activate in different intensity PPAR isotypes (Bionaz *et al*., 2013). Activation of *PPARG* by PUFA (mainly DHA and EPA) results in a positive functional response in tumor cells (Grygiel-Górniak, 2014). Likewise, PUFA can bind to PPARα, at physiologic concentrations, and expression of several genes involved in fatty acid metabolism including their transport, synthesis and β oxidation (Rodríguez-Cruz and Serna, 2017). According to Wolfrum *et al*. (2001), PUFA are more potent agonists than SFA to *PPARA* and, in general, in non-ruminant species that have been studied, *PPARA* has greater affinity for unsaturated fatty acids than for saturated fatty acids (Bionaz *et al*., 2013).

Final considerations

To date, the knowledge shows that gene expression is a metabolic factor affecting marbling and fatty acid profile in ruminant meat. However, it is necessary to understand better this complex mechanism discovering how specific fatty acids act and who are the transcription factors of the transcription factors. The possible effects of fatty acids on DNA and histones or their chemical modifications are other important mechanism to be studied.

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Declaration of interest

There is no conflict of interest.

Ethics statement

Every cited study was carried out according to the ethical guidelines adopted by the international ethics committees on animal use.

Software and data repository resources

None of the data were deposited in an official repository.

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1751731118001933

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