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Review 综 述

# 酿酒酵母高级醇代谢的转录调控研究进展

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CHEN Lu, LIU Yanlin, QIN Yi. Transcriptional regulation of higher alcohol metabolism in *Saccharomyces cerevisiae*[J]. Acta Microbiologica Sinica, 2024, 64(12): 4669-4680.

**摘　要：**高级醇是酿酒酵母在葡萄酒酿造过程中产生的主要代谢副产物，其代谢受到多层次调控体系的精细调节。酿酒酵母高级醇代谢途径中的酶系及其编码基因已基本明确，但酿酒酵母高级醇代谢的转录调控机制仍不清晰。本文在总结酵母高级醇代谢途径及其代谢调控策略的基础上，重点综述了参与酵母高级醇代谢调控的转录因子 Aro80p、GATA 和 Leu3p 及其作用机制。旨在为系统理解酵母高级醇代谢转录调控机制，以及选育高级醇产量适中的酵母菌种提供理论参考。

**关键词：**酿酒酵母；高级醇；转录因子；转录调控

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# Transcriptional regulation of higher alcohol metabolism in *Saccharomyces cerevisiae*

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**Abstract:** Higher alcohols, major metabolic byproducts produced by *Saccharomyces cerevisiae* during winemaking, are intricately regulated by a multilevel system. While the enzymatic machinery and their encoding genes involved in the metabolic pathways of higher alcohols in *S. cerevisiae* have been largely elucidated, the transcriptional regulation underlying this process remains poorly understood. This paper, building upon a summary of the metabolic pathways and regulatory strategies of higher alcohols metabolism in yeast, focuses on the transcription factors Aro80p, GATA and Leu3p implicated in the regulation of higher alcohols metabolism in yeast and their mechanisms of action. The review aims to give theoretical insights into a comprehensive understanding of the transcriptional regulation of higher alcohols metabolism in yeast and facilitate the breeding of yeast strains with moderate production of higher alcohols.
**Keywords:** *Saccharomyces cerevisiae*; higher alcohols; transcription factors; transcriptional regulation

全球气候变暖给葡萄酒产业带来了深刻影响，其中最为突出的是葡萄采收时的含糖量在过去 20 年里逐年攀升[1]。近年我国西北葡萄酒产区主栽红色酿酒葡萄的含糖量普遍超过 260 g/L。葡萄的高含糖量不仅使发酵困难、酒度升高，还会导致葡萄酒高级醇含量显著升高。高级醇也称为“杂醇油”，指含有 3 个及以上碳原子的一元醇，是酿酒酵母的主要代谢副产物[2-5]。研究表明，葡萄酒中的高级醇含量小于 300 mg/L 时，能够赋予葡萄酒令人愉悦的风味，当超过 400 mg/L 则会对葡萄酒带来辛辣、腐臭等不愉悦的杂味，从而导致葡萄酒香气不纯净、感官品质劣变等问题[6]。更重要的是，高级醇含量过高易引发头痛、口渴、醒酒慢等不良症状，对饮用者构成安全隐患[7]。随着葡萄原料含糖量逐年增加，这一问题表现得越来越突出，已成为阻碍我国西北产区葡萄酒质量飞跃的重要问题。因此，亟须在葡萄酒酿造过程中合理控制高级醇含量。

葡萄酒中高级醇的产生与多种发酵环境和工艺条件相关，如发酵基质的同化氮含量和类型[7]、糖含量[8]和添加方法、发酵温度、发酵基质的初始 pH 值及溶氧量等[9-10]。面对复杂的发酵环境条件和多样的工艺措施，酿酒酵母可通过基因转录、转录后翻译和翻译后加工等多层次的调控体系，精细调节高级醇的合成代谢，其中转录水平的调控发生在基因表达的初期阶段，通常是代谢调控的主要方式之一。目前酿酒酵母的高级醇代谢途径已梳理清楚，代谢途径中的酶系及其编码基因已基本明确[11]，针对

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酿酒酵母高级醇代谢的转录调控研究较少，在酿酒酵母高级醇合成代谢中发挥关键作用的转录因子及其转录调控机制尚不全面，这也导致对酿酒酵母的定向代谢工程育种存在代谢调控效果不理想等诸多问题。本文综述了酿酒酵母高级醇代谢途径和参与高级醇代谢的相关转录因子，旨在系统了解酿酒酵母高级醇代谢及转录调控机制，为改良和选育高级醇产量适中的优良酿酒酵母菌种提供理论支持。

# 1 高级醇代谢途径

葡萄酒中高级醇的主体组分为正丙醇、异戊醇、异丁醇、苯乙醇和活性戊醇等，约占高级醇总量的 70%。酿酒酵母的高级醇主要经由糖合成代谢途径(Harris 途径)和氨基酸分解代谢途径(Ehrlich 途径)合成(图 1)[12]。Harris 途径主要指葡萄糖/果糖的糖酵解终产物 α-酮酸，经 2-酮基酸脱羧酶(KDCs)脱羧、脱氢酶(ADHs)脱氢还原成活性戊醇、异丁醇、异戊醇等高级醇；Ehrlich 途径是氨基酸在氨基转移酶(BATs)的催化作用下生成 α-酮酸，α-酮酸在脱羧酶的作用下生成相应的醛和 $CO_2$，醛经还原生成相应的醇。酿酒酵母所产生的高级醇约 75%来自 Harris 途径，约 25%来自 Ehrlich 途径[7]。

酵母的高级醇合成代谢是多基因控制的复杂性生物学过程，涉及多个调控因子。现有研究采用了过量表达/敲除高级醇类物质的代谢途径基因[13]，删除/增强竞争途径[14]，改变辅因子水平[15]，或在线粒体或细胞质重构代谢途径[16]等策略，调控了酵母的高级醇代谢模式。其中，研究人员通过删除非特异性氨基酸转运蛋白编码基因 *GAP1*、*AGP1*[10]以及支链氨基酸分解途径的 *BAT2*[17]，敲除 α-酮酸合成代谢途径的 *LEU1*、*LEU2*、*GDH1*[18]，删除 α-酮酸分解代谢途径的 *HOM2*、*PAD1*、*QCR2*、*SPE1*、*ALD6*[19]，过量表达乙酸酯代谢基因 *ATF1* 或同时敲除 *IAH1* 基因[20]等，均在一定程度上降低了酵母的高级醇产量。

对碳、氮等代谢通路上的单(多)基因敲除或过量表达，在削弱酿酒酵母高级醇合成途径代谢能力的同时，可能会导致乙酸等代谢副产物的增加，这些代谢副产物将严重影响微生物细胞生长和损伤葡萄酒感官品质，以及导致工程菌株发酵特性的改变。因此，通过对高级醇合成途径转录调控的精细优化，可能实现在基因组层面上定向进化或同时改变多个相关基因群，实现精准弱化高级醇合成能力的目的。

# 2 高级醇转录调控

## 2.1 转录因子结构

转录因子(transcription factor, TF)通过识别并结合到 DNA 上的特定序列(顺式作用元件、增强子或沉默子)，激活或抑制相关基因的转录，进而影响高级醇的合成。根据与 DNA 结合结构域类型[21]，TF 可分为 3 类，包括锌簇($Zn^{2+}$)稳定型、螺旋-旋转-螺旋型和拉链型。其中，$Zn^{2+}$稳定型的DNA结合结构域在各种生物体中普遍存在。它的功能域模型如图 2A 所示，整个 DNA 结合结构域(DNA-binding domain, DBD)分为 3 个区域：锌指区、连接体区和二聚区。锌簇蛋白有一个 DBD，其中包含 2 个 $Zn^{2+}$，并以 6 个半胱氨酸(Cys)残基作为配体[22]。在多数锌簇 TF 的结构中存在一个显著特征，即 DBD，位于 TF 的氨基端(N 端)。这一结构域负责识别并结合特定的 DNA 序列，从而调控基因的表达。与此同时，与 DNA 序列直接相互作用并参与特异性结合的残基，则位于 TF 的羧基端(C 端)[23] (图 2B)。这种结构使 TF 能够以高效且特异的方式与 DNA 相互作用，进而调控转录过程。

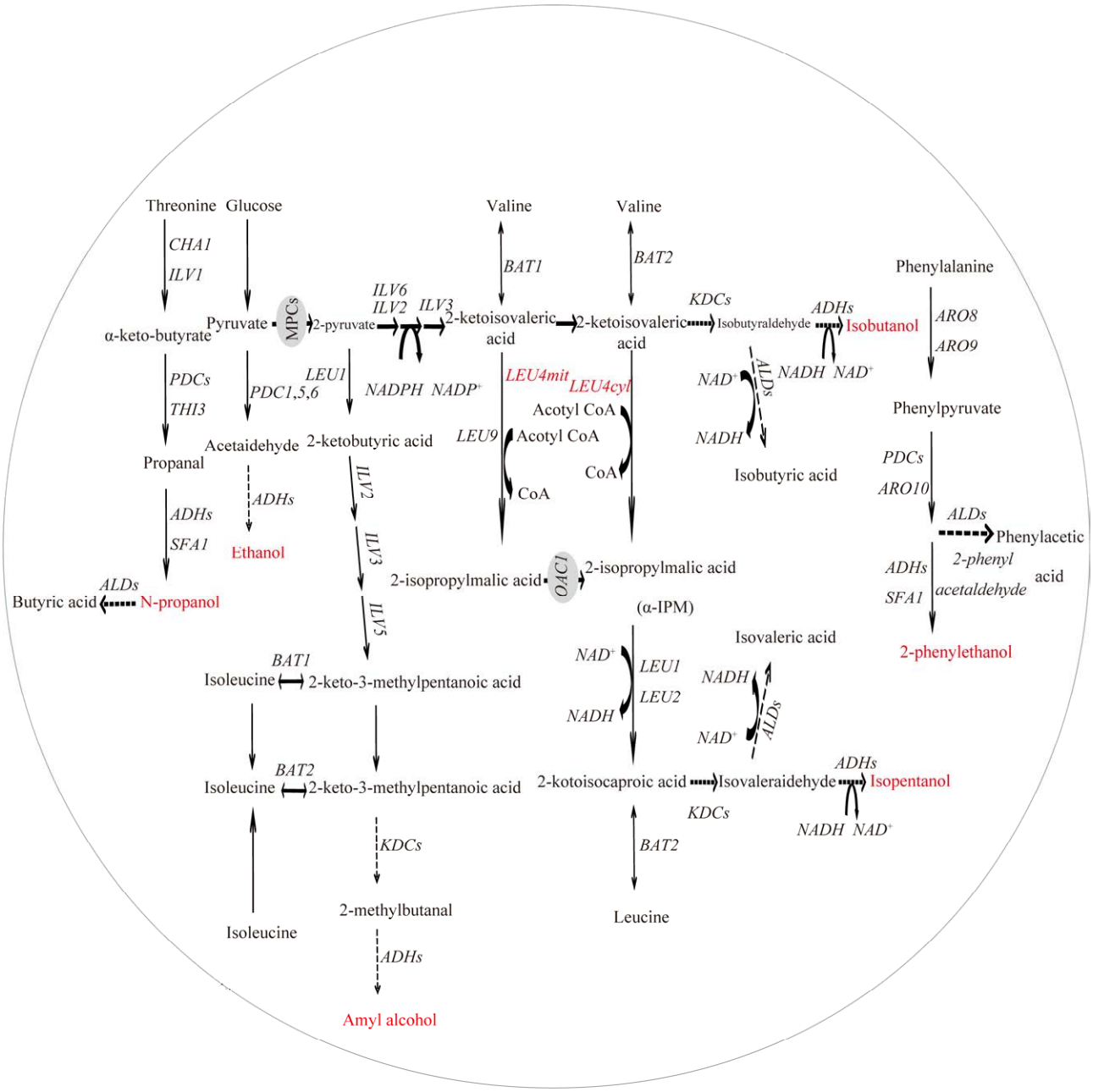


**图 1　高级醇代谢途径[12]**

Figure 1　The metabolic pathway of higher alcohols[12].

## 2.2　与高级醇代谢相关的转录因子

目前已知的与高级醇代谢相关的转录因子有 Aro80p[24]、GATA[25]和 Leu3p[26-29]。

### 2.2.1　Aro80p

Aro80p 属于 $Zn_2Cys_6$ 蛋白家族，由 *ARO80* 基因编码，其能够对芳香族氨基酸作出响应，并促进 *ARO9* 和 *ARO10* 基因的表达[30]。*ARO8* 和 *ARO9* 编码的芳香族转氨酶 I 和 II 催化氨基酸形成相应的 α-酮酸类似物，在 *ARO10* 编码的芳香族脱羧酶的作用下，进一步转化为 2-苯乙醇、色醇和酪醇[31] (图 1)。

Lee 等[32]研究发现，*ARO9* 和 *ARO10* 基因

的表达会被 Aro80p 激活，从而促进 2-苯乙醇的合成；*ARO80* 基因的缺失显著降低 2-苯乙醇的合成。然而同时也发现，利用 *AgTEF1* 启动子过表达 *ARO80*，会导致支链氨基酸分解代谢衍生的异戊醇和异丁醇水平增加 2.5 倍，而 2-苯乙醇的水平基本不变[33]。

Aro80p 的 N 末端具有 1 个 DBD，能够与靶基因启动子序列上一段特定的 36 个碱基对(bp)长度的激活序列相结合。这一激活序列最初在 *ARO9* 和 *ARO10* 基因的启动子序列中被发现，它由 4 组 CCG 序列组成，每组 CCG 之间相隔 7 bp (图 3)；此外，在 *ARO80* 基因的启动子序列中也证实了这一激活序列的存在[30]。若要 Aro80p 与 *ARO9* 和 *ARO10* 启动子上的特定重复序列 CCG 相结合，还需芳香族氨基酸协助触发诱导信号。当培养基中氮源充足时，通过氮代谢物的阻遏抑制氨基酸通透酶编码基因 *GAP1* 表达，导致质膜上 Gap1p 失活。然而，当氮源只有 L-苯丙氨酸存在时，Gap1p 的转运活性将恢复，使得芳香族氨基酸在 Gap1p 的协助下进入细胞并参与代谢过程[34-35]，进而促使 Aro80p 与靶基因启动子的特定重复序列相结合发挥作用(图 4)。这种特定的结合触发了 *ARO9* 与 *ARO10* 基因的表达活性，从而实现对 2-苯乙

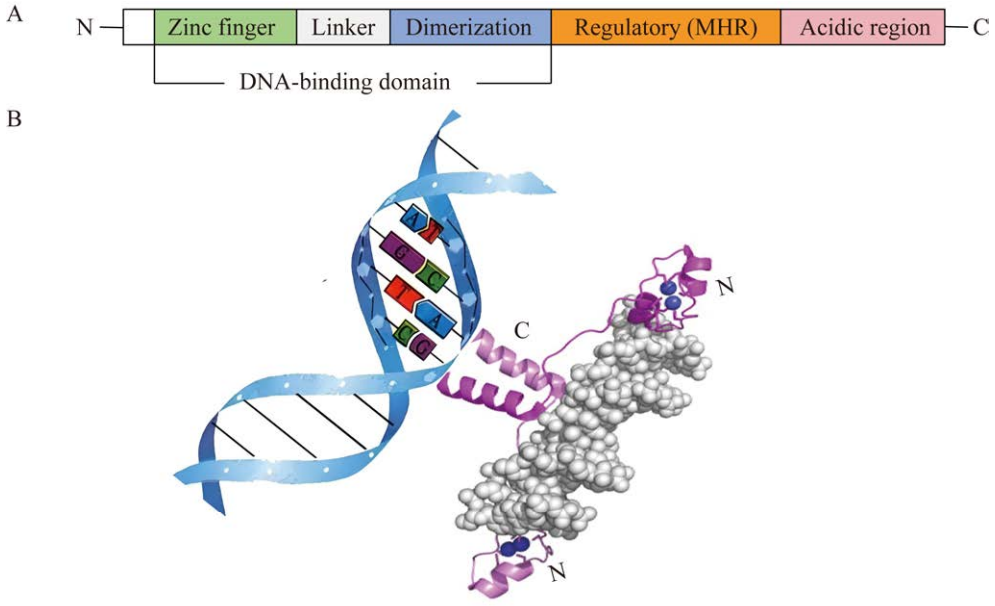


**图 2 锌簇转录因子结构**

Figure 2 The structure of Zinc finger transcription factors. A: Exploring the functional domain of Zinc cluster proteins. B: The TF-DNA binding spatial structure. MHR: Middle homology region.

*GAP1* -550 5′-**TGATAA**GATTGTTAAATGT.....GATTAAATTAAACAT**GATAA**G-3′ -462
*ARO9* -175 5′-GCATTGCCGATGCTTACCGAGATTTGCCGCG**GATAA**CCGAAC-3′ -130
*ARO10* -349 5′-G**GATAA**CCGCG**GATAG**CCGTCATTTACCGAAAATTGCCGAGG-3′ -308
*ARO80* -148 5′-TTCTATCCGAT**GATAA**CCGA**GATAA**ATGAAGATAGTAACTAA-3′ -107

**图 3 基因启动子的上游激活序列[30]**

Figure 3 Upstream activation sequences in gene promoters[30]. CCG triplets, the binding sites of *ARO9*, *ARO10*, and *ARO80*, are underlined and potential GATA factor binding sites (GATAA/G) are indicated in bold.

醇的有效调控。因此，可以看出，Aro80p 不仅直接参与了 *ARO9*、*ARO10* 和 *ARO80* 的调控，也间接影响了氨基酸转运酶。

### 2.2.2 GATA 转录因子

GATA 家族作为一类具有 IV 型锌指结构的转录调控因子，具有特异性识别并结合 GATA 基序(motif)的能力[36]。在酿酒酵母中，氮代谢相关基因的表达由 4 个 GATA 家族转录因子共同调控，它们是 Gat1p、Gln3p、Gzf3p 和 Dal80p[37-38]。这 4 个转录因子具有一个共同的特征性锌指部分，使其能够结合到上游激活序列上，该区域位于受氮调控的基因上游约数百个碱基对处，并激活(Gat1p 和 Gln3p)或抑制(Gzf3p 和 Dal80p)转录的启动。

当敲除酿酒酵母 *GAT1* 和 *GLN3* 基因后，与高级醇代谢相关的基因表达水平显著降低[39]。Wang 等[17]发现，*GAT1* 缺失菌株中高级醇总含量增加 28.36%，达到 615.73 mg/L。*GLN3* 的缺失可增加酵母对异丁醇的耐受性，异丁醇产量提高了 4.9 倍[40]。此外，尽管目前暂未发现 Dal81p 是否参与了酵母的高级醇代谢调控，但有研究显示 Dal80p 可能通过调节尿素代谢参与了氨基甲酸乙酯的调控[41]。Dal80p 的同系物 Dal81p 与前者的作用明显不同，Dal81p 是从尿囊素、尿素和亮氨酸获取氮的正调节因子[42]。

GATA 家族 Gat1p 和 Gln3p 作为转录激活因子调控酿酒酵母中的氮分解代谢物抑制(nitrogen catabolism repression, NCR)。当微生物处于含有多种氮源的环境中时，它们会优先选择利用易于同化且能量效率高的氮源(如氨、谷

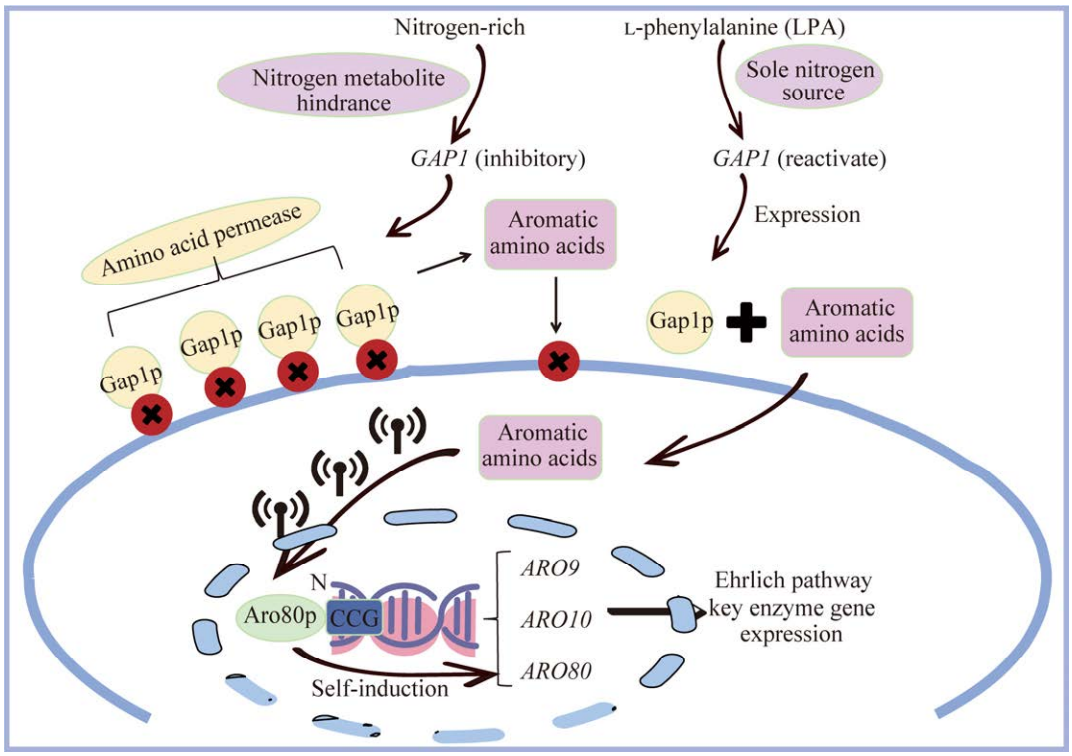


**图 4 转录因子 Aro80p 调控机制**

Figure 4 Mechanism of Aro80p transcription factor regulation. When nitrogen sources are available in abundance, Gap1p becomes inactive, resulting in the inability of Aro80p to function. Conversely, when L-phenylalanine alone serves as the nitrogen source, the transport activity of Gap1p is restored, allowing it to enter the cell and thereby prompting Aro80p to function.

氨酸等)，而抑制利用成本较高或效率较低的氮源相关基因的表达[43]。*GLN3* 基因的分离和测序结果表明，在 306−330 区域，Gln3p 有 1 个锌指结构，与高等生物的 GATA 转录因子具有显著同源性[30]。免疫沉淀实验显示，Gln3p 与 *GLN1* 基因启动子上游 5′-GATAA/G-3′序列相结合[44]。在酵母中，除了已知的 Gln3p 调控因子外，还发现了氮代谢途径中的另一个重要激活因子 Gat1p。该因子与 Gln3p 都具有 GATA 锌指基序，对于 NCR 敏感基因的表达至关重要，并呈现出轻微的转录激活潜力[45]。Gat1p 能够与目标基因的启动子中位于 310−334 区域的特定序列“5′-GATAA/G-3′”进行结合[44]。在氮源充足的情况下，Tor1p 及其他未知的磷酸激酶被激活，致使 Gat1p 和 Gln3p 发生磷酸化，并被核膜排斥至细胞质中，阻碍其参与靶基因的转录调控[46]。当 Gat1p 和 Gln3p 处于非活化状态时，多个基因的转录受到抑制，包括 *DUR1*、*DUR2* (编码脲基酰胺酶)、*DUR3* (编码尿素渗透酶)、*CAR1* (编码精氨酸酶)；而在氮源匮乏时，Gat1p 和 Gln3p 进入细胞核，并与 NCR 敏感基因启动子上的 GATA 序列结合，进而激活转录[47] (图 5)。

### 2.2.3 Leu3p

Leu3p 作为转录调控因子，可能参与了包括异戊醇和异丁醇等高级醇类物质的代谢调控[48-49]。Leu3p 是一个 $Zn(II)_2Cys_6$ 锌簇蛋白转录因子，结合 DNA 翻转重复序列 CCG-N4-CGG，*LEU3* 基因的表达受 Gcn4 介导的通用氨基酸控制 (general amino acid control, GAAC)；Leu3p 自身

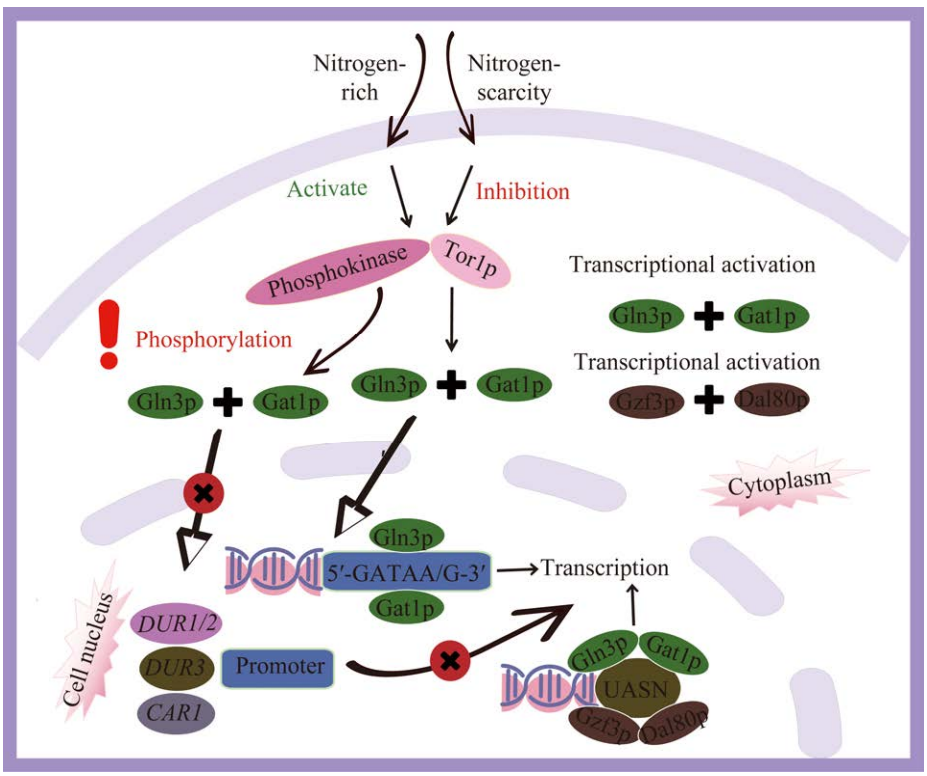


**图 5 GATA 家族转录因子调控机制**

Figure 5 Mechanisms of regulation by GATA family transcription factors. When nitrogen sources are abundant, Gat1p and Gln3p undergo phosphorylation, preventing their entry into the nucleus and impeding their involvement in transcriptional regulation. Conversely, in a condition with limited nitrogen sources, Gat1p and Gln3p are allowed to enter the nucleus to participate in transcriptional regulation.

的激活程度取决于细胞内 Leu3p 浓度，也受酵母细胞内亮氨酸/异戊醇生物合成途径的中间代谢物 α-异丙基苹果酸(α-isopropylmalate, α-IPM)的调控；α-IPM 是 Leu3p 的共激活因子，当 α-IPM 充足时，形成 Leu3-α-IPM 复合物，发挥激活因子功能，反之 Leu3p 则为转录阻遏物[50-51](图 6)。

转录因子 Leu3p 对异戊醇合成途径编码基因 *BAT1* 和 *LEU4* 的调控机制相对清晰。*BAT1* 编码线粒体支链氨基酸转氨酶，催化 Ehrlich 途径第 1 步反应(转氨作用)；Bat1p 主要参与支链氨基酸的生物合成[51]，在对数生长期内表现为快速表达并大量积累，进入稳定期后其表达受到抑制。在生物合成阶段 *BAT1* 的表达主要受到 Leu3-α-IPM 的激活调控，其中，Leu3p 结合于无核小体区域(nucleosome-free regions, NFR)[26]的 *BAT1* 侧翼区。*LEU4* 编码的 α-异丙基苹果酸合酶(Leu4p)是亮氨酸/异戊醇生物合成途径的关键调控酶，受亮氨酸反馈抑制[52]。*LEU4* 启动子的主要调控元件是 Leu3p 结合元件(upstream active sequence, UAS)和 2 个一般控制响应 Gcn4p 结合元件(genetic code expansions, GCEs)[53]。亮氨酸对 *LEU4* 的调节是通过 α-IPM 进行的。当细胞内亮氨酸供应不足时，其对 α-异丙基苹果酸合酶的反馈抑制作用减弱，引起 α-IPM 水平升高并与 Leu3p 相互作用，从而激活 *LEU4* 表达[52]。

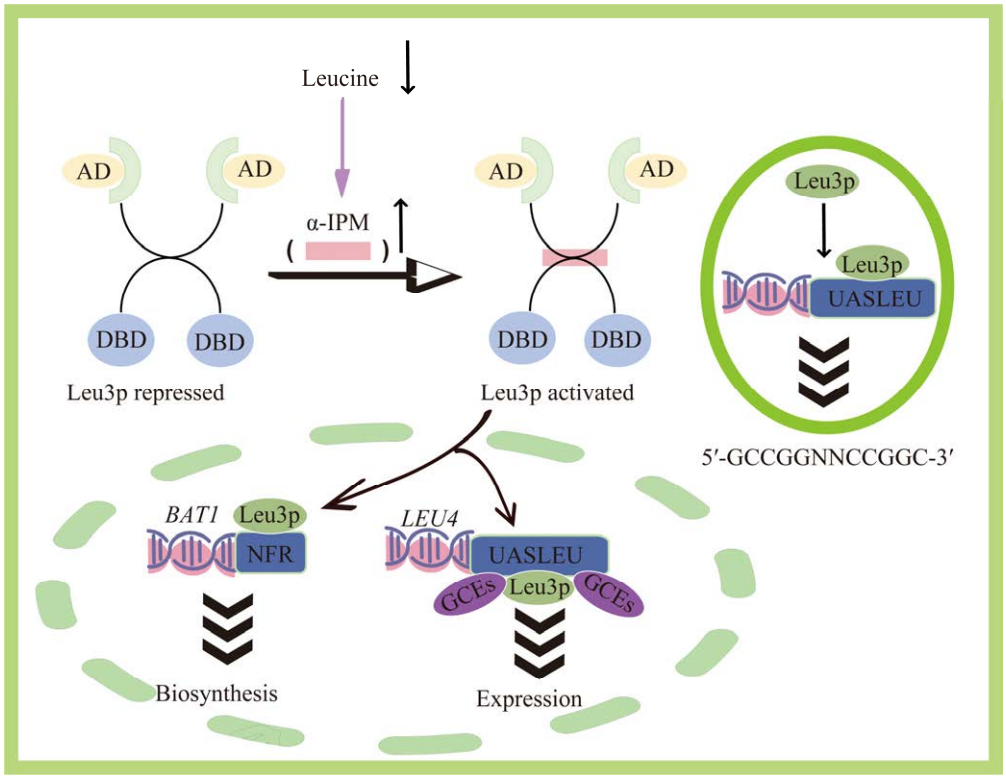


**图 6　转录因子 Leu3p 调控机制**

Figure 6　Mechanism of Leu3p transcription factor regulation. α-IPM serves as a coactivator for Leu3p. When α-IPM is abundant, it forms a Leu3-α-IPM complex, which then functions as an activator. Conversely, when α-IPM is in short supply, Leu3p acts as a transcriptional repressor.

尽管转录因子 Leu3p 对 *BAT1* 和 *LEU4* 的作用机制相对清晰,但通过 YEASTRACT 数据库[54]分析发现，Leu3p 与异戊醇和异丁醇代谢途径的 16 个基因也有直接或间接的关系。其中，Leu3p 激活 *OAC1*、*ALD5*、*BAP2*、*LEU1/2*、*ILV5*、*PDC5/6*、*THI3*、*ADH2/6*、*GAP1* 的表达(或者共表达)，激活或抑制 *BAT2*、*ILV2/3* 表达，抑制 *ILV6* 的表达(图 7)。

## 3 展望

高级醇是包括葡萄酒在内的饮料酒重要风味物质和潜在健康危害因子，主要由酿酒酵母代谢产生。由于酿酒酵母高级醇代谢转录调控机制不明确，导致葡萄酒酿造中针对高级醇含量的控制缺乏有效策略。因此，需要进一步在转录、转录后、翻译和翻译后加工等水平探究高级醇代谢的精细调控。尽管目前已有实验证据表明转录因子 Aro80p、GATA 和 Leu3p 与酿酒酵母高级醇代谢有关，同时借助转录组学、基因组学等组学技术预测了更多与高级醇代谢具有潜在关系的转录因子,但是这些转录因子是在无约束条件下的分析结果,无法明确指出哪些转录因子是调控酿酒酵母高级醇合成代谢的关键转录因子。因此，在全基因组范围内挖掘和验证调控酿酒酵母高级醇的关键转录因子，是首要解决的关键科学问题；其次，通过关键转录因子靶向基因的解析，回答在不同发酵阶段关键转录因子通过何种方式调控酿酒酵母高级醇的合成代谢能力，从而揭示酿酒酵母高级醇合成代谢的调控机制，是需要解决的第 2 个关键科学问题。

对调控酿酒酵母关键转录因子的挖掘及其作用机制的解析，对于深刻系统理解酿酒酵母的高级醇代谢调控机制，为酿酒酵母高级醇代谢的精细调控提供新的思路，也为选育能够产出适量高级醇、适用于包括葡萄酒在内的各类饮料酒生产的优质酿酒酵母菌种，提供了重要的科学依据和实践指导，具有深远的意义。

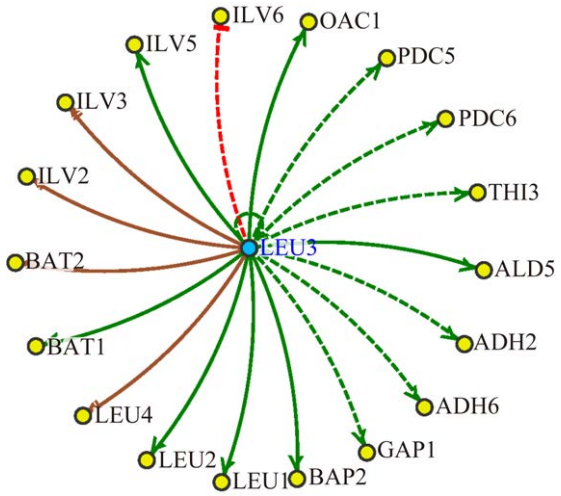


**图 7 酿酒酵母高级醇代谢途径编码基因与酿酒酵母转录因子(Leu3p)的关系**

Figure 7 Relationship between coding genes involved in the higher alcohols metabolic pathway and transcription factors (Leu3p) in *Saccharomyces cerevisiae*. Solid lines indicate direct DNA-binding evidence derived from techniques such as ChIP/ChIP-seq, while dashed lines represent indirect associations inferred from transcriptome sequencing data. Green lines signify activation, red lines indicate inhibition, and brown lines imply a dual role of either activation or inhibition, depending on the context.

## 作者贡献声明

陈璐：构思、论文撰写；刘延琳：修改；秦义：修改。

## 作者利益冲突公开声明

作者声明没有任何可能会影响本文所报告工作的已知经济利益或个人关系。

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