Molecular Regulation of Muscle and Adipose Tissue Development in Relation to Meat Quality

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Abstract

In agriculture production, meat yield and quality depend largely on growth of muscle and deposition of fat. Skeletal muscle growth is governed by myogenesis, while adipogenesis contributes to the development of intramuscular fat, that significantly affects the overall quality of meat. Moreover, the processes of lipogenesis and lipolysis regulate the deposition and mobilization of fat of intramuscular fat. Recent evidence also suggests that muscle cells may transdifferentiate into adipocytes, further influencing fat content in the muscle. This review summarizes the molecular mechanisms underlying myogenesis, adipogenesis, lipogenesis, lipolysis, and transdifferentiation of muscle to fat, with emphasis on their roles in regulating in meat production and quality.

Keywords: Adipogenesis, lipogenesis, lipolysis, muscle, myogenesis

Introduction

In the aspect of nutrition, meat is the main source of protein, providing essential amino acids, and various micronutrients. These nutritional attributes are affected by the skeletal muscle development and deposition of adipose tissue in animal. The skeletal muscle accounts for the huge proportion of carcass yield, while the adipose tissue affects the meat quality and sensory traits such as juiciness, flavour and tenderness, through the intramuscular fat (IMF) deposition (Hocquette et al., 2020; Smith & Johnson, 2020). Originally, both tissues arise from mesenchymal stem cells (MSCs), including several transcription factors and signalling pathways involved in their development and affects the production of balance composition between lean mass and fat content in meat.

The muscle development, or myogenesis, is orchestrated by the myogenic regulatory factors (MRFs) - Myf5, MyoD, Myogenin, and MRF4, together with Pax3/7, which is involved during muscle growth and regeneration (Buckingham and Rigby, 2014; Wang and Rudnicki, 2012). Meanwhile, the composition of muscle fibre type, accounted by the myosin heavy chain (MyHC) isoforms, also play a significant role in myogenesis, as it affects the meat quality traits (Wang et al., 2025; Picard et al., 2015).

Conversely, adipogenesis – the formation of adipose tissue, is primarily governed by PPARγ and C/EBP family transcription factors, which regulate preadipocyte differentiation into adipocyte, and lipid deposition in the cells (Smith & Johnson, 2020). The intramuscular adipose tissue (or marbling) has long been associated with improved sensory traits particularly juiciness, texture and flavor, while the increased in intermuscular fat poses a negative impact on carcass yield (Hirai et al., 2023; Hocquette et al., 2020; Dunshea et al., 2016; Thompson, 2004). Thus, elucidating the regulatory mechanisms underpinning adipose tissue and muscle development is crucial for developing strategies to produce healthier meat with desirable quality traits.

Myogenesis

Myogenesis (formation of muscle), can be defined as a developmental process of myofibres, the structural units for skeletal muscle. This process involves the MSCs committing to the myogenic lineage, differentiating into muscle cells, and subsequently fusing for production of multinucleated fibres or myotubes. Myogenesis begins prenatal. The primary fibres appear during embryonic phase, followed by the emergence of secondary fibres during fetal phase (Yan et al., 2013).

As the MSCs possess the potential to commit to myogenic, adipogenic or chondrogenic lineages, specific protein regulators are responsible in the process of determination, including the wingless (Wnt) and hedgehog (Hh) protein family members, Pax3/Pax7 transcription factors, and bone morphogenetic factors (BMPs) (Yan et al., 2013; Bentzinger et al., 2012). During the determination stage, these MSCs segregate into two populations: expressing and non-expressing myogenic regulatory factor five, (Myf5(+)) and (Myf5(-)), respectively. The Myf5(+) will develop to muscle cells, and Myf5(-) to white adipoblasts (Ladeira et al., 2016). The subsequent progression of both lineages is controlled by the regulators as stated above.

Wnt family protein is an extracellular signalling molecule, canonically through the Fridzzled (Fzd) receptors, transducing the β-catenin-dependent mechanism, forming a complex with nuclear T-cell specific transcription factor (TCF), and non-canonical through β-catenin-independent mechanism (van Amerongen and Nusse, 2009), which ultimately activate the transcription of target genes. Its activity has been widely recognized as a key drive of myogenic differentiation (Sharma et al., 2023; Jin et al., 2016; Ladeira et al., 2016; Cisternas et al., 2014; Bertzinger et al., 2012). Supporting this, Han et al. (2011) demonstrated that activation of Wnt signalling enhanced mRNA expression and activity of Myf5 *in vitro*.

Among the Hh protein, Sonic hedgehog (Shh), instead of Indian hedgehog (Ihh) and Desert hedgehog (Dhh), is also a coactivator in myogenesis, by stimulating the MRFs expression, including Myf5 (Gustafsson et al., 2002; Borycki et al., 1999). Hh signalling begins when the ligand interacts with the Patched receptor, releasing the Smoothened molecule, leading to the activation and nuclear translocation of GLI1/GLI3 transcription factors, which eventually be responsible for the transcription of the target genes, such as upregulation of Myf5 and MyoD expressions (Jin et al., 2016; Bertzinger et al., 2012; Lum and Beachy, 2004; Borycki et al., 2000).

The Pax3 and Pax7, members of the paired box family of transcription factors, contribute to myogenesis during developmental stage as well as adult regenerative myogenesis. They are known as early markers of the developing dermomyotome, which is the source of future myoblasts. Relaix et al. (2005) demonstrated that the double knockout of Pax3:Pax7 leads to profound impairment in skeletal muscle development. This demonstrated their expressions in MSCs induces the MRFs expression, thereby promoting commitment to the myogenic lineage.

Unlike factors that promote myogenesis, the BMPs negatively regulate myogenesis, which inhibits the expression of myogenic genes. As part of transforming growth factor β (TGF-β) superfamily, BMPs are crucial in determining the fate of MSCs, guiding their differentiation into adipogenic and osteogenic lineage, as well as essential for early bone formation (Ladeira et al., 2016; Beederman et al., 2013; Tsumaki and Yoshikawa, 2005).

Myogenic Regulatory Factors (MRFs)

The four Myogenic Regulatory Factors (MRFs) - the myogenic factor 5 (Myf5), myogenic differentiation 1 (MyoD), myogenic factor 6 (MRF4), and myogenin (MyoG) are often categorized as master regulators of myogenic determination and differentiation. They share a conserved basic helix-loop-helix (bHLH) domain that enables sequence-specific DNA binding and heterodimerization with E proteins to the E-box motifs (CANNTG), ultimately driving transcription of myogenic genes (Shirakawa et al., 2022; Sabourin and Rudnicki, 2000; Endo, 2015).

The studies involving the null mutations of these MRFs has demonstrated their effect in the muscle formation. In the MyoD-knockout mice, there was a normal development of muscle phenotype, along with the increase of Myf5 expression (Rudnicki et al., 1992). However, there was a perinatal death in the Myf5-knockout mice, with abnormal rib development (Braun et al., 1992). The MyoD/Myf5-double knockout mice fail to develop any skeletal muscles, and die at birth (Rudnicki et al., 1993). In the effect of MRF4 deficiency, the mice showed normal development of muscle, along with increase in myogenin expression (Braun et al., 1995; Patapoutian et al., 1995; Zhang et al., 1995). However, after the inactivation of myogenin, the mice have normal myoblasts, but fail to develop into myofibres, and die at birth, therefore indicating that myogenin is a differentiation factor rather than a muscle development factor (Eng et al., 2013; Hasty et al., 1993; Nabeshima et al., 1993). Collectively, these knockout studies show that Myf5 and MyoD act as primary MRFs, that are expressed early to specify myogenic precursor cells and commit them to the myoblast lineage, whereas myogenin and MRF4 function as secondary MRFs, that drive myoblast differentiation into mature myocytes and stimulate myotube formation (Yan et al., 2013; Sabourin and Rudnicki, 2000). The developmental process of myogenesis involving MRFs is shown in Figure 1.

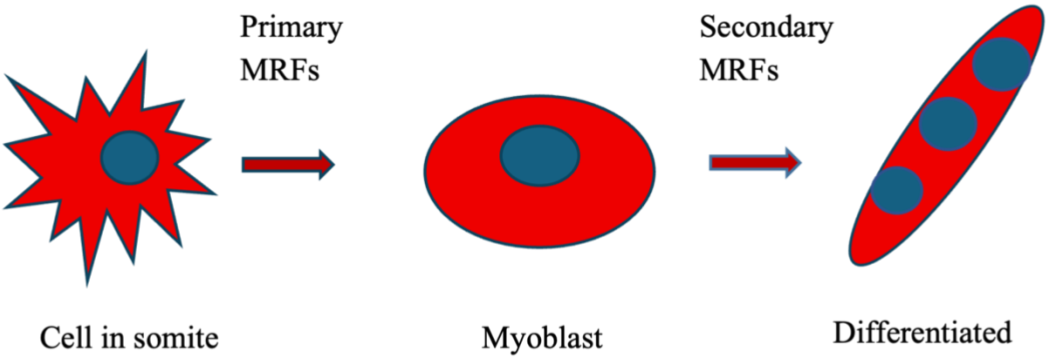

Figure 1: Primary MRFs: MyoD and Myf-5, involved during commitment step of the proliferating somitic cells (progenitor cells) to the myoblasts. The secondary MRFs: myogenin and MRF4 induced the proliferation and differentiation of myoblasts into myocytes, and fusion into myofibers (Adapted from Sabourin and Rudnicki, 2000).

Adipogenesis

Adipogenesis occurs through two major developmental phases. First, pluripotent MSCs commit to the adipogenic lineage and form preadipocytes. These preadipocytes then undergo a second differentiation becoming mature, insulin-responsive adipocytes (Ali et al., 2013). During the initial commitment stage, regarding adipogenesis, the MSC give rise to the non-expressing myogenic factor (Myf5(-)) cells, which will develop into white adipoblasts, instead of expressing myogenic factor 5 (Myf5(+)) cells, which will develop into muscle and brown adipocytes (Ladeira et al., 2016). Further development of these cells to myogenic or adipogenic are controlled by several different regulators such as activating protein-1 (AP-1), single transducers and activators of transcriptors (STATs), sterol regulatory element-binding protein-1 (SREBP-1) such as SREBP-1c, zinc finger protein (ZFP) family, wingless and INT-1 protein (Wnts) family, Kruppel-like factors (KLFs), bone morphogenic protein (BMP) family, fibroblast growth factors (FGFs) family and preadipocyte factor 1 (Pref-1) (Ladeira et al., 2016; Sarjeant and Stephens, 2012; Siersbæk et al., 2011).

During the next stage of adipogenesis, the preadipocytes differentiate into adipocytes, which is controlled by two key regulators, peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT/enhancer binding proteins (C/EBPs) specifically C/EBPα. The PPARγ is predominantly expressed in adipose tissue and induces early differentiation of adipocytes, while C/EBPα, which is expressed in many tissues, induces terminal adipocyte differentiation. When co-expressed, both factors act synergistically to powerfully activate developmental process of adipocytes in fibroblastic cells (Hu et al., 1995). Similar to the differentiation of skeletal muscle cells, adipocyte maturation involves the activation of genes fundamental to the function of adipocyte and are associated with the adipogenesis program. These adipogenesis-associated genes include fatty acids binding protein-4 (FABP4), fatty acid synthase (FAS) and adiponectin, all of which contribute to the development of fully differentiated adipocytes (Moseti, et al., 2016).

PPARs

Peroxisome proliferator-activated receptors (PPARs) belong to the nuclear hormone receptor superfamily, and often characterized as “orphan” receptors which belong to the nuclear receptor group, which includes liver X receptor (LXR), These receptors are activated by the lipophilic molecules, such as the derivatives of long-chain polyunsaturated fat which includes prostaglandins and synthetic arachidonate leukotrienes (such as 5,8,11,14-eicosatetraynoic acid (ETYA)), as well as anti-diabetic drugs such as thiazolidinediones (TZD) including troglitazone, which then promote peroxisome proliferation (Moseti et al., 2016; Siersbæk et al., 2010; Farmer, 2005; Hu et al., 1995). The PPARs family is composed of three different members (PPARα, β/δ, γ). The PPARα is predominantly found in the metabolically active tissues such as heart, kidneys, liver, and bone, where it contributes to nutrient metabolism including amino acid turnover, fatty acid oxidation and gluconeogenesis (Tyagi et al., 2011; Brun et al., 1996). The PPARβ/δ are ubiquitously expressed in many tissues and have been suggested to regulate energy expenditure and differentiation of preadipocyte, whilst PPARγ is most abundance in adipose tissues, where it involves in energy storage, and facilitate early adipogenesis (Moseti et al., 2016; Tyagi et al., 2011, Hu et al., 1995).

A study by Brun et al. (1996) also demonstrated that only PPARγ is the predominant factors when combined with C/EBPα, to promote adipogenesis. The PPARα, at slower rate than PPARγ, is capable of stimulating significant adipocyte differentiation. However, PPARδ does not stimulate adipocyte differentiation possibly because it has the weakest relative binding to the regulatory element sequences (DR-1 type elements) of fat specific genes promoters, as compared to PPARγ (Tontonoz and Spiegelman, 2008).

The treatment of clonal preadipocytes, 3T3-F442A cells from mouse, with PPAR agonist, pioglitazone, resulted in enhanced lipid deposition, leading to higher triglyceride content in the mature adipocytes (Sandouk et al., 1993). In humans, the importance of PPARγ in regulating adipogenesis, is highlighted by its capacity to stimulate FABP4 expression (which will be discussed next), a key protein required for adipocyte function (Qian et al., 2010).

C/EBPs

Along with PPARs, C/EBPs also induce the adipogenic program, by promoting terminal differentiation and maturation of adipocytes (Hu et al., 1995). There are six members of C/EBPs (α, β, δ, γ, ε, and ζ), which belongs to a class of highly conserved basic-leucine zipper (bZIP) DNA-binding proteins for dimerization with other C/EBPs and other transcription factors (Sarjeant and Stephens, 2012). Three members (α, β, δ) have been shown to induce adipocyte differentiation. The C/EBPβ and C/EBPδ act early in adipogenesis and induced by hormonal stimulants 3-isobutyl-1-methylxanthine (IBMX) and dexamethasone, respectively, which are the potent stimulators for terminal differentiation, and inducing the PPARγ activation, along with activation by SREBP1c (Sarjeant and Stephens, 2012; Yeh et al., 1995; Cao et al., 1991). Both can cross-dimerize with one another and transactivate C/EBPα, and in turn activate PPARγ for adipocyte differentiation (Sarjeant and Stephens, 2012; Cao et al., 1991). *In vitro* experiment using 3T3-L1 cells confirmed that inhibition of these C/EBPs blocked the terminal differentiation and attenuated adipogenesis (Yeh et al., 1995). Meanwhile, *in vivo* study by Tanaka et al. (1997) using mice deficient in C/EBPβ and/or C/EBPδ exhibit impaired development of adipose tissue, while Wang et al. (1995) also demonstrated that C/EBPα-deficient mice leads to a reduction in lipid droplets compared with control mice, suggesting the importance of C/EBPs in regulate adipogenesis.

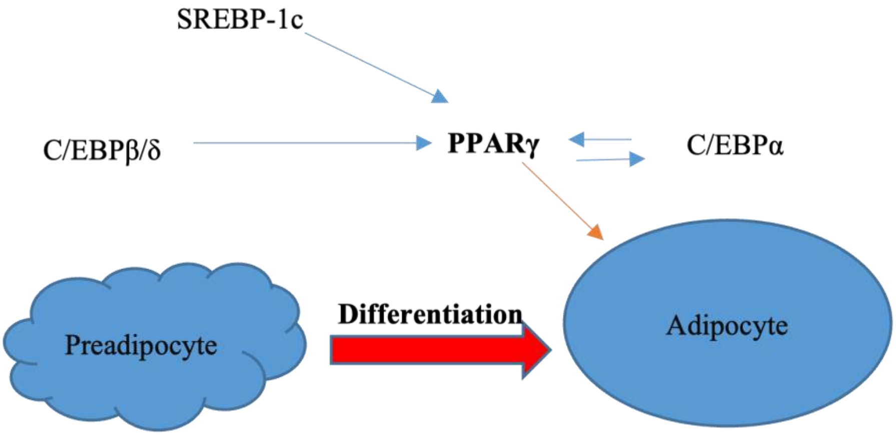

Figure 2: The role of PPARγ in adipogenesis. Ligand stimulated-PPARγ modulates and stimulates C/EBPα expression, which in turn cooperate to allow positive feedback which

maintains PPARγ expression, as well as inducing other adipogenic genes. Both PPARγ and C/EBPα are involved in adipogenesis, including stimulating adipocytes genes and insulin sensitivity. Activation of PPARγ induces terminal differentiation by stimulating other target genes (Adapted from Tontonoz and Spiegelman, 2008).

FABPs

The mammalian fatty acid binding proteins (FABPs) constitute a widespread multigene intracellular or cytoplasmic lipid-binding protein family, which bind hydrophobic molecules including prostaglandins, leukotrienes, eicosanoids, and long-chain fatty acids, with high affinity and mobilize them throughout the cells (Storch and Thumser, 2010; Elmasri et al., 2009). The family includes ten different FABPs, named after the tissue-specific distribution, and have been identified as: liver-(L-FABP; FABP1), intestinal-(I-FABP; FABP2), heart/muscle-(H-FABP; FABP3), adipocyte-(A-FABP; FABP4), epidermal-(E-FABP; FABP5), ileal-(Il-FABP; FABP6), brain-(B-FABP; FABP7), myelin-(M-FABP; FABP8), testis-(T-FABP; FABP9) and newly discovered retina-FABP12 (Smathers and Petersen, 2011; Storch and Thumser, 2010, Liu et al., 2008; Haunerland and Spener, 2004; Hertzel and Bernlohr, 2000). However, FABPs are not only specific for certain tissues, but are also expressed in various locations (Smathers and Petersen, 2011; Haunerland and Spener. 2004). The FABPs are involved in aiding the influx of fatty acids across cell membrane (ingestion) and directing these fatty acids to a specific intracellular compartment and organelles. They also contribute to signal transduction and solubilization of lipid, for the modulation of enzyme reaction and regulation of gene expression (Storch and Thumser, 2010; Elmasri et al., 2009; Chmurzyñska, 2006; Haunerland and Spener, 2004; Zimmerman and Veerkamp, 2002; Hertzel and Bernlohr, 2000).

Adipocyte fatty acid-binding protein (AFABP), also referred to as FABP4 as well as aP2, shares significant homology with the myelin P2 protein (Furuhashi et al., 2014). The FABP4 is expressed primarily in adipose tissue, most abundantly in macrophages and mature adipocytes and thus, the FABP4 might act as an important mediator between these two components in adipose tissue (Queipo-Ortuño et al., 2012; Maeda et al., 2005; Fu et al., 2000; Coe and Bernlohr, 1998). Its expression rises markedly as preadipocyte differentiate into adipocyte and during the induction of myoblasts to transdifferentiate into adipocytes upon the presence of fatty acids, while could also be affected by long-chain fatty acids (LCFA), oxidized low-density lipoprotein (OX-LDL), PPARγ and insulin (Gan et al., 2015; Taylor-Jones et al., 2002; Grimaldi et al., 1997). Therefore, elevated FABP4 expression is widely used as an indicator of cells increasing their “adipogenic” activity.

Lipogenesis

Fat deposition is governed by the dynamic balance between lipogenesis (synthesis of fat) and lipolysis (breakdown or oxidation of fat). *De novo* lipogenesis (DNL) is defined as an enzymatic conversion of excess dietary carbohydrate into fatty acids, which can then be incorporated into triglycerides for storage of energy, phospholipid synthesis for the structural component of the cell membrane or function as signalling molecules (Ameer et al., 2014; Colbert et al., 2010; Hellerstein, 1999). The primary sites of DNL vary across species: in ruminant, it occurs mainly in the adipose tissue, while predominantly hepatic in human, whereas both liver and adipose tissue in rodents and rabbit (Laliotis et al., 2010; Kersten, 2001; Ingle et al., 1972). In avian species chicken and pigeon, the DNL occurs predominantly in the liver with adipose tissue serving mainly as a storage depot for preformed fatty acids. In DNL, the fatty acids are synthesized from various precursors, including glucose and amino acids which generate acetyl CoA during their catabolic metabolism (Schutz, 2004). These metabolites are then channelled into fatty acids biosynthesis within the cytosol by an extra-mitochondrial system, that is responsible for the synthesis of palmitate. Subsequently, fatty acids may undergo further elongation and/or desaturation in the endoplasmic reticulum through the coordinated action of multiple enzymes (Laliotis et al., 2010).

The DNL is regulated by two key regulators, SREBP-1 and carbohydrate responsive element binding protein (ChREBP), which are induced in response to insulin and glucose, respectively (Postic and Girard, 2008). These regulators stimulate the expression of key lipogenic genes, most notably acetyl CoA carboxylase (ACC) and fatty acid synthase (FAS), which facilitate the transfer of acetyl CoA from mitochondria to the cytosol for the fatty acid synthesis (Towle et al., 1997). The ACC is a rate-limiting and biotin containing cytoplasmic enzyme that catalyses carboxylation of acetyl CoA to form malonyl CoA using ATP, whereas FAS catalyses the acetyl CoA and malonyl CoA conversion into palmitic acid in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) as reducing equivalents (Laliotis et al., 2010). The simplified diagram for DNL pathway is shown in Figure 3.

ACC

ACC mediated the rate-limiting and first committed step of DNL, converting acetyl-CoA into malonyl-CoA in an ATP-dependant reaction. Malonyl CoA serves as an important substrate for subsequent reaction by fatty acid synthase (FAS) for long-chain fatty acid synthesis (Brownsey et al., 2006). The ACC is encoded by two major isoenzymes designated ACC-α (or ACC-1, gene) and ACC-β (or ACC-2, gene) in mammals. While ACC-1 is a cytosolic isoform that is thought to be the predominantly controlling fatty acid synthesis, the ACC-2 is mitochondrial and involved in localizing malonyl-CoA production and which can interrupt carnitine palmitoyltransferase (CPT)-1 function, thus preventing the mitochondrial β-oxidation (Svensson et al., 2016; Postic and Girard, 2008). Although both isoforms are expressed in multiple tissues, ACC-1 expression is highly inducible in tissues with highly lipogenic activity, such as liver, adipose tissue and lactating mammary gland, while ACC-2 is predominantly expressed in tissues that rely on fatty acid for energy source, including skeletal muscle and heart (Laliotis et al., 2010; Postic and Girard, 2008). Thus, it is believed that only ACC-1 is committed in DNL.

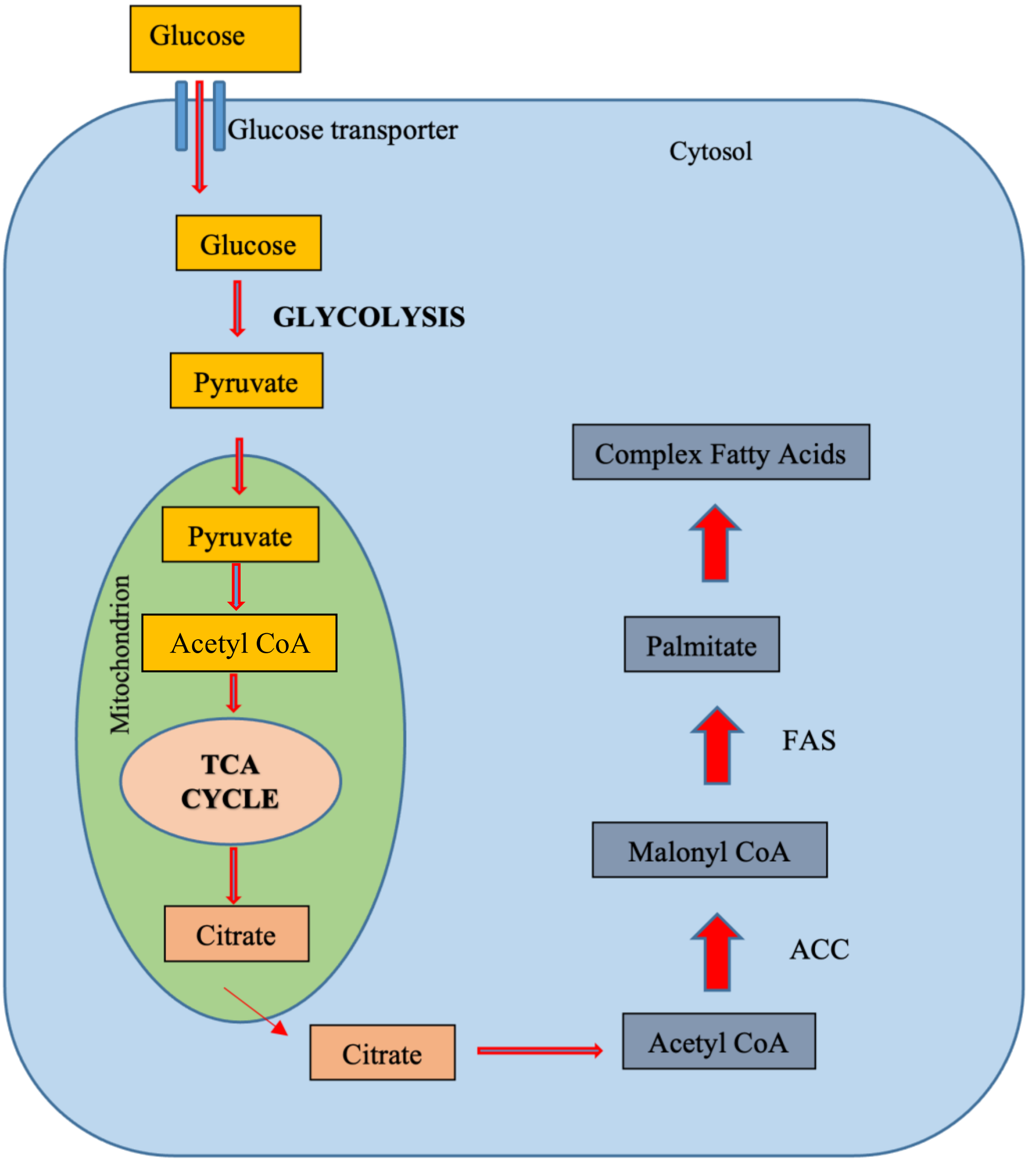

Figure 3: The process of *de novo* lipogenesis (DNL): The glucose enters the cell through glucose transporters for the glycolysis and subsequent pyruvate formation, which is then converted into acetyl CoA, and can enter the tricarboxylic acid (TCA) cycle. The acetyl CoA condenses with oxaloacetate (OAA) for the formation of citrate from TCA cycle. The citrate is then transported to the cytosol, where ATP-citrate lyase (ACLY) catalyses the conversion of citrate back into acetyl CoA. This cytosolic acetyl CoA serves as a substrate for ACC to generate malonyl CoA and then utilized by FAS to generate palmitate. Palmitate

can then undergo further modifications through elongation and desaturation to form more complex fatty acids (Adapted from Ameer et al., 2014).

FAS

Fatty acid synthase (FAS) is a key multi-enzyme complex in DNL, catalysing the condensation of acetyl CoA and malonyl CoA, initiated by the covalent binding with the enzyme, to synthesize palmitate, a 16-carbon saturated fatty acid, in the presence of NADPH (Hogan and Stephens, 2005; Chirala et al., 2001; Katiyar et al., 1975). However, other products are also generated from the reaction such as stearate, myristate, laureate, and even shorter-chain fatty acid (Ameer et al., 2014; Zhu et al., 2014). These fatty acids then undergo modification by subsequent elongation and/or desaturation reaction to form complex lipids that serve diverse roles including energy storage, cell membrane formation, and signalling molecule production (Svensson et al., 2016).

The expression of FAS is primarily regulated at the transcriptional level and influenced by both nutritional and hormonal signals. Study by Claycombe et al. (1998) using human adipocytes demonstrated the increase by five-fold in FAS mRNA and induced FAS gene transcription and expression with the treatment of insulin, suggesting FAS mRNA expression also act as a marker of DNL activity.

Lipolysis

Lipolysis refers to the breakdown or hydrolysis of triacylglycerols (TAG) stored within cellular lipid droplets, resulting in the release of non-esterified fatty acids (NEFAs) and glycerol (Zechner et al., 2012; Duncan et al., 2007). More specifically, it involves the step-by-step cleavage of the ester bonds connecting long-chain fatty acids to the glycerol backbone (Lass et al., 2011). Although this process occurs in many tissues, it is most active in white and brown adipose tissue, with white adipose tissue serves as primary energy reservoir in mammals. Complete TAG hydrolysis requires the coordinated action of three major enzymes, classified as lipases: adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL) and monoacylglycerol lipase (MGL). The ATGL, a member of patatin-like phospholipase family, catalyses the first step of lipolysis, by converting TAG into diacylglycerols (DAG) and NEFAs. The HSL then act as rate-limiting for DAG catabolism but also possesses as versatile lipase as it can hydrolyse a variety of acylesters including TAG, DAG, and monoacylglycerols (MAG), while MGL completes the process by hydrolysing MAG to yield glycerol and fatty acid (Zechner et al., 2012). The overall lipolytic cascade is shown in Figure 4.

ATGL

Adipose Triglyceride Lipase (ATGL), also referred to as patatin-like phospholipase domain containing protein-2 (PNPLA-2), is selectively responsible for initiating lipolysis. It catalyses the rate-determining step in the breakdown of TAG producing DAG (the preferred substrate for HSL), along with free fatty acid (Zimmermann et al., 2004). In mice, the ATGL mRNA expression and enzyme activity are most abundant in white and brown adipose tissues but are also detected in skeletal muscle (predominantly in type I or oxidative muscle fibres), liver, cardiac muscle and testis. Similarly, high levels of human ATGL were also found in adipose tissue (Zechner et al., 2009; Zimmermann et al., 2009; Jocken et al., 2008; Reid et al., 2008; Zimmermann et al., 2004). The ATGL expression is markedly upregulated during murine 3T3-L1 adipocyte differentiation (Kershaw et al., 2006; Kim et al., 2006). Meanwhile, the ATGL-knockout mice displayed a reduced fatty acid release from adipose tissue and reduced circulating fatty acid levels, suggesting reduced rate of lipolysis (Haemmerle et al., 2006). These knockout animals also exhibited high TGs accumulation in non-adipose tissues including skeletal muscle, heart and testis (Haemmerle et al., 2006). In human, mutations in the ATGL gene are linked with systemic TAG accumulation, cardiomyopathy, and hepatomegaly, which are the characteristic of the inherited condition known as "*Neutral Lipid Storage Disease with Myopathy* (NLSDM)" (Lass et al., 2011).

The full activation of ATGL activity requires interaction with its coactivator, α/β hydrolase fold domain-containing protein-5 (ABHD5), also known as comparative gene identification-58 (CGI-58) (Lass et al., 2006), while its activity is decreased by a peptide called G0/G1 switch gene 2, isolated from mononuclear cells (Yang et al., 2010).

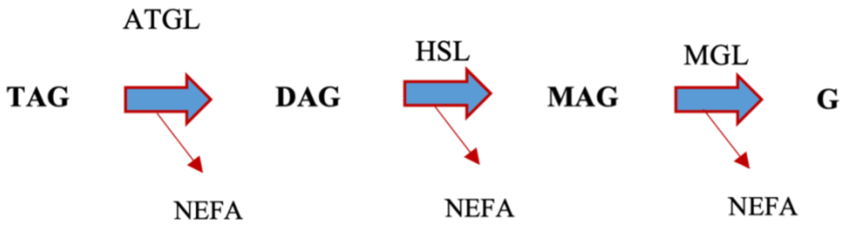

Figure 4: Schematic delineation of the coordinate breakdown of triacylglycerols (Adapted from Lass et al., 2011).

HSL

Earlier in 1960s, lipase in white adipose tissue (WAT) was discovered which was thought to be stimulated by hormones and therefore given the name hormone sensitive lipase (HSL). The HSL was believed to be the sole enzyme responsible for in TAG breakdown (Vaughan, et al., 1964; Hollenberg et al., 1961). Review by Lass et al. (2011) showed that the hydrolysis rates by HSL of DAG is ten times fold faster than TAG and MAG, indicating that HSL functions primarily as a DAG lipase rather than TAG lipase. This was supported by the findings in HSL-deficient mice, which showed no accumulation of TAG, instead of large accumulation of DAG in many tissues (Haemmerle et al., 2002; Osuga et al., 2000). Currently, HSL is recognized as a key rate-limiting enzyme capable for hydrolyse DAG, TAG, MAG, short-chain carbonic acid esters, retinyl esters and cholestryl esters (Zechner et al., 2012; Bezaire et al., 2009; Fredrikson et al., 1986). Its expression is highest in adipose tissue, and lower levels are found in muscle, testis, steroidogenic cells/tissues, pancreatic islets, and macrophages (Zechner et al., 2012; Holm et al., 2000).

The activity of HSL is strongly enhanced by beta-adrenergic stimulation, while insulin acts as a strong inhibitor (Zechner et al., 2012; Lass et al., 2011). During beta-adrenergic stimulation, HSL activity is regulated by two different mechanisms: 1) Reversible phosphorylation of HSL at a number of serine residues by PKA, extracellular-signal-regulated kinase (ERK), glycogen synthase kinase-4, Ca^{2+}/calmodulin-dependent kinase II, and AMP-activated protein kinase (Watt and Hoy, 2012; Lass et al., 2011); 2) HSL translocation to the lipid droplets, which is regulated by perilipin-1 (Lass et al., 2011).

MGL

Monoglyceride lipase (MGL) is involved in the final step of lipolytic cascade, converting MAG into glycerol and free fatty acid. MGL is abundantly expressed across tissues, particularly in adipose tissue, kidney, and testis, which display high MGL mRNA expression (Lass et al., 2011). Study by Rakhshandehroo et al. (2007) demonstrated upregulation of MGL, along with other lipases (ATGL and HSL) transcripts, by PPARα stimulation in liver, thereby indicating PPARα as a negative regulator of steatosis. However, whether MGL is predominantly regulated at post-transcriptional or post-translational level is not known as evidence of phosphorylation has yet to be determined (Labar et al., 2010).

The relationship between muscle metabolism and meat quality

In common, meat is referred as edible animal tissues, including both muscle (flesh) and organs. The meat from cattle, sheep and pigs is typically classified as red meat, while the meat from poultry (such as chicken, duck, turkey, pigeon and guinea fowl) is classified as white meat (FAO, 2013). This includes all processed and manufactured products that might be prepared from these tissues. Generally, the composition of meat, after rigor mortis but prior to post-mortem degradative changes, can be broadly estimated as approximately 75% water, 19% protein (including myofibrillar proteins, sarcoplasmic proteins that consists of myoglobin, and stroma proteins that consists of collagen and elastin), 3.5% soluble, non-protein substances (amino acids, vitamins, carbohydrate (organic), and minerals such as phosphorus, potassium, and small amount of sodium, magnesium, calcium and zinc) and 2.5% fat (Frontera and Ochala, 2014; Olaoye, 2011). Thus, meat is a rich source of high-quality protein, essential amino acids, vitamins and minerals. These variability plays a significant role in determining meat quality.

Meat quality is partly influenced by its compositional traits, particularly the lean tissue to fat ratio, which includes the amount of marbling, as well as the palatability characteristics such as visual appearance, aroma, texture, juiciness, tenderness and flavour (Bender, 1992). The mechanism controlling meat quality development is often associated with altered post-mortem muscle metabolism, which is involved in the changes of glycolysis rate, leading to unfavourable decline in muscle pH, and subsequently, may cause protein denaturation and negatively affect the quality attributes (Ryu and Kim, 2005). Meanwhile, recent evidence also demonstrated that the mitochondria would sustain their function after post-mortem, which could contribute the generation of reactive oxygen species, ultimately influence the lipid and protein oxidations, thus would affect meat quality such as tenderness and colour stability (Zou et al., 2023). In addition, the metabolomics intervention also demonstrated the postmortem metabolite changes in the muscle metabolism, including citric acid cycle and redox $NAD^+/NADH$, which could be associated with other metabolic pathways including carbohydrate and protein breakdown, and in turn significantly affect the meat water holding capacity (WHC), colour and flavour (Muroya, 2023; Ijaz et al., 2022).

The myofibrillar protein make up roughly 11.5% of total protein content in meat. Numerous studies have reported the association between meat quality and muscle fibres characteristics. The total amount of slow, type I fibre is negatively correlated with drip loss and lightness and positively associated with WHC and redness (Joo et al., 2013; Choi and Kim, 2009). Meanwhile, it has been reported that lower fast, type IIb and higher slow, type I fibres improve the pork quality, while higher percentage of fast, type IIb fibre exhibit lighter and tougher meat (Kim et al., 2018; Kim et al., 2013). In addition, recent study on lamb demonstrated that higher composition of slow, type I fibre is positively linked with higher redness, WHC, essential amino acids and unsaturated fatty acids, while reduction of redness was observed with higher fast, type IIb fibre (Fu et al., 2025).

Several studies also demonstrated the positive correlation between proportion of fast, type I fibre and intramuscular fat content, as it is associated with higher phospholipid content, which is involved as major flavour determinant in meat (Joo et al., 2017). The intramuscular fat (located within the perimysium which surrounds muscle fibres) also is a major factor in meat quality and associated with tenderness, juiciness and palatability. It also contains flavour-forming precursor material and positively correlated with meat quality and taste (Jeong et al., 2012; Liu et al., 2012; McPhee et al., 2008). Fatty acids, especially polyunsaturated fatty acids (PUFA), are major flavour precursors of meat (Yu et al., 2013).

Intramuscular fat (IMF) development

The fattening phase always refers to the normal maturation phase, which involved changes in the lipid metabolism, while the growth phase, refers to the pre-fattening phase (Vernon, 1980). During the fattening phase, the nutrient that initially directed for skeletal and muscle growth were also diverted to the lipid anabolism activity, resulted in increased fat deposition, which align with the early characterization of developmental sequence of tissue deposition, beginning with skeletal, muscle and fat (Hocquette et al., 2010). In addition, the order of adipose tissue deposition in ruminant is abdominal, intermuscular, subcutaneous, and finally intramuscular (Pethick et al., 2006).

Intramuscular adipose tissue, or intramuscular fat (IMF) or marbling, consists of accumulation of adipocytes, appearing as lipid droplets, located within the muscle, specifically in the perimysium (within intramyocellular and extramyocellular) in the muscle fibres. This is distinctly different to intermuscular fat, which is adipocytes and subsequent fat which occur in the spaces between the muscles) (Rahemi et al., 2015). Generally, the IMF deposition also includes uptake of fatty acid from the plasma in the form of NEFAs, or from fatty acid pools by the lipoprotein lipase (LPL) action, followed by transportation into muscle mediated by fatty acid translocase (FAT/CD36). The glucose utilization also contributed to the acetyl-CoA production (building block for fatty acid synthesis) in the muscle (Tokach et al., 2010; Frayn et al., 2006). Meanwhile, the HSL mediated the oxidative activity of IMF (Frayn et al., 2006). The IMF have been widely implicated to play an important role in meat quality. The amount of IMF was positively correlated with sensory quality characteristics such as taste, flavour, firmness, juiciness, and tenderness of the meat, while lower IMF produced less tasty and dry meat (Hocquette et al., 2010; Pethick et al., 2006).

As reviewed by Hocquette et al. (2010), the deposition of IMF varies between species, including individual in given species, and between muscles and cuts. The activity and fibre type also influence the IMF level. Muscle with high muscularity and high glycolytic fibre types generally appear in reduced fat content in the muscle (Pethick et al., 2006). However, the development of IMF might also result from the balance between uptake, formation and breakdown of fat in the muscle, which involved an interrelation between intramuscular adipocytes and muscle fibre’s metabolic activities (Hocquette et al., 2010). Hocquette and colleague also suggested that fat deposition might also resulted by the high fat turnover (Hocquette et al., 2003). The transdifferentiation of muscle cells and/or satellite cells into fat cells also might favour the IMF development in the muscle, as demonstrated by Huang et al. (2022), mediated by fatty acid transport-1 (FATP1).

Many studies reported that IMF content increases with feeding periods, until plateau (Tokach et al., 2010). During early growth, the rate of fat deposition is lower, while during maturation, the rate is higher than lean tissues, which might later increase IMF level (Pethick et al., 2004). The IMF development can be represented using the S-shaped curve, which consists of early period (no change in IMF level), followed by linear growth and then reached the plateau (saturation of fat deposition at maturation). Adding to that, the curved might be shifted to the right after stimulation with certain metabolic modifiers, which stimulates muscle growth (Figure 5) (Pethick et al., 2006).

The identification of the key determinants in IMF development since early growth can be assessed by the expression of certain markers, which involved in the adipocyte differentiation such as PPARγ and SREBP-1, along with lipogenic enzyme such as ACC, FAT/CD-36 and LPL, which are involved in lipid mobilization and uptake by the muscle (Hocquette et al., 2010; Hausman et al., 2009). However, as explained earlier, the fat turnover might be affecting IMF deposition and should be considered. Study by Underwood et al. (2008) reported that key mediator in fat metabolism, AMP-activated protein kinase (AMPK) is negatively correlated with IMF level in *longissimus dorsi* muscle of beef cattle. This suggested that as AMPK promotes lipolysis or oxidation and impedes lipogenesis, lower oxidative activity promotes fat deposition (Hocquette et al. 2010). By this reason, some researchers included blood analysis along with the enzyme activity studies to ascertain IMF development, noted that the different metabolic markers are included (Gondret et al, 2004b; 2004a). Review by Frayn et al. (2006) reported that the expression of FAS is small or undetectable, which suggested that the IMF might entirely developed from NEFAs.

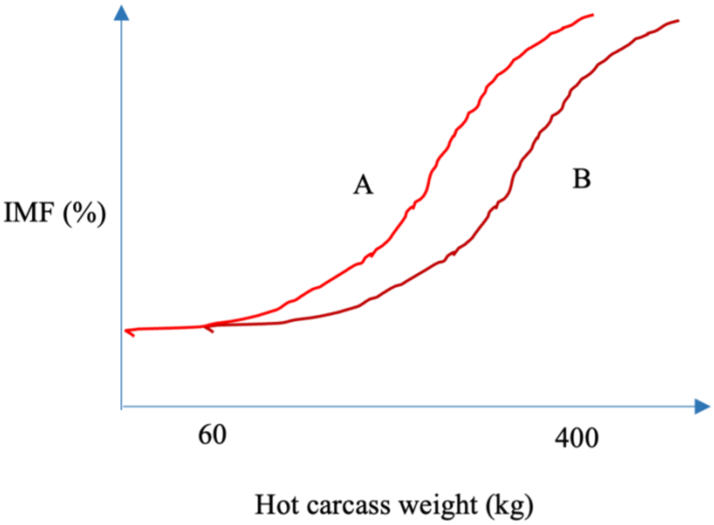

Figure 5: The IMF development. The S-shaped developmental curve hypothesized by Pethick et al. (2006), showing the IMF development at two different muscle weights; A = with metabolic modifiers; B = without metabolic modifiers (Adapted by Pethick et al., 2006).

Transdifferentiation - muscle cells to adipocytes

Transdifferentiation is an irreversible switching process of differentiated cell type to another, which both cells are related in terms of ancestor-descendent relationship (Shen et al., 2004). It has been reported that transdifferentiation is likely to happen when there are any changes in the expression of the master regulator/switch genes that affect the developmental process, and can be induced by environmental changes, such as modification in cell culture media with certain inductive agents (Eguizabal et al., 2013; Shen et al., 2004).

As myoblasts and adipocytes are from the same origin (from mesoderm layer during embryogenic development), the transdifferentiation of myoblasts into adipocytes is possible and has been discussed widely, particularly in *in vitro* (Singh et al., 2007; Li et al., 2005), which commonly used C2C12 or G8 myoblast cell lines as model (Grimaldi et al., 1997, Hu et al., 1995). Two key adipogenic transcription genes, PPARγ and C/EBPβ are involved in this process. In a study by Hu et al. (1995) using G8 myoblast cell lines, the co-expression and synergistic action of both genes suppressed the expression of myogenic genes such as MyoD, myogenin, MRF4 and Myf5, blocked further development into myotubes, induced the accumulation of lipid droplets-containing cells, and upregulated adipogenic markers such as aP-2, adipsin, LPL, and PEPCK. In terms of intramuscular fat development, both genes were reported to induce adipocyte numbers in the skeletal muscle of bovine (Torii et al., 1998) and pig (Poulos and Hausman, 2006).

The myoblast transdifferentiation into adipocytes can be induced by thiazolidinediones (TZD) family, such as rosiglitazone, pioglitazone, BRL49653, and unsaturated fatty acids (Grimaldi et al., 1997), which both are the natural and synthetic activators/ligands for the PPARγ receptor, respectively (Grygiel-Górniak, 2014). Both activators induced adipogenic markers expression, such as glycerophosphate dehydrogenase (GPDH), FAT/CD-36 and FABP, and suppressed myogenic markers expression, such as creatine kinase, myogenin and α-actin (Grimaldi et al., 1997). Treatment of C2C12 with TZDs inhibit MyHC and induced PPARγ and C/EBPα expressions, along with decreased fusion into myotube (Singh et al., 2007). The TZDs also induced the expression of the GLUT-4 for the uptake of glucose, which is the substrate in the IMF development (Mukherjee et al., 2000).

The adipogenic media in cell culture, which is formulated with insulin, dexamethasone (DEX) and isobutylmethylxanthine (IBMX), along with the supplementation with TZDs, have been used in the myoblast transdifferentiation into adipocytes (Ryan et al., 2013; Singh et al., 2007). The DEX induces C/EBPβ transcription, which is the factor for adipogenesis, IBMX stimulates cAMP levels and promotes adipogenesis, via cAMP response binding factor (CREB), while insulin acts through IGF-1R for lipid filing enhancement (Singh et al., 2007). Singh et al. (2007) also reported the exposure of adipogenic mixture and another TZDs, ciglitazone, to muscle satellite cells from porcine induced formation of lipid droplets-containing cells, and increased its number with increased incubation time, along with the expression of CEBP/α and PPARγ genes and activities.

Conclusion

The increase in global population would expect an increase in food demands, particularly for animal protein such as meat. This challenge necessitates the understanding of molecular processes underpinning the muscle and fat development in the animals, particularly myogenesis, lipogenesis and lipolysis, and how these processes could be modulated in enhancing the meat production efficiency. Meanwhile, the usage of metabolic modifiers has been proven to increase production, improve feed efficiency and animal growth rates, as well as improve economic benefits, by modulating those three key processes. In conclusion, understanding the molecular levels of myogenesis, lipogenesis, and lipolysis is important to improve livestock efficiency, while developing an innovative strategy to sustainably increase meat production. These advancements must align with ethical practices, sustainability goals, and consumer expectations to create a resilient and equitable food system for the future.

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