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肠癌肝转移机制与类器官模型研究进展

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广东省消化系统恶性肿瘤研究重点实验室项目(2021B1212040006)资助

摘要 结直肠癌(colorectal cancer, CRC)是消化道系统最常见的恶性肿瘤之一, 其发病率随生活方式改变呈逐年上升趋势. 肝脏是结直肠癌最常见的转移部位, 而结直肠癌肝转移(colorectal liver metastases, CRLM)是导致患者死亡的主要原因之一. 目前结直肠癌的发生机制尚未完全阐明, 深入研究CRLM的机制将有助于优化患者的诊疗策略. 近年来, 患者来源类器官(patient-derived organoids, PDOs)因其在疾病建模、机制研究及药物筛选中的应用优势, 成为肿瘤研究的热点模型. 自2013年首次成功培养以来, 肿瘤类器官技术发展迅速. 该类模型通过体外三维(3D)基质胶培养患者活检或手术组织, 形成高度模拟体内器官结构和功能的组织类似物, 为原代细胞(包括正常细胞和肿瘤细胞)的高效培养提供了新平台. 本文结合本中心经验, 综述结直肠癌肝转移机制及类器官模型的研究进展.

关键词 结直肠癌, 肝转移, 类器官, 进展

结直肠癌是全球最常见的消化道恶性肿瘤之一, 其发病率居全球第三位, 致死率位列第四[1]. 全球结直肠癌发病率呈持续上升趋势, 年增长率达3.2%, 病例数从1999年的78.3万例增至2020年的180万例[2~4]. 这种增长与经济发展水平密切相关, 发展中国家的发病率约为发达国家的四分之一[3].

远处转移作为结直肠癌治疗的首要挑战, 标志着肿瘤进入晚期(IV期), 导致患者生存率显著降低, 是重要的致死危险因素. 根据门静脉系统的解剖特点, 肝转移成为最常见的转移类型. 约50%的结直肠癌患者病程中会出现肝转移, 根据发生时间可分为同时性和异时性肝转移[5]. 研究显示, 左半结肠癌肝转移发生率较高[6], 但右半结肠癌一旦发生肝转移, 病灶范围往往更广泛.

值得注意的是, 肝转移发生率存在性别差异: 男性患者风险更高, 25%~50%会出现肝转移, 其中约30%在初诊时即已存在[7,8]. 种族差异也值得关注, 美国研究显示不同族裔的肝转移发生率存在显著差异[9], 提示基因变异可能是重要风险因素. 有研究已发现, *BRAF*、*KRAS*、*NRAS*、*PI3KCA*、*TP53*、*CDK12*、*EBF1*等基因与肝转移相关[10], 且突变类型影响预后: n*OTCH1*和*PIK3C2B*突变患者预后最佳, 而*SMAD3*突变患者预后最差[11].

1 结直肠癌肝转移治疗

结直肠癌肝转移(colorectal liver metastases, CRLM)的治疗方案需根据患者全身状况及疾病进展程度制定, 可采用单一疗法、联合治疗或多学科诊疗模式(multidisciplinary diagnosis and treatment model, MDT). 治疗选择主要取决于患者整体健康状况、原发

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肿瘤特征(大小/位置/淋巴结转移情况)及肝转移灶特征(大小/位置/数量). 基于精准医学和转化医学原则, 临床常根据患者状态及肿瘤分子特征制定个体化方案: 例如对可切除CRLM且体能状态良好者采用手术联合化疗, 体能欠佳者则选择新辅助治疗序贯手术及化疗. 目前CRLM治疗主要分为局部治疗(手术切除/射频或微波消融/栓塞治疗)和全身治疗(化疗/靶向治疗/免疫治疗), 前者适用于局限性肝转移, 后者用于弥散性病灶[12].

CRLM化疗方案与原发肿瘤一致, 无特异性药物. 根据美国国立综合癌症网络(national comprehensive cancer network, NCCN)指南, 可依据患者病情阶段及全身状况选择以下方案: xELOX(卡培他滨+奥沙利铂)、FOLFOX(5-Fu+奥沙利铂+亚叶酸钙)、FOLFIRI(5-Fu+伊立替康+亚叶酸钙)、FOLFOXIRI(5-Fu+奥沙利铂+伊立替康+亚叶酸钙)或氟尿嘧啶单药治疗[13]. 靶向治疗包括抗EGFR抗体(如西妥昔单抗)、抗血管生成药物(如贝伐珠单抗), 免疫治疗包括免疫检查点抑制剂(PD-1/PD-L1/CTLA-4抑制剂).

2 结直肠癌肝转移机制研究

尽管诊疗技术持续进步, 结直肠癌肝转移患者的长期生存率和治愈率仍不理想. 近十年来, 相关机制研究取得显著进展, 尤其在细胞信号通路、分子调控、肿瘤微环境及免疫逃逸等领域, 为优化治疗策略提供了新思路.

*Wnt/β-catenin*信号通路在结直肠癌肝转移中起关键作用. 该通路通过调控β-catenin蛋白(肿瘤发生发展的核心调控因子)激活下游靶基因异常转录[14]. 研究表明, Wnt通路不仅参与细胞生长分化调控[15], 更通过诱导上皮-间质转化(epithelial-mesenchymal transition, EMT)促进肿瘤侵袭转移[16]. EMT涉及细胞极性改变、骨架重塑及黏附能力减弱等多阶段过程, 是肿瘤转移的重要驱动因素. 此外, *MAPK*和*PI3K*/*AKT*等通路的异常激活也与转移密切相关[17].

分子调控层面, *Snail*、*Twist*等转录因子通过调控EMT促进肿瘤迁移[18]. 非编码RNA(如*miRNA-330*)通过靶向*HMGA2*致癌基因, 抑制肿瘤细胞增殖迁移并诱导凋亡, 其机制涉及下调EMT标志物(*Snail-1*、*E-cadherin*等)、*TGF-β*及*AKT*/*STAT3*磷酸化水平[19].

结直肠癌肝转移是多重机制协同作用的结果, 深入解析其分子网络可为临床转化提供新靶点[20]. 当前研究需进一步阐明调控细节, 并推动类器官模型等研究工具的临床应用, 以提升治疗效果.

3 结直肠癌肝转移体内外模型研究

3.1 细胞及动物模型研究

在疾病演变研究中, 构建肿瘤细胞系为机制探索提供了重要手段常用结直肠癌细胞系包括*HCT15*、*HCT116*、*SW480*等. 针对结直肠癌肝转移(CRLM)研究, Boot等人[21]利用患者转移灶组织成功构建了6种低传代CRLM细胞系(*JVE103*、*JVE114*、*JVE187*、*JVE253*、*JVE371*、*KP283T*), 这些细胞系在突变谱和基因表达谱上呈现多样性特征. 新型CRLM细胞系可作为体外实验的有力工具, 用于揭示结直肠癌发生机制及开发新疗法.

CRLM动物模型以小鼠为主[22], 按造模方法分为两类: 自发性肝转移模型: 通过原位移植结直肠癌细胞或肿瘤组织, 使小鼠自发形成原发灶并继发肝转移; 实验性转移模型: 经静脉/脾脏注射肿瘤细胞直接模拟血行转移, 具有操作简便、成本低、效率高等优势[23]. 但该模型仅能反映转移晚期阶段, 缺乏早期过程特征, 限制了肿瘤转移全程机制的研究.

3.2 类器官模型研究

结肠癌类器官(图1)可精准模拟肿瘤干细胞生物学行为[24,25], 为评估关键调控基因/信号通路、解析基因变异谱及探索肿瘤发展机制提供理想平台. 患者来源肿瘤类器官(PDOs)具有以下特点: 取材量少且培养成功率高; 保留原始肿瘤形态及遗传特征; 可反映患者治疗临床反应[25]. 重要研究进展: Wang等人[26]基于57例患者77份样本构建PDOs模型, 其预测IV期结直肠癌化疗反应的敏感性、特异性和准确率分别达63.33%、94.12%和79.69%; 牛津大学[27]成功培养13例CRLM类器官, 证实其表达*EpCAM*、*CEA*、*CAM1*等标志物及*CD24*/*CD44*干细胞特征, 并验证其化疗耐药性评估功能; 复旦大学Mo等人[28]建立50例原发/转移配对肠癌PDOs库, 通过多组学分析证实类器官可反映肿瘤异质性, 体外药敏实验显示其在预测化疗方案(FOLFOX/FOLFIRI)反应及预后评估中的应用潜力.

Fujii等人[29]运用类器官与*CRISPR-Cas9*技术成功模拟消化道恶性肿瘤的早期形成及进展过程, 深化了对消化系统恶性肿瘤的认知. 2015年, Matano等人[30]

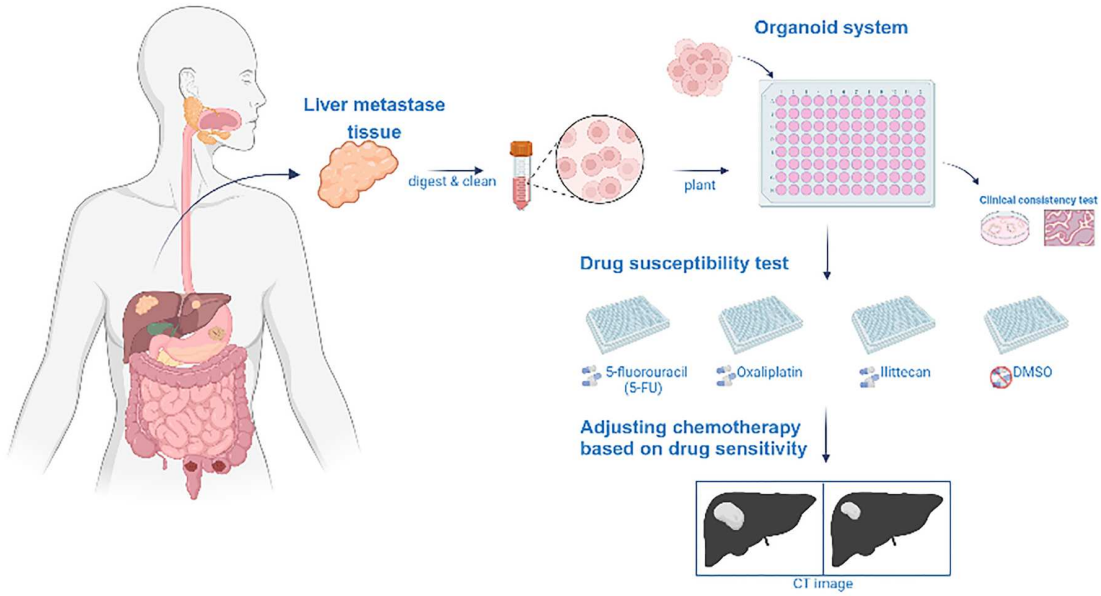

图 1 器官培养过程(Created by BioRender.com)
Figure 1 The process of organoid culture (Created by BioRender.com)

通过*CRISPR-Cas9*在正常人肠上皮类器官中引入结肠癌常见突变基因(*APC*、*AD4*、*TP53*、*KRAS*、*PIK3CA*),模拟肠道微环境构建出多表型结肠癌模型,证实了类器官在研究结直肠癌分子机制中的价值. Fumagalli等人[31]利用人结肠类器官原位移植模型,通过设计携带不同突变组合的类器官,揭示*WNT*、*EGFR*、*P53*和*TGF-β*信号通路突变的连续积累促进肿瘤生长与转移. Xu等人[32]则通过*APC*杂合缺失类器官模拟家族性腺瘤肉病,发现*Rad21*是*APC*缺陷的关键调控因子,在癌变过程中起决定性作用.

当前类器官技术已成为抗癌药物筛选的关键模型. Cho等人[33]利用患者来源结直肠癌类器官证实,5-氟尿嘧啶通过激活*WNT*/*β-catenin*通路促进肿瘤干细胞增殖,提示其与*WNT*抑制剂联用可能预防复发. Ganesh等人[34]通过小鼠移植模型发现,低侵袭性直肠癌类器官对5-氟尿嘧啶或FOLFOX方案更敏感. Pauli等人[35]基于类器官生物样本库筛选发现,阿法替尼联合伏立诺他可显著抑制*APC*突变肿瘤生长,疗效达FOLFOX方案的10倍. Costales-Carrera等人[36]在患者类器官中验证*Plocabulin*□有显著细胞毒性. Fernández-Barral等人[37]则揭示骨化三醇在正常类器官中上调干性基因并抑制增殖,而在肿瘤类器官中主要诱导分化表型. 这些突破为结直肠癌药物研发提供了新方向.

尽管类器官模型已成为肿瘤研究的首选模型,但仍存在局限性. (1) 类器官构建受限于细菌污染、肿瘤特性及特定培养基要求,导致*MSI*、*BRAF*突变、低分化或黏液型肿瘤的类器官建系困难[38]. (2) 肿瘤在患者体内呈动态演变过程,尤其在化疗或放疗后,特定时间节点构建的类器官仅反映肿瘤瞬时状态,现有方法无法准确模拟组织动态变化,难以预测患者预后. (3) 体外类器官模型与体内微环境存在差异,无法完全复刻肿瘤细胞外基质等成分,影响模型有效性. (4) 类器官缺乏多器官互作机制,而卡培他滨等结直肠癌药物需经肝脏和肠道代谢才能起效,需多器官联用模型才能完整模拟药物作用过程. (5) 类器官培养过程中基因表达存在自发变异,如何控制基因突变类型仍需突破. (6) 取材因素显著影响培养成功率: Zeng等人[39]通过1231份结直肠癌组织样本(含1130例患者)的单因素及多因素Logistic回归分析发现,内镜活检样本及接受新辅助放化疗者培养成功率低,而恶性腹水样本成功率较高. 当前类器官模型在个体化药敏检测中存在三类关键局限性及临床影响: (1) 培养污染可能通过诱导异常死亡(假阳性: 误判无效药物为有效)或掩盖真实药效(假阴性: 漏检有效药物),从而导致错误用药方案; (2) 传代过程中关键亚克隆丢失(如耐药突变)及培养基选择压力诱导非生理表型,导致耐药风险低估和药物

反应偏离; (3) 免疫微环境缺失(如PD-1抑制剂需T细胞共培养)及代谢异常(如肝酶缺乏致前药失活)引发的药物反应失真. 针对上述问题, 本研究提出系统性解决方案: 在质量控制方面, 通过GMP标准培养、多组学动态监测(*WES*/*scRNA-seq*)和传代次数限制(≤5代)维持肿瘤异质性; 在模型优化方面, 采用免疫共培养体系(自体T细胞/巨噬细胞)、个性化培养基(患者血清/*TGF-β*等)及代谢补偿策略(肝类器官共培养); 在临床转化层面, 构建多模型交叉验证体系(类器官-PDX-AI校正模型)、生物标志物分层系统(*EGFR*/*KRAS*基因型联合磷酸化蛋白检测)以及标准化操作指南(MINEO共识/IC50阈值设定). 通过技术创新与标准化整合, 可显著降低假阳性/假阴性率(预计从当前~30%降至<10%), 为实现类器官模型从实验室预测向临床决策的可靠转化提供实践路径. 在未来, 或许可以通过流控芯片、3D生物打印方式来解决上述问题.

4 结论与展望

结直肠癌肝转移是结直肠癌患者常见的严重晚期表现, 显著影响患者生存及预后. 近年来, 其机制及模型研究取得重要进展. 结直肠癌肝转移涉及复杂细胞信号通路、分子调控及肿瘤微环境改变, 促进肿瘤细胞侵袭、迁移、血行播散、肝脏定植及微转移灶形成等关键步骤. 通过基因突变、细胞外基质重塑、免疫逃逸等机制, 结直肠癌细胞获得促肝转移能力.

为深入探究机制并开发新疗法, 研究者已建立多种模型: 从啮齿类化学诱导模型、基因工程小鼠模型到患者来源异种移植模型, 以及新型类器官模型. 类器官模型不仅可作为药物筛选工具, 延长晚期患者生存期, 更在个体化治疗领域展现广阔前景. 然而, 类器官在结直肠癌肝转移研究中仍存在诸多未知领域需深入探索.

随着分子生物学与交叉学科的发展, 基于多组学技术构建的新型类器官模型不断推动肿瘤建模技术的革新. 针对传统类器官缺乏功能性血管网络的局限, 未来可通过内皮细胞共培养诱导血管生成(如激活*VEGF*信号)、生物3D打印构建含预成型血管的支架并联合微流控动态灌注, 或移植人源类器官至小鼠体内利用宿主血管实现血管化. 针对肿瘤免疫细胞体外功能维持难题, 可采取患者来源免疫细胞共培养保留个体化互作, 或通过添加*IL-2*/*IFN-γ*等细胞因子及*CRISPR*编辑技术增强免疫细胞活性与靶向性. 在耐药机制研究中, 类器官可揭示基因突变(如*EGFR T790M*)、药物外排泵上调等肿瘤内在机制, 以及免疫抑制微环境、基质细胞分泌保护因子(*HGF*/*IL-6*)、缺氧代谢适应等外在机制. 药物筛选方面, 可通过阶段药物暴露模拟临床耐药演化, 结合单细胞测序追踪耐药亚群, 在血管化模型中评估抗血管药物(如贝伐珠单抗)及免疫检查点抑制剂(如PD-1抗体)的疗效, 并利用空间组学解析耐药区域细胞互作网络. 未来需整合AI预测模型与高通量类器官筛选, 构建涵盖血管、神经及肿瘤微环境的仿生体系, 为结直肠癌肝转移等精准治疗提供新策略.

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Summary for “肠癌肝转移机制与类器官模型研究进展”

Research progress of liver metastasis mechanism and organoid model of colorectal cancer

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Colorectal cancer (CRC), one of the most prevalent malignancies of the digestive system, has shown a steady annual rise in incidence linked to evolving lifestyle patterns. The liver serves as the most common metastatic site for CRC, with colorectal liver metastases (CRLM) representing a leading cause of mortality among affected individuals. While the molecular pathogenesis of CRC remains incompletely understood, elucidating the mechanisms underlying CRLM holds significant potential for refining diagnostic and therapeutic approaches. In recent years, patient-derived organoids (PDOs) have emerged as a transformative research model in oncology due to their unique advantages in disease modeling, mechanistic exploration, and drug sensitivity testing. Since their inaugural successful cultivation in 2013, tumor organoid technology has undergone rapid advancement. This innovative platform utilizes three-dimensional (3D) Matrigel culture systems to propagate biopsy or surgical specimens into tissue analogs that faithfully recapitulate the architectural and functional complexity of native organs, thereby establishing a robust methodology for high-efficiency expansion of primary cells, including both normal and malignant populations. The distinctive value of PDOs lies in their preservation of tumor heterogeneity and microenvironmental interactions, enabling researchers to investigate cancer biology while maintaining critical cell-cell and cell-matrix communication networks. Particularly in CRLM research, organoid models permit longitudinal observation of metastatic processes under controlled experimental conditions, facilitating mechanistic studies of invasion, angiogenesis, and hepatic colonization. Furthermore, these systems demonstrate remarkable translational potential in personalized medicine, as drug response profiles generated from patient-specific organoids frequently correlate with clinical outcomes, offering opportunities for tailored therapeutic strategies. Current progress in organoid technology has significantly enhanced our understanding of CRLM pathogenesis. Studies utilizing this model have identified key molecular pathways involved in epithelial-mesenchymal transition (EMT), immune evasion, and metabolic reprogramming during hepatic metastasis. Notably, the integration of organoid co-culture systems with hepatic stromal components has provided novel insights into tumor-stroma crosstalk mechanisms that promote metastatic niche formation. From a clinical perspective, the establishment of organoid biobanks from CRLM patients has enabled large-scale pharmacological screens, accelerating the discovery of targeted therapies and overcoming traditional limitations associated with conventional 2D cell cultures. Building upon our institutional experience, this review comprehensively examines recent advancements in CRLM pathophysiology and the expanding applications of organoid models. We highlight technical innovations in organoid generation from metastatic lesions and discuss remaining challenges in standardized protocol implementation. As the field progresses toward multi-omics integration and microphysiological system development, organoid technology promises to bridge critical gaps between bench research and clinical practice, ultimately advancing precision oncology in CRLM management.

colorectal cancer, liver metastasis, organoids, progress

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