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Review 综述

微生物衍生物在细胞精准营养中的调控作用研究进展

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摘　要：传统细胞培养依赖血清，但血清存在成分不明确、成本高昂、具有污染风险等问题。微生物衍生物来源清晰、成本低廉、成分安全及促增殖效果明确，成为替代血清的理想选择。为开发适用于细胞农业生产的培养基提供新资源参考依据，本文首先总结微生物衍生物的制备工艺对无血清培养基研发的影响，进而阐述其在细胞农业中的应用现状，最后深入解析微生物衍生物在提供细胞精准营养、促进细胞增殖中的作用机制，以期为细胞培养摆脱血清依赖、推动细胞精准营养体系构建及细胞农业的发展提供新的技术支撑。

关键词：微生物衍生物；细胞培养；精准营养；细胞增殖；制备工艺

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Research progress in the regulatory effects of microbial-derived additives on cellular precision nutrition

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Abstract: Conventional cell culture relies on serum, which has the problems of unclear composition, high cost, and contamination risks. Microbial-derived additives, with clear sources, low costs, safe components, and obvious pro-proliferative effects, have become an ideal alternative to serum in cell culture. To provide a basis for the development of new sources for the culture media of cells in agricultural production, this review first summarizes the role of microbial-derived additives in the research and development of serum-free media, and then elaborates on the application status of microbial-derived additives in cellular agriculture. On this basis, it probes into the mechanisms through which microbial-derived additives provide precision nutrition and promote cell proliferation. This review aims to provide technical support for the research and development of serum-free culture media, the establishment of cellular precision nutrition, and the sustainable development of cellular agriculture.

Keywords: microbial-derived additives; cell culture; precision nutrition; cell proliferation; preparation process

细胞农业(cellular agriculture, CA)已成为全球范围内新兴且发展势头迅猛的领域，其核心技术是细胞培养[1]。营养供给是传统细胞培养的基础，其中胎牛血清(fetal bovine serum, FBS)因富含激素、生长因子及各类营养物质，能模拟细胞在体内的生长环境并促进细胞增殖，是目前细胞培养体系中的核心成分[2-3]。然而，FBS存在成分复杂、成本昂贵、批次间成分差异大、易引入污染物，以及动物福利等固有缺陷，阻碍了CA产品的大规模生产应用[3-5]。

为了解决FBS依赖所带来的技术与产业化瓶颈问题，近年来研究者逐步开发了各类血清替代物，用以满足CA生产中高效、稳定、安全以及无伦理争议的产品需求。目前主流的血清替代品主要包括动物源衍生物和植物源衍生物。动物源衍生物以人血小板裂解物(human platelet lysate, HPL)为代表，其通过对人类血小板进行裂解制备，富含与FBS类似的生长因子和营养成分。在间充质干细胞、免疫细胞等培养中，HPL展现出优异的促增殖效果，且具有较高的生物相容性与细胞适配性[6]。然而，这类替代物仍存在显著局限：一方面，其制备依赖血液资源，来源受限且成本高昂，难以满足大规模产业化需求；另一方面，存在传播病原微生物的

潜在风险，且需严格控制批次差异，质量控制难度较大[7]。植物源衍生物是另一类重要的血清替代选择，主要包括大豆水解物、豌豆水解物、小麦提取物等，这类替代物通过酶解或物理方法从植物原料中获取氨基酸、多肽及少量生物活性物质[8]，其核心优势在于来源广泛、成本低廉、无动物伦理争议，且能有效规避动物源病原体污染风险。植物源衍生物的应用同样面临挑战：植物原料易受种植环境、农药残留等因素影响，导致产物批次稳定性不足；部分植物成分(如植酸、凝集素等)可能对细胞生长产生抑制作用[9]。

上述 2 类替代物虽然在减少 FBS 依赖方面取得了一定进展，但均未能同时兼顾成分明确性、批次稳定性、规模化生产可行性及高效促增殖活性等多重需求。这一困境促使细胞培养营养供给理念向精准化方向升级，即不再依赖复杂的天然提取物，而是根据不同细胞类型的代谢特征与生长需求，系统解析并定制核心营养成分，实现培养体系的效率最大化、成分明确化及安全标准化[10]。

微生物源衍生物恰好契合这一精准化发展需求。源于真菌、细菌和微藻的微生物衍生物，既规避了动物源衍生物的安全及伦理风险，又克服了植物源衍生物制备周期长、批次稳定性不佳的问题，不仅来源清晰，而且可通过发酵工艺实现规模化量产[11]。更重要的是，通过调控菌种选育、发酵参数及提取工艺微生物衍生物可实现营养成分的定向调控与精准匹配，为无血清培养基的定制化开发提供了理想原料[12]。

为了推动微生物源衍生物在细胞培养中的创新应用，本文归纳了目前已知具有促进细胞增殖作用的微生物衍生物，并解析这些微生物衍生物促进细胞增殖的作用机制。在此基础上，本综述总结了微生物衍生物的关键制备流程，并且比较了不同制备工艺对微生物衍生物促细胞增殖效应的影响。通过对微生物衍生物在细胞精准营养中的调控作用进行系统综述，以期为开发能支撑 CA 高质量发展的无血清培养基提供全新的解决方案。

1 微生物衍生物的制备工艺对无血清培养基研发的影响

微生物衍生物是一类来源于微生物，通过可控的加工工艺制备获得的复杂混合物。微生物衍生物的制备工艺直接决定其活性成分的保留、含量与生物活性，进而影响其在无血清培养基中的应用效果与产业化前景。根据其制备工艺，目前可用于细胞培养的微生物衍生物分为 3 种类型：无细胞上清液(cell-free supernatant, CFS)、菌体裂解物和菌体水解物[13]。CFS 富含微生物分泌的活性代谢物，其功能侧重于细胞通路的精准调控；菌体裂解物因包含全部胞内组分，能模拟完整的胞内微环境，提供广泛而全面的支持；菌体水解物则以小分子肽和氨基酸为主，充当高效营养底物，直接驱动细胞生物合成。通过精准控制工艺路径定向获得目标形态的衍生物，从而实现对细胞培养功能的设计和调控。

目前，微生物衍生物的制备过程包括菌种活化、发酵生产与提取纯化。制备这些微生物衍生物的主要方法如图 1 所示。其中，对微生物衍生物促增殖效应影响最明显的制备过程是提取与分离。在微生物衍生物的提取过程中，目前产业中常用的技术包括超临界 CO_2 提取(supercritical carbon dioxide extraction, SCDE)、亚临界水提取(subcritical water extraction, SWE)等现代提取技术；而在纯化过程中，产业链中最常用的技术是膜过滤、色谱分离等纯化技术。这些技术的应用，能最大限度保留微生物衍生物中对细胞生长至关重要的关键生物活性化合物，与细胞无血清培养基的配方设计、批次稳定性、规模化生产密切相关，从而为生物技术领域相关应用的产品安全性与质量稳定性提供可靠保障[14-15]。

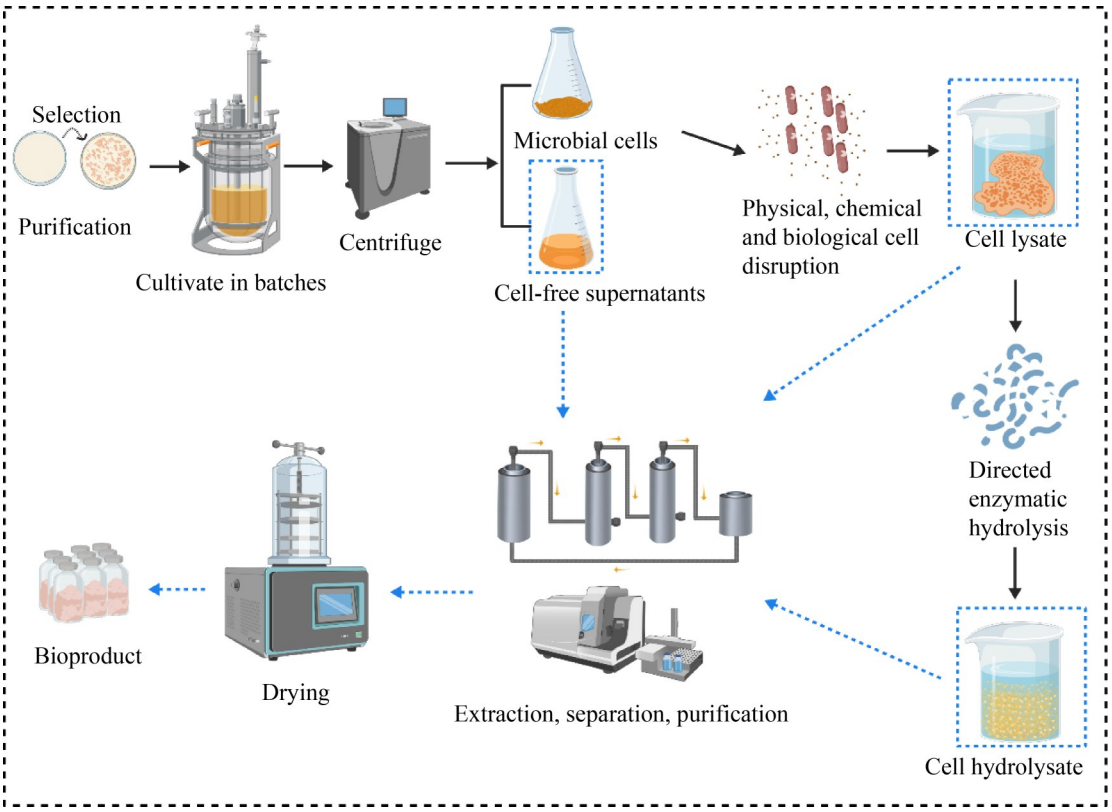


图1　微生物衍生物制备的工艺流程示意图

Figure 1　Schematic diagram of the preparation process of microbial-derived additives. Created with BioGDP.com.

1.1　微生物衍生物的制备方式及其在无血清培养基研发中的应用

目前，通过不同制备方式获得的微生物衍生物也有所不同，主要包括 CFS、菌体裂解物以及菌体水解物。CFS 主要通过离心技术将含有代谢活性产物的上清液与菌体分离，得到粗上清液；菌体裂解物的制备核心在于通过物理、化学、生物方法实现菌体的高效破壁；菌体裂解后，利用酶法进一步水解即可得到菌体水解物。不同制备方式获取的微生物衍生物蕴含的营养因子各不相同，因此在无血清培养基配方研发中可针对性减少某些营养因子的添加量，与微生物衍生物形成营养互补，实现细胞的精准营养供给。

1.1.1　无细胞上清液(CFS)

CFS 指微生物发酵结束后，通过离心或过滤等方法去除菌体后得到的澄清液体部分，不含胞内物质，主要为微生物分泌型代谢物，如多糖、有机酸、功能性蛋白等[13]。

CFS 通常具有明确的信号通路调控功能，如免疫调节、抗炎、抗凋亡等，可用于细胞功能的精准调控。Lee 等[16]研究发现，罗伊特氏黏液乳杆菌(*Limosilactobacillus reuteri*) DS0384 的 CFS 中代谢物 *N*-氨基甲酰谷氨酸不仅能显著促进肠干细胞生长，还可保护由干扰素-γ (interferon-γ, IFN-γ)与肿瘤坏死因子 α (tumor necrosis factor-α, TNF-α)共同诱导的肠类器官炎症反应。含丁酸盐的丁酸梭菌 CFS 处理 Caco-2 细胞时可通过上调肝素结合表皮生长因子

(heparin-binding epidermal growth factor, HB-EGF)与双调蛋白(amphiregulin, AREG)的表达活化肠上皮细胞表皮生长因子受体(epidermal growth factor receptor, EGFR)信号通路，进而实现肠屏障保护并缓解葡聚糖硫酸钠(dextran sulfate sodium, DSS)诱导的实验性结肠炎[17]。此外，嗜酸乳杆菌(*Lactobacillus acidophilus*)的CFS能诱导肿瘤坏死因子的表达与分泌，促进免疫细胞增殖，同时加速血管生成[18]。发酵粘液乳杆菌(*Limosilactobacillus fermentum*)上清液中含高浓度的烟酰胺，其可以通过降低活性氧(reactive oxygen species, ROS)水平、稳定线粒体膜电位和增加NAD/NADH比率来保护细胞免受氧化损伤[19]。

与菌体裂解物和菌体水解物相比，CFS的制备工艺相对简单，主要涉及固液分离，活性成分功能明确，易于进行机理研究和靶向应用，不含菌体碎片与复杂胞内物质，成分背景相对清晰，下游纯化目标明确。然而其产量受限于微生物的分泌能力无法获取具有重要功能的胞内物质，上清中活性成分浓度可能不高，且稳定性易受发酵条件和储存影响。

1.1.2 菌体裂解物

菌体裂解物指通过物理、化学、生物方法将微生物菌体细胞打破、裂解，使其内部物质释放出来，但不进行深度水解所得到的混合物，成分最复杂，包含所有胞内物质，如蛋白质、肽、核酸、糖、脂等[13]。目前常用的物理破碎技术有高压均质、超声、微波、珠磨、冷等离子体、脉冲电场和水力空化[20-21]以及蒸汽蒸馏[22]，而化学方法主要包括酸碱法[23]和离子液体法[24]，细胞破碎的生物方法主要是酶解与自溶[25]。

物理破碎法通用性强、效率高、易于放大，尤其是高压均质和珠磨[26-27]，且多数不引入外源化学物质，产物纯净。例如，使用高压均质对小球藻进行细胞破碎，破碎率达到99.9%，提取水不溶性蛋白的含量为(2.2±0.1) g/100 g[28-29]；利用珠磨法对啤酒酵母进行裂解提取β-葡聚糖，酵母破碎率可达99.8%，提取β-葡聚糖含量为78.53%[30]。此外，部分物理技术(如脉冲电场、冷等离子体)对热敏物质较友好，能较好保留活性[31]，如使用脉冲电场技术破碎钝顶螺旋藻(*Arthrospira platensis*)提取热敏性物质C-藻蓝蛋白(c-phycocyanin, C-PC)，钝顶螺旋藻细胞破碎率可达85%，C-PC提取产量为115 mg/g DW[32]。然而，物理技术能耗通常较高，某些技术如超声、微波、蒸汽蒸馏等还可能产生局部高温，导致热敏成分失活[33]。

化学法操作相对简单，成本较低，破碎效率高[34]，如利用盐酸破坏雨生红球藻(*Haematococcus pluvialis*)细胞，可使虾青素提取率达到(99.00±0.48)%[35]。然而其环境友好性差，易产生化学废物，需额外去除，且极易导致蛋白质变性、维生素破坏等[36]。

生物法条件温和，适中的温度及pH能最大程度保护生物活性物质，且选择性高，可根据细胞壁成分选择特异性酶[37]。如可以利用壳聚糖酶和溶菌酶共同作用于小球藻细胞壁[37]；通过β-1,3-葡聚糖酶和蛋白酶组合对雨生红球藻(*Haematococcus pluvialis*)进行细胞破壁，实现了类胡萝卜素最高83.9%的可提取率[38]。然而，酶成本高，大规模应用经济性待提升，且反应时间较长，可能存在外源酶残留问题，增加纯化负担[39]。

选择裂解物制备方法时需在破碎效率、活性保全、产物纯度、成本及规模化可行性之间进行权衡。对于高附加值、对活性保全要求严格的产物，温和的物理法(如脉冲电场)或生物法是优选；而对于大规模、对成本敏感的工业制备，高压均质等高效物理法仍是主流，但需注意其对热敏成分的潜在影响。

菌体裂解物营养全面，成分复杂，功能多样，可模拟细胞生长微环境，尤其适用于支持初始接种、干细胞维持或机制不明确的复杂培养体系。微藻裂解物中提取的岩藻黄素具强效

抗炎与抗氧化活性，可淬灭活性氧、提升内源性抗氧化酶活性、上调 Nrf2，同时抑制核因子 κB (nuclear factor kappa-B, NF-κB)与丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK)通路，减少促炎介质产生[40-41]；贝莱斯芽孢杆菌(*Bacillus velezensis*) Kh2-2 裂解物可通过上调 NF-κB 和 MAPK 信号通路、促进免疫相关细胞因子分泌实现巨噬细胞的免疫激活，体外实验中该裂解物可诱导脾细胞产生白细胞介素-2 (interleukin-2, IL-2)和 IFN-γ，抑制 IL-10 表达，从而促进脾细胞增殖并诱导 Th1 型免疫应答极化[42]；低血清培养条件下，小球藻裂解物可促进中国仓鼠卵巢(Chinese hamster ovary, CHO)细胞与间充质干细胞(mesenchymal stem cells, MSC)生长，该效果在 2D、3D 2 种培养模式中均能实现，最长培养周期达 21 d[43]。

与 CFS 相比，菌体裂解物集成了微生物全部胞内活性物质，能提供协同的营养支持和生物信号，完美模拟细胞生长的天然微环境。与水解物相比，菌体裂解物避免了深度酶解对蛋白质等大分子高级结构的破坏，能保留许多依赖完整结构的生物活性。当细胞培养(如某些原代细胞、干细胞)的确切需求未知时，其“全谱”支持特性通常比成分明确但单一的添加物更有效。

尽管菌体裂解物在模拟天然微环境与保留完整生物活性方面展现出显著优势，但其复杂的组分同时也为研究和应用带来了多重挑战。菌体裂解物含有大量未知或功能不明确的物质，可能包含核酸、细胞膜碎片等潜在干扰物，给作用机理研究、产品质量控制和标准化带来巨大挑战；可能含有内毒素、宿主细胞 DNA、蛋白酶等对培养细胞不利的成分，存在引入污染或引发非预期免疫反应的风险，对纯化工艺要求极高，某些裂解释放的物质，如特殊的次级代谢产物可能对特定细胞类型有抑制作用。

1.1.3 菌体水解物

菌体水解物是在菌体裂解的基础上使用特定的水解酶，如蛋白酶、糖苷酶等来处理裂解液，将不易直接利用的大分子(主要是蛋白质)转化为细胞可直接高效吸收利用的小分子，菌体水解物中小肽、氨基酸含量高，成分相对明确[44]。

菌体水解物的制备核心是定向酶水解，根据目标产物选择不同的单一或复合酶进行水解，需要考虑酶浓度、温度、pH 值和孵育时间等因素以确保高效水解[38]。使用不同蛋白酶对蛋白核小球藻蛋白质进行水解，碱性蛋白酶效果最好，可获得超过 62 g/100 g 的必需氨基酸[45-46]；采用碱性蛋白酶和复合酶(包含木聚糖酶、β-葡聚糖酶、半纤维素酶和阿拉伯糖苷酶)水解普通小球藻(*Chlorella vulgaris*)，几乎实现碳水化合物和蛋白质的完全溶解[47]。蛋白质水解还会产生生物活性肽，无花果蛋白酶水解蛋白质易释放具有抗氧化特性的肽，而木瓜蛋白酶水解蛋白质易产生具有降压特性的肽[48]。另外，水解微藻得到的肽具有抗氧化、抗炎以及免疫调节的活性[49-50]。

菌体水解物可作为高效氮源、碳源为细胞增殖提供良好的营养供给，显著提高细胞密度和重组蛋白产量。酵母水解物已被证实是可靠的动物血清替代物[11,51-52]，现为生物技术产业重要细胞培养添加剂，尤其在重组蛋白生产核心细胞株 CHO 的培养中应用广泛[53]，能促进 CHO 细胞体积增大与脂质合成能力提升，进而提高目标重组蛋白合成效率，支撑规模化生产。此外，从裂蹄木层孔菌(*Phellinus linteus*)中提取制备的水解物，经研究证实具有特定生物活性：一方面可增强派尔集合淋巴结介导的骨髓细胞增殖过程，为免疫相关细胞的生成提供支持；另一方面能刺激细胞合成 IL-2 等细胞因子，而这类细胞因子在调节免疫应答、维持细胞生理平衡中发挥关键作用，这也凸显了真菌源水解物在细胞功能调控中的独特价值[54-55]。

与 CFS 和菌体裂解物相比，菌体水解物营养组分生物利用度极高，能快速满足细胞生长

需求，提升细胞密度和产物得率；通过酶的选择性，可实现对产物肽段组成和功能的初步定向调控；成分相对裂解物更简单，有利于下游加工和质控。然而，深度水解可能破坏某些天然大分子(如完整功能蛋白、多糖复合体)的特定高级结构与生物活性，过度水解可能产生一些不期望的降解产物；制备过程至少包括“破壁”和“水解” 2 步，工艺更复杂，成本增加。

1.2 微生物衍生物的提取、纯化工艺及其对无血清培养基的质量水平控制

为了确保微生物衍生物的产品功效、安全性与批次间一致性，需要通过高效的提取方法和纯化技术去除杂质(如菌体碎片、核酸、内毒素等)和富集目标活性成分，实现产物标准化并确保其长期稳定储存。在无血清培养基规模化生产中，微生物衍生物的高效提取与纯化不仅简化了培养基的生产工艺，还降低了培养基的质量控制难度。

1.2.1 微生物衍生物的提取方法

对于微生物衍生物而言，提取技术的核心目标是在更短时间、更低能耗和更温和条件下实现更高效率、更高选择性和更高活性的目标成分获取。完整的微生物衍生物提取工艺可分为胞内活性成分释放和目标成分靶向富集 2 个关键环节，对应形成 2 类核心技术：一类是作为提取前处理的传统破壁提取方法(物理、化学、生物破壁)，主要实现微生物胞内成分的充分释放；另一类是作为提取核心工艺的新型绿色提取技术，重点实现目标活性成分的高效富集与分离，目前常用于微生物衍生物的绿色提取方法有超临界 CO_2 提取、亚临界水提取和深共熔溶剂提取(deep eutectic solvents, DESs)。前处理及提取是微生物衍生物生产工艺的上下游环节，且在提取效率、规模化放大可行性、综合成本等核心维度存在显著差异，而这些方面直接决定提取工艺的产业化应用价值，因此本文首先对这 2 类技术的显著特征与优劣性进行整体对比(表 1)[28-31,33-38,56-60]，为提取工艺的组合优化提供基础依据。

表 1 的整体对比结果显示，传统破壁提取方法与新型绿色提取技术并非替代关系，而是互补耦合的上下游工艺，传统破壁的效率决定了胞内成分的释放上限，是后续提取的基础，新型绿色提取方法的靶向性决定了目标成分的富集效果，是提升产品价值的核心。

为进一步明确新型绿色提取方法的工艺特征与适用场景，实现提取工艺的精准选择，本文对目前常用的 SCDE、SWE 及 DESs 3 类绿色提取方法进行了更深入的比较(表 2)[56-60]。

SCDE 作为超临界流体萃取(supercritical fluid extraction, SFE)技术的典型代表，是一种公认的绿色、高效分离方法，尤其适用于天然产物与生物活性成分的提取[61]。SCDE 利用超临界状态下 CO_2 兼具气体高扩散性和液体强溶解能力的特性，能快速渗透样品并高效提取目标成分，提取时间远短于传统溶剂萃取[62]。

SCDE 因无毒、环保、稳定等优势广泛用于微藻油提取[63]。研究表明，提高提取压力可增加 CO_2 密度与溶解能力，从而提升得率。例如，从雨生红球藻中提取虾青素时，65 MPa 下的提取率比 45 MPa 和 25 MPa 分别高 1.25 倍和 2.32 倍[64]；此外，添加适量乙醇作为共溶剂，从小球藻中萃取类胡萝卜素等化合物时不仅能显著提高萃取物抗氧化活性，还可将提取时间缩短至传统方法的 1/7[65]。

然而，SCDE 的产业化应用面临两大挑战：(1)维持超临界状态所需的高压设备导致初始投资与维护成本高昂；(2)纯 CO_2 对强极性物质溶解能力有限，常需添加共溶剂，这增加了后续分离纯化的复杂性[36]。

SWE 作为一种环境友好型提取技术，其优势在于能够有效保留提取物的生物活性与营养品质[66]。SWE 利用在 100–374 ℃的温度和高达 22 MPa 的压力下仍保持液态的水作为溶剂，此时水的介电常数、极性、黏度和表面张力等物

表1　不同微生物衍生物提取前处理方法的比较

Table 1　Comparison of pretreatment methods for the extraction of microbial-derived additives

Comparison dimension	Traditional cell disruption extraction	Novel green extraction
Extraction efficiency	(1) Cell disruption efficiency: physical>chemical>biological (2) No component selectivity; only intracellular total components released; no targeted enrichment for target components	(1) Targeted extraction efficiency: SCDE≈SWE>DESs (2) High selectivity; effective component extraction rate increased by 30%–80% *vs*. traditional processes
Scalability	(1) Physical/chemical: industrially mature, continuous amplification for ten-thousand-ton basic raw material production (2) Biological/pulsed electric field: pilot scale, efficiency fluctuates after amplification	(1) SCDE: extremely mature, for large-scale high-value-added products (2) SWE: gradually industrialized, pilot mature, scalable to thousand-ton scale (3) DESs: Lab/bench scale, solvent separation bottleneck in amplification
Comprehensive cost	(1) Equipment cost: physical>biological>chemical (2) Operating cost: chemical<physical<biological (3) Overall: relatively low, for low-value-added basic raw materials	(1) Equipment cost: SCDE>SWE>DESs (2) Operating cost: DESs<SWE<SCDE (3) Overall: relatively high, added value covers cost *via* improved purity/bioactivity
Bioactive component retention	(1) Physical (except pulsed electric field)/chemical: easy denaturation/degradation by high temperature/acid-base (2) Biological only: mild conditions, excellent retention	(1) SCDE/DESs: almost no thermal damage, retention rate>90% (2) SWE: minor thermosensitive component loss, better than traditional methods
Environmental impact	(1) Chemical: severe pollution (acid-base/organic waste), need extra treatment (2) Physical/biological: no chemical pollution, eco-friendly	All eco-friendly: SCDE (CO_2 recyclable, no residue); SWE (water only); DESs (biodegradable, low toxicity)
Process positioning	Extraction pretreatment; provides raw materials for subsequent enrichment, needs combination with purification	Core extraction process; synchronous “targeted enrichment+preliminary purification”, simplifies subsequent steps
Applicable scenarios	Preparation of basic nutritional components (crude amino acids/polysaccharides/hydrolysates) for general serum-free medium additives	Extraction of high-value-added bioactive components (C-PC/peptides/terpenoids) for precision serum-free medium additives

理化学性质发生显著改变，使其能溶解在常温常压下不溶或难溶的物质[67]。

在 200 ℃下利用 SWE 提取雨生红球藻衍生物，提取物表现出高抗氧化活性[68]；SWE 适用于蛋白质和氨基酸的提取，在对蛋白核小球藻衍生物进行提取时获得最大蛋白质浓度为 4.13 mg/mL，氨基酸约为 17.52 mg/g，其中谷氨酸是含量最高的氨基酸(4.96 mg/g)，其次是脯氨酸、丙氨酸、缬氨酸、亮氨酸、甘氨酸、异亮氨酸、苯丙氨酸和蛋氨酸[69]。

SWE 以水为唯一溶剂，来源广泛、成本低廉、安全无毒且无环境负担，但在产业化应用中其较高的操作温度对热不稳定成分(如维生素)构成了显著威胁，从而影响最终产品的功能品质[70]。

DESs 通常由氢键受体和氢键供体组成，二者结合形成低共熔混合物，这类溶剂具备低毒、可生物降解、成本较低及可设计性强等特点[71]，其内部的三维氢键网络能与目标成分有效作用，促进溶解[72]。

在各种 DESs 配方中，以氯化胆碱为基础的 DES 因其能够在保持蛋白质结构完整性的同时

表2 三种常用微生物衍生物绿色提取方法的比较

Table 2 Comparison of three common green extraction methods for microbial-derived additives

Extraction methods	SCDE	SWE	DESs
Core solvent	CO_2	H_2O	HBA+HBD
Green attributes	Non-toxic, non-flammable, recyclable, but itself is an industrial emission gas	Non-toxic, harmless, safest	Biodegradable, low toxicity
Operating temperature	Low (31–60 ℃)	High (100–374 ℃)	Ambient temperature
Operating pressure	High (10–40 MPa)	Medium-high (2–10 MPa)	Atmospheric pressure
Mechanism	Utilizes high diffusivity for penetration and dissolution	Polarity of water decreases, expanding dissolution range	Strong hydrogen bonding interacts with and dissolves target compounds
Best for	Low-polarity, lipophilic, small molecules	Medium-to-high polarity, water-soluble, or components releasable *via* hydrolysis	Broad spectrum, especially effective for medium-to-high polarity and complex systems
Thermal sensitivity compatibility	Excellent	Poor	Good
Post-processing & solvent recovery	Simplest and most thorough. CO_2 turns into gas upon depressurization, leaving no solvent residue in product	More complex and energy-intensive. Extract is a hot dilute solution requiring concentration and drying	Most complex. High viscosity makes separation difficult
Equipment & cost	Highest equipment investment	Moderate equipment investment	Lowest equipment investment
Industrial maturity	Very mature	Gradually maturing	Largely at laboratory research and pilot stages

溶解蛋白质被广泛关注[73]，使用 DES 进行蛋白质提取相比传统碱法可提高 10%–50% 的产率[74]。例如，采用 DES 氯化胆碱-尿素 DESs 提取小球藻源蛋白质，回收率可达 32.79%，且必需氨基酸含量占 37.45%[75]；此外，利用由 2 种 DESs (氯化胆碱-葡萄糖和氯化胆碱-尿素)、磷酸二氢钾盐和水组成的体系从雨生红球藻中成功提取超过 99% 的虾青素[76]。

DESs 可通过调整组分可实现针对特定分子(如特定蛋白质和肽)的高选择性提取[77]。然而其产业化瓶颈在于 DESs 通常黏度较高，且与目标物之间可能存在强相互作用，导致后续分离困难，从 DESs 相中回收高纯度产物往往需要抗溶剂沉淀、膜分离等多步复杂工艺，增加了操作成本与技术难度[78]。

1.2.2 微生物衍生物的纯化方法

为了提高微生物衍生物的纯度，从而增加其市场竞争力，提取过后通常会进行纯化处理，常用的纯化方法主要有膜过滤和色谱技术[79]。

膜过滤是目前应用最广泛的物质分离纯化技术，操作条件简单温和，且不需要添加任何化学试剂[80]，膜过滤的分离机制以筛分效应为主，依据分子尺寸实现选择性截留以提高目标产物的纯度，膜过滤技术主要包括微滤和超滤[81]。微滤的膜孔径范围为 0.1–10 μm，超滤技术的膜孔径范围为 0.01–0.1 μm，超滤操作压力要求高于微滤，通常为 0.5–5.0 bar，而微滤的操作压力仅需 0.1–2.0 bar[82]。微滤用于截留悬浮颗

粒、细胞、细胞碎片等大尺寸物质，超滤可截留蛋白质、多糖、胶体等大分子物质，在索氏小球藻裂解物的膜过滤纯化中先用 0.22 μm 滤膜去除细胞碎片和截留蛋白质，后用 3 kDa 膜超滤浓缩，蛋白的回收率可达初始含量的 12%[83]；在原始小球藻水解物的制备过程中最后一步通过膜截留分子量<5 kDa 的超滤技术获得蛋白质含量占干重的 80%[84]；在酵母水解物制备中常利用特定截留分子量的超滤膜分离具有生物活性的功能肽段，分子量低于 500 Da 的酵母水解物组分能显著提升 CHO 细胞培养性能[85]。在大规模工业使用中，微生物细胞碎片、溶解性有机物或颗粒物的累积均可能造成膜污染，进而降低过滤效率，目前的解决方法主要有反冲洗、化学清洗、旋流结构(可提升通量 40%)[86-87]和电导膜过滤[88]。

虽然膜过滤易于规模化，但产物选择性略低于色谱法，色谱技术是分离纯化活性物质最常用的方法之一。色谱法可分为凝胶色谱法、硅胶色谱、离子交换色谱法、羟基磷灰石色谱法、疏水相互作用色谱法、超临界流体色谱法、高效液相色谱法等多种类型[89]。常用的纯化色谱法主要有凝胶色谱、硅胶色谱和离子交换色谱[33]。凝胶过滤色谱基于分子尺寸进行筛分，常用于脱盐、分子量分级及复合物分离；硅胶色谱主要基于目标化合物与硅胶表面硅羟基之间的极性相互作用差异实现不同极性组分的依次洗脱与分离，尤其在中低极性天然产物、脂溶性色素及有机小分子的精细分离中起核心作用；离子交换色谱依据分子表面电荷差异进行分离，适用于蛋白质、多肽、核酸等带电生物分子的纯化[36]。通过离子交换色谱及葡聚糖凝胶色谱成功从普通小球藻中分离纯化出抗氧化叶黄素-蛋白质复合物[90]；利用硅胶柱色谱法和亲水亲油平衡型固相萃取从三角褐指藻(*Phaeodactylum tricornutum*)中分离纯化岩藻黄素，最终获得了 92.03% 的高纯度和 76.67% 的回收率[91-92]。尽管色谱法在选择性方面优于膜过滤，但其大规模应用仍面临操作复杂、设备成本高、处理通量有限、消耗有机溶剂等问题。

2 微生物衍生物在细胞农业中的应用

人口的持续增长与饮食结构的升级对全球粮食供给体系尤其是优质动物蛋白的生产提出了严峻挑战。据联合国粮食及农业组织统计，预计到 2050 年全球人口将突破 97 亿，肉类需求将较当前增长 70% 以上，而传统畜牧业作为动物蛋白的主要来源，正面临着资源消耗大、环境负荷重、可持续性不足等突出问题。传统畜牧业不仅占用了全球约 30% 的陆地面积和 70% 的淡水资源，其产生的温室气体排放量占全球总排放量的 14.5%，同时还存在抗生素滥用、人畜共患疾病传播等公共卫生隐患[93]。

为满足高价值动物蛋白需求、解决畜牧业可持续性难题，细胞培养肉技术作为开创性方案，正成为替代传统畜牧生产的环保型动物蛋白生产方式，兼具营养价值与环境友好性[94-95]。传统的血清培养基作为细胞增殖分化的核心支撑，其高成本(占比超 99%)是制约培养肉规模化生产的关键，因此开发低成本、高性价比的无血清培养基组分及配方是降低培养肉总成本的核心突破口[96-97]。

微生物生长速度快、培养条件简单，可通过发酵技术实现高效量产，其衍生物中富含蛋白质、多肽、氨基酸、维生素、生长因子等细胞生长必需的营养物质，能够有效替代 FBS 的部分功能，为细胞的增殖分化提供必不可少的营养支撑[44]。同时还能避免 FBS 的伦理和安全隐患，为 CA 的可持续发展提供了新路径。

2.1 微生物衍生物在陆生动物细胞培养肉中的应用

陆生动物细胞培养肉主要以牛、猪、鸡等畜禽细胞为培养对象，是目前细胞培养肉领域的研究重点，其中牛源细胞因肌肉组织含量高、

营养价值丰富，成为培养基优化的核心参考体系[98]。

近年来，大量研究证实，不同类型的微生物源衍生物(包括酵母、乳酸菌、海洋细菌、微藻、大型真菌等来源)均可作为血清替代品，有效支持牛源细胞的增殖、分化，且能显著降低培养基成本，展现出巨大的应用潜力。例如，Andreassen 等[99]的研究证实，在无血清培养环境中添加浓度为 0.000 1−1 mg/mL 的酵母水解物可使牛骨骼肌细胞的代谢活性提升超 100%，细胞增殖能力提高近 50%；Celebi-Birand 等[100]在牛肌肉卫星细胞(bovine muscle satellite cells, bSCs)的培养中添加乳酸菌海氏肠球菌水解物，有效促进了细胞增殖；Dolgin 等[101]同样对牛肌肉卫星细胞进行培养，证明了海洋细菌需钠弧菌(*Vibrio natriegens*)水解物的添加，优化了培养基的效果，可以对细胞进行长期培养；Okamoto 等[102]用小球藻提取物对原代牛成肌细胞进行培养，研究结果证明小球藻提取物可以维持细胞的增殖和分化；Yu 等[103]利用大型担子菌灰树花(*Grifola frondosa*)水解物对牛肌肉卫星细胞进行培养，实验结果表明灰树花水解物可以促进细胞增殖和分化，其效果显著高于含 20% FBS 培养基。

这些研究充分证实了微生物衍生物在替代血清、实现陆生动物培养肉低成本化方面的巨大潜力，为后续无血清培养基的优化和规模化应用提供了重要的理论支持。

2.2 微生物衍生物在水生动物细胞培养肉中的应用

随着全球水产品需求的不断增长，传统渔业捕捞和水产养殖面临着过度捕捞、水体污染、病害频发等问题，90% 的世界鱼类资源处于过度开发或枯竭状态[101]。因此，细胞培养海鲜作为替代传统水产品的新型生产方式，成为 CA 领域的另一研究热点。

目前，相关研究主要围绕斑马鱼胚胎干细胞、Mack1 细胞系等鱼类细胞模型展开，重点探讨微生物源水解物作为胎牛血清可持续替代品的可能性，已取得了一系列突破性成果。例如，在 Amirvaresi 等[9]的研究中将斑马鱼胚胎干细胞作为鱼类细胞的培养基优化参考系统，探讨了微生物衍生物代替胎牛血清用于细胞培养的可行性，实验证明酵母水解物和食用菌双孢蘑菇(*Agaricus bisporus*)水解物可以有效支持斑马鱼胚胎干细胞生长代谢和提高细胞活力。此外，Mack1 (也称为 Atlantic mackerel cell line)是一种来源于大西洋鲭鱼(*Scomber scombrus*)骨骼肌的连续、自发永生化细胞系，可分化为肌肉细胞，也可表现出脂肪样表型，是首个公开发布的鱼类肌肉细胞系，为细胞培养海鲜(如培养鱼肉)研究提供了关键工具[104]。Lim 等[105]在 Mack1 的低血清培养基的研发中证实了酿酒酵母(*Saccharomyces cerevisiae*)水解物、小球藻和螺旋藻微藻水解物可以支持 Mack1 在低血清培养条件下的生长增殖；Dolgin 等[101]同样对 Mack1 培养基中的低成本血清替代物进行了研究，发现酿酒酵母水解物对 Mack1 的短期培养有促进作用。

上述研究表明，微生物衍生物在鱼源细胞中的应用展现出良好的促细胞增殖的潜力，能为细胞的生长发育分化提供营养支持，同时可显著降低培养基成本。

2.3 微生物衍生物在培养肉基质与风味调控中的应用

培养肉的基质构建与风味形成是其实现产业化、贴近传统肉类感官特性的核心环节，传统培养肉体系多依赖动物源胶原蛋白、明胶作为基质支架，通过化学试剂进行风味调控存在风味单一、安全性存疑等问题[95]。微生物衍生物凭借其成分多样、功能可控、来源环保的优势，成为培养肉基质构建与风味调控的新型优质原料，实现了细胞营养供给、基质支撑和风味调控的多功能协同作用[11]。

在基质构建方面，微生物源多糖、微生物源蛋白等可通过静电纺丝、凝胶成型等技术制备具有良好生物相容性、机械韧性的三维支架，模拟传统肉类的肌肉纤维结构[106]。例如，作为细菌多糖和细菌异多糖代表的细菌纤维素和结冷胶是很有前景的增强基质支架机械强度的生物材料[107]，研究表明，细菌纤维素是促进骨骼肌成肌细胞增殖和分化的良好支架，其性能优于商业基质材料[108]；将 1% 结冷胶与 0.5% 明胶按 2:3 比例复合，经 0.18 mol/L 钙离子交联制备的支架能有效促进鸡骨骼肌卫星细胞的黏附、增殖与分化[109]。此外，利用酵母蛋白制备细胞培养支架，实验结果显示支架具有优异的机械性能和生物相容性，支持牛成肌细胞的细胞增殖与分化，且该酵母蛋白培养肉油炸后颜色和味道与牛肉相当[110]。

在风味调控方面，微生物衍生物可通过 2 种途径实现培养肉的风味增强。(1)微生物代谢产物直接提供风味物质，如乳酸菌发酵产生的乳酸、乙酸等有机酸可调节培养肉的酸度，赋予其柔和的风味[111]；酵母提取物中富含的呈味核苷酸是天然的鲜味剂，可与培养肉中的氨基酸协同作用提升鲜味强度[112]；此外，微藻提取物中的不饱和脂肪酸还可丰富培养肉的风味层次，同时提升产品的营养价值[102]。(2)微生物衍生物调控细胞代谢，促进风味前体物质合成，如在 C2C12 小鼠成肌细胞培养中添加传统药用真菌白桦茸(*Inonotus obliquus*)多糖，该真菌多糖可调控 AMPK-ACC1 信号通路，直接影响肌肉细胞内脂肪酸的合成代谢，而脂质及其热反应产物是肉类风味的重要前体[113]。

总的来说，微生物衍生物既为培养肉基质提供了安全稳定的支架构建，又能丰富其味道，为培养肉实现天然肉类的感官特性与产业化落地提供了重要支撑。

2.4 微生物衍生物在细胞培养辅料制备中的应用

CA 的产业化不仅依赖于核心的肌肉细胞培养技术，还需要低成本、标准化的细胞培养辅料作为支撑，包括细胞贴壁剂、抗氧化剂、渗透压调节剂等。微生物衍生物凭借其发酵量产的优势成为细胞培养辅料规模化制备的理想原料，可适配不同细胞类型的培养需求。

在细胞贴壁剂制备方面，微生物源黏附蛋白可替代传统的动物源纤连蛋白、明胶，为贴壁依赖性细胞提供贴壁位点。例如，酵母提取物中的多肽组分可提升细胞的贴壁能力与传代稳定性，在 Vero 细胞培养中已实现规模化应用[114]，此外，细菌纤维素与蘑菇壳聚糖、藜麦蛋白复合制备的微载体可使细胞初始黏附率达到 95% 以上，在动态悬浮培养中实现 60 倍扩增[115]。在抗氧化剂制备方面，微生物衍生物中富含的天然抗氧化物质可替代传统的化学抗氧化剂，清除细胞培养过程中产生的 ROS，缓解氧化应激对细胞的损伤，同时提升培养肉的货架期。例如，植物乳植杆菌(*Lactiplantibacillus plantarum*) CFS 显著增强激酶插入区受体(kinase-insert domain-containing receptor, KDR)细胞的超氧化物歧化酶(superoxide dismutase, SOD)和谷胱甘肽过氧化物酶(glutathione peroxidase, GSH-Px)功能，降低 NO 产生和 ROS 水平，1,1-二苯基-2-三硝基苯肼自由基(1, 1-diphenyl-2-picrylhydrazyl radical, DPPH)自由基清除率可达 95% 以上[116]；泡菜乳酸菌来源的胞外多糖可增加血清和肝脏中过氧化氢酶、GSH-Px、SOD 的活性，并抑制丙二醛的形成[117]。另外，真菌多糖也被证实可通过上调抗氧化酶活性来增强培养体系的抗氧化能力[118]。此外，微生物衍生物还可用于制备渗透压调节剂等辅料，这些辅料与无血清培养基体系兼容性好，且可通过发酵工艺实现连续化生产，批次稳定性高。例如，氧化葡糖杆菌(*Gluconobacter oxydans*)在高渗条件下可积累甘露醇作为渗透压调节物质，外源添加甘露醇可缓解渗透胁迫并促进细胞生长[119]。

总体而言，微生物衍生物通过规模化发酵实现了贴壁剂、抗氧化剂等关键辅料的高效制

备，为 CA 的标准化、低成本生产筑牢了辅料基础，加速了细胞培养技术的产业化转化。

3 微生物衍生物促细胞增殖的作用机制

微生物衍生物成分丰富、功能多样，它们能替代 FBS 的各类促细胞增殖功能，为细胞农业生产提供细胞增殖必需的营养底物、激活细胞增殖相关分子通路、促进细胞蛋白质合成与分泌、维持细胞活性及抵抗细胞损伤，从而有效支持细胞农业生产过程中种子细胞的活性维持与增殖[13]。研究指出，不同来源的微生物衍生物在不同细胞的培养中发挥着不同的促增殖作用，因此明确不同微生物衍生物的具体促增殖作用机制是开发面向不同细胞类型的精准营养适配型培养基的关键前提，具有重要的研究与应用意义。微生物衍生物促进细胞增殖的分子机制见图 2。

根据微生物来源的不同，微生物衍生物主要分为真菌衍生物、细菌衍生物及微藻衍生物三大类，各类衍生物在活性成分组成、功能侧重及适用场景上呈现鲜明特点。在真菌衍生物中，真菌源衍生物，如酵母提取物、酵母水解物等应用最为广泛，其富含氨基酸、多肽、核酸等营养成分，无论是对昆虫细胞还是哺乳动物细胞，均能显著提升细胞密度、促进蛋白产量或维持细胞活性，是目前验证最可靠的血清替代物之一；其他一些大型真菌如灵芝、灰树花的提取物则凭借独特的多糖、黄酮类成分在抑制细胞凋亡、抵抗毒素损伤、促进肌肉卫星细胞增殖分化等方面表现突出，部分甚至比 20% FBS 的效果好。细菌源衍生物中，乳杆菌、丁酸梭菌等益生菌的代谢产物，如短链脂肪酸、特定功能蛋白 p75/p40 等，在调控肠道上皮细胞生长、激活免疫细胞增殖、促进抗体生成等方面具有精准作用，而海洋细菌(如 *Vibrio natriegens*)和大肠埃希氏菌的裂解物则以高含量蛋白为核心优势，能支持细胞长期传代或短期快速生长。微藻衍生物则凭借兼具营养供给与抗氧化的双重特性脱颖而出，小球藻、螺旋藻等提取物不仅能为细胞提供葡萄糖、氨基酸等基础营养，其含有的藻蓝蛋白、不饱和脂肪酸等成分还能有效清除活性氧、维持干细胞增殖特性，在培养肉制造、皮肤细胞培养等场景中展现出独特价值。上述不同来源微生物衍生物的具体活性成分与效果见表 3。

综上所述，微生物源衍生物是来源丰富多样、功效明确、极具开发潜力的血清替代物。在实际细胞培养应用中需根据培养目标精准选择，若以提高细胞密度、增加蛋白产量为核心，酵母源衍生物是经过验证的可靠选择；若需精确调控特定信号通路以促进分化或抑制凋亡，可添加含有明确活性成分的细菌源衍生物；若培养体系面临氧化应激等挑战，微藻来源的衍生物可提供额外的抗氧化保护。

3.1 提供增殖必需的营养底物

氨基酸、糖类、维生素等是细胞增殖所必需的营养物质[137]，微生物衍生物可以提供这些营养物质。

文献报道，Bio Springer 公司生产的酵母提取物中富含赖氨酸和精氨酸的肽能够使 CHO-AMW 细胞密度增长 4 倍[85]；Spearman 等[138]也有同样发现，酿酒酵母裂解液中分子量小于 3 kDa 的组分含有多条含精氨酸和赖氨酸的肽段，以及 2 种多胺(精胺和亚精胺)，能够使 CHO-Luc 细胞密度增加至 2.6×10^6 cells/mL；Xiu 等[139]发现干酪乳酪杆菌(*Lacticaseibacillus casei*)的 CFS 中含有分子量为 37.37 kDa 的特征性多糖，能增强 RAW264.7 细胞的增殖并且改善其作为免疫细胞的吞噬活性；Dong 等[133]研究发现，每 100 g 蛋白核小球藻裂解物含有约 51 g 粗蛋白和 22 g 可溶性糖，在低血清条件下使金鱼肌肉细胞(*Carassius auratus* muscle cells)可以连续培养至少 4 代；此外，Wu 等[140]从肠道内常驻乳酸杆菌的代谢物中发现的维生素 C 具有

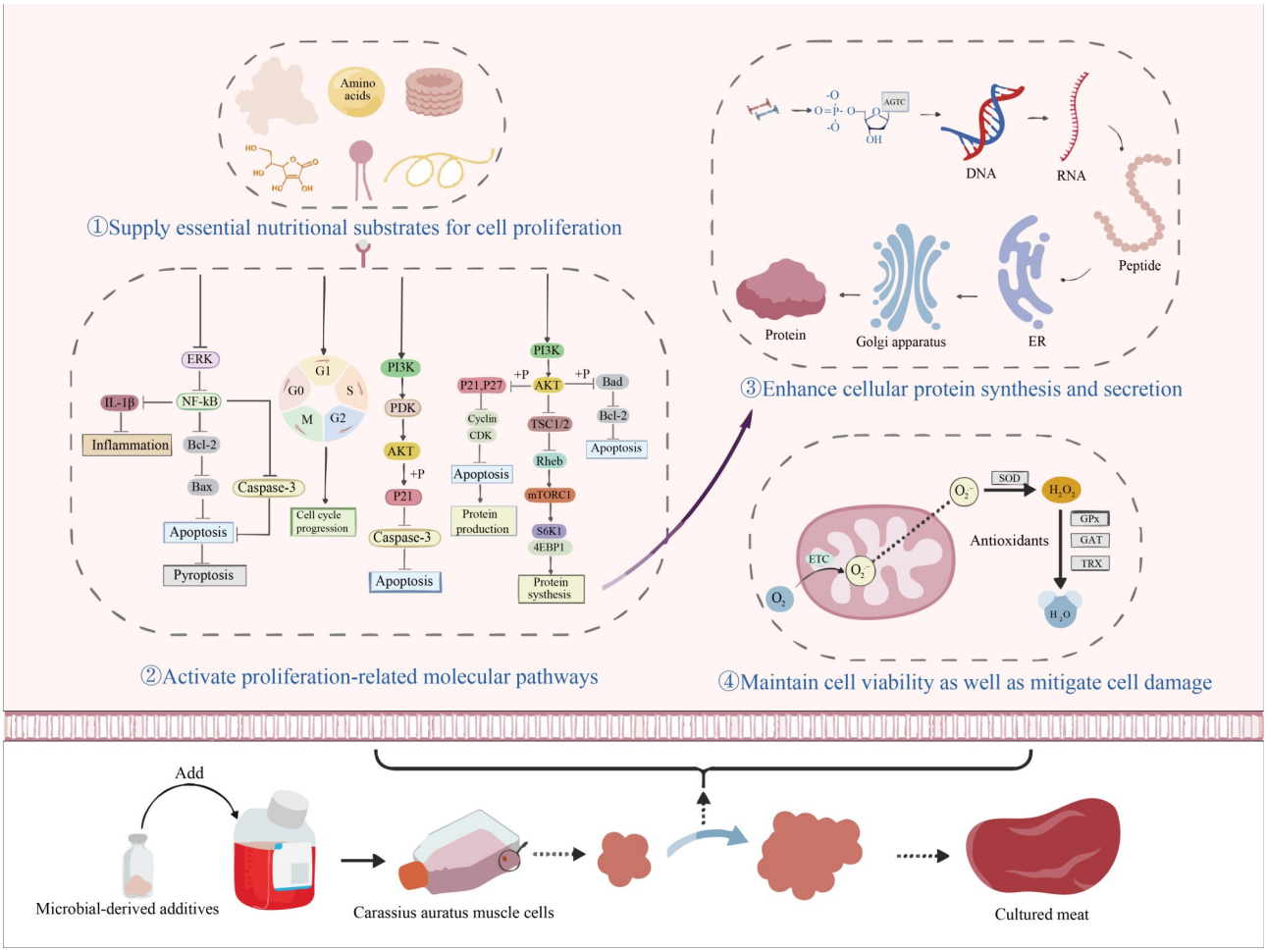


图2　微生物衍生物促进细胞增殖的分子机制

Figure 2　Molecular mechanisms of cell proliferation promotion by microbial-derived additives. AKT: Protein kinase B (PKB); Bad: Bcl-2-associated death promoter; Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; CDK: Cyclin-dependent kinase; Caspase-3: Cysteine-aspartic protease 3; ERK: Extracellular signal-regulated kinase; 4EBP1: 4E-binding protein 1; IL-1β: interleukin-1 beta; mTORC1: Mammalian target of rapamycin complex 1; NF-κB: Nuclear factor kappa B; p21: Cyclin-dependent kinase inhibitor 1; p27: Cyclin-dependent kinase inhibitor 1B; PDK: Pyruvate dehydrogenase kinase; PI3K: Phosphatidylinositol 3-kinase; Rheb: Ras homolog enriched in brain; S6K1: Ribosomal protein S6 kinase 1; TSC1/2: Tuberous sclerosis complex 1/2. Created with BioGDP.com.

抗氧化特性，能有效减轻肠道细胞损伤、增强细胞功能并促进细胞更新。

上述研究表明，微生物衍生物能够为细胞生长增殖提供丰富的氨基酸、糖类和维生素等来源，是潜力巨大的细胞营养补充剂。

3.2　激活增殖相关分子通路

研究证实，微生物衍生物通过激活多条增殖相关的分子通路有效促进细胞生长与增殖。

微生物衍生物富含多种生理活性成分，如肽类和生长因子，它们通过与细胞表面受体结合激活细胞内信号通路，从而促进增殖。例如，酵母水解物中的碱性亲水肽及阳离子肽是推动CHO细胞生长与代谢的核心成分，不仅促进养分运输与大分子摄取，还可间接增强细胞增

表3 不同来源微生物衍生物作为培养基组分促进不同细胞增殖的效果

Table 3 Proliferation-promoting effects of microbial-derived additives from diverse sources on various cell types as medium components

Type	Sources	Cell line	Active component	Addition amount	Effect	References
Fungi-derived Additives	YL	Sf-9	<30 kDa peptides	5% *V*/*V*	Result in a 60.6% increase in cell density	[120]
	YE and YP.A, (Bio Springer)	CHO-AMW	Amino acids, carbohydrates, nucleic acids	YE (1 g/L) and YP.A (4 g/L)	Increase IgG production by 180%	[121]
	YE (Bacto^{TM})	Vero	NA	0.1 g/L	Maintain cellular growth and proliferation	[122]
	Yes (FNI100, FNI 105, and Nucel)	DF-1	FAAs	Nucel 24–781 μg/mL; FNI100 & FNI105<1.56 g/L	Enhance cellular viability	[123]
	Ganoderma lucidum spores	CHO K1	NA	NA	Boost growth, prevent apoptosis, maintain cell cycle in low-serum	[124]
	Grifola frondosa	NHDFs	Naringin, hesperidin, chlorogenic acid, and kaempferol	100 μg/mL	Shield fibroblasts from BPA toxicity *via* antioxidant/anti-inflammatory action, boost proliferation	[125]
Bacteria-derived additives	Fermented skim milk supernatant (11 LAB+yeast)	HB4C5	19.0 kDa protein	530 μg/mL	Enhance IgM production of the hybridoma cells by 2.8-fold	[126]
		PBL		530 μg/mL	Facilitate IgM production by 2.8-fold, enhance IgG production by 5.4-fold	
		PBL		50 μg/mL	Stimulate IFN-γ production by 6.0-fold	
	Lacticaseibacillus rhamnosus GG	YAMC, HT 29	p75 and p40	p75 100 ng/mL, p40 10 ng/mL	Block TNF apoptosis and boosts gut epithelial growth	[127]
	LAB	CD^{3+}, CD^{4+}	Glu, P, Na, K	NA	Boost $CD3^{+}$/$CD4^{+}$ T cells>80% in 3 days	[128]
	Rhodobacter sphaeroides	HeLa	Arg, Leu	10% *V*/*V*	Reach 1.5× cell count in 5% FBS medium	[129]
	Rhodobacter sphaeroides	HS27	Gly, Glu, Ala, Asp, His, Arg, Cys, Thr, Tyr, Met, Asn	0.5% *V*/*V*	Outperform FBS for growth/viability, cuts ROS, and boosts lysosomes	[130]
Microalgae-derived additives	*Chlorella vulgaris*	RL34	Glucose, amino acids	10%–15% *V*/*V*	Increase the survival rate of cells	[131]
	Chlorella vulgaris	EBTr	NA	10 g/L	Increased cell viability	[132]
	Auxenochlorella pyrenoidosa	*Carassius auratus* muscle cells	Protein, sugar	NA	Support continuous culture of the cells for at least 4 passages	[133]
	Spirulina platensis	PMMSC	NA	NA	Promote cellular proliferation	[134]
	Oscillatoria okeni	HaCaT	C-PC, Protein	1% *V*/*V*	Enhance cell viability	[135]
	Chlorococcum littorale	C2C12	Glucose, proteinogenic amino acids, Glu	5% *V*/*V*	Enhance cellular proliferation by 4.5×, matching 10% FBS-DMEM	[136]

Ala: Alanine; Arg: Arginine; Asn: Asparagine; Asp: Aspartic acid; C-PC: C-phycocyanin; Cys: Cysteine; FAAs: Free amino acids; Glu: Glutamic acid; Gly: Glycine; His: Histidine; LAB: Lactic acid bacteria; Leu: Leucine; Met: Methionine; NA: Not available; Thr: Threonine; Tyr: Tyrosine; YE: Yeast extract; YL: Yeastolate; YP.A: Yeast peptone-A; YUF: Yeastolate ultrafiltrate.

殖[85]。这类直接触发信号往往能快速诱导增殖相关表型标志物的表达，是增殖启动的早期指标。例如，Lee 等[141]研究发现，经菠萝蛋白酶水解的酵母提取物在 25–100 μg/mL 浓度下可显著提高成骨细胞碱性磷酸酶活性，该成分是成骨细胞定向分化与矿化成熟的核心因子。

此外，微生物衍生物也可通过调节 MAPK、NF-κB 等关键信号节点影响细胞命运。例如，富硒酵母肽能够抑制皮肤细胞 HaCaT 和巨噬细胞中 MAPK 与 NF-κB 信号通路的激活[142]，参与生长、分化与存活等过程[143]；另外，大型真菌的衍生物也同样具有良好的促细胞增殖作用，Kim 等[125]研究发现，舞茸提取物则通过抑制 NF-κB 活性下调 Bax、Bcl-2、Caspase-3 及 IL-1β 等因子，抑制皮肤成纤维细胞焦亡，为增殖创造了有利环境。

雷帕霉素靶蛋白(mechanistic target of rapamycin, mTOR)信号通路在细胞增殖中也发挥关键作用。研究发现，酵母水解物可上调 CHO-K1 细胞中 PI3K 的表达，激活 PI3K/Akt/mTOR 通路，从而促进细胞增殖、维持稳态并提高蛋白产量[53,144-146]。Guan 等[147]研究同样指出，长双歧杆菌(*Bifidobacterium longum* subsp. *longum*)水解物可通过激活 PI3K/Akt/mTOR 和 Wnt/β 通路调节细胞周期并抑制肠上皮细胞凋亡。类似地，Yan 等[127]研究发现，鼠李糖乳酪杆菌(*Lacticaseibacillus rhamnosus*) GG 来源的 p75 和 p40 蛋白则通过 PI3K/Akt 通路抑制 Caspase-3 激活，减轻细胞损伤。

3.3 促进细胞蛋白质合成与分泌

除了具有维持细胞增殖的作用外，微生物衍生物还可有效提升细胞中蛋白合成的产量。研究表明，通过在 CHO 细胞培养基中添加酵母水解物可使细胞合成的 Fc 融合蛋白产量提高 1 倍[53,148]；Sung 等[51]利用酵母水解物作为 CHO 细胞的培养基添加物，当添加浓度超过 5 g/L 时细胞所合成的人血小板生成素产量最高可提升 11.5 倍；Hermes 等[149]在 NS0 细胞培养中添加酵母水解物使单克隆抗体滴度提升 20%。

研究指出，微生物衍生物能通过促进蛋白质的正确折叠与加工来保障重组蛋白的有效生成。例如，酵母提取物能通过提高基因转录效率增强重组蛋白 mRNA 表达，并利用其所含的 Ca^{2+}和富含精氨酸的寡肽缓解内质网应激及未折叠蛋白积累，从而兼顾表达提升与细胞保护[148]。酵母水解物还可上调内质网中伴侣蛋白 CRP55 和蛋白质二硫键异构酶的表达，从而促进蛋白质折叠和重组蛋白的合成[150]。

另外，蛋白质糖基化是影响重组蛋白安全性与有效性的关键质量属性。酵母水解物中的核苷和碱基成分可通过调节细胞内核苷酸代谢、增强能量供应并促进蛋白质糖基化，从而支持高效蛋白合成[151]。研究表明，在 CHO 细胞无血清培养中添加酵母水解物会显著改变单克隆抗体中半乳糖基化聚糖的类型与分布，而对高甘露糖、岩藻糖基化和唾液酸化聚糖影响较小，说明微生物源成分能够定向调控糖基化修饰，进而影响抗体功能[8]。

3.4 维持细胞活性及抵抗细胞损伤

微生物衍生物通过提高细胞存活率和发挥抗氧化作用可有效维持细胞活性及抵抗细胞损伤，为细胞正常生理功能及目标产物表达提供保障。

在提高存活率方面，研究表明微生物衍生物有助于延长培养时间并提升细胞活力。例如，在干细胞培养中添加小球藻水解物可将其表型稳定维持长达 21 d，并使二维和三维培养条件下的细胞活力提升 120%[43]。除此之外，细胞形态的稳定性也与存活率密切相关。在 CHO 细胞培养中添加微生物源水解物可使其直径由 14–18 μm 增大至 16–20 μm，这一形态变化反映了细胞生理状态的改善，并有助于增强其蛋白合成能力[53,152]。此外，本团队在前期研究也发现，从灵芝中提取的多糖组分 F31 能够减轻肝脏炎症，维持肝细胞正常形态，支持肝脏损伤修复继而提高存活率[153]。

在抗氧化方面，微生物衍生物通过清除自由基、抑制 ROS 生成及增强抗氧化酶活性等多种机制缓解氧化应激对细胞的损伤。Chen 等[19]在前期研究中证实，发酵粘液乳杆菌 XJC60 的 CFS 中提取的烟酰胺，能降低活性氧水平、稳定线粒体膜电位以及增加 NAD/NADH 比率，从而保护 HaCaT 细胞免受紫外线诱导的氧化损伤；Wu 等[154]研究发现，秀珍菇蛋白水解物在大鼠 PC12 细胞模型中表现出神经保护作用，其机制涉及调控内源性抗氧化酶表达及清除细胞内 ROS；Mirdamadi 等[155]研究指出，来自马克斯克鲁维酵母(*Kluyveromyces marxianus*)的抗氧化肽 VLSTSFPPK (VL-9)及其类似物能通过清除自由基、激活 Keap1-Nrf2 通路，并与过氧化氢酶、超氧化物歧化酶及谷胱甘肽过氧化物酶相互作用，增强这些酶的活性，从而提高 Caco2 细胞抗氧化能力。此外，本团队研究发现，灵芝多糖 F31 也能上调肝细胞中谷胱甘肽过氧化物酶和超氧化物歧化酶的活性，缓解糖尿病引发的肝脏细胞的氧化损伤[156]。

4 总结与展望

微生物衍生物作为一类重要的培养基补充剂，在克服传统胎牛血清应用的局限性方面展现出显著潜力[13]。其作用机制涵盖营养供给、信号通路激活、抗氧化保护等多个环节[44]。近年来，研究表明若能在细胞培养体系中精准选用适宜的微生物衍生物可有效支持细胞生长、维持细胞功能并促进目标产物表达，从而提升培养体系的整体性能[138,157-158]。因此，开发成分明确、功能稳定的微生物衍生物，对于推动无血清培养技术发展、实现细胞精准营养调控以及保障生物制品安全生产具有重要意义。

从产业化视角来看，微生物衍生物在应对 CA 规模化生产的关键挑战方面展现出独特优势。首先，在成本控制层面，微生物衍生物通过发酵工艺实现规模化生产，其原料成本远低于动物源血清及 HPL。其次，在放大生产可行性方面，微生物发酵工艺本身已具备成熟的工业化基础，菌种选育、发酵参数优化及下游纯化流程均可实现标准化控制，有效规避了动物源血清批次间差异大、供应不稳定等产业化瓶颈。此外，微生物衍生物作为无动物源成分，不仅符合细胞农业产品的伦理要求，也降低了病原体污染风险，简化了后续纯化与监管审查流程。更重要的是，通过代谢工程与合成生物学手段，可对微生物菌株进行定向改造，使其精准合成特定活性成分，如特定结构的多糖、重组生长因子、功能性肽段等，从而实现培养基添加剂的精准定制，这一特性为不同细胞类型、不同培养工艺的个性化需求提供了灵活解决方案[159]。

目前，多种来源的微生物衍生物已被证实对动物细胞培养具有明确的促进作用。研究显示，酵母来源的衍生物可通过提供必需营养、激活增殖相关信号通路、优化蛋白合成与分泌等机制有效支持细胞的高密度生长与重组蛋白的高效表达[43,51,148]；某些益生菌来源的组分能够调节培养环境的免疫平衡，抑制应激相关细胞凋亡[127,147]；此外，微藻与真菌提取物通过其特有的抗氧化与抗炎活性有助于维持细胞在长期培养过程中的稳定性[125,156,160]。然而，目前微生物衍生物的生产与质量控制仍面临挑战，其高质量活性组分的分离与鉴定仍需依赖复杂的纯化工艺，成本较高。因此，未来亟需建立标准化的微生物衍生物功能评价体系，通过规范其活性成分鉴定、作用机制解析及功能验证流程，将有力促进微生物衍生物在生物制药与 CA 等领域的精准应用，为实现细胞精准营养调控、开发性能优异且成本可控的新型细胞培养基策略提供重要支持。

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