Meat Science 86 (2010) 103–109

Contents lists available at ScienceDirect

Meat Science

journal homepage: www.elsevier.com/locate/meatsci

Review

Cellular signaling pathways regulating the initial stage of adipogenesis and marbling of skeletal muscle

Min Du [a,*], Jingdong Yin [b], Mei J. Zhu [a]

[a] Department of Animal Science, University of Wyoming, Laramie, WY 82071, USA
[b] College of Animal Science and Technology, China Agricultural University, Beijing 100193, China

ARTICLE INFO

Article history:
Received 26 January 2010
Received in revised form 19 March 2010
Accepted 8 April 2010

Keywords:
Adipogenesis
Meat
Skeletal muscle
Mesenchymal stem cells
Signaling
Marbling

ABSTRACT

Due to extensive efforts to increase lean growth, intramuscular fat (marbling) is reducing in beef, pork and chicken breast, which impairs the eating quality of meat. Because fat is the major contributor to meat flavor, the presence of intramuscular fat is indispensible for the high eating quality of meat. However, up to now, our understanding of adipogenesis (formation of fat cells) in skeletal muscle is limited. Adipocyte differentiation in skeletal muscle initiates from multipotent mesenchymal stem cells, which are abundant in skeletal muscle at early developmental stages. In this review, the known cellular mechanisms regulating adipogenesis from multipotent cells are summarized, which include hedgehog, Wingless and Int (Wnt)/β-catenin, and bone morphogenesis protein (BMP) mediated signaling pathways, as well as AMP-activated protein kinase. Promoting adipogenesis within skeletal muscle will effectively increase intramuscular fat, improving the quality of meat.

Contents

1. Introduction

Intensive genetic selection of animals for their lean growth has dramatically reduced intramuscular fat (marbling) and impaired the eating quality of meat. Intramuscular fat is crucial for meat palatability (Hausman et al., 2009; Tong et al., 2008). In recent years, huge efforts have been exerted to enhance intramuscular fat but only obtained very limited success. Intramuscular fat can be enhanced through the enlargement of existing adipocytes (hypertrophy) and increase in the number of adipocytes (hyperplasia) (Du et al., 2010b). The majority of available studies on intramuscular fat focus on the conversion of pre-adipocytes to adipocytes, adipocyte lipid metabolism and hypertrophy through nutritional management (Hausman et al., 2009; Smith et al., 2009). Mechanisms regulating the initial stage of adipogenesis, the conversion from a multipotent mesenchymal stem cell to pre-adipocytes, are far less studied especially in livestock (Fig. 1). The poor understanding of such mechanisms limits our ability to effectively enhance marbling in beef cattle and other livestock.

Both muscle cells and adipocytes (fat cells) are derived from mesenchymal stem cells (MSCs), which are abundant in the skeletal muscle at early developmental stages, especially during the fetal and neonatal stages, but wanes as animals become older. The majority of MSCs develop into myogenic cells, but a small portion of these cells differentiate into adipocytes which are the basis for intramuscular fat

* Corresponding author. Tel.: +1 307 766 3429; fax: +1 307 766 2355.
E-mail address: mindu@uwyo.edu (M. Du).

0309-1740/$ – see front matter © 2010 The American Meat Science Association. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.meatsci.2010.04.027

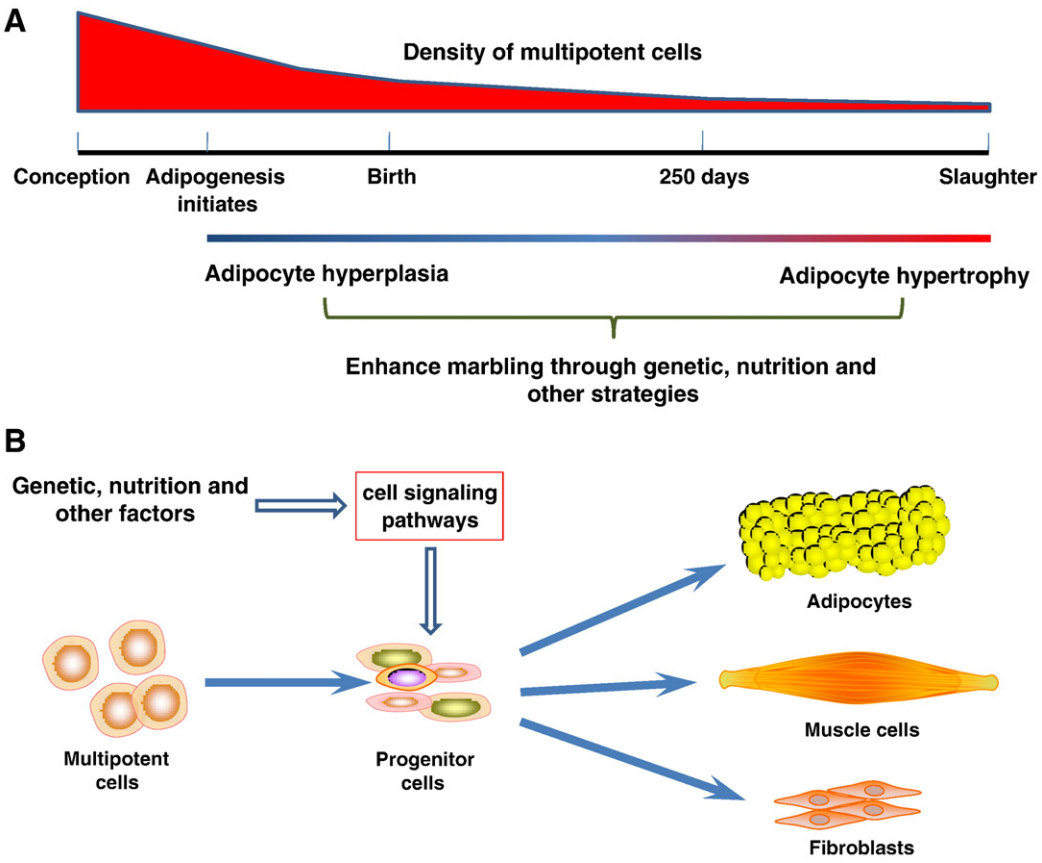

Fig. 1. Strategies to increase intramuscular fat (marbling) in beef cattle. Panel A: early stage development of intramuscular fat is characterized by adipocyte hyperplasia through adipogenesis from multipotent cells, while late stage development is characterized by hypertrophy; Panel B: Adipogenesis from mulitpotent cells within skeletal muscle is regulated by complex cell signaling pathways, and genetic, nutrition and other factors regulate adipogenesis via altering these pathways.

accumulation that produce marbling in offspring (Du et al., in 2010b). Adipogenesis is regulated by genetic, nutrition and environmental factors, all of which dictate the key signaling pathways regulating adipogenesis in skeletal muscle and, thus, marbling in resulting meat (Harper & Pethick, 2004). Japanese black cattle is well known for its extremely high marbling, which is apparently mainly due to increase in the number of intramuscular adipocytes, though an increase in adipocyte size was also detected when compared to European cattle (Gotoh et al., 2009). Because the association between the late stage adipogenesis, lipid metabolism and marbling has been the subject of several excellent previous reviews (Fernyhough, Okine, Hausman, Vierck, & Dodson, 2007; Hausman et al., 2009; Hocquette et al. 2010; Smith et al., 2009), in this review, we only discuss important cell signaling pathways regulating the initial stage of adipogenesis (Fig. 1). We first describe the key transcription factors regulating adipogenesis, followed by the discussion of important cell signaling pathways regulating these key transcription factors and the early stage of adipogenesis.

2. Adipogenesis

In the bovine fetus, primary muscle fibers form within the first two months post-conception (Russell & Oteruelo, 1981), and the majority of muscle fibers form during the secondary myogenesis which occurs in the fetal stage between 2 and 7 months of gestation in cattle (Russell & Oteruelo, 1981). In fetal cattle and sheep, maternal nutrient fluctuation during late gestation reduces muscle fiber size but not number (Du et al., 2010a; Greenwood, Slepetis, Hermanson & Bell, 1999). However, this stage is crucial for intramuscular adipogenesis. Adipogenesis is initiated around mid-gestation in ruminant animals (Feve, 2005; Gnanalingham, Mostyn, Symonds & Stephenson, 2005; Muhlhausler, Duffield, & McMillen, 2006), which partially overlaps with the period of secondary myogenesis (Du & Zhu, 2009). The mid to late gestation is a period critical for adipogenesis in cattle, and maternal nutritional management to enhance the number of MSCs committed to adipogenesis will increase the number of intramuscular adipocytes and thus marbling.

Adipogenesis is regulated by several key transcription factors, including CAAT/enhancer binding proteins (C/EBPs) and peroxisome proliferator-activated receptor γ (PPARγ) (Hausman et al., 2009). C/EBPβ and -δ are first induced by adipogenic stimuli and followed by an increase in PPARγ and C/EBPα expression. C/EBPα is induced during the initial phase of adipogenesis and directly binds to the PPARγ promoter to induce its expression (Clarke, Robinson, & Gimble, 1997; Wu et al., 1999). The expression of PPARγ further promotes the expression of C/EBPα, providing a self-reinforcing regulatory loop. Terminal differentiation of an adipocyte needs the concerted action of PPARγ and C/EBPs to turn on lipid synthesis and other adipocyte-specific programs (Fernyhough et al., 2007; Hausman et al., 2009). PPARγ, but not C/EBPα alone can stimulate adipocyte differentiation, clearly showing the critical role of PPARγ in adipogenesis (Rosen et al., 2002). The basic helix–loop–helix protein, adipocyte determination and differentiation-dependent factor-1/sterol regulatory element-binding protein-1 (ADD-1/SREBP-1), is another important protein induced during the early stages of adipogenesis (Kim & Spiegelman, 1996). Activation of PPARγ promotes terminal differentiation through the induction of a range of genes important for triglyceride uptake and storage, such as fatty acid-binding protein (aP2), acyl-CoA synthetase, fatty acid transport protein-1, lipoprotein lipase and others (Frohnert, Hui, & Bernlohr, 1999; Rosen & MacDougald, 2006).