



牦牛乳腺发育及其泌乳调控机制研究进展

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摘 要: 牦牛适应青藏高原低温、强紫外、缺氧和营养胁迫为主要特征的极端环境, 是高海拔牧区的优势畜种。牦牛属于多功能型牛种, 兼具产肉、产绒、乳用及役用性能, 其乳用性能未经过高强度选育。牦牛产奶量低, 但乳脂率、乳糖和乳蛋白含量均显著高于普通牛。乳汁由乳腺分泌, 泌乳是复杂生物过程, 依赖于多种细胞协调维持生理功能。乳腺是哺乳动物特有的器官, 其发育和功能转换受复杂基因网络的调控。随着组学技术的发展和功能基因组学研究的深入, 人、小鼠和普通牛等物种乳腺发育的核心调控因子得到解析, 控制泌乳过程和乳脂分泌等关键过程的调控网络逐渐清晰。虽然产乳性状是牦牛重要的经济性性状, 但关于牦牛乳腺和泌乳基因调控网络的研究相对较少。本文系统总结了牦牛乳腺在形态、发育、泌乳机制、泌乳性能等方面与其它物种的相似性和异质性, 提出了牦牛相关方面亟需解决的关键科学问题, 以期对乳腺生物学研究和牦牛产乳性状功能基因的鉴定提供重要的信息。

关键词: 牦牛; 乳腺; 发育; 泌乳机制

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Molecular Regulation Mechanisms of Mammary Gland Development and Lactation in Yak (*Bos grunniens*)

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Abstract: Yaks are well-adapted to the extreme environment of the Qinghai-Tibet Plateau, characterized by low temperatures, intense ultraviolet radiation, hypoxia, and nutritional stress, making them the dominant livestock species in high-altitude pastoral areas. Yak are multi-functional cattle breeds, possessing the performance of meat production, cashmere production, service use and

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milk production, however, their milk production performance has not undergone high-intensity breeding. Yaks have low milk yield but significantly higher milk fat, lactose and milk protein content. As the core organ for milk secretion, the development of yak mammary gland is regulated by complex network of genes, and the maintenance of its homeostasis and lactation is an intricate biological process of the organism, which relies on the coordinated functioning of multiple cells. With the development of omics technology and the deepening of functional genomics research, the core regulators of mammary gland development in human, mouse and common cow species have been analyzed, and the regulatory networks controlling key processes such as lactation and milk lipid secretion have been clarified. Although milk production is an economically important trait in yak, relatively few studies have been conducted on the regulatory network of mammary gland and lactation-regulating genes in yak. In this paper, the similarities and heterogeneity of yak mammary glands in terms of morphology, development, lactation mechanism, lactation performance and other aspects compared with mammary glands of other species were systematically summarized, and key scientific issues that need to be urgently addressed in yak-related aspects are presented with a view to providing important information for mammary gland biology research and identification of functional genes for milk production traits in yaks.

Keywords: yak; mammary gland; development; lactation mechanism

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乳腺是哺乳动物一种高度特化的器官,其发育和功能受自身和外在环境的显著影响。乳腺发育和泌乳机制在物种间存在显著差异。牦牛是生活在青藏高原及其毗邻地区的牛种,能适应高海拔牧区独特的自然环境,尤其是漫长的冷季和饲草匮乏导致的营养胁迫。许尚忠等^[1-3]研究发现,牦牛乳腺形态和泌乳性能与奶牛甚至黄牛存在显著差别。牦牛乳日产量低,为娟姗牛的13.3%,仅为高产奶牛的6.25%。但牦牛乳营养价值高,比如,牦牛乳中的乳糖、乳蛋白和乳脂率显著高于普通牛。由于在高寒牧区有特殊的经济价值,研究牦牛乳腺发育和产乳性状的分子调控机制具有极其重要的科学和产业意义。但目前,牦牛乳腺发育和泌乳过程的关键调控因子还不清楚,调节牦牛乳脂和乳蛋白合成的通路尚未得到解析,基因组互作调节乳腺发育和泌乳过程还不明确^[4]。

哺乳动物乳腺由实质和间质组成,实质部的乳小叶是泌乳的重要组成单元,维持正常泌乳及乳汁输送^[5]。乳小叶由导管和腺泡组成,其中,腺泡为乳脂合成和分泌的核心,由肌上皮细胞发挥收缩功能,管腔上皮细胞发挥泌乳功能^[6-7]。乳腺发育经历3个重要时期,即胚胎期、青春期和成年期。在成年期,乳腺经历泌乳早期、泌乳中期、泌乳后期、干奶期或退化期循环,在此期间,乳腺结构和细胞代谢

发生剧变^[8]。近期的研究表明,在胚胎期,乳芽可延伸至乳导管结构,颠覆了乳腺在出生后才发育的传统观点。出生后,乳腺在雄激素、雌激素和催产素等多种激素的协同下完成导管在周围基质的延伸和分支,最终形成乳腺基本结构。成年动物乳腺形态和功能在生殖周期发生动态变化^[6,8]。形态学分析表明,牦牛乳腺形态异于奶牛和黄牛,其乳房轮廓较小,呈现碗碟状,乳头短小,乳静脉不明显^[1-2]。近年来,多组学技术和基因编辑技术逐渐成熟,人和小鼠等动物乳腺发育及泌乳调控机制的相关研究已经较为深入,乳腺细胞的起源、异质性和基因表达模式均得到解析^[6,9]。但人们对牦牛乳腺发育、泌乳机制及泌乳性能的研究相对较浅。因此,本文尝试收集牦牛和其它牛在乳腺形态、泌乳机制和泌乳性能等方面的共性和差异,解析牦牛泌乳调控的遗传机制,为深入开展牦牛泌乳生物学研究提供重要的资料,为牦牛遗传育种及高价值乳产品开发提供有价值的信息。

1 牦牛乳腺发育形态异质性

1.1 乳腺特征

牦牛的乳腺有着特定的形态学特征,其形态轮廓偏小,整体呈碗碟状。具体而言,牦牛乳腺的乳头短小,乳静脉也不明显,这些结构隐匿于腹毛之

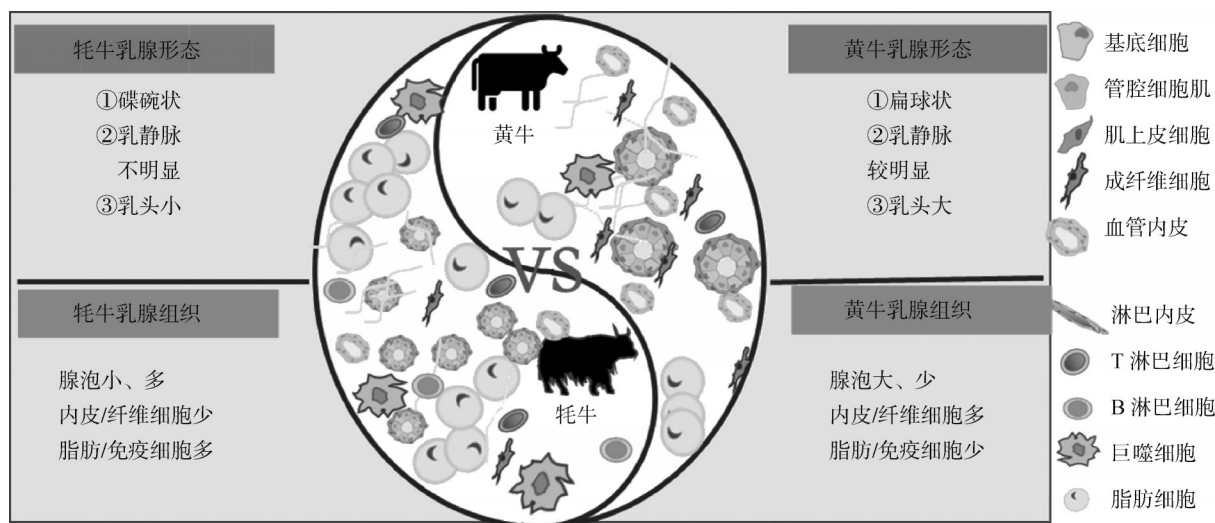
下,通常很难直接观察到。虎业浩等^[10]研究发现,奶牛乳房的轮廓偏大,呈现出明显的悬垂状,其乳头表现为细长形态,并且乳静脉清晰可见。形态轮廓上的差异往往与泌乳量有着必然且紧密联系。不仅如此,此类差异还会使乳腺微环境发生诸多改变,像活性分子的分布、内部压力以及空间结构等方面均会受到影响,而乳腺微环境的变化最终又会造成泌乳性能的差异。

1.2 牦牛乳腺组织形态

乳腺主要是由腺泡、脂肪细胞以及叶间导管共同构成。其中,腺泡大多呈现出规则的圆形,而叶间导管形态多为不规则状。王志强等^[11]研究发现在牦牛处于发情期时,其腺泡和叶间导管的数量相较于未发情期有着极为显著的增加,增加幅度达到2倍多。与奶牛相比,牦牛乳腺的腺泡和导管系统发育程度相对不发达。牦牛乳腺具体表现为腺泡的体积偏小,数量较多。比如,发情期的腺泡数量

为1159个,未发情期为455个;发情期的叶间导管数量为133个,未发情期为54个^[11]。刘占龙^[12]发现这种结构特点与牦牛乳产量较低以及乳腺整体呈现出的较小形态轮廓特征是相互契合、彼此印证的。

奶牛经过长期的杂交选育以及分子育种,其泌乳优势性状得到了高强度筛选,乳腺组织发育充分,具体表现为腺泡和导管构建起了完备且发达的体系,可高效完成乳汁的合成和分泌^[13-14]。泌乳期时,乳腺上皮细胞呈现多样化特征,为柱状、立方状等形态。同时,乳腺上皮细胞胞质内富含内质网,为乳汁合成提供重要物质基础。在靠近腺腔的部位存在明显的大分泌颗粒,这些分泌颗粒是即将分泌出乳汁的重要物质储备形式^[15](图1)。刘占龙^[12]发现,牦牛乳腺中免疫细胞数量多于普通牛,推测可能与高原抗病需求相关,但免疫细胞对乳腺上皮细胞泌乳功能的调控作用尚不明确。



左侧为牦牛乳腺形态描述,右侧为黄牛乳腺形态描述

The text on the left is the description of the yak mammary gland morphology, and the text on the right is the description of the cattle (*Bos taurus*) mammary gland morphology

图1 牦牛和黄牛乳腺形态和细胞组成的对比分析

Fig. 1 Comparative analysis of mammary gland morphology and cellular component of yak and cattle

2 牦牛乳腺发育的分子机制

“乳腺发育-泌乳”是一个复杂的生理过程,受机体多种激素和因子协同调控,推动乳腺组织进行周期性结构重构与退化。宋嘉哲等^[16]提出乳腺发育可分为6个有序阶段:胚胎期、青春期、性成熟期、妊

娠期、泌乳期和退化期。Nan等^[17-19]研究发现,在性成熟期后,乳腺组织经历周期性的重塑(发育、分化与退化),其泌乳性能受机体遗传背景、肠道菌群以及外界环境(如饲养管理)等因素的综合调控。吴家劲等^[20-23]研究表明,在泌乳高峰期,细胞增殖和分化活跃,上皮细胞的基因表达受到精密调控。

Turner 等^[24-25]研究发现,腺泡上皮细胞摄取血液中的营养物质,合成乳汁并分泌至腺泡腔内储存,之后乳汁经由导管系统运输,最终通过乳头排出体外。牦牛的乳腺发育过程显著区别于奶牛或黄牛,表现为成年期(性成熟期后)乳腺体积较小且组织学特征存在明显差异,比如腺泡小但基质比例高。这些典型的形态学特征受基因表达的严密调控,可能在牦牛适应高原,抵抗高寒环境中发挥重要功

能。比较基因组分析显示,和普通牛相比,牦牛基因组有 6 733 个受选择的结构变异,在其适应性进化中发挥重要作用^[26]。基因组结构变异是否在这些性状发育中发挥作用,还需要进一步研究。目前,随着测序技术的飞速发展,牦牛乳腺基因表达逐渐得到解析,同时,模式动物和奶牛的数据为研究者们了解牦牛乳腺生物学提供了重要的参考(图 2)。

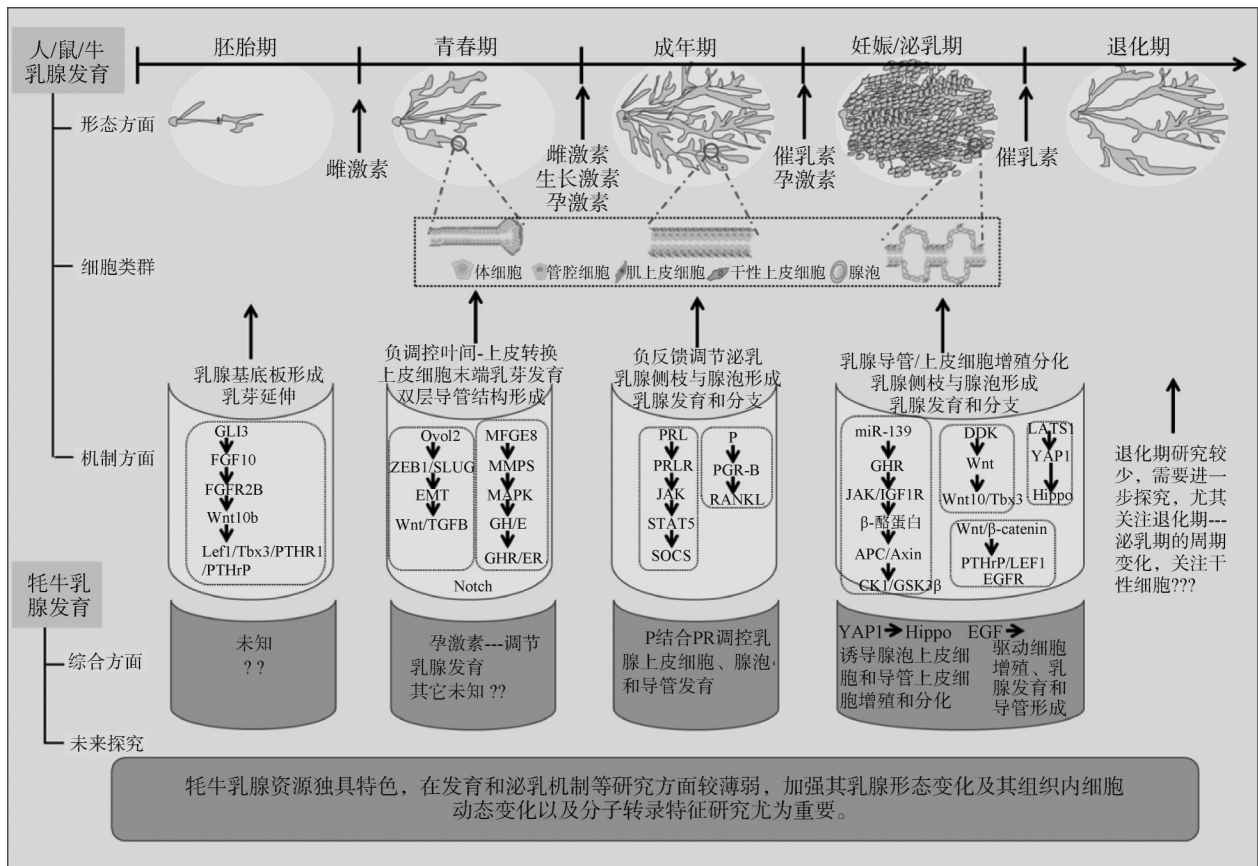


图 2 牦牛乳腺发育

Fig. 2 Yak mammary gland development

2.1 胚胎期

胚胎期是乳腺发育的起始阶段,这一阶段的发育状况直接为乳腺后续泌乳奠定基础,因此,解析其分子调控机制是泌乳生物学的核心科学内容之一^[6]。Faulkin 等^[27-28]研究发现,哺乳动物乳腺起源于胚胎期的外胚层,其发育经历乳条-乳腺-顶状乳丘-球状乳芽-乳池-乳导管系统等连续形态演变阶段。王雯竞等^[29-33]研究发现,胚胎外胚层通过表达 *Wnt10b* 及其下游转录因子 *Lef1* 和 *Tbx3* 协同调控乳腺发育。Mailleux 等^[34-35]研究表明,在胚胎期乳腺发育阶段,转录因子 *Gli3* 激活成纤维生长因

子 10(*FGF10*)表达,发挥关键作用。*FGF10* 与 *FGFR2B* 结合后,诱导 *Wnt10b* 表达,进而促进乳腺基板形成。Hiremath 等^[36]研究发现,在小鼠胚胎期,乳腺上皮细胞表达的 *PTHrP* 与间充质细胞表达的 *PTHrP* 协同调控乳芽的形态发生及延伸。此外,乳腺发育受雌、雄激素的严密调控。雄性胚胎中若缺失雄激素受体(AR),其乳腺芽发育会与雌性胚胎呈现相似表型。

2.2 青春期

青春期乳腺发育受雌激素、生长激素(GH)等多激素调控,表现为基质组织(结缔组织与脂肪组

织)快速增长,导管侵入脂肪垫并广泛分支,形成复杂有序的导管系统,此阶段腺泡尚未发育^[37-38]。Bonadeo等^[39]发现NOTCH信号系统在青春期牦牛乳腺发育过程中呈现动态变化,随着青春期启动,乳腺中NOTCH1和NOTCH2活性结构域增加,而NOTCH3和NOTCH4活性结构域减少,表明NOTCH旁系同源物在牛乳腺发育和分化中的参与程度存在差异。NOTCH配体JAGGED1和DELTA1的mRNA水平在发育过程中也逐渐增加。NOTCH靶基因HEY1和HEY2的mRNA表达水平在青春期期间增加,HES1 mRNA水平的变化未发生显著变化。

青春期乳腺导管中,转录因子*Ovol2*通过负向调控小鼠上皮-间质转化(EMT)相关基因表达,影响乳腺的形态结构演变^[40]。生长激素(GH)、雌激素(E)与其相应受体(生长激素受体(GHR)和雌激素受体 α (ESR α))分别结合后,可诱导并协同促进胰岛素样生长因子1(IGF1)的生成,以此调节乳腺发育。此外,E-ESR α 复合物还能诱导双调蛋白(amphiregulin,AREG)的表达。Jenkins等^[41-42]研究发现,AREG作为旁分泌信号分子,与基质细胞表达的表皮生长因子受体(EGFR)结合,进而促进导管上皮的侧枝分支及末端乳芽(terminal end buds,TEBs)的发育。此外Li等^[43-44]研究发现,雌激素(E)还可驱动乳腺上皮细胞增殖、促进基质细胞有丝分裂、增强葡萄糖代谢、上调孕酮受体(PR)表达、介导脂质合成,以及诱导组胺释放及免疫细胞募集。神经发育相关蛋白Netrin1(NTN1)和Slit2(SLIT2)协同促进乳腺双层上皮管状结构的形成,而Reelin(RELN)则促进导管分支的形态发生延伸^[45-46]。Spina等^[47-48]研究发现,MFGE8与MMPs可激活MAPK信号通路,促进导管分支及基底膜重塑。转化生长因子 β 1(transforming growth factor β 1,TGF β 1)抑制乳腺导管分支,维持导管结构稳态^[49]。青春期牦牛乳腺的腺泡上皮与导管上皮表达孕激素受体(PR),调控乳腺发育^[43]。基于模式动物上的结果推测,转录因子*Ovol2*、雌激素、生长激素及表皮生长因子可能形成重要的调控网络,在牦牛乳腺发育中发挥核心作用。Bonadeo等^[39]的研究揭示了牦牛乳腺中NOTCH、WNT、雌激素等与其它牛种存在差异,推测牦牛乳腺为适应青藏高原恶劣的环境,会释放一些因子激活相关通路。

2.3 成年期

性成熟后,乳腺经历泌乳和复原的周期性变化,其结构也会发生显著重塑。在妊娠期,受多种激素驱动,导管系统与腺泡结构快速生长,小叶内及小叶间结缔组织比例下降^[50-52]。乳腺小叶腺泡经分化成熟,上皮细胞由扁平状转变为柱状;妊娠期乳腺的发育程度决定泌乳细胞数量,直接影响产奶性能^[53-54]。孕激素(P)与其受体亚型B(PGR-B)诱导乳腺侧支及腺泡形成,并通过促进RANKL与其受体RANK(TNFRSF11A)的特异性结合来介导旁分泌信号,进而调控邻近细胞的生长与分化^[55]。在妊娠期,孕激素(P)促进牦牛乳腺细胞发育,它与受体(PGR)结合后调控上皮细胞及导管-腺泡结构发育。若PGR缺失,则会导致腺泡与二级导管发育受阻^[56-58]。雌激素与孕激素共同构成乳腺发育的核心调控网络^[59],二者可能在牦牛乳腺发育(尤其是导管分支)中起主导作用。催乳素(PRL)协同孕激素促进腺泡分化^[60]。比如,Mcnally等^[61-64]研究发现,PRL结合PRLR激活JAK-STAT通路,磷酸化STAT5以启动靶基因转录,促进乳汁合成;同时诱导SOCS蛋白表达,负反馈抑制该通路,维持泌乳稳态。此外Wnt通路是调控乳腺导管及腺泡小叶发育的另一关键通路:妊娠早期,Wnt-2、Wnt-5a与Wnt-7b表达下调,而Wnt-4、Wnt-5b及Wnt-6显著上调,协同维持乳腺小叶发育^[65]。

泌乳期乳腺腺泡增生达到峰值,结缔组织包括成纤维细胞与脂肪细胞含量锐减。泌乳早期与中期腺泡泌乳活跃,至晚期泌乳量逐渐下降^[66]。Huang等^[67-68]研究发现,Hippo通路通过介导乳腺细胞增殖与凋亡,直接决定腺体形态大小。Du等^[69]构建了成年牦牛乳腺中HIPPO信号通路关键蛋白和mRNA的表达谱并发现MST1、LATS1、YAP1和TEAD1在GP乳腺组织中均显著上调,且该阶段细胞增殖最为迅速。因此,LATS1可能通过调节YAP1的活性参与乳腺发育。YAP1和TEAD1可能在乳腺发育过程中发挥促进增殖和抑制凋亡的作用。Li等^[70-72]研究发现,Yes相关蛋白(YAP1)作为Hippo通路的关键下游效应因子,通过激酶级联磷酸化反应调控乳腺等器官的大小。YAP基因缺失可致腺泡发育障碍,显著阻碍乳腺组织生长^[73]。杜培岩等^[74]研究发现,YAP1在牦牛乳腺妊娠期、泌乳期及干奶期均有表达,其蛋白水平在妊娠期与泌乳期显著高于干奶期,且妊娠期表达高于泌乳期。

这表明 YAP1 可能通过调控腺泡及导管上皮细胞的增殖与分化,推动乳腺体积增长,进而促进妊娠期乳腺的发育。Hippo-Yap 信号可靶向调控骨桥蛋白,而 Bai 等^[75]研究发现牦牛骨桥蛋白(OPN)的转录从初乳期到干奶期普遍呈下降趋势,与泌乳高峰期相比,泌乳后期 OPN 表达明显增加。综上, YAP1 靶向调控牦牛乳腺腺泡及导管上皮细胞,参与其增殖与分化调控。

Wnt 家族成员在乳腺发育的青春期、妊娠期、泌乳期及退化期均广泛表达。Veltmaat 等^[76]研究发现 Wnt 蛋白与其受体 Frizzled(Fzd)结合后,激活下游信号通路。该通路促使激酶 CK1 和 GSK3 β 与支架蛋白 APC、Axin 形成复合体,介导 β -catenin 降解。信号激活导致 β -catenin 在胞核内积累,进而调控靶基因表达。Chu 等^[30,77-78]利用 *Dkk1* 抑制 Wnt 信号通路后, *Wnt10* 和 *Tbx3* 基因表达下调,并伴随乳腺发育异常。Yu 等^[79-80]研究发现, Wnt/ β -catenin 信号通路通过靶向调控乳腺细胞内 *PTHrP* 和 *LEF1* 基因的表达,在决定乳腺上皮细胞命运、调控导管后期发育及介导乳腺芽基形成中发挥关键作用。此外, *Lrp5* 和 *Lrp6* 蛋白对乳腺导管形成与分支至关重要。*Lrp5* 和 *Lrp6* 敲除小鼠出现乳腺导管发育缺陷及终末芽(TEB)数量显著减少的表型^[81-82]。杨玉莹等^[83]定量分析显示,牦牛乳腺组织中表皮生长因子(EGF)及其受体(EGFR)的表达水平在泌乳早期最高,泌乳中期次之,退化期(involution)最低。马跃^[84]研究发现,EGF-EGFR 通过激活雌激素信号通路,促进细胞增殖与分化,进而调控乳腺发育及导管形成。此外,非编码 RNA 也可能参与牦牛乳腺发育和泌乳功能的调控。Shi 等^[85]构建了环状 RNA 数据库,并发现环状 RNA 作为竞争性非编码 RNA 网络中的关键分子,可作为促进泌乳和乳腺发育的潜在靶点,有望应用于改善牦牛的产奶性状。长链非编码 RNA 也可通过调控邻近基因来调节泌乳、乳汁合成及乳腺发育^[5]。LNC_000763 可靶向调控 AKT 丝氨酸/苏氨酸激酶 1(AKT1),进而参与了泌乳和乳腺发育过程^[86]。

在成年乳腺泌乳和复原过程中,雌激素、生长激素、孕激素及其受体(PR)、催乳素及其受体(PRLR)、YAP1 蛋白以及 Wnt 和 JAK-STAT 信号通路发挥着关键调控作用,特别是在乳腺腺泡发育、导管分支形成及泌乳维持方面。综上,牦牛乳腺受到多种激素和基因的网络调控,在胚胎期、青

春期、成年期呈现出特异性发育模式,直接决定了其腺泡数量、导管分支程度等结构特征,进而影响成年后泌乳量与乳成分合成效率,具体泌乳性能差异见下节详细描述。

3 牦牛泌乳性能

3.1 泌乳量

不同牛种的泌乳性能存在显著差异,例如,娟姗牛年产量约为 5 300 kg,日均产奶量约 15 kg^[87]。徐云祥^[88]研究发现,西门塔尔牛年产量约 1 200 kg,日均产奶量约 3.2 kg。荷斯坦牛年产量约 12 000 kg,日均产奶量约 32.5 kg^[89]。牦牛年产量约为 250 kg,日均产奶量约 2 kg^[90],明显低于其它牛种。牦牛日均泌乳量约为荷斯坦牛的 1/16,而年产量仅为其 1/48。这种差异与牦牛对高原极端环境的适应性进化紧密相关,表现为乳腺发育相对受限,体积较小。值得注意的是,牦牛群体内个体间泌乳量差异显著,主要受遗传因素、饲养管理水平和环境刺激影响。采用科学的优质精料补饲方案并优化挤奶制度,能够有效提升牦牛个体的产奶性能^[91-94],但依然无法达到奶牛的水平。

3.2 乳成分

3.2.1 乳蛋白 路畅等^[95-99]研究发现,乳蛋白含量是评价牦牛乳品质与营养价值的重要指标之一。娟姗牛平均乳蛋白含量约为 4%,显著高于荷斯坦牛的 2.8%^[100],而西门塔尔牛的乳蛋白约为 3.5%^[101]。牦牛乳蛋白含量平均约 5%,均高于其它牛乳^[102],且富含多种必需氨基酸。酪蛋白是主要成分,它不仅能促进钙(Ca)、磷(P)的吸收,还有助于增强免疫力^[103-105]。

3.2.2 乳脂 牦牛乳脂肪含量为 5.5%~7.5%,脂肪球直径约为 4.39 μ m,显著大于普通牛乳^[106],西门塔尔牛、娟姗牛和荷斯坦牛的乳脂率分别为 3.9%、6% 和 3.4%^[89,105]。相比之下,牦牛乳脂含量更高,具有开发为优质乳制品的潜力。

3.2.3 脂肪酸 脂肪酸是维持机体稳态的重要组成部分。Toledo-Alvarado 等^[107]研究发现,牦牛乳的饱和脂肪酸含量(约 71.5%)高于荷斯坦奶牛(69.64%)和西门塔尔牛(69.96%)。牦牛乳中含有特殊不饱和脂肪酸,如二十碳五烯酸(EPA)和二十二碳六烯酸(DHA),而其它牛乳中几乎不存在或含量极低^[108-109]。这些物质在增强机体免疫功能、延缓衰老进程、促进胎儿发育、预防心血管疾病及抑

制肿瘤细胞增殖等方面具有重要作用^[110]。

3.2.4 乳糖 牦牛乳中乳糖含量为 5.2%,比荷斯坦牛乳(4.97%)和西门塔尔牛乳(4.67%)略高^[105]。牦牛乳中的乳糖是风味形成的关键成分,也具有调节肠道健康的生理功能^[111-114]。

3.2.5 矿物质 矿物质是牛乳的重要组成部分,兼具营养与生理调节功能。Chi等^[115]采用微波消解结合电感耦合等离子体发射光谱法(ICP-OES)和石墨炉原子吸收光谱法(GFAAS)分析表明,牦牛乳中钾(K)、磷(P)和钠(Na)为主要矿物元素,平均含量分别为:K 1 532 mg·L⁻¹、P 1 297 mg·L⁻¹、Na 512 mg·L⁻¹。牦牛乳富含铁元素(Fe),其含量显著高于其它常见乳品。因此,牦牛乳可作为潜在的优质膳食铁来源,有助于预防缺铁相关疾病并维持正常免疫功能^[116]。此外,牦牛乳中钠(Na)和钙(Ca)含量均高于其它牛乳。其中,钙含量尤为突出(牦牛乳:1 475 mg·L⁻¹;荷斯坦牛乳:1 102 mg·L⁻¹)。同时,其钾(K)、磷(P)、镁(Mg)含量也高于荷斯坦牛乳,表明牦牛乳在矿物质营养方面具有优势。

3.2.6 活性小分子 Korhonen等^[117]研究发现,免疫球蛋白(immunoglobulin, Ig)是动物免疫系统中的关键活性物质,通过形成免疫屏障抵御病原体入侵。牦牛乳中主要含有IgG、IgA和IgM三类免疫球蛋白,其中IgG在含量及生物活性上均占主导地位。牦牛乳中免疫球蛋白含量显著高于普通牛乳,其中IgG(0.362 2 mg·mL⁻¹)、IgA(0.490 7 mg·mL⁻¹)和IgM(0.041 6 mg·mL⁻¹)均高于奶牛乳及水牛乳^[118-119]。其中IgA含量尤为突出,约为水牛乳(0.047 1 mg·mL⁻¹)的10倍。此外,转化生长因子-β2(TGF-β2)作为牦牛乳中丰度较高的生长因子,参与细胞增殖调控、胚胎发育和免疫调节等生理过程^[120]。研究显示,牦牛乳中TGF-β2含量(76.41 ng·mL⁻¹)也显著高于奶牛乳(12~71 ng·mL⁻¹)^[121]。在分子水平, Ma等^[122]研究发现,牦牛 $ATF6$ 基因内的两个单核苷酸多态性位点——g. 3_9812652G>T和g. 3_9900243C>T与蛋白质、酪蛋白、脂肪、无水固形物及乳糖含量等多项乳质性性状显著相关。酪蛋白基因家族(CSN)和胰岛素样生长因子结合蛋白3基因($IGFBP3$)是调控泌乳的关键因子。Wu等^[5,96-97]研究发现, $CSN2$ (与 $CSN3$ 同属该家族)的I变体与牦牛产乳量及乳蛋白含量呈显著正相关。

4 牦牛泌乳机制

4.1 乳脂合成

牦牛乳脂合成和分泌受多基因协同调控,尤其是乳腺上皮中脂肪酸代谢相关基因的调控,包括脂肪酸合成、摄取、储存以及甘油三酯合成与调控基因,其中, DBI 、 LEP 、 $SREBP$ 、 $mTORC1$ 和 $TRIB3$ 等基因在牦牛乳脂合成过程中发挥重要作用(图3)。FABP家族成员(如FABP4和FABP5)负责将脂肪酸转运至特定的细胞亚群。随后,这些脂肪酸被长链脂酰辅酶A合成酶(如ACSL1和ACSL4)捕获并激活,转化为其辅酶A硫酯形式($acyl-CoAs$),从而促进脂肪酸的摄取与利用。在转录调控方面,Meng等^[123-125]研究发现乳腺中表达的地西洋结合抑制因子(DBI)参与脂肪酸代谢过程,同时调控孕酮及雌激素等类固醇激素的合成,进而影响乳腺发育。董宝霞^[126]研究发现, $TRIB3$ 基因对脂质代谢相关基因具有显著的负向调控作用,进而抑制乳脂合成。 $TRIB3$ 主要调节甘油三酯合成、脂滴形成以及脂肪酸的摄取和转运^[127-128]。在牦牛乳腺上皮细胞中,过表达 $TRIB3$ 能使脂肪酸代谢相关基因的表达显著下调,如脂肪合成基因(ACC 、 $FASN$)及摄取转运基因($ACSS2$ 、 $ACSL1$ 、 LPL)表达极显著下调,储存转运基因 $FABP3$ 表达显著降低^[129]。同时,甘油三酯(TAG)合成相关基因($GPAM$ 、 $DGAT2$ 、 $PLIN1$)表达受到抑制,乳脂合成关键转录因子 $PPAR\gamma$ 及其调控因子 $SCAP$ 表达极显著抑制。综合分析, $TRIB3$ 过表达对TAG合成相关基因的抑制作用最为显著,提示牦牛乳脂合成可能主要依赖于TAG相关基因的调控。在细胞内信号转导方面,雷帕霉素靶蛋白(mTOR)信号通路参与调控乳腺乳脂合成。胰岛素与其细胞表面受体特异性结合后,激活PI3K-Akt信号轴。活化的Akt通过磷酸化激活mTORC1复合物,进而促进转录因子固醇调节元件结合蛋白1($SREBP-1$)的活化,最终驱动脂质合成相关基因的转录^[130-132]。Porstmann等^[133-134]研究发现Akt作为mTORC1信号通路的关键调控枢纽,通过以下多维度机制发挥核心作用:1)代谢底物供应: Akt上调葡萄糖转运蛋白(GLUT)表达并促进其膜转位,增加葡萄糖摄取;2)增强糖酵解:通过诱导缺氧诱导因子1α($HIF1\alpha$)表达,增强糖酵解速率,为脂质合成提供充足前体;3)调控SREBP-1稳定性: Akt磷酸化后可抑制糖原合成激酶3(GSK3)介导的

SREBP-1 降解, 稳定 SREBP-1 蛋白水平; 4) 调控 SREBP-1 活化: 通过磷酸化修饰调控 SREBP-1 切割激活蛋白(SCAP), 促进无活性的 SREBP-1 前体与 SCAP 形成复合物, 并介导该复合物从内质网向高尔基体的转运, 进而实现 SREBP-1 的蛋白水解加工与活化。mTORC1 还通过磷酸化调控 TAG 合成通路中的关键磷脂酸磷酸酶(PAP) Lipin1 功能, 使其发生核转位, 进而在细胞核内调控 SREBP 的转录活性^[135-136]。在激素方面, 瘦素(leptin, LEP) 是调控乳脂合成的一个重要激素。瘦素主要由脂肪细胞合成, 可通过激活 JAK-STAT (特别是 STAT5 和 STAT3) 信号通路调控乳腺上皮细胞增殖与分化。该信号级联反应可诱导乳腺中酪蛋白(casein) 基因的表达, 促进乳蛋白合成, 并同时影响乳脂含量^[137]。此外, *CIDE* 基因通过抑制脂解(lipolysis) 促进胞内脂质储存。在乳腺组织中, 过表达该基因可显著增加脂滴含量; 反之, 敲低其表达则导致脂滴含量下降^[138-139]。

在牦牛上, *CSL1*、*ACSS1*、*ACSS2* 和 *FABP3* 的表达量在产后 30 天达到峰值, 并在 30~120 天内维持高水平, 这种表达模式与泌乳高峰期及相应的营养需求密切相关^[140]。1-酰基-sn-甘油-3-磷酸转酰基酶 6 (*AGPAT6*)、二酰甘油酰基转移酶 1 (*DGAT1*) 和二酰甘油酰基转移酶 2 (*DGAT2*) 在牦牛泌乳期呈现特征性表达模式。*DGAT1* 的表达量于产前 15 天开始升高, 在产后第 1 天达到峰值。*DGAT2* 的表达量在产后第 60 天达到峰值, 随后逐渐降低。*AGPAT6* 的表达量在产后 30 天前存在波动, 于产后第 30 天达峰值后缓慢下降。与奶牛相比, 牦牛 *AGPAT6*、*DGAT1* 和 *DGAT2* 的表达峰值均提前出现在泌乳早期。邓霄禹等^[141] 研究发现这一独特的表达模式可能归因于高海拔环境、牧草质量差异以及犏牛早期营养需求等多因素的协同作用。在牦牛乳腺细胞中, HIF1 信号通路被激活, *HIF1 α* 通过激活糖酵解通路为乳脂合成提供能量, 同时调控 *VEGF* 基因表达促进血管生成^[133-134]。牦牛乳的乳脂率显著高于其它牛乳, 这也是牦牛在遗传上适应高海拔环境的结果。比如, 脂蛋白脂肪酶基因(*LPL*) 在牦牛基因组存在单核苷酸多态性(SNP) 位点, 不同 SNPs 和乳脂率显著相关。该基因的表达受 *SREBF1* 基因调控, 且在牦牛中的活性高于奶牛同源基因^[125]。

4.2 乳蛋白合成

乳蛋白来源多样, 主要来源于乳腺上皮细胞合成的蛋白质。此外, 像白蛋白、免疫球蛋白等其他蛋白质, 分别由肝脏和脾脏/淋巴组织合成, 并通过血液循环系统运输至乳腺组织。万善霞等^[142] 发现这些外源性蛋白质是乳中 IgG 的主要来源。乳蛋白合成遵循经典分泌途径, 受多种激素和基因调控。前体氨基酸借助转运系统被细胞吸收, 在粗面内质网中合成新生肽链(形成分泌蛋白或膜结合蛋白), 接着转运至高尔基体进行加工修饰, 最后通过分泌囊泡释放到腺泡腔^[143]。核糖体是蛋白质合成的核心场所, 可合成胞内驻留蛋白(如结构蛋白、酶)、分泌蛋白(如乳清蛋白) 及膜结合蛋白^[144]。催乳素(PRL) 与血清因子、生长因子及其它激素协同作用, 不仅促进乳腺上皮细胞的增殖活性, 同时刺激氨基酸的吸收, 并能特异性促进乳清酸性蛋白(WAP)、 β -酪蛋白和 β -乳球蛋白的合成^[145]。胰岛素样生长因子(IGF) 与其结合蛋白(IGFBP) 通过相互结合调控细胞增殖、凋亡及迁移等生物学过程。Erickson 等^[146-148] 研究发现, IGF 结合蛋白 5(IGFBP5) 在奶牛乳汁中呈高表达状态, 受生长激素(GH) 和催乳素(PRL) 调控, 并参与 IGF 信号通路的调节。泌乳早期, α -乳白蛋白表达上调。这需要血液来源的氨基酸优先用于合成 β -乳球蛋白、酪蛋白及 α -乳白蛋白^[149]。牦牛乳蛋白合成机制的研究较为匮乏。因此, 有必要借鉴奶牛等物种的前沿研究成果, 深入剖析牦牛乳腺上皮细胞中乳蛋白合成相关基因及其调控网络(图 3)。

4.3 乳糖合成

乳腺摄取葡萄糖的量与乳糖合成量、产奶量均呈显著正相关^[150-152]。乳糖主要在乳腺上皮细胞中合成, 其合成依赖于乳腺上皮细胞对血液中葡萄糖的摄取, 并最终将其合成为乳糖^[153-154]。上皮细胞吸收葡萄糖后, 一部分葡萄糖会被转运至高尔基体加工并形成囊泡; 另一部分则在胞质中经磷酸化生成葡萄糖-6-磷酸, 进而转化为 UDP-半乳糖。之后, UDP-半乳糖与 α -乳白蛋白(α -lactalbumin, LALBA) 以及 β -1,4-半乳糖基转移酶 I (β -1,4-galactosyltransferase I, β -4-GalT-I) 共同组装形成乳糖合酶复合物^[155-161], 最终以葡萄糖和半乳糖为底物催化合成乳糖^[162-163]。

4.4 乳铁蛋白合成

牦牛乳含有多种生物活性物质, 乳铁蛋白(lactoferrin, LF) 是其中之一, 它是一种铁结合糖蛋

白,具备抗菌、抗炎、抗病毒以及抗肿瘤等多种生物活性。裴杰等^[164-165]研究发现,与奶牛相比,牦牛 *LF* 基因存在 7 个碱基的差异,导致空间结构(α 螺旋、 β 折叠)改变进而影响免疫调控活性,开发乳产品具有较高的潜力。催乳素(PRL)通过激活 JAK2/STAT5 信号通路,促进乳腺上皮细胞乳铁蛋白(LF)的合成与分泌。此外 Cutone 等^[166-167]研究发现,雌激素和糖皮质激素分别通过与雌激素受体(ER)和糖皮质激素受体(GR)结合,激活相应信号通路,共同促进奶牛乳腺上皮细胞 LF 的合成与分

泌。关键转录因子 *CTCF* 参与调控乳铁蛋白(LF)的表达。在小鼠模型中,*CTCF* 在妊娠期乳腺组织中的表达量显著升高,其表达谱的动态变化提示其可能参与乳腺发育及泌乳过程的调控^[168]。乳腺感染牛白血病病毒(bovine leukemia virus, BLV)后,通过抑制 *c-Jun* 的磷酸化及 *SP1* 的表达,降低 *c-Jun* 和 *SP1* 与 *LF* 基因启动子区调控位点的结合活性,进而抑制 *LF* 基因的转录,最终降低其表达水平^[169-170]。因此,探究雌激素(E)及转录因子对解析乳铁蛋白的调控机制具有重要意义(图 3)。

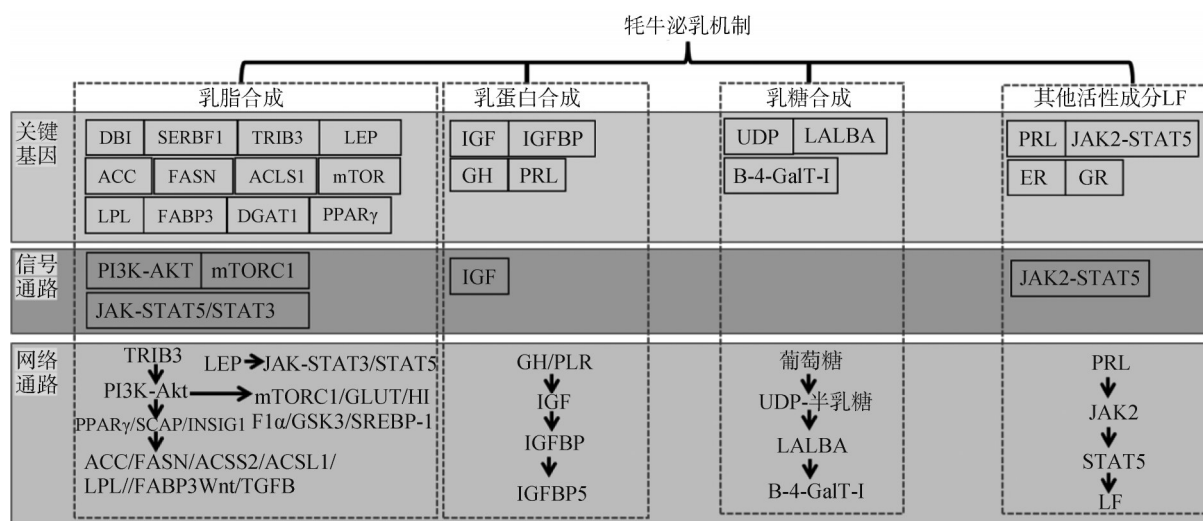


图 3 牦牛乳腺泌乳的重要调控因子

Fig. 3 Key factors regulating lactation in mammary gland of yak

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综上,牦牛在乳腺形态、发育机制、泌乳性能等方面均与普通牛存在显著差异。参考普通牛(尤其是奶牛)的相关研究成果,结合牦牛产业发展的需求,以下问题亟待重点关注。

第一,牦牛乳腺形态呈碗碟状,乳静脉发育程度较低,其体积显著小于普通牛。青春期中牦牛乳腺组织中的腺泡较小,这与其泌乳量低的特点相关。然而,关于牦牛其它发育阶段乳腺形态的研究较少,且乳腺组织中细胞的空间分布、内环境(微环境)差异及其调控机制尚不明确,亟待深入探究。

第二,乳腺发育过程受多种基因与激素协同调控。转录因子、生长因子、激素及其受体、关键信号通路蛋白以及信号通路等在乳腺发育和泌乳中发挥关键作用。据此推测,上述因子在牦牛乳腺的腺泡发育、导管分支形成及泌乳过程中亦可能具有重

要功能。然而,目前对牦牛乳腺的研究仍需加强,特别是在胚胎期和泌乳期等关键阶段乳腺结构的形成机制,以及调控这些过程(如细胞增殖、分化、导管分支)的关键基因(包括前述基因与激素)方面。深入阐明牦牛乳腺发育的调控网络,将为优化牦牛育种策略、开发乳腺疾病防治方法及提升乳品质提供坚实的理论基础。

第三,牦牛乳以其高乳脂率备受关注,一直是研究热点。研究表明, *DBI*、*LEP*、*SREBP*、*mTORC1* 和 *TRIB3* 等基因在牦牛乳脂合成中发挥关键作用,主要通过调控 PI3K-Akt 和 JAK2-STAT5 等信号通路实现。这些基因和通路是解析乳腺泌乳调控的核心靶点。乳腺合成乳脂、乳蛋白、乳糖及活性成分乳铁蛋白或小肽等的核心功能单元位于上皮细胞系统。因此,通过多组学技术深入研究牦牛乳腺上皮细胞群(特别是导管与腺泡细胞)的差异基因表达,并拓展探究其与周围基质细

胞(如脂肪细胞、免疫细胞)的互作网络,将为全面揭示牦牛泌乳机制奠定基础。

综上,牦牛乳腺发育和功能维持有独特的形态学特征及基因表达模式,牦牛乳在乳蛋白、矿物质、乳脂、乳糖及脂肪酸等基础营养成分方面优势显著,尤其在功能性活性成分乳铁蛋白或小肽等方面潜力巨大。因此,基于其独特组分,开发优质乳制品,特别是以高附加值功能性乳基原料(如富含特定活性分子的添加剂)为目标的产品,具有广阔的应用前景。

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