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遗传性肿瘤易感综合征的iPSC模型：通往肿瘤进展与早期干预的机制路径

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摘　要

遗传性肿瘤易感综合征(hereditary cancer predisposition syndromes, HCPS)源于胚系致病性变异，这类变异在肿瘤发生之前的很长阶段内，即可重塑细胞应激反应、基因组维护能力以及组织特异性的稳态调控。传统研究模型——包括经典肿瘤细胞系、动物模型及患者来源的肿瘤类器官——能够较好反映疾病进展期的表型特征，但在解析癌前阶段的早期事件、谱系依赖的分子机制以及患者间差异性方面存在明显局限。诱导多能干细胞(induced pluripotent stem cells, iPSCs)为此提供了一种可扩增且遗传背景明确的研究平台，可与定向分化、类器官、微生理系统(microphysiological systems)以及等基因基因组编辑技术相结合，用于模拟癌前状态、建立基因型与表型之间的因果联系，并评估预防或治疗干预策略的效果。

关键词

诱导多能干细胞，遗传性肿瘤综合征，类器官，多组学，早期生物标志物

iPSC Models of Hereditary Cancer Predisposition Syndromes: Mechanistic Pathways to Tumour Progression and Early Intervention

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Abstract

Hereditary cancer predisposition syndromes (HCPS) arise from germline pathogenic variants that reshape cellular stress responses, genome maintenance and tissue-specific homeostasis long before tumour initiation. Conventional research models—including established tumour cell lines, animal models, and patient-derived tumour organoids—can effectively recapitulate phenotypic features of advanced disease stages, but they have clear limitations in elucidating early events during the pre-cancerous stage, lineage-dependent molecular mechanisms, and inter-patient heterogeneity. Induced pluripotent stem cells (iPSCs) provide an expandable, genetically defined platform that can be combined with directed differentiation, organoids, microphysiological systems and isogenic genome editing to model premalignant states, map genotype-to-phenotype links and test preventive or therapeutic strategies.

Keywords

Induced Pluripotent Stem Cells, Hereditary Cancer Syndromes, Organoids, Multi-Omics, Early Biomarkers

1. 前言

遗传性肿瘤易感综合征源于胚系致病性变异，这类变异使个体在其一生中对肿瘤发生具有组织选择性的易感风险。从临床表现来看，此类综合征通常呈现家族聚集性、发病年龄提前、多原发肿瘤发生风险增加以及情境依赖性的治疗敏感性差异，多数遵循常染色体显性遗传模式[1]-[3]。典型代表包括遗传性乳腺癌和卵巢癌综合征(hereditary breast and ovarian cancer syndrome, HBOC)，其中 *BRCA*1/2 与 *PALB*2 具有明确的风险评估价值和临床实用性，而大量提出的“候选基因”在普通人群中仅贡献有限的肿瘤风险[4] [5]。由错配修复(mismatch repair, MMR)基因(*MLH*1、*MSH*2、*MSH*6、*PMS*2)胚系缺陷所致的 Lynch 综合征，可显著增加结直肠癌及多种胃肠道和泌尿生殖系统肿瘤的发生风险，而构成性错配修复缺陷综合征(constitutional mismatch repair deficiency, CMMRD)则代表一种尤为侵袭性的易感状态，常在儿童期即出现多肿瘤发生[6]-[8]。胚系 TP53 突变导致 Li-Fraumeni 综合征，其特征为肿瘤谱系广泛且发病极早[9] [10]。由 *APC* 突变引起的家族性腺瘤性息肉病(familial adenomatous polyposis, FAP)通常在青少年期出现数百至数千枚腺瘤，如不干预几乎不可避免发展为结直肠癌，且常伴随结直肠外病变[11] [12]。随着临床遗传检测的普及，携带者数量不断增加，迫切需要阐明肿瘤发生的早期机制，并发展真正个体化的预防策略。

传统肿瘤研究模型——包括经典细胞系、基因工程小鼠或患者来源异种移植(PDX)模型，以及患者来源培养体系(如类器官)——在肿瘤生物学研究和治疗评估中不可或缺，但其并未针对重建胚系条件约束下、跨组织的最早致癌步骤进行优化[13] [14]。成熟的肿瘤细胞系具有良好的可扩展性和实验可操作性[15]，但通常来源于晚期病灶，并在长期传代中发生克隆选择及基因组或转录组演化，从而改变表型和药物反应，掩盖由胚系变异所决定的早期致癌轨迹[13]。患者来源类器官在一定程度上保留了关键的组织学和基因组特征，并可用于伴随临床的药物反应测试，但其通常建立于已发生转化的病灶，长期培养同样

可能引入选择性偏移；此外，在同一胚系背景下构建涵盖多种高风险及非高风险组织的匹配类器官面板仍然具有技术挑战性[16]-[18]。

诱导多能干细胞(induced pluripotent stem cells, iPSCs)技术为弥补上述不足提供了互补性的实验框架。通过建立可扩增的患者来源体系，iPSC 模型能够完整保留胚系遗传背景，并可被可重复地分化为疾病相关的人类细胞谱系[19]。结合精准的基因组编辑以构建等基因对照，基于 iPSC 的模型能够在多种人类组织中对胚系变异进行因果性解析，并在受控条件下重建早期“第一击/第二击”致癌动力学过程[20] [21]。iPSC 衍生体系已被广泛应用于二维培养、三维类器官以及整合免疫与基质成分的共培养平台，从而支持对微环境相互作用的实验性研究，并在遗传背景明确的人类体系中评估治疗效果与毒性[22] [23]。此外，iPSC 衍生模型具备良好的可扩展性，适用于大规模遗传或化学扰动筛选，以揭示基因型特异性的依赖关系，包括合成致死相互作用。同时，具备谱系分辨率的 iPSC 模型为识别肿瘤发生前的早期分子异常提供了可操作的平台，有助于提出候选生物标志物和风险分层假设[24] [25]。

2. 遗传性肿瘤易感综合征的 iPSC 模型构建、表征与应用

在疾病建模中，iPSC 的两项核心优势尤为关键：其一是可持续扩增的细胞来源，其二是完整保留供体的胚系遗传背景，在遗传性肿瘤易感研究中，正是胚系变异定义了最早的“起始状态”。

由于后续生物学推断的可靠性高度依赖 iPSC 质量，其建立与质量控制(QC)应被视为“按研究目的定制”的流程，在通量、基因组完整性风险及预期生物学/临床读出之间取得平衡。重编程效率、谱系偏倚及变异负荷均受供体细胞类型、递送方式及培养微环境的影响[26]。因此在遗传性肿瘤易感背景下，分层 QC 尤为必要，因为涉及基因组维护通路(如 *MMR*、*TP*53、*DDR*)的胚系缺陷可能放大克隆漂移及获得性变异的影响。

在功能层面，患者来源的 iPSC 模型通过捕捉携带胚系突变但尚未恶变的起始状态，并支持向疾病相关谱系的受控分化，从而补充了肿瘤来源模型的不足[22] [27]。这些模型完整保留胚系遗传背景，能够在匹配分化和 QC 条件下支持跨 iPSC 衍生谱系的系统比较，这对于多器官受累的综合征尤为重要[28] [29]。iPSC 衍生的二维和三维体系可用于基于基因型的药物测试，而 iPSC 衍生的正常组织则支持对靶向疗效与组织毒性的并行评估[22] [30]。iPSC 模型并非取代动物模型，而是在最具优势的情境下用于提出可检验的早期状态假说，随后在肿瘤类器官或 PDX 中进行验证，并充分认识各模型的固有偏倚[31]。

从应用角度看，iPSC 模型在遗传性肿瘤易感综合征研究中愈发核心，其关键优势在于能够在相关人类谱系中重建“疾病前”或癌前状态[22] [27]。一项重要应用是利用匹配的 iPSC 衍生免疫/基质细胞，与来源于特定胚系背景的上皮前体或类器官共培养，以模拟和解析微环境影响[32]。原代组织图谱研究表明，胚系易感性可与非肿瘤组织中可检测的免疫状态差异相关，支持“易癌微环境(cancer-prone niches)”的概念[28] [29]。iPSC 多谱系分化可生成巨噬细胞和基质细胞，并将其整合入类器官共培养体系中，用于检验肿瘤微环境(TME)的机制性假说[32]。例如，整合巨噬细胞的 PDAC 类器官体系已被用于阐明巨噬细胞状态与肿瘤生长及治疗反应之间的关系[32]。同时，工程化的 iPSC 衍生 NK 细胞平台在临床前研究中显示出可规模化生产及增强的抗肿瘤活性，且 iPSC 衍生 CAR-NK 产品的早期临床研究已观察到疗效[33] [34]。第二个重要应用方向是利用等基因 iPSC 模型进行变异功能解析，包括在匹配分化条件下对致病变异与意义未明变异(VUS)的功能比较[35]。更复杂的设计还可引入多位点组合及工程化“第二击”，以探索修饰因子、外显率差异及胚系－体细胞协同效应[36]。全基因组 CRISPR 筛选已在多能干细胞中实现，并逐步扩展至类器官体系，从而支持系统性发现情境依赖的脆弱性[30]。这些优势同时要求严格的安全措施，因为 CRISPR 编辑可在 hPSC 中触发 p53 介导的选择，并可能引入较大的非预期基因组改变，因此必须进行深度基因分型和克隆级 QC [37]-[39]。

最后，iPSC 模型应被定位为肿瘤来源模型的互补而非竞争体系。肿瘤类器官和 PDX 能够捕捉已形

成肿瘤的复杂性，并在特定情境下与患者治疗反应表现出一致性[14] [40]；相比之下，iPSC 体系最擅长重建携带胚系突变的正常状态及早期癌前演化轨迹，包括在谱系相关类器官中构建工程化“第二击”[27] [36]。一种切实可行的迭代工作流程是：首先利用 iPSC 界定早期谱系程序和潜在脆弱性，随后在来自同一患者或基因型定义队列的匹配肿瘤类器官/PDX 中检验其转化相关性[14] [40]。这一逻辑同样适用于具体综合征。在 BRCA1/2 相关 HBOC 中，iPSC 衍生的相关上皮谱系可用于解析复制应激和 DNA 修复缺陷，并测试基因型特异性的药物敏感性[22] [41]；在 Li-Fraumeni 综合征中，多谱系分化支持在胚系 TP53 变异背景下比较不同组织的应激反应，而等位基因编辑体系可用于模拟具有明确定义“第二击”的早期演化步骤[27]；在 APC 驱动的 FAP 中，肠道分化及类器官体系可定量评估 Wnt 失衡和腺瘤样程序，并支持利用通路调节剂进行化学预防假说检验[42]；在 Lynch 综合征/MMR 缺陷中，上皮分化可追踪突变累积、MSI 相关程序及早期免疫原性，而免疫共培养体系则有助于解析免疫监视和免疫治疗敏感性的机制[29]。总体而言，这些综合征特异性的 iPSC/类器官研究表明，通过严格的 iPSC 构建与 QC、整合单细胞分析以及精准编辑，可将胚系易感性转化为可检验的癌前程序和具有转化潜力的研究假说(表 1)。

Table 1. Exemplar hereditary cancer predisposition syndromes: iPSC-derived lineages, premalignant readouts, and translational hooks

表 1. 代表性遗传性肿瘤易感综合征：iPSC 衍生谱系、癌前读出指标与转化切入点

综合征/基因	最相关的 iPSC 衍生谱系/模型	关键癌前读出指标(示例)	转化切入点(进展/干预)
遗传性乳腺癌/卵巢癌综合征(HBOC) BRCA1/BRCA2/PALB2	输卵管分泌上皮(FTSEC)样模型；乳腺上皮谱系；3D 类器官[22] [35] [41] [43]-[46]	复制压力与同源重组(HR)缺陷程序；谱系分化异常；DNA 损伤信号特征；在特定应激和/或工程化“第二击”条件下出现早期染色体不稳定性	可操作的早期 DNA 损伤应答(DDR)生物标志物；对恶性进展前的组织特异性演化轨迹进行排序；基因型匹配的脆弱性位点(如 PARP/ATR 轴)及耐药通路建模
Lynch 综合征/错配修复缺陷 MLH1，MSH2，MSH6，PMS2	患者来源工程化 PSC/CRISPR 模型[20] [47]	MSI 样不稳定性与突变累积的纵向出现；炎症/干扰素程序；在特定微环境背景下的癌前免疫原性状态和抗原呈递特征	与 MMR 缺失相关的早期检测生物标志物；免疫预防/早期干预假说；影响肿瘤进展及免疫治疗反应的基因型－微环境互作
Li-Fraumeni 综合征(LFS) TP53	多谱系面板(如乳腺、造血、神经/间充质)；用于测试情境依赖性的类器官[27] [48]	检查点与凋亡阈值减弱；谱系依赖性的应激反应；代谢适应；对基因组损伤耐受性增加，从而促进早期克隆选择	对变异/谱系风险进行功能分层；识别情境特异性脆弱性；预测胚系携带者的治疗敏感性/毒性
家族性腺瘤性息肉病(FAP) APC	具有隐窝样组织结构的肠道/结肠类器官；可选基质/免疫共培养以模拟生态位效应[42] [49] [50]	WNT/β-catenin 通路过度激活；干/祖细胞扩增；腺瘤样转录程序；隐窝动力学改变；与炎症刺激协同	在癌前人源上皮中开展化学预防/早期干预测试；腺瘤起始/进展的生物标志物；优先评估 WNT/COX/炎症调节策略

缩略语：iPSC，诱导多能干细胞；MMR，错配修复；MSI，微卫星不稳定性；HR，同源重组；DDR，DNA 损伤应答。

3. 基于 iPSC 的遗传性肿瘤易感模型的局限性与防护边界：安全性、保真度与标准化

尽管 iPSC 模型在遗传性肿瘤易感研究中的应用价值不断提升，其更广泛的转化仍受到技术变异性、

生物学保真度以及临床级流程质量与监管标准尚在演进等因素的限制[51]。除建系阶段外，长期培养过程中可能选择性富集反复出现的基因组异常，包括染色体核型改变和培养适应性变异[52]。这些改变可发生克隆性扩增，从而干扰疾病建模并对转化安全性构成潜在风险[52]。

在生物学层面，一个核心局限是发育成熟度不足：许多 iPSC 衍生上皮组织在转录和功能层面仍保留胎儿样程序，与成年组织存在差异，这在模拟成人起病的癌前演化轨迹及肿瘤易感上皮的应激反应时可能降低模型保真度[53]。对于多数具有年龄依赖外显率的 HCPS 而言，肿瘤易感并不只取决于胚系 first hit 本身，还取决于复制压力、DNA 损伤累积、端粒与表观遗传漂移、细胞衰老以及衰老相关分泌表型(SASP)等时间依赖过程；因此，一个“年轻化”的 iPSC 模型往往更适合捕捉最早期的谱系偏移，却不足以单独替代成年阶段的风险推断[54]-[56]。也正因如此，未在体外观察到显著癌前表型，并不必然意味着胚系变异在成体组织中生物学沉默，也可能仅仅反映模型尚未获得足够的成熟度、应激负荷或年龄相关微环境输入[53] [57]。未来 HCPS-iPSC 研究应将“年龄维度”作为实验设计变量而非背景噪声，结合长期培养、诱导衰老操作(如端粒缩短、DNA 损伤刺激或衰老相关 ECM 条件)、异龄共培养、气液界面或灌流微生理系统，以及必要时的体内移植成熟化策略，比较同一基因型在“发育早期－成熟－加速衰老”连续谱中的表型变化[54] [57]。与此同时，还应在解释层面明确区分“发育窗口表型”与“真正的年龄相关癌前机制”：前者有助于揭示胚系 first hit 如何在组织建立阶段重塑谱系程序，后者则更接近成年携带者的真实外显率与干预时机，这两类信息都重要，但不应被混为一谈[53] [55] [57]。对于面向转化的应用，残留未分化 iPSC 杂质仍是关键安全隐患，因为其可能驱动肿瘤形成；因此，放行检测日益依赖灵敏、定量化的残留多能性标志物检测方法，并理想情况下需在不同实验流程和中心间完成验证[58]。因此，稳健的因果推断依赖于多克隆设计、测序驱动的验证流程，以及在条件允许时进行全基因组层面的评估，以排除大尺度结构重排或选择性偏倚[59]。

4. 结论

基于 iPSC 的谱系模型为遗传性肿瘤易感综合征提供了一个人源、胚系语境明确的研究框架，用以解析肿瘤发生之前最早期的细胞状态[22] [41]。当与等基因工程和多组学分析相结合时，这些模型能够对变异效应进行因果归因，提名癌前生物标志物，并在跨组织层面系统性检验以预防为导向的研究假说[35] [47]。

下一阶段更值得优先推进的，不只是继续增加单个模型案例，而是建立可比较、可累积、可复用的基础平台：建议优先针对 BRCA1/2 相关 HBOC、Lynch/MMRD/CMMRD、Li-Fraumeni 综合征和 FAP，建设标准化的多克隆、等基因、跨谱系 iPSC 资源库，并统一多组学及药物反应读出体系[27] [42] [47] [48]。与此同时，计算生物学方面亟需发展三类分析框架：其一是面向跨批次、跨中心和跨谱系比较的参考图谱映射与整合方法[60]；其二是能够联合转录组、表观组、空间组学与谱系追踪信息的多组学整合模型[61] [62]；其三是能够区分克隆漂移、编辑伪影与真实致癌信号的基因型感知分析流程[37]-[39] [59]。只有当标准化资源库、年龄/成熟度建模、单细胞与空间多组学、以及患者队列和肿瘤来源模型的交叉验证同步推进时，iPSC 平台才有可能从“机制演示工具”真正升级为支持 VUS 解释、风险分层、监测策略优化以及化学预防优先级排序的转化工具[14] [35] [55] [57]。

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