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肿瘤类器官培养中条件培养基与化学定义培养基的比较及应用前景

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摘要 肿瘤类器官(TOs)是体外三维培养物, 可以较好地保持原发肿瘤生物学特性, 在药物敏感性和新药开发方面得到广泛应用。培养基配方直接影响类器官建立效率、表型稳定性和遗传真实性。该文对比了肿瘤类器官培养过程中使用条件培养基(CM)和化学定义培养基(CDM)的区别: CM含有大量天然成分、价格低廉并且能够很好地复现肿瘤微环境, 有利于早期筛选和大规模扩增, 但是其组成不确定且不同批次之间存在较大差异; 而CDM成分明确、批次一致, 便于进行标准化药物敏感性以及相关机制的研究工作, 但是其生产成本较高并且某些肿瘤不能长时间在其中生长并出现克隆选择现象。该文认为, CM与CDM的主要区别在于“生物学复杂性”与“工程学可控性”之间的取舍, 而这种取舍取决于肿瘤类型、培养阶段以及目的等。之后, 在对二者适用性和证据水平进行批评性评价后, 该文进一步讨论针对性配方设计、利用AI进行配方设计、动态培养适配以及实现符合GMP标准的临床级质控等途径来指导培养基的选择和改进。

关键词 肿瘤类器官; 条件培养基; 化学定义培养基; 肿瘤异质性; 药物筛选; 临床转化; 培养体系标准化

Comparative Study of Conditioned and Chemically Defined Media on Tumor Organoid Culture and Their Clinical Applications

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Abstract TOs (tumor organoids) are three-dimensional *in vitro* cultures that effectively preserve the biological characteristics of primary tumors and have been widely applied in drug sensitivity testing and new drug development. The composition of the culture medium directly influences the efficiency of organoid establishment, phenotypic stability, and genetic fidelity. This review compares CM (conditioned medium) and CDM (chemically defined medium) used during tumor organoid culture: CM contains abundant natural components, is cost-effective, and closely recapitulates the tumor microenvironment, making it advantageous for early-stage screening and large-scale expansion; however, its composition is undefined and exhibits significant batch-to-batch variability. In con-

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trast, CDM features well-defined components and consistent batches, facilitating standardized drug sensitivity assays and mechanistic studies, but it entails higher production costs and may support only limited growth duration for certain tumor types, leading to clonal selection. The fundamental distinction between CM and CDM lies in the trade-off between "biological complexity" and "engineering controllability", a balance that depends on tumor type, culture stage, and experimental objectives. Following a critical evaluation of their applicability and levels of evidence, this review further discusses strategies to guide medium selection and improvement, including targeted formulation design, AI-driven formulation optimization, dynamic culture adaptation, and implementation of GMP (good manufacturing practice)-compliant clinical-grade quality control.

Keywords tumor organoids; conditioned medium; chemically defined medium; tumor heterogeneity; drug screening; clinical translation; standardization of the culture system

肿瘤类器官(tumor organoids, TOs)是能够再现原发肿瘤生物学行为的三维体外模型，在外观、标志物以及基因型上类似于真实的肿瘤，可以预测患者对于化疗药物的敏感性从而为个体化治疗提供合理的选择[1]。包含超过1 000名患者的泛癌肿瘤类器官平台[使用化学定义培养基(chemically defined medium, CDM)]表明类器官在基因型和转录组层面均高度类似于其来源的肿瘤[2]。而在肝癌、前列腺癌、胶质母细胞瘤(glioblastoma, GBM)中，患者来源肿瘤类器官(patient-derived tumor organoids, PDTOs)的药敏结果与患者的实际情况相吻合[3-5]，因此类器官是连接基础研究与临床应用的良好纽带，尤其是在弥补二维细胞系以及动物模型不足之处方面发挥重要作用[6]。但是，类器官成功构建在很大程度上取决于培养条件，在各种因素中，培养基配方是最重要的可调控因素。

培养基是影响类器官能否形成、能传代并保持其功能的关键因素。不同的培养基对于生长速度、干细胞维持、分化以及药物敏感性都有很大差别。在结直肠癌(colorectal cancer, CRC)中，最初的培养基决定了转录本模式[7]；而在胃上皮祖细胞中，单细胞测序表明条件培养基(conditioned medium, CM)和CDM对不同干细胞亚群的维持作用存在差异[8]；在非小细胞肺癌(non-small cell lung cancer, NSCLC)中，许可型培养基(permissive culture medium, PCM)可以实现高效的长期培养，而最低基础培养基(minimum basal medium, MBM)则有利于防止正常细胞污染[9]。因此，培养基不仅作为基础的物质与能量来源，而且可作为一种手段来调节信号通路从而改变类器官生物学特性。

CM是由特定细胞(成纤维细胞、间充质干细胞或者肿瘤细胞)培养后所得的上清液，含有大量的生长因子、细胞因子以及外泌体等生物活性物质。L-WRN细胞CM含有Wnt3a、R-spondin和Noggin，常用于生成肠道类器官；甲状腺癌细胞原代细胞CM可支持甲状腺类器官培养长达10个月[10-11]。而CDM的所有成分都是明确的并且没有任何动物源性或者未鉴定成分，包括定量重组蛋白、小分子还有基础养分，在子宫内膜癌、脑类器官以及儿童胃上皮类器官的研究中均被使用[1,12-13]。二者在实际应用中也有交集——一些"CDM"仍然含有不明成分的血清替代品，同时一些"CM"也可以通过冻干实现标准化存储[14-15]。目前的趋势是越来越多地用"CDM"代替"CM"，以便进行大规模生产和临床转化[16-17]。但是不同的文章对于什么是"CDM"有不同的定义。严格意义上的"CDM"应该是所有成分及其比例都清楚且没有任何未知物质的加入。但实际上很多文章中使用的含有B27或者N2(包含维生素A、视黄酸等，但其确切的比例并未给出)的培养液也被称作"CDM"，这实际上就是一种"无血清培养基"(serum-free medium, SFM)而不是严格意义下的"CDM"。"无动物源培养基"(animal component-free medium, ACFM)虽然无动物来源物质，但也有可能存在植物水解物，而且其具体组成不清楚。这给比较不同研究结果带来困难，在下文我们将鉴别所引用文献中使用的培养基类型是什么。

1 培养基成分与作用原理对比

1.1 条件培养基的主要成分与功能

CM含有大量的天然多样化的生物活性物质，可以模仿体内的微环境。它有三种作用方式：基质替代——成纤维细胞CM制备的海藻酸钠水凝胶可以代替Matrigel用来培养膀胱癌患者来源类器官

(patient-derived organoids, PDOs), 同样有效而且更便宜[18]; 节省费用——在胃肠道类器官中, CM可以用作重组HGF的替代品来显著减少成本[19]; 通路调节——在低级别胶质瘤中, CM与ROCKi联合使用可以激活Akt/Erk1/2通路, 从而促进肿瘤细胞大量扩增[20]; 而在输卵管上皮类器官中, CM可以提高干细胞标志物(如LGR5、OLFM4)以及促血管生成因子(如VEGF、bFGF等)的水平[21]。

1.2 化学定义培养基的配方与优势

由于组分选择严格, CDM重现性良好并且不存在动物源污染问题。泛癌肿瘤类器官平台(>1 000个样本)利用CDM构建类器官, 其基因组和转录组与相应原发肿瘤非常接近[2]。在肝细胞癌(hepatocellular carcinoma, HCC)中降低生长因子含量的CDM可以成功构建23个PDTOs, 同时保留肿瘤组织学以及遗传异质性, 发现非经典信号改变与对塞瑞替尼敏感有关(P<0.000 1)[4]。工业细胞系研究对CDM优化有指导意义——Plackett-Burman实验可筛选重要组分[22], 多变量数据分析(multivariate data analysis, MVDA)与氨基酸比例优化使单克隆抗体(monoclonal antibody, mAb)产量提高约80%[23], 150多个配方筛选出某些成分增加抗体滴度[24], 这些方法可以应用于肿瘤类器官CDM的开发上; 另外, CDM中的胰岛素会被CHO细胞分泌的胰岛素降解酶(insulindegrading enzyme, IDE)水解, 敲除*IDE*基因即可解决该问题[25], 说明需要考虑生长因子稳定性问题。

1.3 两种培养基对信号通路的调控差异

CM和CDM所含生长因子不同, 对信号通路的影响也不同。CRC类器官中CM比CDM更适合进行长期培养, 转录谱型与初始使用的培养基有关[7]。肺腺癌中过表达补体因子H(complement factor H, CFH)的CM通过JAK2/STAT3通路促进细胞增殖、迁移[26]。而CDM则通过精确调控比例起到作用——优化后的CDM即使生长因子降低到原来的1/10仍然可以维持间充质干细胞(mesenchymal stem cell, MSC)的增殖以及免疫调节的能力[27]。在输卵管上皮类器官中CM可以提高干细胞相关基因的表达水平但是其Wnt3a/RSPO1水平较低, 需要额外补充才能刺激Wnt信号转导; 传统的CDM有利于细胞增殖[21]。在猪囊胚(非肿瘤模型参考)中, PF4-CDM与牛血清白蛋白(bovine serum albumin, BSA)非定义培养基的基因表达几乎没有区别, 但是它们都与真正的囊胚有较大差别(如细胞周期、溶酶体、代谢等)[28], 说明CDM不能很好地模拟体内微环境。而且前面也有提到, 在CM中Wnt3a/RSPO1虽水平较低, 却可以上调干细胞标志物的表达[21], 意味着CM中可能存在一些未知因素(如外泌体、脂质介质或者非经典的Wnt配体)对下游信号通路起到补偿作用, 而这些都无法通过简单复制CM中的组分实现。因此, CDM设计要由“模拟CM成分”转变为“模拟CM激活的信号网络”, 即以适当比例组合重组因子或小分子等方式激活相应通路, 这也为利用AI进行针对性网络优化提供依据。选择何种培养基需要根据实验目的确定。CM与CDM的综合比较见表1。

2 培养效果的系统性比较

2.1 长期培养与增殖能力比较(存活率/增殖能力)

在肿瘤类器官长期培养过程中, CM和CDM对细胞生存及分裂的作用存在差异, 在来自结直肠癌病人的类器官系中, CM比CDM更能有效促进肿瘤上皮细胞的长期培养, 有利于类器官不断扩增并且保持较高活力[7]。但是并不是所有的CDM都可以成功构建出类器官, 在后续传代过程中会出现生长迟缓或克隆选择的情况。比如在兔盲肠类器官系中, 使用5% L-WRN细胞CM处理的类器官体积较小, 增殖相关标记物水平较低, 而用2Ki CDM处理的类器官则有更强的增殖能力和更高水平的干细胞标记物表达[11]; 但是也有一些文献报道CDM有较好的长期培养潜能, 比如从患有子宫内膜癌患者中分离出的类器官能够在CDM中长时间传代并保留它们最初肿瘤来源组织学及遗传特征[1]; 儿童胃类器官也能在CDM中保持上皮极性并且可传代一年以上[13]。总体上来说, 在部分肿瘤中CM具有更好的长期维持能力, 而改良后CDM也有可能实现长期培养, 但这取决于肿瘤种类以及培养条件。

2.2 肿瘤异质性保持效果对比

本文“肿瘤异质性”包括三个方面内容: (1) 分子异质性——基因组层面采用全外显子测序(whole-exome sequencing, WES), 转录组层面采用单细胞RNA测序(single-cell RNA sequencing, scRNA-seq), 同时分析拷贝数变异(copy number variation, CNV), 表观遗传层面采用单细胞转座酶可及染色质测序(single-cell assay for transposase-accessible chromatin using sequencing, scATAC-seq); (2) 细胞异质性——

表1 CM与CDM综合比较

Table 1 Comprehensive comparison of CM and CDM

对比维度 Comparison dimension	条件培养基 CM	化学定义培养基 CDM
Composition definition level	Contains unknown components, serum/hydrolysates	All components and concentrations are known (strict CDM)
Batch stability	Poor, depends on cell status	High, can be standardized
Primary establishment success rate	Relatively high (especially Wnt-dependent)	Moderate (requires targeted optimization)
Long-term passaging stability	Relatively stable	Clonal selection occurs in some tumors
Clonal selection risk	Low-moderate	Moderate-high
Normal cell contamination risk	Relatively high	Relatively low
Cost	Low	High
Multi-center reproducibility	Poor	Good
High-throughput drug screening applicability	Limited	Applicable
Organoid phenotype	Closer to *in vivo* microenvironment	Relatively uniform
Application scenarios	Primary establishment, low-cost expansion	Drug screening, mechanistic research, clinical translation
Regulatory compliance	Difficult to meet GMP	Complies with GLP/GMP

肿瘤干细胞比例、分化程度、间质/上皮表型(流式、免疫组化等); (3) 功能异质性——各种不同的亚群对于药物的不同敏感性(药敏试验、活细胞成像等)。单细胞测序是对分子以及细胞异质性最准确的方法, 而类器官的形态多样性以及药敏结果的分散性也可以反映一定的功能异质性, 在不同的培养条件下, 这三种类型的类器官对这三层保留的程度可能会有所不同。在CRC类器官中, CM和CDM都可以重现原发肿瘤的转录组[7]。在胃上皮祖细胞中, CM与CDM对干性维持的效果存在差异[8]。泛癌肿瘤类器官平台CDM建立的超过1 000个类器官在基因型以及转录组学上均与各自对应原发肿瘤一致[2]。在兔盲肠正常组织(正常组织对照)中, CM促进分化基因表达, 而CDM则有利于维持干细胞样状态[11]。来自乳腺癌中枢神经系统(central nervous system, CNS)转移灶PDOs可以在某些条件下大量扩增并且保留肿瘤内在异质性。虽然二者都可以保持一定量的异质性但由于细胞的选择性偏好可能会导致转录上的变化。

2.3 药物敏感性测试中的表现差异

CDM培养的子宫内膜癌类器官可以体现患者的化疗敏感性差异, 在小鼠实验中也是一样的, 基因型可以预测其预后[1]。HCC PDTOs在无生长因子CDM中药敏结果与其临床获益有相关性[4]。胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)中不同的培养条件以及不同的培养基对于吉西他滨和紫杉醇的敏感性并没有明显区别[29]。含有胎牛血清(fetal bovine serum, FBS)的类器官培养系统也是有效的——前列腺癌类器官(29个, 成功率为62.07%)体外药敏与临床疗效一致[3]。NSCLC中由于PCM存活率较高更适合进行药物筛选[9]。但是CM中可能含有会影响药物反应的活性成分——骨髓MSC CM提高水通道蛋白1(aquaporin 1, AQP1)表达水平, 促进骨肉瘤和肝细胞癌的迁移与侵袭[30]; 巨噬细胞CM增强肿瘤球侵袭能力[31], 表明在药物敏感性检测过程中CM参与免疫微环境可能导致额外影响因素。需要注意两个限制条件: 第一, 发表偏倚问题, 即报道阳性结果的文章更易被接受而发表; 第二, 大部分药敏试验是在Matrigel上完成的, 但是Matrigel含有许多生长因子, 可能会掩盖培养基本身的作用。因此需要做“培养基×基底膜基质”的正交实验。从证据水平来看, 大多数PDOs药敏试验都处于体外结果(Level III)或者回顾性验证(Level IIb)阶段, 而前瞻性临床验证(Level Ia)则很少见。因此“药敏预测”表述统一修正为“初步证据提示具有预测潜力”

2.4 培养体系中其他因素的协同与混杂效应

培养基只是培养体系的一个组成部分, 在使用时应注意以下几点。(1) 基底膜基质——Matrigel含有转化生长因子-β(transforming growth factor-β, TGF-β)、表皮生长因子(epidermal growth factor, EGF)、碱性成纤维细胞生长因子(basic fibroblast growth factor, bFGF)等多种生长因子而且不同批次

之间存在差异, 部分“培养基效应”可能就是由培养基与Matrigel相互作用或者相互竞争所致的, 在合成水凝胶中缺少Matrigel这种“基质”, 可能会导致培养基成分变化更加明显。(2) 培养条件——静止、气液界面以及微流控流动等不同的培养方式会对细胞周围的氧气浓度、养分供给以及代谢产物积累造成影响从而影响细胞对培养基的需求。(3) 培养时期——初次建立细胞株系、传代、药物筛选等不同阶段对于培养基的要求也是不一样的, 需要不断进行调整。

3 未来技术路径与发展方向

3.1 人工智能优化培养基配方

AI以及机器学习可以用于改进培养基。在CHO-K1中主动学习平台使用364个无血清配方提高细胞浓度约60%[32]。而在肿瘤类器官中AI辅助CDM开发的关键在于: 以CM激活信号网络作为“功能目标”, 从大量重组因子以及小分子中筛选出等价替代品。这可以通过以下方式实现: (1) 单细胞测序获得CM处理下“信号通路活性特征谱”作为训练集目标; (2) 使用主动学习不断优化配方; (3) 利用微流控进行大规模测试。目前已经报道有基于深度学习无标记成像平台结合CDM用于抗肿瘤药物敏感性预测的研究成果[2]。AI也可用于优化培养基组成以与系统生物学相结合[33], 但是需要有标准来保证其有效性[34]。

3.2 动态培养系统的应用前景

静态培养无法复制体内动态微环境, 在灌注生物反应器中CRC肝转移类器官对于5-FU的IC_{50}远小于静态培养[35]。动态系统还可以结合在线气体监测进行培养基在线调整[36-37]。在流动状态下液体剪切应力以及营养梯度会影响细胞消耗培养基中成分的速度, 在静态条件下优化得到的最佳培养基成分并不适合流动条件下的使用, 需要再次优化重要成分的比例、缓冲液以及氧气分压等参数。这方面的研究目前还很少见, 是一个很有前景的方向。将来结合微流控技术、生物反应器及实时监测的动态培养方法能够更真实地反映肿瘤微环境[38-39]。

3.3 临床转化的标准化体系建设

目前, 类器官领域尚缺乏统一的标准体系, 这严重制约了其临床转化进程。尽管CDM相比于CM成分更加清晰, 但是对于其长期稳定性和一致性仍存在问题[7]。目前已经有学者用无血清CDM以及重组R-spondin-1代替CM来大规模制备人类胰腺类器官并且开发出相应的GMP(good manufacturing practice)冻存方法[40]。经济合作与发展组织(Organisation for Economic Co-operation and Development, OECD)已经对无动物源系统是否可以用于毒理学研究进行了评价[41]。未来还需要在多个中心获得相关证据支持后才能使监管机构[如美国食品药品监督管理局(Food and Drug Administration, FDA)、欧洲药品管理局(European Medicines Agency, EMA)]接受类器官作为伴随诊断工具[34,42]。临床转化标准化参数建议见表2。

3.4 肿瘤类型特异性培养基开发策略

并不存在一种普适最优培养基, 在肿瘤细胞对

表2 临床转化标准化质控参数

Table 2 Standardized quality control parameters for clinical translation

环节 Stage	关键参数 Key parameter	建议标准 Recommended standard	评价方法 Evaluation method
Sample acquisition	Cold ischemia time	≤24 h (<12 h)	Timer recording
	Viable cell count	≥10^5	Cell counting
Establishment	Primary passaging success rate	≥70%	Organoid forming unit
Passaging	Maximum recommended passages	10-15 passages	WES monitoring every 5 passages
Cryopreservation and recovery	Recovery viability	≥60% (recommended ≥80%)	Viable cell staining/re-formation rate
Quality control release	Genomic fidelity	Driver genes unchanged	WES every 5 passages
	Pathological consistency	H&E consistent with parental tissue	Pathological evaluation
	Drug sensitivity consistency	Consistent with clinical efficacy (retrospective)	IC_{50} *vs* PFS/ORR
Multi-center	Culture medium batch consistency	CV<15% (key factors)	ELISA/mass spectrometry

表3 不同肿瘤类型类器官培养特征

Table 3 Culture characteristics of organoids for different tumor types

肿瘤类型 Tumor type	推荐培养基 Recommended medium	关键因子 Key factors	建系成功率 Establishment success rate	应用场景 Application scenario
CRC	CM (L-RWN-CM)	Wnt3a, RSPO3, Noggin, EGF	Relatively high	Long-term expansion, CRISPR screening
HCC	CDM (low growth factors)	EGF, FGF10, HGF, A83-01	~70% (23/33)	Drug sensitivity, genomics
Prostate cancer	Modified medium containing FBS	Androgen, EGF, FGF10	~62% (18/29)	Drug sensitivity prediction
PDAC	CDM/DMEM-F12	EGF, FGF10, Noggin, RSPO1	Varies greatly depending on formulation	Drug screening
GBM	CM+ROCKi	EGF, FGF2, ROCKi	Can be passaged long-term	CAR-T, invasion
NSCLC	PCM	EGF, FGF10, RSPO1, Noggin	Relatively high	High-throughput drug screening
Endometrial cancer	CDM	EGF, FGF10, FGF7, Noggin, A83-01	Successful establishment	Prognosis prediction
Thyroid cancer	Primary cell CM	Autocrine factors (unknown)	Can be passaged >10 months	Long-term culture
HGSOC	Optimized CDM	RSPO1, Noggin, NRG1, advanced DMEM/F12	82.8% (24/29), ascites 87.5% (7/8)	Individualized modeling
Breast cancer CNS metastasis	Specific medium	Adjusted according to metastatic origin	Rapid expansion	CNS metastasis research

信号通路依赖程度上存在区别导致培养基组成不同。Wnt依赖型CRC: 高度依赖Wnt/β-catenin, 在CM中Wnt3a/RSPO1自然组合更好, CRC类器官在CM中可存活更长时间[7]; Wnt非/低依赖型HCC: 可以在没有添加外源性Wnt的情况下培养成功(23/33), 应优先使用CDM[4]; 生长因子依赖型PDAC: 需要EGF或FGF, 不同的研究对于CDM成分有所不同, 需要进行比较以确定最佳比例[29]。针对胶质母细胞瘤(GBM)微环境复杂性, 条件重编程+ROCKi的CM方案对保持浸润性表型有优势[5,20]。卵巢癌(high-grade serous ovarian carcinoma, HGSOC): 含有R-spondin-1(250 ng/mL)、Noggin和NRG1的培养基使构建成功率高达82.8%(24/29), 而针对腹水来源的样本, 成功率可达87.5%(7/8)。高Wnt条件可能不利于HGSOC长期存活[43-45]。中枢神经系统(CNS)转移的乳腺癌: 来自胸水或腹水的PDOs容易大量增殖并且保留肿瘤内在异质性[46]。不同肿瘤类型的推荐培养基、关键因子、建系成功率及应用场景见表3。

4 结论与展望

CM和CDM各有利弊, 这与肿瘤类型、培养时间以及目的有关。本文主要观点是二者差别在于“生物学复杂性”与“工程学可控性”。CM可以较好地再现微环境并保留部分肿瘤细胞异质性, 适用于初代建系和探索性研究; 而CDM在批次间一致性、标准化和监管合规方面不可替代, 在机制研究和临床转化中发挥重要作用。现阶段大部分研究报道为基于回顾性和单中心的研究结果, 相同患者的样品同时在CM和CDM中进行头对头对比的研究还未见报道。未来应更多关注以下几方面研究工作: (1) 不同肿瘤类型、多个中心、同一个体的比较; (2) 以信号网络等效性为导向的CDM智能化设计; (3) 培养体系中不同成分之间相互关系的研究。另外我们认为: (1) 探索性工作或样本量不足的情况下CM仍然可靠, 但是需要针对每次实验中的主要因素进行定量的质量控制; (2) 机理研究或者大规模筛选应当首选严格的CDM(无B27/N2); (3) 临床应用相关的工作应当尽早开始构建GMP级CDM; (4) 鼓励公开详细的配方以及质量标准, 提高整个领域的再现率。

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