Postprint: Absorption and Metabolism of Short-Chain Fatty Acids in Rumen Epithelium

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Abstract

Short-chain fatty acids are important products of ruminal fermentation in ruminants, primarily consisting of acetate, propionate, and butyrate, which are mainly absorbed through the rumen epithelium. Propionate generates glucose via gluconeogenesis in the liver to provide energy for the organism. With advancing research on short-chain fatty acids, it has been found that their absorption across the rumen epithelium occurs through passive diffusion and specific carrier-mediated transport, with related transporters including monocarboxylate transporter (MCT), Na+/H+ exchanger (NHE), and anion exchanger 2 (AE2). The transport and absorption of short-chain fatty acids across the rumen epithelium is also associated with pH in the rumen lumen and intracellular pH, with interactions among carriers collectively maintaining pH balance in the rumen lumen and within cells. Following absorption into cells, short-chain fatty acids undergo intracellular metabolism, with the primary metabolic pathways being cholesterol synthesis and ketone body synthesis. Ketone body synthesis occurs in mitochondria, whereas cholesterol synthesis occurs in the cytoplasm and endoplasmic reticulum, with 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) serving as the precursor for both pathways. The synthesized ketone bodies are transported out of epithelial cells by MCT into peripheral tissues for energy supply. This review summarizes the absorption and metabolic regulatory mechanisms of short-chain fatty acids in the rumen epithelium, providing a theoretical foundation for future research.

Full Text

Absorption and Metabolism of Short Chain Fatty Acids in Ruminal Epithelium

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Abstract: Short-chain fatty acids (SCFAs) are important products of ruminal fermentation in ruminants, primarily consisting of acetate, propionate, and butyrate. These SCFAs are mainly absorbed through the ruminal epithelium, with propionate undergoing gluconeogenesis in the liver to produce glucose for energy supply. Recent research has revealed that SCFA absorption across the ruminal epithelium occurs via both passive diffusion and specific carrier-mediated transport. Key transporters include monocarboxylate transporters (MCT), Na+/H+ exchangers (NHE), and anion exchanger 2 (AE2). The transport of SCFAs is closely associated with pH regulation in both the rumen lumen and intracellular compartments, with various transporters working in concert to maintain pH homeostasis. Following absorption, SCFAs undergo intracellular metabolism primarily through cholesterol synthesis and ketone body synthesis pathways. Ketogenesis occurs in mitochondria, while cholesterol synthesis takes place in the cytoplasm and endoplasmic reticulum, with both pathways sharing 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) as a common precursor. Synthesized ketone bodies are exported from epithelial cells via MCTs to provide energy for peripheral tissues. This review summarizes the mechanisms of SCFA absorption and metabolic regulation in the ruminal epithelium to provide a theoretical foundation for future research.

Keywords: ruminal epithelium; short-chain fatty acid; absorption; metabolism
Classification: S852.2

Ruminants produce large quantities of short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, through microbial fermentation of dietary carbohydrates in the rumen. These SCFAs are subsequently absorbed through the ruminal epithelium. Research indicates that a portion of SCFAs enters the bloodstream via ruminal absorption and undergoes gluconeogenesis in the liver to supply energy, while another fraction is metabolized within ruminal epithelial cells to produce ketone bodies and cholesterol. The ruminal epithelium serves as the primary site for SCFA absorption and possesses a stratified structure consisting of four layers from the luminal surface inward: the stratum corneum, stratum granulosum, stratum spinosum, and stratum basale. Within the rumen lumen, SCFAs exist in two forms—dissociated and undissociated—with distinct transport characteristics depending on their type and form. SCFA transport involves both passive diffusion and specific carrier-mediated processes. As weak acids, SCFAs cause acidification whether they dissociate H+ in the rumen lumen or within epithelial cells, which activates membrane transporters such as Na+/H+ exchangers (NHE) to export intracellular H+ into the lumen. Following absorption, SCFAs are extensively metabolized in ruminal epithelial cells, with metabolism rates exceeding 50% and butyrate showing the highest metabolic rate. The primary metabolic pathways include cholesterol synthesis and ketone body synthesis, both utilizing HMG-CoA generated through a series of reactions from SCFAs. Ketone bodies exported via monocarboxylate/H+ co-transporters (MCT) provide energy for peripheral tissues, but excessive ketogenesis can lead to elevated blood ketone concentrations and potentially ketosis. Conversely, excessive cholesterol accumulation can trigger cellular inflammation

and oxidative stress, compromising energy supply and causing inflammatory responses. Therefore, investigating SCFA transport across the ruminal epithelium is crucial for understanding rumen dynamics and developing nutritional regulation models.

1. Morphology and Function of Ruminal Epithelium

The ruminal epithelium performs essential physiological functions including SCFA absorption, metabolism, and rumen protection. This stratified epithelium comprises four distinct layers from the luminal surface: the stratum corneum, stratum granulosum, stratum spinosum, and stratum basale. The stratum basale contains abundant mitochondria, while cells of the stratum granulosum and stratosum spinosum occupy intermediate positions with less distinct boundaries. The stratum spinosum also contains some mitochondria, making both the stratum basale and stratum spinosum primary sites for SCFA metabolism. Cells in the stratum granulosum are tightly connected through gap junctions, whereas the outermost stratum corneum consists of highly keratinized cells that serve as a protective barrier against the physical environment of the rumen. The thickness of the stratum corneum is regulated by SCFA concentration; when dietary concentrate-to-forage ratio increases, the propionate-to-acetate ratio and total SCFA concentration rise, causing ruminal pH to decline and the keratinized cell layers to increase to 15 layers. Conversely, the number of layers may decrease to as few as 4. The ruminal epithelium is covered with papillae that can reach 10–15 mm in length in cattle, substantially increasing the surface area for SCFA absorption. As the primary structures for nutrient absorption, the density and size of these papillae directly influence SCFA uptake. Studies have shown that high-protein and high-energy diets increase insulin-like growth factor 1 (IGF-1) concentrations, which activate the downstream Ras/Raf/MEK/ERK signaling pathway upon binding to its receptor, upregulating cyclin D1 expression and promoting ruminal epithelial cell proliferation to enhance SCFA absorption. Additionally, Yazdi et al. found that heat stress can increase papillae height. Thus, ruminal epithelial morphology and SCFA absorption exist in a dynamically balanced regulatory system that coordinates to maintain rumen homeostasis.

2. SCFA Absorption in Ruminal Epithelium

SCFA absorption is not simply a matter of passive diffusion down a concentration gradient, as SCFAs exist in both dissociated and undissociated forms within the rumen lumen, with the undissociated form predominating and leading to distinct transport characteristics. In vitro studies have demonstrated that butyrate exhibits the highest net absorption rate even without a concentration gradient, while acetate and propionate show lower net absorption rates. Both passive diffusion and specific carrier-mediated transport contribute to SCFA absorption. NHEs represent important membrane transporters; undissociated SCFAs entering cells via passive diffusion release H+, causing cytoplasmic acidification that upregulates NHE expression, increases Na+ uptake rate, and exports H+ into

the rumen lumen. This creates a functional coupling between SCFA-induced cytoplasmic acidification and enhanced NHE activity during ruminal epithelial transport. The NHE family in bovine ruminal epithelium primarily includes NHE1, NHE2, NHE3, and NHE-8, while NHE1 and NHE3 are expressed in goats and sheep. Research indicates that NHE1 maintains extracellular pH near the stratum granulosum, as NHE1 knockout animals exhibit lower local extracellular pH values, highlighting its crucial role in maintaining ruminal fluid pH. MCTs serve as specific carriers for SCFAs, ketone bodies, and lactate in the rumen, with MCT1 and MCT2 expressed in bovine ruminal epithelium. Immunofluorescence localization places MCT1 in the stratum basale, where it co-transports dissociated SCFAs, lactate, and ketone bodies into the bloodstream, removing H+ from epithelial cells and preventing cytoplasmic acidification caused by excessive accumulation of ketone bodies and lactate.

Dissociated SCFAs are transported by anion exchanger 2 (AE2), down-regulated in adenoma (DRA), and putative anion 1 (PAT1), with this transport depending on HCO3- availability. Bicarbonate serves as a crucial buffer for regulating rumen digesta pH, originating partly from salivary secretion but primarily from transporter-mediated export by ruminal epithelial cells. Bilk et al. proposed that DRA and PAT1 neutralize acid by exporting bicarbonate from epithelial cells while importing dissociated SCFAs. AE2 maintains intracellular pH homeostasis in ruminal epithelial cells; when intracellular pH rises, AE2 is activated to export HCO3- and stabilize cellular pH. While the function and localization of DRA, PAT1, and AE2 carriers have been extensively studied in intestinal cells, their specific distribution across ruminal epithelial layers remains unclear . However, based on the role of HCO3-/H+ transporters, they are likely located primarily in the stratum granulosum due to its proximity to the rumen lumen. The stratum spinosum and stratum basale may also contain small amounts, as these metabolic layers produce various metabolites such as lactate and pyruvate that cause cytoplasmic acidification, necessitating pH-regulating carriers.

3. SCFA Metabolism in Ruminal Epithelial Cells

Ruminal epithelial cells exhibit active metabolism, with approximately 75% of propionate and 95% of butyrate being metabolized within these cells before reaching the bloodstream. These cells obtain most of their energy by oxidizing SCFAs—terminal fermentation products—rather than relying on glucose, ketone bodies, or glutamine. Butyrate shows the highest metabolic rate among SCFAs and serves as the primary metabolic substrate. Following uptake, SCFA metabolism begins with the conversion to acyl-CoA esters by the acyl-CoA synthetase family, followed by transformation of acetyl-CoA into HMG-CoA by 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS). HMG-CoA represents a central metabolite in ruminal epithelium, serving as the precursor for both ketone body and cholesterol synthesis, and is distributed in both mitochondria and cytoplasm. HMGCS has two isoforms: HMGCS1 located in the cytoplasm and HMGCS2 specifically localized in mitochondria. HMGCS2 regulates ketone

body synthesis in ruminal epithelial cells and acts as the rate-limiting enzyme. De Rosa et al. found that docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and arachidonic acid (AA) at concentrations of 25 and 50 µmol/L upregulated HMGCS2 expression at both transcriptional and translational levels, whereas treatment with 25 mmol/L fructose and insulin for 24 h decreased mRNA and protein expression in human hepatoma (HepG2) cells.

Polyunsaturated fatty acids (PUFAs) regulate various metabolic pathways including de novo lipogenesis and fatty acid oxidation by binding to peroxisome proliferator-activated receptor (PPAR). The HMGCS2 promoter region contains peroxisome proliferator response elements (PPRE) that initiate HMGCS2 transcription upon binding PPAR . Studies have shown that increased PPAR mRNA expression correlates with elevated HMGCS2 mRNA levels. We therefore hypothesize that PUFAs may regulate ketone body synthesis by directly binding to nuclear receptors such as PPAR to upregulate HMGCS2 expression. The primary sites of ketogenesis in ruminants include the rumen and liver, with the mitochondrial process illustrated in [Figure 1: see original paper]. Excessive ketogenesis in ruminal epithelium due to disordered SCFA metabolism can lead to hyperketonemia and eventually ketosis, seriously compromising animal health. Thus, further investigation of the regulatory mechanisms of ketone body synthesis in ruminal epithelial cells is important for ketosis prevention.

[Figure 1: see original paper]

Beyond serving as substrates for ketogenesis, SCFAs also undergo cholesterol biosynthesis in the cytoplasm and endoplasmic reticulum. The initial phase of cholesterol synthesis occurs in the cytoplasm, where SCFAs are converted to HMG-CoA through a series of reactions. HMG-CoA then translocates from the cytoplasm to the endoplasmic reticulum, which contains HMG-CoA reductase (HMGR). Within the ER, HMG-CoA is reduced by HMGR to mevalonate (the mevalonate pathway). HMGR represents the rate-limiting enzyme in cholesterol biosynthesis and is considered one of the most highly regulated enzymes in nature. Mevalonate is subsequently decarboxylated to isoprenoid intermediates such as farnesyl pyrophosphate (FPP). These isoprenoid intermediates induce cell proliferation, migration, and oxidative stress through attachment to membrane-associated signaling proteins, subcellular localization, and intracellular trafficking. The final branch point of cholesterol synthesis involves squalene synthase (FDPS) catalyzing FPP conversion to squalene, which is further metabolized to lanosterol and ultimately cholesterol. Although cholesterol is a major component of mammalian cell membranes, excessive accumulation of cholesterol and its metabolites (isoprenoids) increases membrane permeability and triggers inflammatory responses. Research has shown that feeding high-concentrate diets increases ruminal epithelial permeability and inflammation by promoting ruminal fermentation, elevating SCFA concentrations, and enhancing cholesterol biosynthesis in ruminal epithelial cells. Steele et al. found that feeding a high-concentrate diet for one week significantly increased ruminal SCFA concentrations, induced ruminal acidosis, and upregulated mRNA expression of choles-

terol synthesis-related genes HMGS1 and HMGR, leading to elevated cholesterol concentrations and inflammation. However, when the experiment continued to three weeks, SCFA concentrations remained significantly elevated but HMGS1 and HMGR mRNA expression decreased markedly, suppressing cholesterol synthesis and alleviating acidosis. Thus, cholesterol synthesis in ruminal epithelium is regulated by both SCFA concentration and exposure duration. Short-term SCFA elevation promotes cholesterol synthesis, increases epithelial permeability, and triggers inflammation, whereas prolonged exposure activates the sterol regulatory element-binding protein (SREBP) pathway to suppress expression of cholesterol synthesis enzymes, thereby reducing cholesterol synthesis and mitigating inflammation and acidosis. SREBPs are transcription factor families that regulate cholesterol and lipid gene expression in bovine liver and mammary gland. The bovine genome encodes three SREBP isoforms: SREBP-1a, SREBP-1c, and SREBP-2, with SREBP-2 preferentially activating cholesterol biosynthesis. Under high cholesterol conditions, SREBP in the ER binds to SREBP cleavage-activating protein (SCAP) and inhibits cholesterol synthesis gene expression at the transcriptional level [Figure 2: see original paper]. Under low cholesterol conditions, the SREBP-SCAP complex translocates from the ER to the Golgi apparatus, where proteolytic cleavage releases the N-terminus to initiate nuclear gene expression and enhance cholesterol synthesis. Therefore, investigating the molecular regulatory mechanisms of SCFA-driven cholesterol synthesis in ruminal epithelial cells is essential for developing strategies to prevent and alleviate ruminal acidosis by maintaining intracellular cholesterol homeostasis and reducing cholesterol accumulation-induced permeability and inflammation.

[Figure 2: see original paper]

4. Summary and Outlook

Due to the unique fermentation characteristics of the ruminant rumen, SCFAs serve as the primary energy substrate, making their absorption and metabolism in ruminal epithelium critically related to systemic energy metabolism and animal health. Elucidating these mechanisms facilitates nutritional regulation of rumen health. While numerous studies have investigated the types and mechanisms of various specific carrier proteins in ruminal epithelial cells, the interactions between different carriers and their responses to different physiological states such as heat stress and ruminal acidosis remain unclear. Future research should integrate SCFA metabolism in ruminal epithelial cells with hepatic metabolism and blood circulation to comprehensively clarify the regulatory mechanisms of SCFA absorption and metabolism in ruminal epithelium.

References

[1] ANDERSON K L, NAGARAJA T G, MORRILL J L. Ruminal metabolic development in calves weaned conventionally or early[J]. Journal of Dairy Science,

1987, 70(5): 1000-1005.

[2] 卢劲晔, 黄智南, 沈赞明. 反刍动物瘤胃上皮的结构特点 [J]. 黑龙江畜牧兽医, 2014(16): 50-52.

[3] 杨春涛, 刁其玉, 司丙文, 等. 挥发性脂肪酸在反刍动物瘤胃上皮吸收转运及调节作用 [J]. 中国畜牧杂志, 2015, 51(7): 78-83.

[4] CONNOR E E, LI R W, BALDWIN R L, et al. Gene expression in the digestive tissues of ruminants and their relationships with feeding and digestive processes[J]. Animal, 2010, 4(7): 993-1007.

[5] NAEEM A, DRACKLEY J K, STAMEY J, et al. Role of metabolic and cellular proliferation genes in ruminal development in response to enhanced plane of nutrition in neonatal Holstein calves[J]. Journal of Dairy Science, 2012, 95(4): 1807-1820.

[6] XIANG R D, HUTTON O V, ARCHIBALD L A, et al. Epithelial, metabolic and innate immunity transcriptomic signatures differentiating the rumen from other sheep and mammalian gastrointestinal tract tissues[J]. PeerJ, 2016, 4(3): 1762-1793.

[7] GRAHAM C, SIMMONS N L. Functional organization of the bovine rumen epithelium[J]. American Journal of Physiology, 2005, 288(1): R173-R209.

[8] DENGLER F, RACKWITZ R, BENESCH F, et al. Both butyrate incubation and hypoxia upregulate genes involved in the ruminal transport of SCFA and their metabolites[J]. Journal of Animal Physiology and Animal Nutrition, 2015, 99(2): 379-390.

[9] GAEBEL G, MARTENS H, SUENDERMANN M, et al. The effect of diet, intraruminal pH and osmolarity on sodium, chloride and magnesium absorption from the temporarily isolated and washed reticulo-rumen of sheep[J]. Quarterly Journal of Experimental Physiology, 1987, 72(4): 501-511.

[10] SHEN Z, SEYFERT H M, LÖHRKE B, et al. An energy-rich diet causes rumen papillae proliferation associated with more IGF type 1 receptors and increased plasma IGF-1 concentrations in young goats[J]. The Journal of Nutrition, 2004, 134(1): 11-17.

[11] 卢劲晔, 卢炜, 刘静, 等. IGF-1 促进山羊瘤胃上皮细胞增殖的机制 [J]. 南京农业大学学报, 2014, 37(5): 106-110.

[12] YAZDI M H, MIRZAEI-ALAMOUTI H R, AMANLOU H, et al. Effects of heat stress on metabolism, digestibility, and rumen epithelial characteristics in growing Holstein calves[J]. Journal of Animal Science, 2016, 94(1): 77-89.

[13] YADAV B, SINGH G, VERMA A K, et al. Impact of heat stress on rumen functions[J]. Veterinary World, 2013, 6(6): 992-996.

[14] GRAHAM C, GATHERAR I, HASLAM I, et al. Expression and localization of monocarboxylate transporters and sodium/proton exchangers in bovine ru-

men epithelium[J]. American Journal of Physiology, 2007, 292(2): R997–R1007.

[15] KIRAT D, SALLAM K I, KATO S. Expression and cellular localization of monocarboxylate transporters (MCT2, MCT7, and MCT8) along the cattle gastrointestinal tract[J]. Cell and Tissue Research, 2013, 352(3): 585–598.

[16] HERRMANN J, HERMES R, BREVES G. Transepithelial transport and intraepithelial metabolism of short-chain fatty acids (SCFA) in the porcine proximal colon are influenced by SCFA concentration and luminal pH[J]. Comparative Biochemistry and Physiology Part A, 2011, 158(1): 169–176.

[17] ASCHENBACH J R, PENNER G B, STUMPFF F, et al. Ruminant nutrition symposium: role of fermentation acid absorption in the regulation of ruminal pH[J]. Journal of Animal Science, 2011, 89(4): 1092–1107.

[18] PENNER G B. The role of short-chain fatty acid (SCFA) absorption in the regulation of ruminal pH[J]. Memoirs of Shiraume Gakuen College, 2015, 26(4): 47–67.

[19] LU Z Y, YAO L, JIANG Z Q, et al. Acidic pH and short-chain fatty acids activate Na+ transport but differentially modulate expression of Na+/H+ exchanger isoforms 1, 2, and 3 in omasal epithelium[J]. Journal of Dairy Science, 2016, 99(1): 733–745.

[20] YANG W, SHEN Z, MARTENS H. An energy-rich diet enhances expression of Na+/H+ exchanger isoform 1 and 3 messenger RNA in rumen epithelium of goat[J]. Journal of Animal Science, 2012, 90(1): 307–317.

[21] RABBANI I, SIEGLING-VLITAKIS C, NOCI B, et al. Evidence for NHE3-mediated Na+ transport in sheep and bovine forestomach[J]. American Journal of Physiology, 2011, 301(2): R313–R919.

[22] BEHNE M J, MEYER J W, HANSON K M, et al. NHE1 regulates the stratum corneum permeability barrier homeostasis. Microenvironment acidification assessed with fluorescence lifetime imaging[J]. Journal of Biological Chemistry, 2002, 277(49): 47399–47406.

[23] CUFF M A, LAMBERT D W, SHIRAZI-BEECHEY S P. Substrate-induced regulation of the human colonic monocarboxylate transporter, MCT1[J]. Journal of Physiology, 2002, 539(2): 361–371.

[24] YAN L, ZHANG B, SHEN Z M. Dietary modulation of the expression of genes involved in short-chain fatty acid absorption in the rumen epithelium is related to short-chain fatty acid concentration and pH in the rumen of goats[J]. Journal of Dairy Science, 2014, 97(9): 5668–5675.

[25] WANG Z H, PETROVIC S, MANN E, et al. Identification of an apical Cl-/HCO3- exchanger in the small intestine[J]. American Journal of Physiology, 2002, 282(3): G573–G579.

[26] YU Q, XIA W, RIEDERER B, et al. The anion transporter SLC26A6 (putative anion transporter-1) regulates murine small intestinal Na+HCO3- ab-

sorption[J]. Gastroenterology, 2013, 144(5): S131-S131.

[27] CASEY J R, GRINSTEIN S, ORLOWSKI J. Sensors and regulators of intracellular pH[J]. Nature Reviews Molecular Cell Biology, 2010, 11(1): 50-61.

[28] GÄBEL G, BESTMANN M, MARTENS H. Influences of diet, short-chain fatty acids, lactate and chloride on bicarbonate movement across the reticulorumen wall of sheep[J]. Zentralblatt für Veterinärmedizin A, 2010, 38(1-10): 523-529.

[29] BILK S, HUHN K, HONSCHA K U, et al. Bicarbonate exporting transporters in the ovine ruminal epithelium[J]. Journal of Comparative Physiology B, 2005, 175(5): 365-374.

[30] STEWART A K, KURSCHAT C E, ALPER S L. Role of nonconserved charged residues of the AE2 transmembrane domain in regulation of anion exchange by pH[J]. Pflügers Archiv: European Journal of Physiology, 2007, 454(3): 373-384.

[31] GÄBEL G, ASCHENBACH J R, MÜLLER F. Transfer of energy substrates across ruminal epithelium: implications and limitations[J]. Animal Health Research Reviews, 2002, 3(1): 15-30.

[32] FIRKINS J L, HRISTOV A N, HALL M B, et al. Integration of ruminal metabolism in dairy cattle[J]. Journal of Dairy Science, 2006, 89(1S): E31-E51.

[33] HUHN K, MÜLLER F, HONSCHA K U, et al. Molecular and functional evidence for a Na+-HCO3- cotransporter in sheep ruminal epithelium[J]. Journal of Comparative Biochemistry and Physiology B, 2003, 173(4): 277-284.

[34] SEHESTED J, DIERNÆS L, MULLER P D, et al. Ruminal transport and metabolism of short-chain fatty acids (SCFA) in vitro: effect of SCFA chain length and pH[J]. Comparative Biochemistry and Physiology Part A, 1999, 123(4): 359-368.

[35] KRISTENSEN N B, HARMON D L. Effect of increasing ruminal butyrate absorption on splanchnic metabolism of volatile fatty acids absorbed from the washed reticulorumen of steers[J]. Journal of Animal Science, 2004, 82(7): 2033-2042.

[36] ASH R, BAIRD G D. Activation of volatile fatty acids in bovine liver and rumen epithelium. Evidence for control by autoregulation[J]. Biochemical Journal, 1973, 136(2): 311-319.

[37] MARTINEZ-OUTSCHOORN U E, LIN Z, WHITAKER-MENEZES D, et al. Ketone bodies and two-compartment tumor metabolism: Stromal ketone production fuels mitochondrial biogenesis in epithelial cancer cells[J]. Cell Cycle, 2012, 11(21): 3956-3963.

[38] HEGARDT F G. Mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase: a control enzyme in ketogenesis[J]. Biochemical Journal, 1999, 338(3): 569-582.

[39] KOSTIUK M A, KELLER B O, BERTHIAUME L G. Palmitoylation of ketogenic enzyme HMGCS2 enhances interaction with PPARalpha and transcription at the Hmgcs2 PPRE[J]. The FASEB Journal, 2010, 24(6): 1914-1924.

[40] HELENIUS T O, MISIOREK J O, NYSTRÖM J H, et al. Keratin 8 absence down-regulates colonocyte HMGCS2 and modulates colonic ketogenesis and energy metabolism[J]. Molecular Biology of the Cell, 2015, 26(12): 2298-2324.

[41] RESCIGNO T, CAPASSO A, TECCE M F. Involvement of nutrients and nutritional mediators in mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase gene expression[J]. Journal of Cellular Physiology, 2017, 232(8): 1-9.

[42] JUMP D B. N-3 polyunsaturated fatty acid regulation of hepatic gene transcription[J]. Current Opinion in Lipidology, 2008, 19(3): 242-247.

[43] KINOSHITA M, SUZUKI Y, SAITO Y. Butyrate reduces colonic paracellular permeability by enhancing PPAR gamma activation[J]. Biochemical and Biophysical Research Communications, 2002, 293(2): 827-831.

[44] KIROVSKI D, BLOND B, KATIĆ M, et al. Milk yield composition, body condition, rumen characteristics, and blood metabolites of dairy cows fed diet supplemented with palm oil[J]. Chemical & Biological Technologies in Agriculture, 2015, 2: 6.

[45] DE ROSA M C, CAPUTO M, ZIRPOLI H, et al. Identification of genes selectively regulated in human hepatoma cells by treatment with dyslipidemic PUFAs[J]. Journal of Cellular Physiology, 2015, 230(9): 2059-2066.

[46] PUCHALSKA P, CRAWFORD P A. Multi-dimensional roles of ketone bodies in metabolism, signaling, and therapeutics[J]. Cell Metabolism, 2017, 25(2): 262-284.

[47] VITURRO E, KOENNING M, KROEMER A, et al. Cholesterol synthesis in the lactating cow: induced expression of candidate genes[J]. Journal of Steroid Biochemistry and Molecular Biology, 2009, 115(1/2): 62-67.

[48] 孙玲伟, 包凯, 李影, 等. 奶牛临床和亚临床酮病的血浆代谢组学研究 [J]. 中国农业科学, 2014, 47(8): 1588-1599.

[49] MATSUHASHI T, MARUYAMA S, UEMOTO Y, et al. Effects of bovine fatty acid synthase, stearoyl-coenzyme A desaturase, sterol regulatory element-binding protein 1, and growth hormone gene polymorphisms on fatty acid composition and carcass traits in Japanese Black cattle[J]. Journal of Animal Science, 2011, 89(1): 12-22.

[50] LIAO P, HEMMERLIN A, BACH T J, et al. The potential of the mevalonate pathway for enhanced isoprenoid production[J]. Biotechnology Advances, 2016, 34(5): 697-713.

[51] FAUST L, KOVACS W J. Cholesterol biosynthesis and stress in peroxisome deficiency[J]. Biochimie, 2014, 98: 75-85.

[52] ONTSOUKA E C, ALBRECHT C. Cholesterol Transport and Regulation in the Mammary Gland[J]. Journal of Mammary Gland Biology and Neoplasia, 2014, 19(1): 43-58.

[53] KHAFIPOUR E, KRAUSE D O, PLAIZIER J C. A grain-based subacute ruminal acidosis challenge causes translocation of lipopolysaccharide and triggers inflammation[J]. Journal of Dairy Science, 2009, 92(3): 1060-1070.

[54] ZHOU J, DONG G Z, AO C J, et al. Feeding a high-concentrate corn straw diet increased the release of endotoxin in the rumen and pro-inflammatory cytokines in the mammary gland of dairy cows[J]. BMC Veterinary Research, 2014, 10: 172.

[55] STEELE M A, VANDERVOORT G, ALZAHAL O, et al. Rumen epithelial adaptation to high-grain diets involves the coordinated regulation of genes involved in cholesterol homeostasis[J]. Physiological Genomics, 2011, 43(6): 308-316.

[56] HORTON J D, GOLDSTEIN J L, BROWN M S. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver[J]. Journal of Clinical Investigation, 2002, 109(9): 1125-1131.

[57] 柳童斐, 宋保亮. 胆固醇合成途径的负反馈调控机制 [J]. 中国细胞生物学学报, 2013(4): 401-409.

[58] BROWN M S, GOLDSTEIN J L. The SREBP pathway: regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor[J]. Cell, 1997, 89(3): 331-340.

[59] TAO R Y, XIONG X W, DEPINHO R A, et al. Hepatic SREBP-2 and cholesterol biosynthesis are regulated by FoxO3 and Sirt6[J]. Journal of Lipid Research, 2013, 54(10): 2745-2753.

[60] CHEN Z, DING Z, MA G S, et al. Sterol regulatory element-binding transcription factor (SREBF)-2, SREBF cleavage-activating protein (SCAP), and premature coronary artery disease in a Chinese population[J]. Molecular Biology Reports, 2011, 38(5): 2895-2901.

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