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Review 综述

从 C1/C2 底物到单细胞蛋白：生物制造路径与挑战

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摘　要：单细胞蛋白(single-cell protein, SCP)作为一种高效、可持续的蛋白质来源，在缓解传统农业资源约束和降低食品制造碳足迹方面展现出重要潜力。二氧化碳、甲醇、乙酸等低碳 C1/C2 底物具有来源广泛、成本低廉、碳足迹小等优势，但其同化效率与蛋白高效积累仍受限于底盘细胞适配性不足、代谢通量分配失衡以及能量供给效率低下等关键瓶颈。近年来，围绕 C1/C2 底物的高效生物转化，研究者已在微生物底盘的挖掘、评价与理性改造方面取得显著进展，并通过代谢工程、合成生物学及实验室适应进化等手段，持续提升菌株对 C1/C2 底物的耐受性、同化效率及胞内蛋白质积累能力。在此基础上，多种基于 C1/C2 底物的 SCP 生产工艺正逐步向中试及规模化应用推进。本文系统综述了 C1/C2 底物高效利用底盘细胞的构建策略、代谢工程驱动 SCP 高效生产的关键技术，以及不同 C1/C2 底物生产 SCP 的技术发展与产业化现状，并进一步探讨了能量效率、营养品质、安全性及规模化放大等方面面临的挑战，以期为 C1/C2 底物生产 SCP 的可持续发展与工业应用提供理论依据与技术参考。

关键词：C1/C2 底物；单细胞蛋白；合成生物学；代谢工程；产业化

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From C1/C2 feedstocks to single-cell proteins: biomanufacturing routes and challenges

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Abstract: As efficient and sustainable proteins, single-cell proteins (SCPs) demonstrate significant potential in alleviating the constraints of traditional agricultural resources and reducing the carbon footprint of food manufacturing. Low-carbon C1/C2 feedstocks, such as carbon dioxide, methanol, and acetate, offer distinct advantages, including broad availability, low costs, and minimal carbon footprints. However, the assimilation of these feedstocks and the accumulation of proteins are still limited by key bottlenecks such as poor host cell adaptability, imbalanced metabolic flux distribution, and inefficient energy supply. In recent years, remarkable progress has been achieved in the discovery, evaluation, and rational engineering of host strains for the efficient bioconversion of C1/C2 feedstocks. The application of synthetic biology, metabolic engineering, and laboratory adaptive evolution has enabled the continuous improvements of the strain tolerance to C1/C2 feedstocks, assimilation efficiency, and intracellular protein accumulation capacity. On the basis of these advancements, various SCP production processes utilizing C1/C2 feedstocks are gradually advancing toward pilot-scale and industrial applications. This review systematically summarizes the strategies for constructing chassis cells that efficiently utilize C1/C2 feedstocks, key metabolic engineering technologies driving efficient SCP production, and the current technological and industrial status of SCP production from different C1/C2 feedstocks. Furthermore, it discusses challenges related to energy efficiency, nutritional quality, safety, and downstream scale-up, aiming to provide a theoretical foundation and technical reference for the sustainable development and industrial application of SCPs produced from C1/C2 feedstocks.

Keywords: C1/C2 feedstocks; single-cell protein; synthetic biology; metabolic engineering; industrialization

由全球人口不断增长导致的粮食危机，使得人们有必要寻找一种高效可持续的食品生产方式。蛋白质作为三大营养素之一，预计到2050年全球对其需求量将达到3 700万t，相比2024年增长2 400万t[1]。现阶段蛋白质主要通过传统畜牧业、渔业和种植业生产，其面临的耕地、气候危机以及较低的生产效率，让科研团队将目光转移至更具可持续性的细胞农业[2]。

近年来，“向微生物要资源”正式成为中国保障粮食安全、实现农业可持续发展的重要战略。单细胞蛋白(single-cell protein, SCP)，又称菌体蛋白，是一类由藻类、酵母、细菌和真菌生物质积累产生的终产品。其生产无需占用大量土地和水资源，不受季节及环境变化的影响，

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且同时具备糖类、脂肪、微量元素和膳食纤维的供给能力。在这 4 类微生物中，细菌的粗蛋白含量较高，通常可达 50%−80%，其氨基酸谱最接近鱼粉；藻类粗蛋白含量处于 40%−60%，其氨基酸组成接近人类需求；酵母粗蛋白含量处于 45%−60% 之间，其赖氨酸含量优越，富含风味氨基酸；真菌的粗蛋白含量相对较低，约在 30%−50% 之间，氨基酸平衡性存在劣势。然而，上述来源的 SCP 均面临含硫氨基酸丰度较低的营养学限制。截至目前，国内外已有多家公司开展不同微生物的 SCP 生产业务。受限于安全性、较高的监管门槛和消费者的接受度，SCP 产品目前主要服务于饲料行业，仅有少数食品案例成功在部分国家销售。

随着对低碳经济的重视以及对微生物代谢特征的深入研究，研究团队鉴定出了许多天然能利用 C1/C2 碳源(如二氧化碳、甲烷、甲醇、乙酸等)生长的微生物，包括乙醇梭菌(*Clostridium autoethanogenum*)、荚膜甲基球菌(*Methylococcus capsulatus*)、巴斯德毕赤酵母(*Pichia pastoris*)、产碱菌属(*Alcaligenes*)等。通过代谢工程策略，这些天然的 C1/C2 利用途径如 Wood-Ljungdahl 途径、磷酸核酮糖途径(ribulose monophosphate pathway, RuMP)、乙酸激酶-磷酸转乙酰酶(acetate kinase-phosphotransacetylase, ACK-PTA)途径等也被引入常见模式菌株中用于 SCP 生产。然而，微生物利用 C1/C2 底物时面临着较低的生物转化率以及能量效率，使得生物质积累、胞内蛋白质积累和生产效率难以达到与传统碳源相当的水平。

近年来，诸多研究团队报道了提高微生物 C1/C2 底物利用效率及促进 SCP 生产的策略，包括代谢工程优化、电化学偶联等，大幅推进了利用 C1/C2 底物生产 SCP 从概念到应用的进程。基于现阶段的研究，本文从生产底盘、提升微生物 C1/C2 底物利用能力、优化蛋白质合成效率等方面全面总结了 C1/C2 底物 SCP 生产的关键方法，并对其挑战及未来研究方向进行全面评估，以推动 C1/C2 底物 SCP 的产业化发展(图 1)。

1 C1/C2 底物高效利用微生物底盘的挖掘与设计构建

1.1 天然利用 C1/C2 底物微生物底盘的挖掘

相较于依赖糖类等传统原料代谢模式的微生物，天然具备 C1/C2 底物同化能力的微生物在代谢网络完整性、能量利用效率以及碳原子经济性方面展现出独特优势[3]。因此，对这些天然 C1/C2 底物原料利用微生物的系统性挖掘不仅有助于拓展可持续生物制造的原料边界，也为构建新一代低碳、高效的工业微生物底盘奠定了重要基础。

基于传统的生态位环境样本采集，已成功在富含 C1/C2 化合物的自然或化工环境中分离得到高效 C1/C2 利用微生物，如嗜甲基菌属(*Methylophilus*)高效利用甲醇菌株[4]、耶氏酵母属(*Yarrowia*)高效利用乙酸菌株[5]等。这些微生物在长期自然选择压力下形成稳定的 C1/C2 底物耐受和利用能力，在 C1/C2 条件下具有较高的比生长速率和生物量积累。通过以 C1/C2 底物为唯一或主要碳源，优化培养条件，进一步结合高通量培养技术可实现对目标功能微生物的快速富集。例如 Qi 等[6]通过高通量微孔板培养筛选出乙醇耐受型嗜热细菌；Mukherjee 等[7]利用高通量半自动化机器人筛选高乙醇耐受酵母。此外，随着组学技术和生物信息学的发展，数据驱动的新物种挖掘逐渐兴起。通过基因组、宏基因组及转录组分析识别关键 C1/C2 底物同化通路及其调控特征，难培养或低丰度微生物得以被系统地发现。Woodcroft 等[8]通过大规模宏基因组和转录组分析识别了在多年冻土环境中参与甲烷和乙酸循环的关键微生物及其代谢通路；Parks 等[9]在超过 1 500 个公开宏基因组数据集中重构出 7 903 个细菌和古菌基因组，识

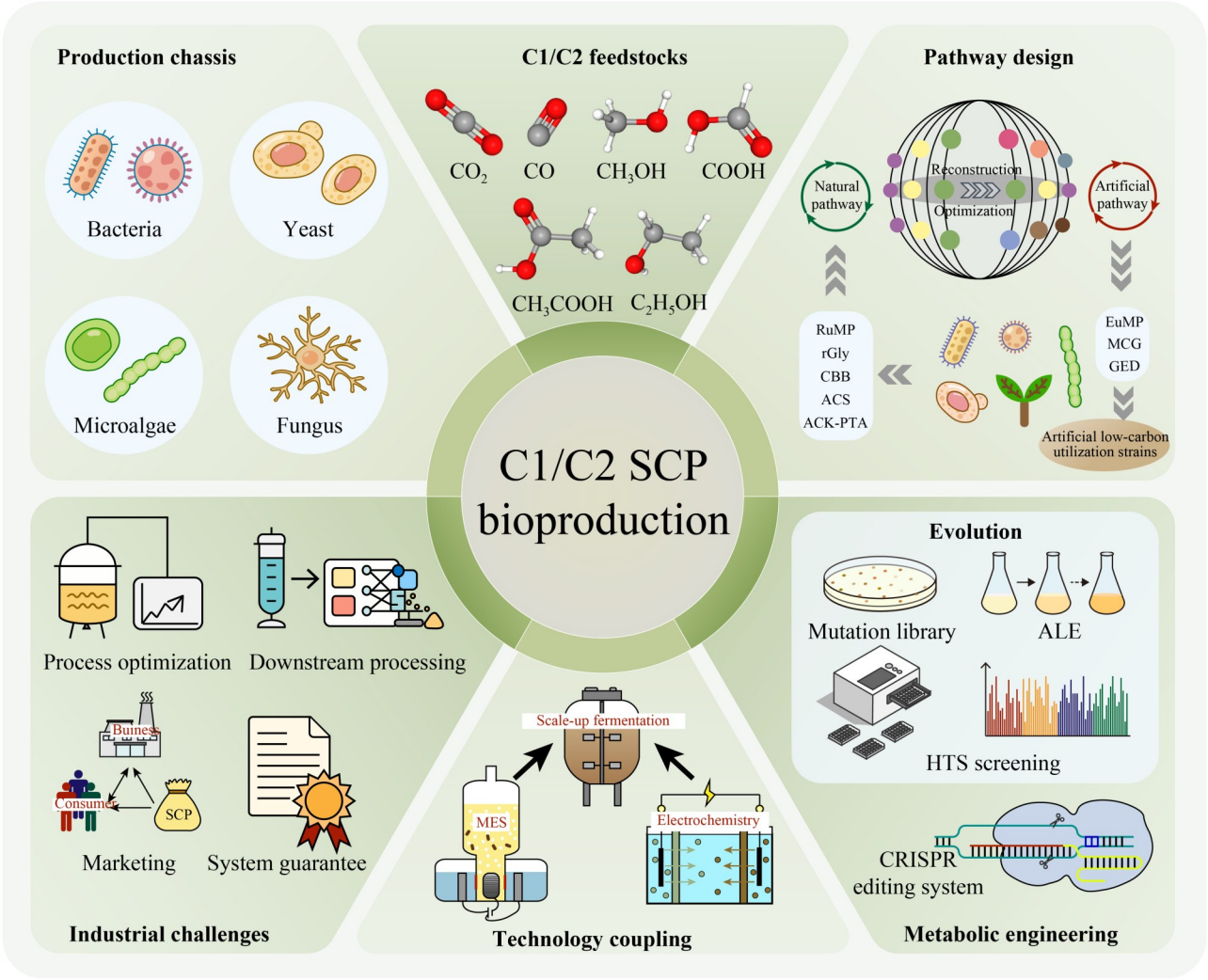

图1　C1/C2底物单细胞蛋白生产总览

Figure 1　Overview of single-cell protein production from C1/C2 feedstocks. The production of SCP from C1/C2 feedstocks is primarily achieved through the assimilation of carbon dioxide, carbon monoxide, methanol, formate, acetate, or ethanol by bacteria, yeasts, fungi, and microalgae. Metabolic engineering strategies have successfully integrated heterologous C1/C2 assimilation pathways into conventional microbial cell factories. To date, synthetic pathways with enhanced carbon assimilation efficiency and reduced energetic requirements have also been developed. The performance of these C1/C2 feedstocks SCP producers can be further augmented through evolutionary and gene-editing strategies, as well as coupling with electrochemical technologies. However, the industrialization of SCP still faces critical challenges regarding scale-up fermentation optimization, downstream processing development, regulatory approval systems, and market penetration. SCP: Single-cell protein; RuMP: Ribulose monophosphate pathway; rGly: Reductive glycine pathway; CBB: Calvin-Benson-Bassham cycle; ACS: Acetyl-CoA synthase pathway; ACK-PTA: Acetate kinase-phosphotransacetylase pathway; MES: Microbial electrosynthesis system; ALE: Adaptive lab evolution; HTS: High-throughput screening.

别出 6 个潜在的乙酸营养型微生物和 2 个低丰度甲基营养型微生物。

1.2 非天然利用 C1/C2 底物微生物底盘的设计构建

近年来，随着代谢工程与合成生物学技术的快速发展，研究团队通过异源通路引入、理性途径设计以及宿主代谢网络系统性重构，突破天然代谢边界，构建出多种能够利用 C1/C2 底物的微生物底盘菌株，进一步拓宽了 C1/C2 底物生物制造的应用范围。

在 C1 底物利用方面，早期工程策略集中于天然固碳途径或甲基营养途径的异源表达。例如卡尔文(Calvin-Benson-Bassham, CBB)循环被引入多种异养模式生物以实现 CO_2 的固定[10]；RuMP、磷酸木酮糖(xylulose monophosphate, XuMP)途径和丝氨酸循环被广泛用于构建甲醇同化微生物底盘菌株[11]。受限于高能量消耗、菌株自身调控系统复杂等问题，这些天然途径在工业应用方面存在限制。因此，近年来有大量研究转向已有途径的优化或人工 C1 途径设计。代表性策略包括优化的 CBB 循环和丝氨酸循环、苹果酰辅酶 A-甘油酸(malyl-CoA-glycerate, MCG)途径、还原甘氨酸途径(reductive glycine pathway, rGly)、去氧酮糖酸(Gnd-Entner-Doudoroff, GED)循环等[12]。这些途径在理论上具有更高的碳转化效率和更低的能量需求，并可通过模块化方式与宿主中心代谢网络耦合。此外，基于算法辅助，分析天然 C1 同化途径，结合大量生化反应数据，研究者设计出了多条基于 16 个中心反应的二氧化碳利用途径，为更高效的 C1 同化途径的构建提供了依据[13]。

在 C2 底物利用方面，研究主要基于天然乙酸和乙醇同化途径进行代谢工程改造。构建非天然乙酸同化微生物常用策略为表达乙酰辅酶 A 合成酶(acetyl-CoA synthetase, ACS)途径或 ACK-PTA 途径，强化乙酸向乙酰辅酶 A 的转化，并进一步进入乙醛酸循环和三羧酸(tricarboxylic acid, TCA)循环[14]。乙醛酸循环是 TCA 循环的一条辅助通路，为乙酸同化时中心代谢物如苹果酸、草酰乙酸的补充以及糖异生反应提供了简便且高效的策略，促进生物质形成，而 TCA 循环则用于能量和还原力的补充[15-16]。此外，乙酸还可被用作辅助碳源，与二氧化碳固定途径相结合构建混合营养体系，从而在能量供给与碳骨架补充方面实现协同优化[17]。

相较于乙酸，乙醇具有优越的能量密度，1 g 乙醇完全氧化为二氧化碳和水产生高达 0.3 mol 的 ATP，且 1 分子乙醇转化为乙酰辅酶 A 可额外产生 2 分子还原力[18]。Liang 等[19]在大肠埃希氏菌(*Escherichia coli*)中整合来自玉米迪克氏菌(*Dickeya zeae*)的乙醛脱氢酶和来自酿酒酵母(*Saccharomyces cerevisiae*)的乙醇脱氢酶，成功构建两步式异源乙醇利用途径，能够在不消耗 ATP 的前提下将乙醇转化为乙酰辅酶 A，进入后续乙醛酸循环与 TCA 循环。

2 代谢工程驱动蛋白质高效生产

尽管仅有极少部分的研究直接聚焦于利用 C1/C2 底物生产 SCP 的代谢工程优化，但基于提升 SCP 生产能力的底层逻辑，C1/C2 底物驱动的蛋白质高效生产可从提升菌株生长速率、增强细胞生物量积累与提高胞内蛋白质含量等层面协同推进。当前，通过提升微生物对 C1/C2 底物的耐受性及同化能力，在促进生长速率提升和生物量增长方面已取得显著进展；而在提高胞内蛋白质含量方面，则主要依托代谢工程对蛋白质积累过程的系统优化，并结合适应性实验室进化(adaptive lab evolution, ALE)与高通量筛选等手段加以实现。

2.1 强化 C1/C2 底物耐受能力

部分 C1/C2 底物(如甲醇、甲酸、乙酸)具有

细胞毒性，可改变细胞膜流动性、扰乱细胞内环境稳态等[20-22]。这导致在以它们为碳源生产SCP时，细胞生物量无法快速、大量积累，生产效率受到限制。突变库筛选、定向进化、组学分析等策略成为获得高耐受菌株和识别关键耐受基因靶点的主要方式。目前，这些策略已在小球藻属(*Chlorella*)、酿酒酵母(*S. cerevisiae*)、解脂耶氏酵母(*Yarrowia lipolytica*)、巴斯德毕赤酵母(*P. pastoris*)、大肠埃希氏菌(*E. coli*)、谷氨酸棒状杆菌(*Corynebacterium glutamicum*)等多种微生物的C1/C2底物耐受性提升中得到应用，并取得良好进展。表1整理了相关研究进展及识别的关键基因靶点，这些靶点有潜力被应用到具有优秀蛋白质含量表型的菌株中，以提高C1/C2底物驱动的蛋白产量。

2.2 提升C1/C2底物同化效率

2.2.1 二氧化碳

天然或人工设计的二氧化碳同化途径主要通过还原和羧化反应使二氧化碳进入中心碳代谢，但其固碳效率并不理想，且高度依赖厌氧条件以及高二氧化碳分压[53-54]。因此，有必要强化二氧化碳固定途径，挖掘更具鲁棒性的还原酶和羧化酶，或是结合计算设计与合成生物学手段构建新型人工途径，以实现在更温和条件下兼具高碳效率与高能量效率的二氧化碳固定。

甲酸脱氢酶(formate dehydrogenase, FDH)催化二氧化碳和甲酸之间的可逆反应，其中金属依赖性的FDH更倾向于催化二氧化碳生成甲酸的还原反应[55]。底物口袋宽度的提高有助于增加FDH的还原活性[56]。筛选不同来源的FDH，并对高效FDH的活性位点构建突变文库，研究团队获得具有更高二氧化碳还原活性、偏好性和催化效率的酶，使得甲酸生产速率提高5.8倍，二氧化碳-甲酸转化率高达91.0%[57-58]。同时，Nielsen等[59]详细总结了不同来源的FDH的反应效率，以及不同电子供体对二氧化碳还原反应的影响，为FDH的初步筛选提供参考。

挖掘、设计与表征高效的羧化酶为构建高效人工固碳系统奠定基础。在多种羧化酶中，烯酰辅酶A羧化酶/还原酶对氧不敏感，仅需辅因子NADPH即能实现高效二氧化碳固定[60]；巴豆酰辅酶A羧化酶/还原酶是最快的二氧化碳固定酶之一，已被用于高效人工二氧化碳体外固定[61]。通过理性设计，结合高通量液滴微流控筛选技术，一种固碳效率提升900倍的全新乙醇酰辅酶A羧化酶被成功开发[62]。进一步通过机器学习策略，该乙醇酰辅酶A羧化酶的羧化效率提升2倍、能量需求降低60.0%，从而有效缓解固碳途径热力学限制[63]。

通过计算组合模拟自然界已知的多种代谢酶反应是开发新固碳途径的有效方式。尽管预设的途径在实施方面仍面临酶在表达水平、活性、稳定性、亚细胞定位和调控层面的严峻挑战[64]，还原性途径相较于大多数羧化途径具有更低的ATP成本，更有助于生物质积累[53]。相较于目前常见的厌氧和低氧化还原电位的二氧化碳固定途径，合成的CO_2-reduction (CORE)循环能够在有氧、常压条件下高效固碳，降低生物碳减排对环境条件的严苛要求[54]。尽管现阶段已挖掘出大量高效固碳酶，但仍需进一步开发更多在碳效率、能量效率方面超越天然固碳通路的人工固碳体系。

2.2.2 甲醇

尽管甲醇同化途径已经被成功应用到多种非天然甲醇利用微生物中，但其同化效率仍远低于天然甲醇营养微生物。甲醇同化的主要瓶颈包括异源表达甲醇脱氢酶(methanol dehydrogenase, Mdh)的氧化动力学和热力学特性较差、胞内高$NADH/NAD^+$比值不利于反应进行、下游反应速率不平衡导致甲醛积累产生的细胞毒性，以及Ru5P较低的再生速率[65]。

Woolston等[66]通过同位素标记识别同化途径限速酶Mdh，通过过表达*glpX*激活七景酮糖-1,7-二磷酸酶介导的RuMP途径，结合Mdh的高通量筛选，实现甲醇同化途径的精准调控，

表1 提升菌株C1/C2底物耐受性的进化策略

Table 1 Evolution strategies for improving C1/C2 feedstock tolerance of strains

C1/C2 feedstocks	Strains	Evolution strategies	Results and achievements	References
Carbon dioxide	*Synechococcus elongatus* PCC7942	Gradient ALE from 5.0% to 20.0% CO_2	Identified potential key genes: *pbsA*, *pyk*, *dnaA*, *MutS*	[23]
	C. autoethanogenum	Chemostat ALE at 23.0% CO_2 in a bioreactor	Identified potential key genes: *perR*, *gerKA*, *prfB*, *thrB*, *argR*	[24]
	Desertifilum sp.	Gradient ALE from 5.0% to 15.0% CO_2	Increased chlorophyll a, carotenoid, and enhanced antioxidant systems contribute to CO_2 tolerance	[25]
	Nannochloropsis oceanica	Stationary and gradient ALE from 6.0% to 99.0% CO_2	Mutations tend to be directed toward light-harvesting proteins	[26]
	Cupriavidus necator	Atmospheric and room temperature plasma (ARTP) mutagenesis combined with strain screening under atmosphere of H_2:O_2:CO_2 at 7:1:1	Identified key mutations *LysS* (C437T) and key gene *gapdh*	[27]
Formic acid/ formate	*Methylorubrum extorquens* AM1	Gradient ALE from 30.0 to 90.0 mmol/L sodium formate	Identified key genes: *META1_0287*, *META1_3027*, *META1_3028*, *META1_3029*, *META1_1261*, *META1_1418*, *META1_2965*	[28]
	Y. lipolytica	Gradient ALE from 4.0% to 6.6% formate	Identified key gene *Ftl1*	[29]
	E. coli	Stationary ALE at 60.0 mmol/L formate	Identified key mutation *lacO* (G8A)	[30]
	E. coli	Stationary ALE at 90.0 mmol/L formate	Inhibition of acetate metabolism is beneficial for improving formate metabolism	[31]
	Vibrio natriegens	Gradient ALE from 20.0 to 140.0 g/L formate	Identified potential key mutations: *fumA* (A44E) and *sdhC* insertion	[32]
	Chlamydomonas reinhardtii	Gradient and stationary ALE from 50.0 to 60.0 mmol/L formate	The alleviation of formate inhibition is associated with increased carbonic anhydrase activity	[33]
	E. coli	Gradient and stationary ALE from 70.0 to 120.0 mmol/L formate	Identified potential key genes: *ptnAB* and *thrA*	[34]
	S. cerevisiae	CRISPRi library screening combined with the “Scan-o-Matic” platform	Identified key genes: *RPL33A*, *RPL30*, *RPL5*, *RPS3*, *TIF5*, *TIF34*, *TIF35*, *RVB1*, *RVB2*, *SNF2*, *SNF6*, *SWI3*, *HSF1*, *YPI1*, *SEC23*, *SEC24*, *RPT5*, *RPN8*, *RPT3*, *RPT4*, *RPN7*, *RPN12*	[35]
Methanol	*P. pastoris*	Stationary ALE at 5.0% and 7.0% methanol	Identified key genes: *PSR1* and *BFA1*	[36]
	E. coli	NTG mutagenesis combined with gradient ALE from 1.0 to 3.0 mol/L methanol	Identified key genes: *rpsL* and *rpsQ*	[20]
	Rhodotorula toruloides	Stationary ALE at 3.0% and 3.5% methanol	Carbon flux toward the biosynthesis of glycerolipid-related metabolites was regulated	[37]
	Methylobacterium extorquens	Gradient ALE from 0.5% to 2.5% methanol	Identified key mutations: *metY* (F36L, S383L) and a premature stop codon in *kefB*	[38]
	S. cerevisiae	Cyclic ALE between 0.0 and 2.0% methanol	Identified key mutation in *YGR067C* and key genes *AHD2* and *ACS1*	[39]
	P. pastoris	Gradient ALE from 6.0% to 10.0% methanol	Identified key gene *PET2*	[40]
	Corynebacterium glutamicum	Stationary ALE at 15 g/L methanol	Identified key mutations: *cgl0653* (G1256 A) and *cgl0833* (C1439T)	[41]
Acetic acid/ acetate	*Halomonas bluephagenesis*	Gradient ALE from 20.0 to 120.0 g/L acetate	Enhanced flux of the TCA cycle and poly-(3-hydroxybutyrate) biosynthesis alleviates acetate toxicity	[42]

(待续)

(续表 1)

C1/C2 feedstocks	Strains	Evolution strategies	Results and achievements	References
	S. cerevisiae	Gradient ALE from 3.0 to 12.0 g/L acetic acid	Identified key genes: *HSF1*, *SKN7*, *BAS1*, *WAR1*, *ASC1*, *GPA2*, *RAS2*, and *IRA2*	[43-44]
	Chlorella vulgaris	Gradient ALE from 30.0 to 45.0 mmol/L sodium acetate	Acetate stress simultaneously improves carotenoid accumulation and wastewater treatment efficiency	[45]
	Papiliotrema laurentii	Gradient ALE from 0.7 to 1.5 g/L sodium acetate	Identified key enzyme: glucan 1,3-β-glucosidase	[46]
	Saccharomyces pastorinous	Stationary ALE at 0.6% acetic acid	High concentrations of acetate trigger *ACS* expression	[47]
	Y. lipolytica	CRISPRi library screening	Identified key gene: *YALI1_F12842g*	[48]
	S. cerevisiae	CRISPRi/CRISPRa library screening	Analyzed mechanisms of Pdr1 and Yap1 in acetate tolerance	[49]
Ethanol	*S. cerevisiae*	Cyclic ALE with increasing ethanol shock	The evolved strain significantly accelerated wine fermentation	[50-51]
	S. cerevisiae	Cyclic ALE with increasing ethanol shock	Identified key mutations: *cyr1* (A1474T) and *usv1*Δ	[52]

甲醇同化效率提高 4 倍。Price 等[67]采用自组装策略构建同化途径的超分子酶复合物，如缩短途径酶 Mdh、3-己酮糖-6-磷酸合酶(3-hexulose-6-phosphate synthase, Hps)及 6-磷酸-3-己酮糖异构酶(D-arabino-hex-3-ulose 6-phosphate, Phi)之间的空间距离，显著提高甲醇向果糖-6-磷酸(fructose 6-phosphate, F6P)的转化效率；该研究进一步利用乳酸脱氢酶作为 NADH 清除剂，抑制甲醛的逆向还原反应，使得 F6P 含量提高 97 倍。整体调控层面，下调糖酵解途径基因 *Gap* 和 *Gpma*，上调 TCA 循环基因 *Acl*、*Mdh* 和 *Suc* 以及氨基酸生物合成途径基因 *Glt1*、*ilvB*、*AroF*、*Trp3* 等有助于平衡甲醇代谢[68]。

构建协同体系可有效推进甲醇同化反应持续进行，并缓解甲醛毒性压力。Qi 等[69]协同 rGly 途径缓解甲醛积累导致的代谢压力，甲醇利用效率提高 2.3 倍；Yuan 等[70]偶联丝氨酸循环和 RuMP 途径，甲醇消耗速率提高 13.1%，NADPH 水平提高 1.3 倍。Liu 等[71]在 *E. coli* 中整合来自肺炎克雷伯氏菌(*Klebsiella pneumoniae*)的超氧化物歧化酶和铜绿假单胞菌(*Pseudomonas aeruginosa*)的过氧化氢酶组成的活性氧解毒系统，使得甲醇同化效率提高 30 倍。

2.2.3 甲酸

天然甲酸利用微生物主要通过 Wood-Ljungdahl 途径、丝氨酸循环和 rGly 途径实现甲酸同化。其中，四氢叶酸(tetrahydrofolic acid, THF)循环是这些途径的核心模块[32]。因此，为了提供充足的 5,10-亚甲基-THF、丝氨酸和甘氨酸供给，强化甲酸-THF 连接酶以及下游 THF 循环相关酶成为提升甲酸同化效率的主要策略[32,72-74]。

也有部分研究通过优化现有途径或开发人工途径，实现非天然菌株代谢甲酸时更少的酶和能量需求、更高的中心碳代谢通量和碳转化率。如 solar formic acid/pentose (SFAP)途径耦合了二氧化碳固定与糖类分解反应，使得由甲酸氧化产生的还原当量能驱动碳同化从糖酵解途径转向戊糖磷酸途径[75]；重构的丝氨酸-三羧酸(serine-tricarboxylic acid cycle, STCA)闭合循环，使得高通量的 TCA 循环能够牵引上游丝氨酸循环和 THF 循环的碳源供应，进而增强甲酸的同化与转化能力[32]；丝氨酸-苏氨酸循环(serine-threonine cycle, STC)能将甲酸作为唯一的碳源和能源，并在常压二氧化碳的培养环境下实现菌株正常生长，提高固碳反应鲁棒性[34]；甲醛缩合酶(formolase, FLS)途径，由人工设计的新酶 FLS 将一碳碳源直接固定，并通过 5 个反应转化为三碳单元磷酸二羟丙酮汇入中心碳代谢，实现在整个反应序列中保持化学驱动力在 3.0 kcal/mol 以上，确保反应高效顺向进行[76]；

辅酶 A 合成(synthetic acetyl-CoA, SACA)途径，通过对乙醇醛合酶和乙酰磷酸合酶进行功能重塑提升碳得率至 50%，且该途径具有不依赖 ATP、对氧不敏感的显著优势[77]。此外，耦合基于甲醇代谢的能量供应模块也具有潜力被运用到构建高效甲酸同化途径中[34]。

2.2.4 乙酸

乙酸同化效率受摄取方式、同化途径选择及能量供给水平的协同制约，针对关键酶、调控因子与能量代谢进行系统性的代谢工程改造是实现乙酸高效利用与提升产物合成能力的核心策略。

大多数工业微生物能够以乙酸为单一碳源生长，通过被动扩散摄取未解离形式的乙酸，或主动运输游离的乙酸根离子摄取碳源，进一步通过 ACS 或 ACK-PTA 途径转化为乙酰辅酶 A 进入乙醛酸循环、TCA 循环以及下游反应[78]。ACS 途径对乙酸具有更高的亲和力，但是其需要消耗 2 个 ATP；而较低乙酸亲和力的 ACK-PTA 途径仅需要 1 个 ATP 即能实现乙酸至乙酰辅酶 A 的同化[79-80]。强化同化途径 ACS 和 ACK-PTA 相关酶的表达水平、实现双途径协同利用、敲除乙醛酸循环基因转录抑制因子 *iclR* 可实现乙酸转化率的大幅提升[14,80-82]。此外，可通过调节异柠檬酸裂解酶表达水平平衡乙醛酸和 TCA 循环通量，以精细调控微生物生长和生产水平[15]。能量供应是限制乙酸高效利用的最主要因素，1 分子乙酸仅产生 10 分子 ATP，因此通过过表达 *pck* 促进 ATP 再生反应、引入 *pntAB* 和 *fdh* 用于 NADPH 再生等代谢工程策略进行有效地能量补充，对于乙酸同化和产物生产至关重要[81-83]。

2.3 优化胞内蛋白质积累过程

菌体胞内蛋白质积累是全局性过程，相关研究已从多个维度开展，实现胞内蛋白质含量与质量的协同提升(图 2)。对于真菌和酵母，细胞壁的合成会消耗部分碳源。为降低碳源在非目标代谢途径中的消耗并促进碳通量向蛋白质合成方向分配，Hong 等[84]通过敲除威尼斯镰孢菌(*Fusarium venenatum*)中的细胞壁几丁质合酶 *Chs3* 基因，不仅显著提高了单细胞蛋白质含量，还使碳源转化效率提升 40.0%。在酿酒酵母(*S. cerevisiae*) 中，敲除 *TIR4*、*SBE2*、*SBE22*、*ECM25* 以弱化细胞壁合成，同样对蛋白质含量提升产生积极作用，菌株粗蛋白含量提高 21.6%[85]。类似地，Gao 等[86]在巴斯德毕赤酵母中鉴定并敲除了由细胞壁传感器激活的关键靶点 *PAS_0305*，由此引发的全局应激信号重构提高了细胞壁通透性并降低了几丁质含量，最终获得粗蛋白含量高达 67.2%、干生物质转化率 46.0% 的甲醇蛋白生产菌株。

强化含氮底物的摄取与同化过程有利于提高胞内蛋白质水平。在 Meng 等[87]的研究中，过表达谷氨酰胺合酶或谷氨酸脱氢酶被认为是一种有效提升氨基酸供给、支撑蛋白质合成并提高粗蛋白含量的策略。然而，该研究也指出，此代谢调控可能伴随生物量积累受限的风险，进而在一定程度上导致总体产量下降。通过扩大细胞体积以增强其对蛋白质的容纳与积累能力，同样被认为是一种有效策略。例如，在酿酒酵母(*S. cerevisiae*)中过表达 *GIC1* 抑制细胞骨架收缩，或敲除 *CLN3* 以延长细胞分裂的 G_1 期，均可实现细胞体积的增加，从而为蛋白质积累提供更大的细胞空间[88-89]。破坏高渗透压甘油(high osmolarity glycerol pathway, HOG)通路以减少压力诱导的代谢负担，可促使菌株成为蛋白积累偏好型菌株，粗蛋白含量提升 16.0%[85]。Lee 等[90]通过紫外随机诱变筛选的 PAN2 突变体提升了菌株翻译效率与 mRNA 稳定性，氨基酸含量提高 16.0%。此外，过表达 GCN4 以增强胞内氨基酸的可利用性，具有提升 SCP 生产的潜力，该策略被证明可使高巴斯德毕赤酵母(*P. pastoris*)重组蛋白生产水平提高 2.6 倍[91]。

支链氨基酸(branched-chain amino acids, BCAAs)是 SCP 中决定营养价值和功能特性的关键组分，其含量水平直接影响 SCP 在动物营养

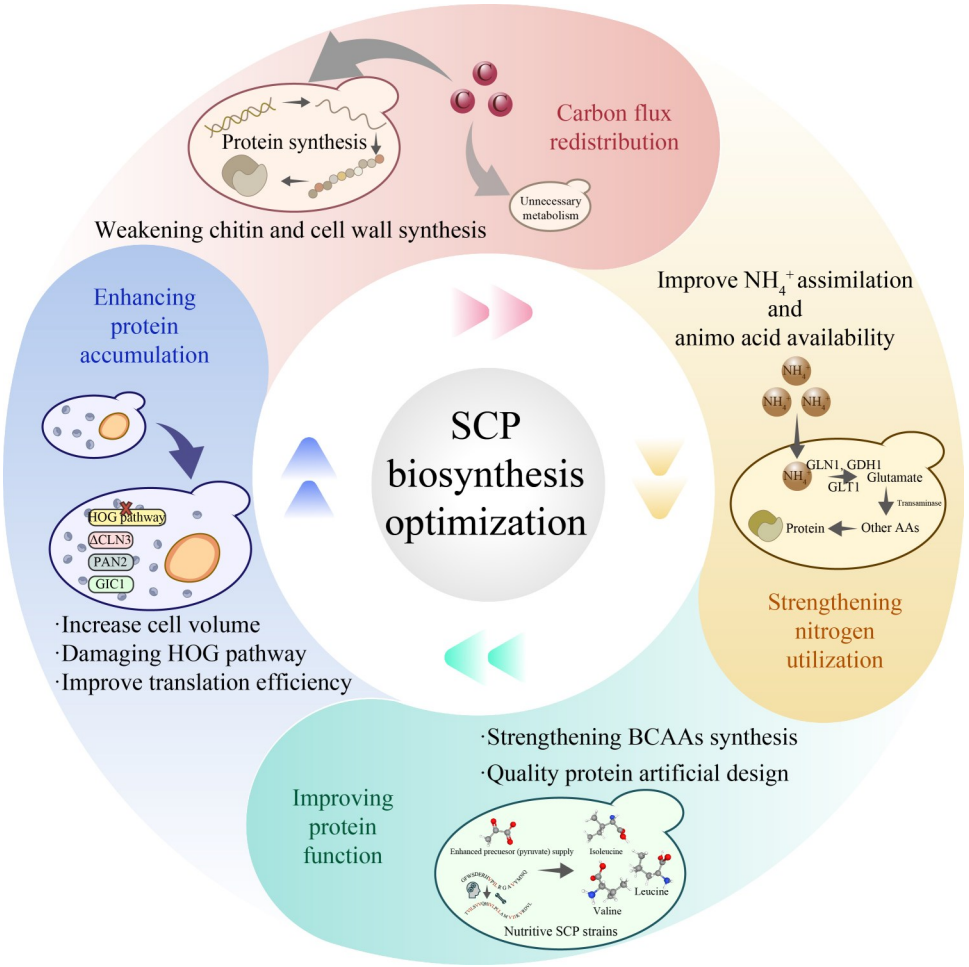

图2　优化单细胞蛋白合成的代谢工程策略

Figure 2　Metabolic engineering strategies for optimizing single-cell protein biosynthesis. In terms of carbon metabolism, redirecting carbon flux toward protein synthesis can be achieved by disrupting non-essential carbon metabolic pathways. For nitrogen metabolism, reinforcing the expression levels of key pathway enzymes and optimizing inter-amino acid conversions provide sufficient substrates for protein biosynthesis. To enhance the protein quality, promising strategies include strengthening branched-chain amino acid biosynthetic pathways or de novo designed proteins with high BCAAs content. Furthermore, global regulatory approaches, such as blocking the HOG signaling pathway, increasing cell volume, and enhancing translation efficiency can be implemented to achieve efficient protein accumulation within the strains. SCP: Single-cell protein; AA: Amino acids; HOG pathway: High-osmolarity glycerol pathway; BCAAs: Branched-chain amino acids.

和人类食品中的应用潜力。然而，天然微生物菌株中 BCAAs 的合成能力及其在胞内蛋白中的比例通常受限于代谢通量分配、反馈抑制调控及前体物质供给等多重因素。通过强化 BCAAs 前体合成途径关键酶 *Ilv3* 的表达水平，提升 α-酮异己酸、α-酮-β-甲基戊酸的供应，并结合人工设计实现高 BCAAs 比例蛋白的高水平表达，在应用中已实现 9.8 mg/100 mg 的高水平 BCAAs 积累，相比野生型菌株产量提升 26.4%[92]。此外，辅因子工程改造平衡氧化还原

反应与动态调节三羧酸循环以平衡生长和生产，也有望成为构建高 BCAAs 含量 SCP 产品的有效手段[93]。

2.4 高蛋白质菌株进化策略与高通量筛选

依赖理性代谢工程通常难以挖掘现有认知体系之外可促进 SCP 生产的关键基因靶点。相比之下，结合随机突变与适应性进化，并辅以高通量筛选和反向工程验证的方法，不仅能够获得高产菌株，还可为后续的理性工程改造以及代谢途径功能注释提供重要启示与指导。常用的进化策略包括紫外诱变、室温常压等离子体 (atmospheric and room temperature plasma, ARTP)诱变、以蛋白质合成抑制剂为压力的 ALE 等；通过全基因组测序识别突变位点并结合反向工程，已在酵母中识别出促进蛋白质合成和胞内积累的关键基因靶点 *SUT1*、*CNM67*、*PAN2*、*CCT4*，同时证实蛋白质高产菌株的翻译能力、氨基酸生物合成途径均发生显著上调[90,94-95]。

为获取优良表型菌株，需要对进化的菌群进行高效、精准的高通量筛选。然而，常用的蛋白质定量方法普遍存在效率低下的问题，存在不可避免的限速步骤。例如，凯氏定氮法中消化和蒸馏需要大量时间；二辛可酸 (bicinchoninic acid, BCA)法、考马斯亮蓝法需要提取菌体总蛋白方可定量；有机元素分析法对样品称量精度要求高，且单个样品的分析时长约为 12 min。近期，Liu 等[94]基于中心法则，提出采用 RNA 染色及流式分选技术实现高蛋白质含量菌株的高通量初步筛选，进一步对高 RNA 含量菌株完成单细胞蛋白质含量的定量，极大程度上提高筛选效率并降低人工劳动强度。

3 C1/C2 底物生产单细胞蛋白发展现状

目前，被用于 SCP 生产的 C1/C2 底物包括气态一碳化合物(二氧化碳、一氧化碳、甲烷)、液态一碳化合物(甲醇、甲酸)和二碳化合物(乙酸、乙醇)。气态一碳化合物主要来源于化石燃料燃烧、重工业生产废气、生物转化等，其在下游生产过程中面临运输复杂性以及传质障碍。相比之下，通过合成气催化氢化法、甲醇羰基化法、发酵法、电化学法等生产的液态一碳和二碳化合物在 C1/C2 底物发酵中更具优势。现阶段，各研究团队已开发多项关键技术，支撑多种微生物利用这些 C1/C2 底物生产 SCP。

3.1 气态 C1 底物生产单细胞蛋白

3.1.1 直接生物转化

微藻通过光合作用直接捕获二氧化碳用于生长，且对工业烟气具有较高的耐受性，成为被广泛用于利用二氧化碳生产 SCP 的研究对象[96]。微藻类群预估有 20 万种，其蛋白质含量通常占干物质的 40.0%–60.0%[97-98]。其中，小球藻和螺旋藻以高蛋白质含量(占 50.0% 以上细胞干重)、与世界卫生组织和联合国粮食及农业组织参考标准相近的氨基酸分布，成为常用的 SCP 生产菌种[98-99]。在利用微藻生产 SCP 时，培养基中营养素的比例、培养温度、光照强度以及 pH 对不同种类微藻的 SCP 质量具有较大的影响[100-102]。然而，微藻固有的鱼腥味与青草味，限制了其直接作为食材的接受度[103]。此外，微藻复杂的细胞壁结构可能影响蛋白质的消化性和生物利用率，因此有必要通过进一步精加工提取微藻蛋白[104]。

氢氧化细菌 (hydrogen-oxidizing bacteria, HOB)利用 H_2 作为能量来源，O_2 作为电子受体，以及 CO_2 作为碳源，展示出卓越的固碳能力[105]。其中，杀虫贪铜菌(*Cupriavidus necator*)蛋白质含量高达 70.0%，必需氨基酸含量均衡，接近鱼粉和猪肉的品质，是一种理想的 SCP 来源[106]。此外，由于 HOB 具备高效的甲烷合成能力，常被用于同步实现 SCP 和以沼气为底物的甲烷生产[107]。然而 HOB 在培养时需要通入易燃气体，同时还需要维持一定的压力以保证

充足的气体溶解度，使得控制气体分布和组成在爆炸极限内成为 HOB 高密度发酵时的核心障碍[108-109]。目前，芬兰的 Solar Foods 公司已着手推广由 HOB 生产的 Solein®蛋白产品，其蛋白质含量高达 80.0%[110]。

乙醇梭菌(*C. autoethanogenum*)是最有效固定 CO_2 和 CO 的微生物之一，可以将气态 C1 废物转化为生物燃料和化学品，如乙酸和乙醇[111]。其单细胞蛋白是一种安全有效的渔业、畜牧业替代蛋白来源，不会对养殖对象的生长表现、抗氧化和消化酶活性产生不良影响[112-114]。2021 年，中国农业科学院饲料研究所与北京首钢朗泽新能源科技股份有限公司合作，实现了 CO 到乙醇梭菌蛋白的万吨级工业化生物合成，获得我国第一张饲料原料新产品证书[115]。

甲烷氧化菌 (methane-oxidizing bacteria, MOB)可以以甲烷作为单一碳源生长，其中荚膜甲基球菌(*M. capsulatus*)在工业上常用于 SCP 生产，蛋白质含量通常在 70.0% 以上[116-117]。由于 MOB 单一菌种生长较慢，与小球藻属(*Chlorella*)、短芽孢杆菌属(*Brevibacillus*)、罗尔斯通氏菌属(*Ralstonia*)等微生物构建的共培养体系，既不影响 MOB 的甲烷代谢，还能提升生物量的积累浓度，成为甲烷 SCP 生产的新思路[118-120]。

3.1.2 间接与电化学耦合转化

由于气态底物存在传质、同化效率低等瓶颈，研究团队融合多学科技术，在间接一碳利用模式下，通过偶联产乙酸菌和微生物电合成系统(microbial electrosynthesis, MES)已实现二氧化碳 SCP 的高效生产。不同的是，产乙酸菌并不直接作为 SCP 生产者，而是通过 MES 在两阶段发酵过程中同化二氧化碳产生乙酸，为第二阶段 SCP 生产提供二碳碳源。例如 Molitor 等[121]开发的两阶段生物处理系统：第一阶段通过电解水提供氢气作为电子供体，使产乙酸菌在厌氧条件下固定二氧化碳产生乙酸盐作为中间代谢产物，用于第二阶段有氧培养酵母或真菌，实现了 25.0% 的碳源转化率；Pan 等[122]开发了类似的一阶段二氧化碳-乙酸转化策略，在二阶段生产产碱菌属(*Alcaligenes*) SCP，该研究利用中空纤维膜实现反应器之间无细胞培养基的循环利用。不同于二阶段发酵的异位生产，也有研究报道通过微生物电化学电池和微生物燃料电池的间歇运行，利用二氧化碳原位同时实现废水中化学需氧量(chemical oxygen demand, COD)和氨氮去除，以及杀虫贪铜菌(*C. necator*) H16 的 SCP 生产[123]。

除 MES 外，类似的间接策略还可以通过偶联电化学系统实现多种一碳 SCP 的生产。混合生物无机电合成系统 (bioinorganic electrosynthesis system, BIES)利用可再生能源提供还原力实现二氧化碳到甲烷的转化，进而支撑 MOB 的 SCP 生产[124]。类似地，通过 BIES，丹麦技术大学张翼峰团队实现甲烷和二氧化碳到 SCP 高达 70.7% 的发酵效率[125]。中国科学院天津工业生物技术研究所张玲玲团队设计的 Cu/Cu_2O 电催化剂，实现了二氧化碳还原到甲酸模块和甲酸同化模块的耦合，形成一个集成的电驱动二氧化碳 SCP 转化系统，其中电能转化效率达到 9.2%[126]。类似地，通过金属-有机框架的铜基催化剂 c-Cu-MOF 实现将二氧化碳转化为乙醇，用于酿酒酵母(*S. cerevisiae*) SCP 生产，已实现 4.8 g/L 的生物量积累[88]。这些策略均为电能驱动二氧化碳生物转化和生物制造提供了有前景的思路。

3.2 液态 C1/C2 底物生产单细胞蛋白

3.2.1 甲醇蛋白

甲醇是理想的一碳碳源，其获取成本低、易于运输，且具有高度还原性，能为微生物生长代谢提供充足的还原力，有助于微生物合成蛋白质[87,127]。

早在 1986 年，甲醇便被 PRUTEEN 工厂用于嗜甲基菌属(*Methylophilus*)生产高蛋白含量饲料添加剂[128]。2001 年，左雅慧等[129]从土壤中分离出一株具有极高甲醇同化能力的菌株，该

菌株粗蛋白含量高达 80.9%，甲醇转化率达 41.5%，在 SCP 生产领域具备较大应用潜力。截至目前，已有多种微生物实现以甲醇为单一碳源生产 SCP。巴斯德毕赤酵母(*P. pastoris*)具备天然甲醇同化能力，在 33 ℃中试补料发酵中实现 63.4 g/L 生物质积累，甲醇-干生物质转化率达 43.0%，且菌体富含必需氨基酸[87]。嗜有机物甲基杆菌(*Methylobacterium organophilum*)的蛋白质含量约为 54.1%，拥有天然类胡萝卜素合成途径，在饲料行业中可用于制备功能性蛋白补充剂[130]。Shi 等[4]从中国天津市空港经济区周边的土壤、污泥和树叶样品中，分离得到嗜甲基菌(*Methylophilus* sp.) HN238，其必需氨基酸与总氨基酸的比例达 44.1%，超过 WHO 规定的理想蛋白标准，且该菌株与商业化 SCP 饲料产品 PRUTEEN 对猪生长表现的影响相当。

3.2.2 甲酸蛋白

近年来，发展甲酸生物经济已成为生物制造领域的新趋势，但现阶段针对天然甲酸代谢微生物生产 SCP 的相关研究仍较少。2022 年，Tong 等[131]首次报道了由甲酸合成 SCP 的技术，该团队从土壤中分离出普通副球菌(*Paracoccus communis*) MA5 菌株，通过基因组学和转录组学表征其在不同氮源、不同甲酸浓度培养条件下的 SCP 合成机制，为甲酸 SCP 生产提供了理论基础。该团队与 Cui 等[126]进一步合作，通过偶联电化学技术使普通副球菌(*P. communis*) MA5 以甲酸为单一碳源实现 2.6 g/L 生物量积累，菌体蛋白质含量达 45%。类似地，刘兆鹏[132]制备出稳定高效的双功能催化剂 Cu-Bi-O_{300}，可将二氧化碳还原生成甲酸，用于 HOB 混合菌群的 SCP 电化学生产，最终生物量达到 10.5 g/L。此外，Liu 等[133]提出一种绿色集成工艺，使粘红酵母(*Rhodotorula glutinis*) As2.703 选择性利用琥珀酸发酵液中的甲酸和乙酸生产富含脂质和类胡萝卜素的 SCP，实现发酵液的原位二次利用。然而，这些研究成果相较于甲醇蛋白，在生物量积累和蛋白质含量方面仍存在一定差距。后续研究中，科研团队仍有充足空间开发并构建安全稳定、效能优异的甲酸 SCP 合成生产菌株。

3.2.3 乙酸蛋白

许多微生物拥有天然的二碳代谢途径，如利用乙酸的 ACS 途径和 PTA-ACKA 途径，以及利用乙醇的 Ada-Adh2 途径等[19,134]。因此相较于一碳碳源，二碳碳源更易被微生物摄取和利用。

工业上通过甲醇羰基化法生产的纯乙酸，在精馏、除杂工艺上成本较高，进一步推高了乙酸 SCP 的整体生产成本。通过厌氧消化工业废水获取乙酸、原位利用发酵液中的乙酸副产物，或是直接利用工业废乙酸，成为二碳 SCP 生产降本增效的主要手段，目前上述方法已分别实现酿酒酵母(*S. cerevisiae*)、粘红酵母(*R. glutinis*)、产碱菌属(*Alcaligenes*)等的废乙酸 SCP 生产，菌体蛋白质含量分别达到 59.9%、53.1% 和 80.0%[133,135-136]。然而，受限于乙酸回收率低、废乙酸浓度不足的问题，体系生物质积累水平仍较低，最高不超过 15.2 g/L。为进一步探索更环保、可持续的乙酸供应策略，已有多个研究团队开发出从一碳气体出发，通过电化学或两阶段生物合成策略生产乙酸，再用于下游细菌、酵母或真菌 SCP 生产的技术。本文 3.1.2 节已对相关技术进行总结，此处不再赘述。

3.2.4 乙醇蛋白

与同化乙酸需要消耗 ATP 不同，乙醇转化为乙酰辅酶 A 的过程中可同步生成 NADH，且其能量密度高于葡萄糖，这使得乙醇在过去十年中被广泛用于生产塑料制品、化学品和重组蛋白[18]。尽管早在 1979 年，Watteeuw 等[137]就提出了产朊假丝酵母(*Candida utilis*)利用乙醇补料发酵生产 SCP 的潜力，1996 年 Yech[138]也证实了红酵母属(*Rhodotorula*)的乙醇 SCP 生产潜力，但目前利用乙醇生产 SCP 的相关研究仍十分有限。近期有研究报道，通过 MES 技术结合铜离子诱导系统可实现 3.0 g/L 的酿酒酵母(*S.*

cerevisiae) SCP 产量[88]。

微生物利用乙醇积累生物质可实现 11.0−13.0 g/(L·h)的生产强度，尽管该荟萃分析涉及的研究更关注微生物利用乙醇的生长表征或其他产物合成，而非专门针对 SCP 生产，但仍指明了乙醇在循环、可持续蛋白质生产系统中的重要作用[139]。此外，Almeida Benalcáza 等[140]通过模型结构模拟，分析了乙醇用于工业化 SCP 纯氧发酵的技术可行性，为正式生产前的发酵工艺参数调试提供了有力的模型支撑。

3.3 C1/C2 底物生产单细胞蛋白产业化进程

随着全球蛋白质需求持续增长与碳减排压力不断加大，以 C1/C2 化合物为原料的 SCP 产业化进程已呈现多元化格局，充分践行“不与人争粮、不与粮争地”的可持续发展理念。表 2 对相关代表性案例进行总结和比较。

在二氧化碳 SCP 领域，芬兰 Solar Foods、美国 NovoNutrients 以及荷兰 Aerbio 等企业正推动二氧化碳气体发酵技术向食品级应用转型，

表2 代表性C1/C2底物SCP产业化项目对比

Table 2 Comparation of representative industrialization projects for SCP from C1/C2 feedstocks

Enterprise	Chassis	Carbon source	Productivity	Product application	Current status	Advantages
Shougang Lanzatech	*C. autoethanogenum*	CO	Current: 25 000 t/a	Feed protein	Obtained the certificate of new feed approval Achieve industrialized replication and rollout in Hebei, Ningxia, and Guizhou	Low cost: utilizing industrial waste gas as feeding
GTL Biotech	*Y. lipolytica*	CO_2	Current: 10 000 t/a Factory under construction: 300 000 t/a	Feed protein	Obtained the certificate of new feed approval Completed the industrial-scale trial production	Electrocatalytic carbon fixation coupled with high-density fermentation
Aerbio	HOB	CO_2	Current: 2.4 t/a Factory under construction: 100 000 t/a	Feed protein & pet food	Completed EU feed ingredient registration Conduct applied research on feed formulation in collaboration with BioMar The pilot production line has commenced continuous commercial operation	One-step anaerobic fermentation Zero carbon footprint
Solar Foods	HOB	CO_2	Current: 160 t/a Factory under construction: 6 400 t/a	Functional foods & everyday foods	The product has obtained novel food approval in Singapore and Generally Recognized as Safe (GRAS) certification in the United States	Good food processing properties
JingFuture Biotechnology	*P. pastoris*	Methanol	Current: 10 000 t/a Factory under construction: 200 000 t/a	Feed protein	The demonstration line is operating stably	High-density fermentation

其中 Aerbio 公司的“Proton™”产品后续规划的商业设施年产能预计达到 10 万 t[141]。吉态来博(北京)生物科技发展有限公司于 2025 年获得我国首张以二氧化碳为主要碳源的饲料原料证书，已在内蒙古建成百吨级解脂耶氏酵母(*Y. lipolytica*) SCP 示范装置[142]。我国一氧化碳发酵技术较为成熟，北京首钢朗泽科技股份有限公司已建成全球规模最大的一氧化碳蛋白产业化生产装置，年产饲料蛋白达 2.5 万 t，处于国际领先水平[143]。甲烷蛋白方面，恺迪苏(重庆)有限公司建成全球首个荚膜甲基球菌(*M. capsulatus*)蛋白“斐康蛋白”规模化生产基地，年产能达到 2 万 t[144]；丹麦 Unibio 公司依托独创的 U-Loop 生产装置，实现 Uniprotein®蛋白的高效转化[145]。甲醇蛋白领域，早在 1979 年，英国 ICI 公司已实现年产 5 万 t 的生产规模，后续因成本等问题停产[146]。2012 年，义煤集团依托自主技术建成的甲醇蛋白 U-GAS 气化装置系统，成功完成中试联动试车，打破了俄罗斯、英国在该领域的技术垄断[147]；2024 年，中国科学院天津工业生物技术研究所联合北京竞未来生物科技有限公司、陕西延长石油榆林凯越煤化有限责任公司启动建设年产 10 万 t 级甲醇碳源酵母蛋白细胞工厂[148]；2026 年，伊犁川宁生物技术股份有限公司已获得甲醇蛋白中试结果，并完成下游客户对接[149]。然而，受市场接受度等因素制约，近年来甲醇蛋白未实现大规模商业化供应，多数项目仍处于技术储备阶段。例如，铁岭碳循环生物科技有限公司于 2025 年 10 月完成绿色甲醇蛋白项目备案，预计年产甲醇蛋白 9.2 万 t[150]。类似地，乙酸蛋白同样处于技术布局阶段，已公开信息包括伊犁川宁生物技术股份有限公司的乙酸单细胞蛋白生产底盘开发工作，以及上海振世能源科技有限公司 2023 年公布的乙酸单细胞蛋白生产装置专利[151-152]。

4 总结与展望

C1/C2 底物 SCP 产品在缓解蛋白质资源短缺和实现非粮生物制造方面具有重要潜力。受制于菌株性能、代谢与能量效率、规模化生产以及法规准入等多重挑战，C1/C2 底物 SCP 产业化进程仍面临多方面技术瓶颈。

部分 C1/C2 底物存在毒性，会抑制微生物生长与蛋白质合成，菌株改造需要兼顾胁迫耐受、生长速率、蛋白质含量三者之间的平衡。目前可用于提升胞内蛋白质含量的代谢工程策略仍较为有限，高效精准的高通量筛选方法欠缺，同时蛋白质合成过程中较高的 ATP 和还原力需求，与 C1/C2 底物能量密度不足之间存在固有失衡，使得高蛋白质含量生产菌株的开发仍面临显著挑战。现阶段仅有极少数研究聚焦于通过代谢工程策略实现 C1/C2 底物 SCP 的高效生产，未来可进一步挖掘 C1/C2 碳源代谢过程中有助于胞内蛋白质定向积累的关键功能靶点。

氮源作为 SCP 生产的另一核心底物，在决定菌体生长速率、生物量积累与蛋白质含量等方面起到关键作用，也是提升 SCP 产量与品质的核心调控因素。合理优化氮源组成、碳氮比及供给策略可保障菌体高效增殖，提升粗蛋白含量和必需氨基酸等核心营养指标，同时降低生产成本、减少富营养废水排放。未来研究可重点关注低成本、可再生氮源及精准氮源补料技术的研发。

规模化生产过程中，高密度发酵气液传质效率受限、发酵过程控制烦琐、下游加工工艺复杂，加之从小试到正式生产的未知放大效应，进一步增加了 SCP 产品商业化生产的难度。生产成本层面，精制 C1/C2 底物价格波动空间有限，结合碳源转化率综合测算，其投入产出比相较于葡萄糖底物暂无显著优势，后续应将化工行业的粗产品纳入 C1/C2 底物 SCP 技术开发的考量范畴，从源头降低原料成本。此外，SCP 产品下游加工中的细胞壁脱除、核酸含量控制、干燥等工艺的能耗与成本也需进一步优化。

法规准入方面，现阶段 SCP 纳入新食品或

饲料原料监管体系，面临严格且周期较长的安全性评估。不同国家和地区在适用标准和允许应用范围上存在显著差异，针对基因编辑 SCP 产品的差异化监管要求，在一定程度上限制了其推广应用。在相关政策体系上，美国采用产品导向监管逻辑，依托美国食品药品监督管理局的 GRAS 认证体系，终产品不含外源 DNA 即可获得监管豁免，审批效率较高；中国、欧盟采用过程导向监管逻辑，着重关注生产过程中是否使用基因工程技术。目前我国实行农业转基因生物安全评价、新食品原料申报的双轨审批机制，现有政策正探索简化无外源 DNA 的基因编辑微生物的审批流程。此外，公众长期以来对转基因食品存在排斥心理，对合成生物技术来源食品普遍存在“非天然”的审视态度。消费者的敏感度极易影响供应链各环节的衔接，导致下游企业出于品牌形象考量，不愿主动选择新型食品原料。因此，在严格保障食品和饲料安全的前提下，搭建专项评估框架，简化和标准化新菌株、新底物及新工艺的审批流程，引导正向舆论、提升公众科学认知，可为 SCP 从实验室走向产业化生产提供完善的制度保障。

展望未来，结合人工智能技术，设计高效 C1/C2 底物同化途径、重构偏好胞内蛋白质积累的代谢网络、开发可定制氨基酸比例的膳食营养菌株是 SCP 微生物底盘设计构建的核心方向。构建电能、化学能等多能互补的杂合能量供应体系是提高 SCP 合成效率的潜在路径。系统整合高通量进化筛选与理性代谢工程、开发智能发酵工艺、推动发酵与分离过程的一体化设计，结合配套政策与法规的保障，有望实现低成本 SCP 的大规模可持续制造，从而重塑我国蛋白质供给格局，为粮食安全与碳中和目标贡献中国方案。

作者声明不存在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。

作者贡献声明

邱靖：提出概念，撰写文章，编辑、修改；王钦宏、戴宗杰：获取基金，提出概念，审阅与修改；马延和：总体思路指导。

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