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Hans汉斯

AggreWell^{TM}800板培养乳腺癌肿瘤球模型及其用于盐酸青藤碱药敏实验

王　晗[1*]，张文元[2]，朱　莲[3#]

[1]杭州医学院公共卫生学院，浙江 杭州
[2]杭州医学院检验医学院、生物工程学院，浙江 杭州
[3]杭州医学院基础医学与法医学院，浙江 杭州

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摘　要

目的：通过AggreWell板构建乳腺癌肿瘤球模型，并用于盐酸青藤碱对乳腺癌MDA-MB-231细胞的药敏试验。方法：AggreWell™800板接种MDA-MB-231细胞，构建乳腺癌3D肿瘤球。采用盐酸青藤碱进行药敏试验，CCK-8试剂盒检测。并与2D培养比较。结果：随着加入盐酸青藤碱浓度的升高，MDA-MB-231细胞抑制率逐渐上升，呈剂量依赖性。AggreWell板培养的乳腺癌3D肿瘤球对盐酸青藤碱的药物敏感性显著低于传统2D培养。结论：本实验研究表明，相比于传统2D培养，使用AggreWell板培养的乳腺癌3D肿瘤球对盐酸青藤碱的药敏性显著更低，可能更能反映体内肿瘤的真实情况，在评估抗癌药物方面可能更具优势。

关键词

AggreWell™800板，乳腺癌肿瘤球模型，盐酸青藤碱，药敏试验

Breast Cancer Tumor Spheroid Model Established Using the AggreWell™800 Plate and Its Application in Drug Sensitivity Test of Sinomenine Hydrochloride

Han Wang[1*], Wenyuan Zhang[2], Lian Zhu[3#]

[1]School of Public Health, Hangzhou Medical College, Hangzhou Zhejiang
[2]School of Laboratory Medicine and Bioengineering, Hangzhou Medical College, Hangzhou Zhejiang
[3]School of Basic Medical Sciences and Forensic Medicine, Hangzhou Medical College, Hangzhou Zhejiang

*第一作者。
#通讯作者。

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Abstract

Objective: To construct a breast cancer tumor spheroid model using the AggreWell plate and apply it to the drug sensitivity test of sinomenine hydrochloride on breast cancer MDA-MB-231 cells. Methods: MDA-MB-231 cells were seeded in the AggreWell™800 plate to form 3D breast cancer tumor spheroid. The sinomenine hydrochloride was used for the drug sensitivity test, and the CCK-8 kit was employed for detection. A comparison was made with 2D culture. Results: As the concentration of sinomenine hydrochloride added increased, the inhibition rate of MDA-MB-231 cells gradually rose, showing a dose-dependent manner. The drug sensitivity of the 3D breast cancer tumor spheroid cultured in the AggreWell plate to sinomenine hydrochloride was significantly lower than that of traditional 2D culture. Conclusion: This experimental study indicates that compared with traditional 2D culture, the 3D breast cancer tumor spheroid cultured in the AggreWell plate has significantly lower drug sensitivity to sinomenine hydrochloride, which may better reflect the real situation of the tumor in the body and may have more advantages in evaluating anti-cancer drugs.

Keywords

AggreWell™800 Plate, Breast Cancer Tumor Spheroid Model, Sinomenine Hydrochloride, Drug Sensitivity Test

1. 引言

乳腺癌是全球范围内影响女性健康的最常见实体癌，造成严重的健康问题[1]。传统的二维(2D)单层培养不能充分捕捉实体肿瘤的复杂性，三维(3D)共培养系统提供了更准确的肿瘤微环境表征[2]。乳腺癌研究中常用的模型，包括 2D 培养和动物模型，并不能精确地模拟乳腺肿瘤的所有方面。3D 细胞培养模型是研究乳腺癌的新方法，可成为传统 2D 培养和体内模型之间的纽带[3] [4]。青藤碱是一种从中药青藤中提取的化合物[5]。盐酸青藤碱为青藤碱的盐酸盐形式，在一定剂量下，对乳腺癌具有抗肿瘤和抗转移作用，可通过激活 AMPK-mTOR 通路诱导细胞凋亡[6]。本实验以 AggreWell™800 培养板种植 MDA-MB-231 细胞，构建 3D 乳腺癌肿瘤球，用于盐酸青藤碱药敏实验。通过预实验结果，盐酸青藤碱实验浓度分别选择 0、100、200、400 μg·mL^{-1}，并与传统 2D 培养比较。

2. 材料与方法

2.1. 药品与试剂

乳腺癌 MDA-MB-231 细胞(iCell 赛百慷)；盐酸青藤碱(麦克林)，用含 10%FBS、1%青链霉素的 L15 完全培养基稀释成工作浓度。L15 培养基(Hyclone)；胎牛血清(Gibco)；AggreWell™800 24 孔培养板(STEMCELL Technologies)，使用前在超净台用紫外线照射 30 min。普通 24 孔、96 孔培养板(Corning)，CCK-8 试剂盒(碧云天)。抗粘附漂洗液(STEMCELL Technologies)。倒置相差显微镜(IX73, Olympus)，多功能酶标仪(上海普丹)。

2.2. 2D 药敏试验

参照文献[7]，乳腺癌 MDA-MB-231 细胞使用 L15 完全培养基常规培养。胰蛋白酶消化后，配制成 1×10^5 cells·mL^{-1} 的细胞悬液，加入普通 24 孔培养板中，每孔加 1 mL，培养 24 h，吸弃培养基。然后分别加入不同浓度的盐酸青藤碱(0、100、200、400 μg·mL^{-1})，每孔加 1 mL，每个浓度设 3 个平行孔。继续培养 48 h，倒置显微镜观察，并 CCK-8 检测。

2.3. 3D 药敏试验

参照文献[7]，取 AggreWell™800 24 孔培养板，每孔加入抗粘附漂洗液 1 mL，2000 ×g，离心 5 min，吸弃液体。每孔加入浓度为 1×10^5 cells·mL^{-1} 的 MDA-MB-231 细胞悬液 1 mL，100 ×g，离心 3 min。培养 24 h，吸弃培养基。然后分别加入不同浓度的盐酸青藤碱(0、100、200、400 μg·mL^{-1})，每孔加 1 mL，每个浓度设 3 个平行孔。继续培养 48 h，倒置显微镜观察，并 CCK-8 检测。

2.4. CCK-8 检测细胞抑制率

取上述 2D/3D 药敏试验的两种 24 孔板，更换成新鲜培养基后，每孔加入 100 μL CCK-8 反应溶液，37℃温育 3 h。每孔吸取 100 μL 转移到普通 96 孔板中，450 nm 处读取 OD 值，每个浓度均 3 个平行孔。细胞抑制率 = (1 − 实验组 OD 值/对照组 OD 值) × 100%。

2.5. 统计分析

使用 SPSS 18.0 软件进行统计分析。数据资料以 $\bar{x}\pm s$ 表示，两组间比较采用两独立样本 t 检验，$P<0.05$ 为差异有统计学意义。

3. 结果

3.1. 2D 培养条件下盐酸青藤碱对乳腺癌 MDA-MB-231 细胞增殖的影响

当盐酸青藤碱浓度 100 μg·mL^{-1} 时，MDA-MB-231 细胞受到一定程度的抑制。当浓度 200 μg·mL^{-1} 时，细胞出现明显抑制。当浓度 400 μg·mL^{-1} 时，细胞大量死亡。呈剂量依赖性。当盐酸青藤碱浓度在 200 与 400 μg·mL^{-1} 时，细胞生长抑制率均超过 50%。见图 1、表 1。

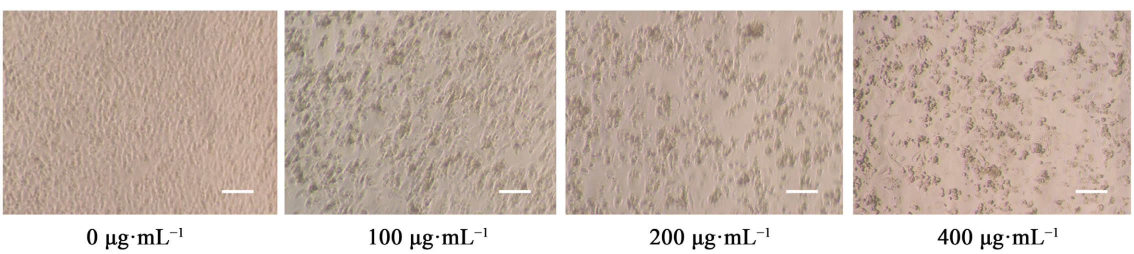

Figure 1. Effects of different concentrations of sinomenine hydrochloride on the survival of 2D-cultured breast cancer MDA-MB-231 cells (100×, scale = 100 μm)
图 1. 不同浓度盐酸青藤碱对 2D 培养的乳腺癌 MDA-MB-231 细胞存活的影响(100×，标尺 = 100 μm)

3.2. 3D 培养条件下盐酸青藤碱对乳腺癌 MDA-MB-231 细胞生长的影响

不同浓度盐酸青藤碱对 3D 乳腺癌 MDA-MB-231 细胞肿瘤球增殖活性的影响情况：随着盐酸青藤碱浓度的增加，MDA-MB-231 细胞生长逐渐受到抑制，死细胞逐渐增多。当盐酸青藤碱浓度在 100 与 200 μg·mL^{-1} 时，细胞受到一定程度的抑制。当盐酸青藤碱浓度在 400 μg·mL^{-1} 作用时，MDA-MB-231 死亡细

胞数量明显增多，抑制率超过 50%。呈剂量依赖性。见图 2、表 1。

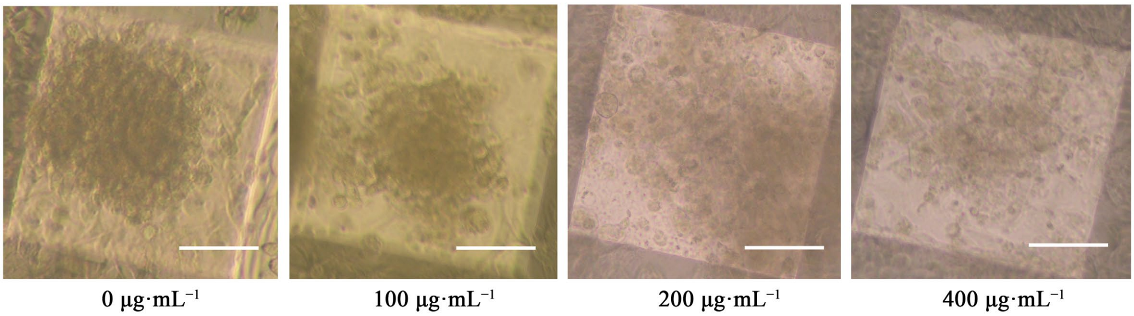

Figure 2. Effects of different concentrations of sinomenine hydrochloride on the survival of MDA-MB-231 breast cancer 3D tumor spheroids (scale = 100 μm)
图 2. 不同浓度盐酸青藤碱对乳腺癌 MDA-MB-231 细胞 3D 肿瘤球存活的影响(标尺 = 100 μm)

3.3. 2D/3D 条件下盐酸青藤碱对乳腺癌 MDA-MB-231 细胞抑制率影响的比较

不同浓度盐酸青藤碱对 2D/3D 条件下乳腺癌 MDA-MB-231 细胞抑制率的影响情况：随着盐酸青藤碱浓度的逐渐升高，MDA-MB-231 细胞生长逐渐受到抑制，死细胞数量逐渐增多，呈剂量依赖性。不同浓度的盐酸青藤碱对 3D 培养条件下乳腺癌 MDA-MB-231 细胞肿瘤球的药物敏感性显著低于 2D 培养。即与 2D 培养相比，3D 肿瘤球的耐药性显著增加。结果见图 1、图 2、表 1。

Table 1. Inhibitory rate of different concentrations of sinomenine hydrochloride on the growth of breast cancer MDA-MB-231 cells under 2D/3D culture conditions ($\bar{x} \pm s$, n = 3)
表 1. 2D/3D 培养条件下不同浓度盐酸青藤碱对乳腺癌 MDA-MB-231 细胞生长的抑制率($\bar{x} \pm s$, n = 3)

盐酸青藤碱剂量($\mu g \cdot mL^{-1}$)	2D 培养细胞抑制率(%)	3D 培养细胞抑制率(%)
100	34.58 ± 3.02	17.35 ± 1.49***
200	67.61 ± 5.35	35.92 ± 2.87***
400	83.34 ± 7.16	54.83 ± 5.20***

注：***：与 2D 培养细胞生长抑制率相比，$P < 0.001$。

4. 讨论

乳腺癌被视为“上个世纪未解决的问题”，迄今尚未确定有效的解决方案[8]。2D 体外培养模型虽然有助于获得初步见解，但始终存在缺陷，并且经常对治疗剂产生夸大反应[9]。肿瘤和微环境异质性阻碍了乳腺癌生物学的研究和治疗策略的评估，给乳腺癌的研究和治疗带来了很大的障碍[10]。癌症生物学研究越来越趋向于创新的体外 3D 培养模型[11]。在这种背景下，需建立能够再现这种异质性以及肿瘤细胞与微环境之间发生动态相互作用的 3D 乳腺癌模型，这对于准确了解肿瘤生物学、行为，以及对治疗反应而言至关重要[12]，从而有助于新靶向治疗策略的开发[13]。

从植物青藤中提取的盐酸青藤碱对人类多种恶性实体瘤具有较强的抗癌活性[14] [15]。青藤碱在抗肿瘤研究中的核心价值，它不仅能够直接杀伤肿瘤细胞，更在抑制肿瘤的转移方面显示出巨大潜力[16]，而肿瘤转移正是导致癌症患者死亡的主要原因[17]。青藤碱的抗肿瘤作用不是通过单一途径，而是多靶点、多通路协同实现的，这正体现了其“独特”之处[18] [19]。从“杀伤肿瘤”转向“控制肿瘤”，特别是抑制其转移，直接从关键环节上抑制癌细胞的侵袭和迁移能力[20]。这使得青藤碱及其衍生物有望成为传统化疗/放疗的增敏剂，预防肿瘤复发和转移的辅助治疗药物，以及针对晚期转移性癌症的潜在治疗选择。

随着临床前研究和未来临床试验的推进，青藤碱类化合物很有希望为癌症治疗策略带来新的突破[21]。盐酸青藤碱的抗肿瘤作用并非通过单一的细胞毒性(直接杀死细胞)，而是通过多靶点、多通路的方式，尤其擅长抑制肿瘤的侵袭、迁移和转移，显示出独特优势与巨大潜力[22] [23]，这与传统化疗药有本质区别。在预防和治疗癌症转移方面具有广阔的应用前景。当前的研究热点正是通过开发新型衍生物，克服其自身缺点，将其从一个有潜力的天然产物活性成分，转化为真正可用于临床高效、低毒抗肿瘤药物，尤其是在联合治疗和抑制转移方面。

AggreWell 是一种专门设计的细胞培养板，其底部有大量微米级微孔。这些微孔的作用是在离心力的帮助下，将细胞捕获并聚集到一个固定的位置，从而形成大小均一、形状规则的 3D 细胞球[24]，可极大地减少实验误差，提高数据的可靠性和重复性。除了在形成胚胎体[25]、类器官培养[26]方面以外，可将肿瘤细胞形成细胞球(肿瘤球)，以模拟实体瘤的 3D 微环境，用于癌症生物学、药物渗透性、放疗抵抗性、抗癌药物筛选等研究[27] [28]，以评估抗癌药物对 3D 肿瘤细胞群体的效力和毒性[29] [30]。

5. 结论

本实验研究表明，相比于传统 2D 培养，使用 AggreWell™800 板培养的乳腺癌 3D 肿瘤球，对盐酸青藤碱的药敏性显著更低，可能更能反映体内肿瘤的真实情况，在评估抗癌药物方面可能更具优势。

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