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微流控芯片分离检测循环肿瘤细胞研究进展

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摘 要

癌症是全球发病率与死亡率最高的恶性肿瘤。循环肿瘤细胞(CTCs)作为液体活检的核心标志物，可无创反映肿瘤异质性与转移潜能，然而，由于CTCs在外周血中含量极低且易受血细胞干扰，因此亟需开发高效的富集与高灵敏度的检测技术。微流控芯片凭借微型化、集成化、低损伤等优势，成为CTCs分离检测的理想平台。文章系统综述肿瘤临床诊疗现状与CTCs生物学意义，分类阐述被动式(尺寸分离、惯性微流控、确定性侧向位移、粘弹性微流控)与主动式(介电泳、磁泳、声泳)微流控细胞分离原理、技术特点及应用进展；对比荧光成像、拉曼光谱、电化学、光电化学等CTCs检测方法的优劣，重点分析光电化学–荧光双模态检测的协同优势。在此基础上，总结当前微流控技术在CTCs富集纯度、检测灵敏度、临床适配性等方面的瓶颈，展望多物理场耦合、智能化集成、单细胞多组学分析等发展方向，以期为肿瘤早期无创诊断、精准分型及预后监测的微流控技术研发提供理论参考，推动液体活检技术向临床转化。

关键词

循环肿瘤细胞，微流控芯片，双模态检测

Advances in Microfluidic Chips for Separation and Detection of Circulating Tumor Cells

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Abstract

Cancer is the malignant tumor with the highest incidence and mortality worldwide. As a core biomarker

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for liquid biopsy, circulating tumor cells (CTCs) can noninvasively reflect tumor heterogeneity and metastatic potential. However, CTCs are extremely scarce in peripheral blood and susceptible to interference from blood cells, creating an urgent demand for efficient enrichment and highly sensitive detection techniques. Microfluidic chips have become an ideal platform for CTC separation and detection owing to their advantages of miniaturization, integration, and low cell damage. This paper systematically reviews the current status of clinical diagnosis and treatment of cancer and the biological significance of CTCs, classifies and elaborates the principles, technical characteristics, and application progress of passive microfluidic cell separation (size-based separation, inertial microfluidics, deterministic lateral displacement, viscoelastic microfluidics) and active microfluidic cell separation (dielectrophoresis, magnetophoresis, acoustophoresis). It compares the merits and drawbacks of CTC detection methods, including fluorescence imaging, Raman spectroscopy, electrochemistry, and photoelectrochemistry, with emphasis on the synergistic advantages of photoelectrochemical-fluorescence dual-mode detection. Furthermore, it summarizes the current bottlenecks of microfluidic technologies in CTC enrichment purity, detection sensitivity, and clinical adaptability, and prospects the future directions such as multiphysical field coupling, intelligent integration, and single-cell multi-omics analysis. This review aims to provide a theoretical reference for the development of microfluidic technologies for early noninvasive diagnosis, precise typing, and prognosis monitoring of cancer, and to promote the clinical translation of liquid biopsy techniques.

Keywords

Circulating Tumor Cell, Microfluidic Chip, Dual-Mode Detection

1. 引言

癌症的全球发病率和死亡率较高[1] [2]，且具有高度异质性。以肺癌为例，其在组织学上主要分为非小细胞肺癌(NSCLC)和小细胞肺癌(SCLC)两大类，其中 NSCLC 约占全部肺癌病例的 85% [3]。该类型可进一步分为腺癌、鳞状细胞癌和大细胞癌三种亚型[4]-[6]。由于癌症进展常伴随上皮－间质转化和远处转移，因此，实现其不同亚型癌细胞的精准鉴别对临床诊疗决策具有重要意义[7]。

目前，癌症的筛查与诊断主要依赖于影像学检查与组织活检，但这些方法存在过度诊断、易出现假阳性、辐射暴露以及侵入性操作等局限性[8]-[10]。若能在临床症状出现前，通过单次检测实现癌症早期识别与亚型区分，则可以降低医疗成本、优化资源分配。但现有技术在此方面存在不足。因此，开发一种具备高灵敏度、高特异性、非侵入性的早期诊断平台，对癌症的精准防治具有重要临床价值。

循环肿瘤细胞作为从原发或转移灶脱落进入外周血的癌细胞，被广泛认为是癌症转移和复发的关键介质，是重要的液体活检生物标志物[11]-[13]。然而，CTCs 在外周血中含量极低，尤其在早期患者中，这使得直接计数并获得准确结果变得困难。因此，检测前通常需对 CTCs 进行高效的富集与分离[14]。目前，多数富集技术仍存在明显局限，如损伤细胞完整性、难以有效捕获间充质表型亚群[15]，且在灵敏度、特异性、稳定性及可重复性等方面亦有不足[16]。本研究针对这些问题，提出利用物理尺寸差异与生物亲和力结合的策略，以实现高纯度富集与精确亚型鉴定，这对于推动精准医疗发展具有重要意义。

2. 微流控芯片中细胞分离的方法

微流控细胞分离技术是在微米级通道网络构成的微流控芯片上，基于细胞尺寸、变形性、密度、介电性、惯性等物理特性或表面抗原、亲和性、免疫识别等生物化学特性实现细胞精准分选与纯化的技术[17] [18]。其原理主要依据微尺度流体力学、场间相互作用及分子识别动力学等理论[19] [20]。

微流控分离细胞可分为被动分离与主动分离两大类[21]。被动分离主要依靠通道结构与流体力学实现分选[22]。主动分离则借助电场、声场、磁场等外场对细胞进行精确操控[23]。微流控芯片能够将进样、反应、分离、检测等实验室功能集成在微小载体上，具有样本消耗量小、分离速度快、对细胞损伤低、分辨率高、易于微型化与集成化等突出优点[24]。在循环肿瘤细胞分选、临床无创、干细胞与免疫细胞纯化、单细胞分析以及药物筛选等领域应用广泛[25]。但该技术也存在处理通量相对较低、芯片加工工艺要求较高、复杂生物样本易发生通道堵塞、标准化与商业化体系不完善等局限[26]。综上所述，微流控细胞分离技术理论基础扎实、应用前景广阔，是现代生物医学研究与临床精准诊疗中不可或缺的细胞处理技术。

2.1. 被动式细胞分离方法

基于被动式细胞分选方法是通过芯片通道中的几何结构设计与微尺度流体力学效应实现细胞分选，无需借助电场、磁场、声场等调控，主要依据细胞之间的尺寸、变形性、密度等物理特性之间存在的差异完成分离[27]。该类方法具有结构简单、无需外接驱动设备、操作稳定性高、系统集成成本低等优势。分离过程温和，避免外场损伤细胞，较好地维持了细胞的生物活性，同时具有高通量、连续化分离与重复性好等特点，适用于快速、大批量的细胞富集与纯化[28] [29]。然而，被动式分离方法也存在局限，例如，分离机制与通道结构高度相关、不能灵活调控不同类型细胞的筛分、对物理特性相近的细胞难以实现高精度的分选、通道结构和适用场景相对固定。面对成分复杂、黏度较高或杂质较多的生物样本时容易出现通道堵塞问题，难以实现多目标细胞的同步分选与动态实时调控，在分选精度与功能扩展性上仍存在一定瓶颈[30]-[32]。

基于尺寸分离的微流控芯片是根据细胞直径差异实现分离，是最直观的物理分离机制[33]。该方法是在微流控通道内设计微柱阵列、筛网结构、狭缝结构或蜂巢阵列等结构，利用目标细胞与背景细胞的尺寸差异实现筛分[34]-[37]。当混合细胞样本随流体流经筛分结构时，直径大于通道或筛分结构临界尺寸的细胞会被阻挡，而直径小于临界尺寸的目标细胞可顺利穿过筛分结构，随主流流体流出，从而实现不同尺寸细胞的分离[38]。该方法的优势是分离速度快、芯片加工难度低，可快速实现细胞样本的初步分级与富集，适用于细胞悬液中杂质去除、大小不同细胞的初步分离[39]。但同时也存在通道堵塞、分离精度有限、临界尺寸调整较难、适用范围相对固定等局限[40]。典型研究如 Cima 及其同事利用硅微筛从术前结直肠癌患者的血液中提取 CTCs [41]。

惯性微流控基于流体惯性升力实现细胞聚焦与分离，如图 1 所示，主要包括剪切梯度升力与壁面效应升力[42]。在矩形或弯曲微通道中，当雷诺数处于中低区间时，细胞在惯性作用下自动迁移至平衡位置，形成聚焦流。该方法通量高、结构简单、无需标记，适用于血细胞、肿瘤细胞等快速分选。由于其高通量和结构简单的优势，该技术在生物医学检测、临床诊断、环境监测等领域得到了广泛应用。例如 Si 等人利用惯性微流控从全血中分离 EVs。实验结果表明，该方法可在 1 小时内从 2 毫升全血中分离 EVs，同时最大限度地减少非特异性吸附[43]。

确定性侧向位移分离(DLD)是基于周期性微柱阵列的高精度被动分离技术，其理论核心为流体流线与粒子运动轨迹的确定性偏移[45]。如图 2 所示，微柱按照特定角度排列，将流体分割为固定宽度的流线，小于临界尺寸的粒子随流线运动，大于临界尺寸的粒子发生侧向位移，从而实现连续和高精度的分离[46]。DLD 分离精度极高、重复性好，可实现微米级差异细胞的分选[47]。

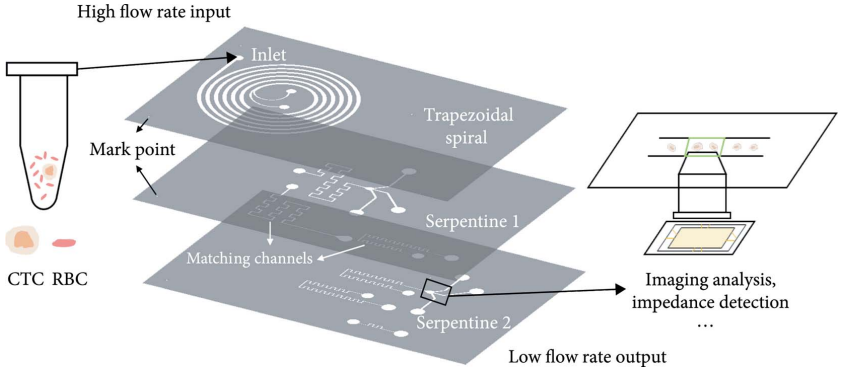

Figure 1. 3D-stacked multistage inertial microfluidic cell sorting chip [44]
图 1. 三维堆栈多级惯性微流控单元分选芯片[44]

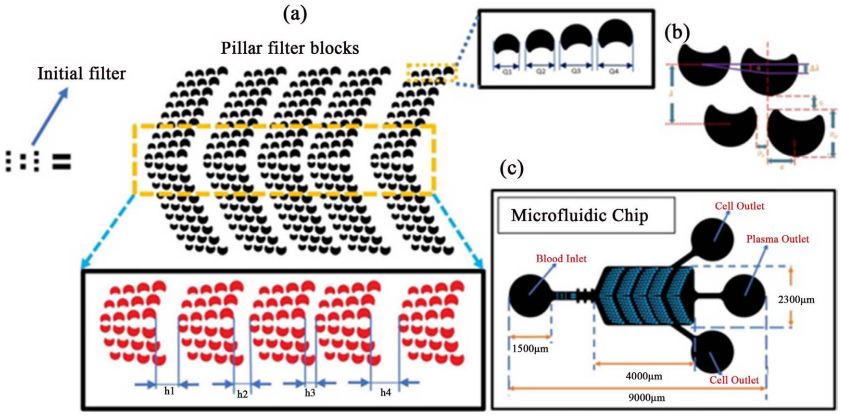

Figure 2. The detailed filter design in a silicon microfluidic structure [48]
图 2. 硅微流控结构中的详细滤波器设计[48]

如图 3 所示，粘弹性微流控是一种被动式微流控分离聚焦技术：在粘弹性非牛顿流体中，利用弹性力和惯性力的协同作用，驱动粒子或细胞发生侧向迁移并聚焦到通道特定平衡位置，实现无鞘流、三维聚焦、高分辨率分选。主要运用于亚微米、纳米颗粒(如外泌体、病毒)与细胞分离[49]。

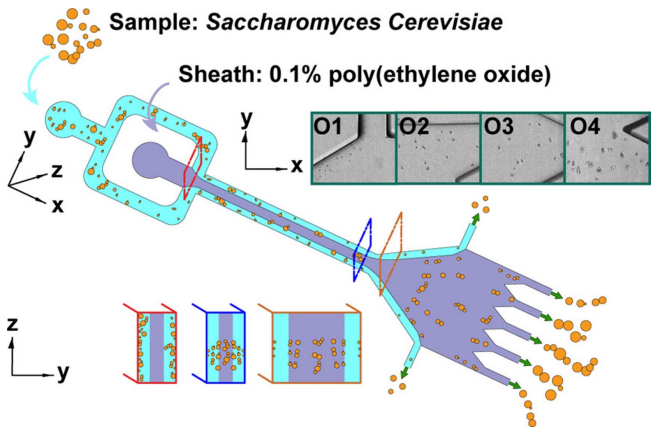

Figure 3. Separation and enrichment of yeast *Saccharomyces cerevisiae* by shape using viscoelastic microfluidics [50]
图 3. 利用粘弹性微流控技术对酿酒酵母的形状进行分离与富集[50]

2.2. 主动式细胞分离方法

主动式细胞分离技术通过在微流控通道外部引入电场、磁场、声场等可控物理场(如图 4 所示)，对不同类型细胞施加差异化场力，从而实现细胞运动轨迹的调控与高效分离[51]。相较于被动式分离，该类方法不受通道几何结构的单一限制，调控自由度更高、分选选择性更强、分辨率更突出，能够有效区分物理特性相近的细胞，尤其适用于成分复杂、基质干扰较强的生物样本分离[52]。

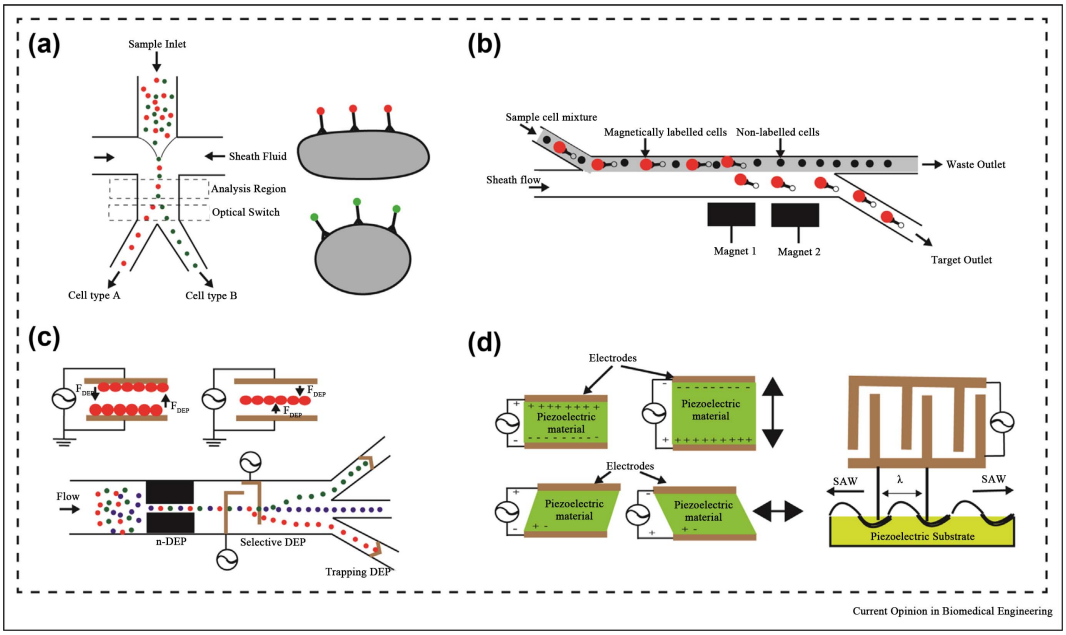

Figure 4. Schematic representation of various active microfluidic systems [53]
图 4. 各种主动微流控系统的示意图[53]

介电泳分离(DEP)：介电泳是细胞在非均匀电场中因极化效应产生定向运动的现象(如图 5 所示)，理论基础为麦克斯韦－瓦格纳极化理论[54]。细胞的介电泳力大小与方向由细胞尺寸、介电常数、电导率及介质特性决定[55]。通过设计微电极阵列产生非均匀电场，可实现肿瘤细胞、血细胞的高选择性分选[56]。DEP 可实现无标记、单细胞精度分离，但需引入电场，可能对细胞活性产生影响。Li 等人开发了一种整合介电泳与磁光技术的装置，用于连续分离悬浮在稀释血浆中的四种 CTC 和血小板，为将 CTC 与血液成分有效分离提供了可靠的方法[57]。

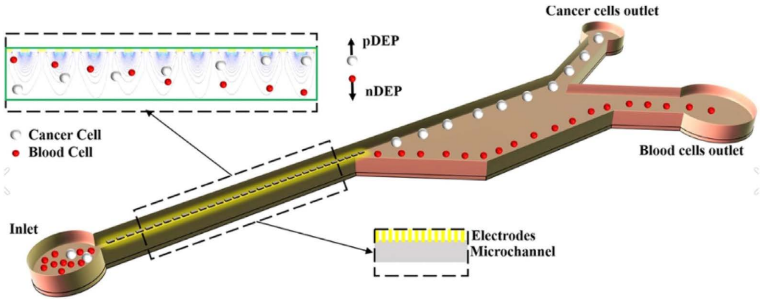

Figure 5. eDEP based microfluidic for separation of CTC from blood cells [58]
图 5. 基于 eDEP 的微流控技术用于从血细胞中分离 CTC [58]

磁泳分离基于细胞与磁性颗粒的免疫磁标记，在外部磁场中实现分离[59]。目标细胞与磁珠特异性结合后，在磁场梯度中受力迁移，未标记细胞随流体通过(如图 6 所示)。磁泳分离选择性极高、条件温和，是临床免疫细胞分离的常用方法，但需要免疫标记与磁珠修饰，流程相对复杂[60]。Fu 等人制造了一个简便的级联负磁分流微流控芯片，并在线连接感应耦合等离子体质谱(ICP-MS)，以快速分离和检测血液样本中罕见的 CTC。该装置可在高通量 100 μL·min^{-1} 的速率下实现 CTCs 的浓缩并具备直接下游分析和重建能力(细胞存活率为 99.27%) [61]。

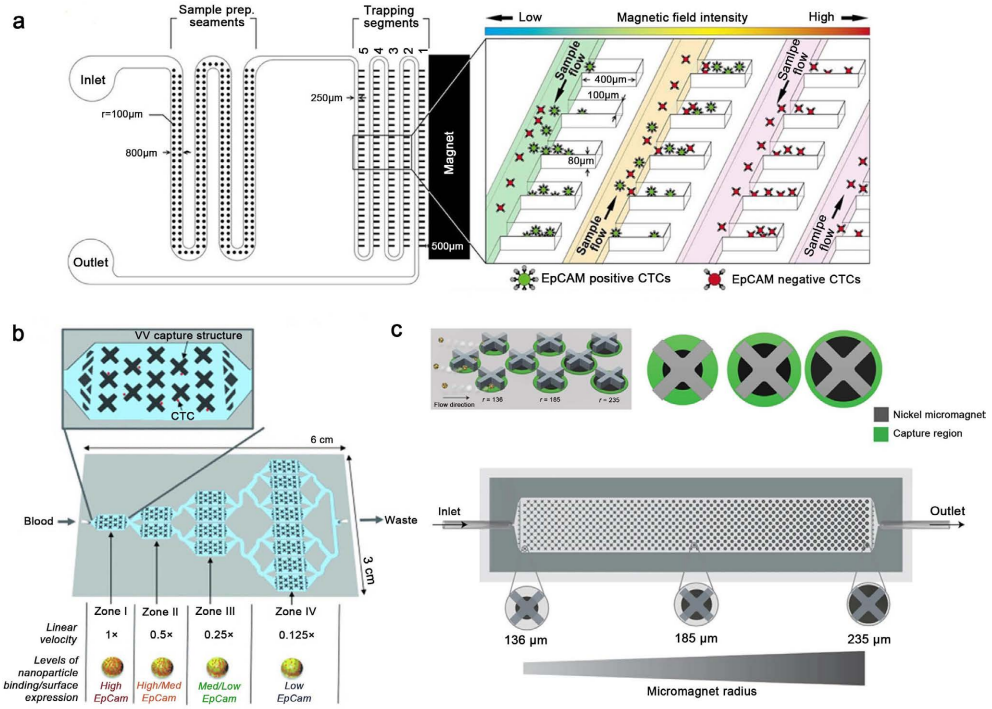

Figure 6. Magnetic nanoparticlemediated separation devices [62]
图 6. 磁性纳米颗粒介导分离装置[62]

声泳分离技术利用超声驻波场中的声辐射力实现细胞分离[63]。密度与压缩系数不同的细胞在声场中迁移至不同平衡位置，实现无接触、无损伤、高活性分离(如图 7 所示)。声学驻波与微流控设计的结合使声流体平台能够通过声波辐射力实现高精度单元分选，为 CTCs 的隔离提供了有前景的方法[64]。然而，声辐射力在作用小于 5 μm 的生物靶点(如小细胞和微生物)时面临固有挑战，限制了其在 CTCs 隔离中的广泛应用，声泳具有生物相容性好、分离效率高、易于集成等优势，适用于血细胞、细菌、肿瘤细胞分选[65]。Eva 等人开发了一种两步顺序声学传送方法，从红细胞(RBC)溶解的全血中分离出癌细胞。这两个步骤基于细胞和颗粒的声学易位，先进行初级分离，再通过二次净化步骤，利用负选择声泳技术去除污染的白细胞[66]。

3. 检测 CTCs 的主要方法

在全球范围内，癌症是危害人类健康的最严重的恶性疾病之一[68]。相关临床研究表明，大多数患者在确诊时已经进入癌症晚期或者伴有肿瘤转移，无法达到根本治愈，这是癌症患者死亡的主要原因[69]。目前，早期诊断肿瘤细胞的方法有影像学、组织活检和液体活检[70]。其中，影像学检查微小肿瘤存在局限性，依赖高分辨率成像系统导致设备体积大、成本高[71]。组织活检需要采用微创方法从肿瘤组织中提

取细胞进行病理检查，成像速度与通量难以兼顾，易受光照、通道透光性及样本非特异性吸附干扰[72]。而液体活检通过检测体液中循环的生物标志物来检测肿瘤[73]。目前常见的 CTCs 检测方法有荧光检测、光谱检测、电化学检测、光谱检测、光电化学检测等[74]。

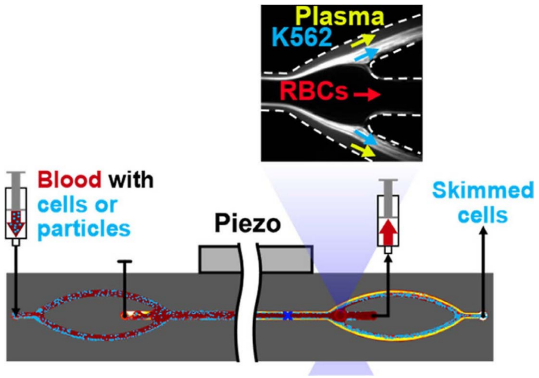

Figure 7. Separation of cancer cells directly from whole blood [67]
图 7. 从全血中进行癌细胞的声流分离[67]

3.1. 荧光成像检测

CTCs 荧光成像检测技术利用荧光标记的特异性抗体，与循环肿瘤细胞(CTCs)表面或胞内的特征性抗原特异性结合，并辅以荧光染料标记以排除干扰。随后，通过荧光显微镜或全自动成像系统获取样本图像，依据荧光信号的位置、强度及组合特征，实现对 CTCs 的可视化识别、定位与定量检测[75]。

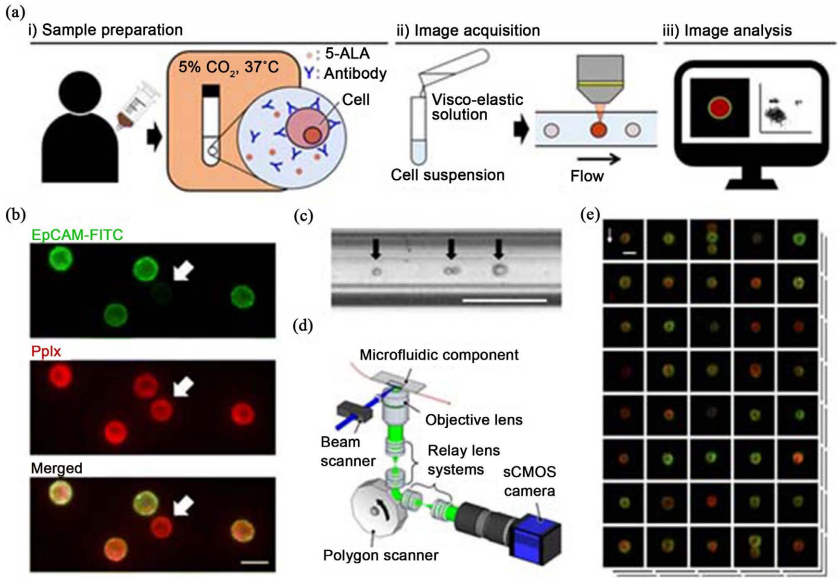

Figure 8. Schematic of fluorescence imaging and flow cytometric detection [80]
图 8. 荧光成像及流式细胞数检测[80]

如图 8 所示，荧光成像检测技术可实现循环肿瘤细胞的可视化观察，能在单细胞水平上直观分析细胞形态与标志物表达[76]。通过多色荧光标记具有较高特异性的目标细胞，可有效区分肿瘤细胞与其他细胞，操作较为成熟，能够对循环肿瘤细胞进行定性与定量检测，适用于肿瘤疗效评估、复发监测等临床

场景[77]。但该技术依赖肿瘤细胞抗原表达，易漏检抗原表达下调的细胞，检测通量较低、耗时较长，且荧光信号易发生光漂白，背景干扰较强，影响检测稳定性与准确性[78]。Luo 等人报告了一种多功能的金纳米探针温泳测定法，用于特异性区分前列腺癌 CTCs 和细胞内微 RNA (miR-21)。并进行灵敏成像，实现了前列腺癌快速且精准的检测[79]。

3.2. 拉曼光谱检测

拉曼光谱检测是利用肿瘤细胞与正常细胞在分子组成、结构上的差异，通过分析其散射或分子振动特征实现无标记检测的一类技术[81]。拉曼光谱依托分子振动产生的特征散射信号，可实现无标记、非破坏性、快速的分子指纹检测，特异性高，能准确识别化学成分、生物分子结构和细胞组成[82]。且样品前处理简单，几乎不受水的干扰，与微流控液体环境高度兼容[83]。但拉曼光谱也存在明显局限：其固有的拉曼散射信号极弱，导致灵敏度相对较低，易受样品或基底的背景噪声与荧光信号干扰[84]。此外，检测效率易受激光功率、采集时间和芯片材料影响，且配套光谱仪与激光器成本较高，阻碍了其在便携化、低成本即时检测系统中的进一步应用[85]。

3.3. 电化学检测

电化学检测是基于肿瘤细胞与传感界面相互作用后引发的氧化还原反应，将细胞识别信息转化为可量化的电流、电压或阻抗信号的检测技术。如图 9 所示，其核心原理是通过在工作电极表面修饰特异性识别单元(如抗体、适配体)，实现目标肿瘤细胞的特异性捕获[86]。捕获后细胞对电极表面电子传递过程产生阻碍或促进作用，或通过酶催化、纳米材料增敏等方式放大氧化还原信号，最终通过电化学工作站采集并分析信号强度，实现肿瘤细胞的定性识别与定量分析[87]。该技术具有设备结构简单、操作便捷、响应速度快、成本低廉、易于微型化与微流控芯片集成的显著优势，可快速实现肿瘤细胞的初步检测[88]。但受生物样本(如全血、组织液)中蛋白质、电解质等基质成分的影响较大，易发生非特异性吸附，导致检测信号干扰，同时其检测选择性主要依赖识别单元的特异性，整体选择性有限，难以在复杂基质中实现痕量肿瘤细胞的精准检测[89]。Tian 等人开发了一种闭合双极电极阵列电化学发光(c-BPE-ECL)芯片，用于同时检测肿瘤细胞表面的癌胚抗原(CEA)和 α 胎蛋白(AFP)。c-BPE-ECL 系统对 CEA 和 AFP 检测具有很高的灵敏度，计算出的检测限为 6.12 pg·mL^{-1} 以及 0.25 pg·mL^{-1} [90]。

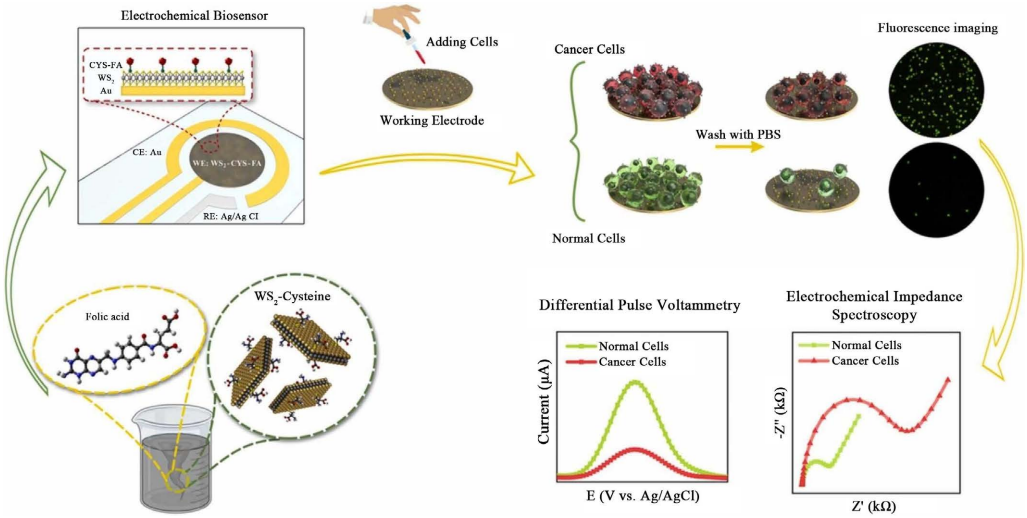

Figure 9. Label-free and high-efficiency electrochemical biosensor [91]
图 9. 无标记高效电化学生物传感器[91]

3.4. 光电化学传感器检测

光电化学检测以光敏材料(如半导体纳米材料、金属有机框架材料)在特定波长的光照下会产生光生电子－空穴对，通过光生载流子的分离与转移形成稳定的光电流信号，实现肿瘤细胞的高灵敏检测[92]。光电化学传感器将特异性识别单元修饰在有光敏材料的工作电极表面，当目标肿瘤细胞被特异性捕获后，会阻碍光生电子－空穴对的分离与界面电子传递，导致光电流信号发生显著变化(图 10)，通过检测光电流的变化值，可以实现肿瘤细胞的定量分析[93]。该技术最突出的优势是激发源(光照)与检测信号(电流)相互分离，有效避免了激发光对检测信号的干扰，背景信号极低，检测灵敏度远高于传统电化学与单一光谱检测技术[94]。同时，其检测系统结构相对简单、响应速度快、生物相容性好，且易于与微流控芯片的微通道、富集单元集成，非常适合构建微型化、高灵敏的肿瘤细胞检测系统，是痕量肿瘤细胞检测的优选技术之一。Ren 等人设计了一种基于智能手机的光电化学传感器，基于氧空位(Ovs)驱动的信号增强，用于汞离子检测。传感器对 Hg^{2+}表现出良好的线性度，浓度范围为 0.1 nM~1.0 μM [95]。

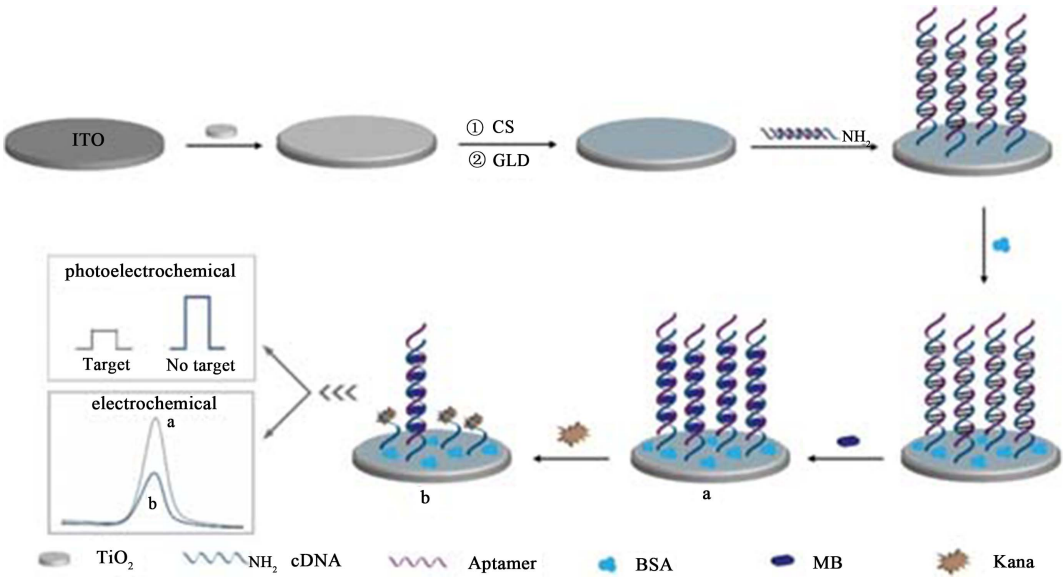

Figure 10. Schematic diagram of the dual-model PEC sensor [96]
图 10. 双模光电化学传感器原理图[96]

综上所述，单一检测技术均存在各自的优势与局限。电化学检测易于集成但抗干扰能力弱，光谱检测无标记但灵敏度与集成性不足，荧光检测可视化、高灵敏但易受光漂白与背景干扰，化学发光等简易检测技术操作便捷但定量能力有限。而光电化学检测与荧光检测双模态联用可实现优势互补，既借助光电化学检测的低背景、高灵敏度实现痕量肿瘤细胞的精准定量，又依托荧光检测的可视化优势实现肿瘤细胞的定位、成像与表型分析，且两者均易于与微流控芯片集成，能够完美适配肿瘤细胞分离与痕量检测的双重需求，是构建高效、精准、微型化肿瘤细胞检测系统的理想组合。

4. 未来微流控芯片发展前景与瓶颈

4.1. 芯片材料选型与规模化低成本高重复性制造瓶颈

材料是生物芯片性能稳定、批量生产的基础，也是区别实验室原型与工业化产品的第一道核心关卡。实验室原型芯片多以研发验证为核心目标，对材料成本、生产效率、批次一致性要求较低，可选用高纯

度、定制化小众材料，依托精密手工、小批量微纳加工工艺完成制备。但面向临床应用的商业化产品，必须兼顾生物相容性、检测稳定性、成本可控性与批量一致性，材料选型和制造工艺的适配难题成为首要壁垒。

在材料选型层面，当前主流生物芯片材料各有短板，尚无完全适配全临床场景的通用材料。玻璃材料透光性好、生物惰性强、表面修饰工艺成熟，是核酸、蛋白检测芯片的常用材料，但存在脆性大、不易封装集成、难以批量微加工的问题，不适合便携式临床检测设备的开发。聚二甲基硅氧烷(PDMS)材料具备良好的弹性、透气性和微结构成型能力，是实验室微流控芯片的核心材料，但其材质疏水，易吸附生物样本中的蛋白、脂质等杂质，会导致检测信号干扰、结果偏差，且材料批次差异大、耐溶剂性差，无法满足临床长期稳定检测需求。聚苯乙烯、环烯烃共聚物等工程塑料成本低廉、易注塑成型、适合大规模生产，但存在表面改性难度大、生物特异性修饰稳定性不足的问题，难以适配高精度、高灵敏度的临床微量检测场景。此外，针对活体检测、植入式芯片等特殊生物材料，还需兼顾抗凝血、抗炎症、组织相容性等特殊属性，材料选型的适配难度进一步提升。

4.2. 临床应用全流程质量控制策略缺失与优化方向

临床检测结果直接指导疾病诊断、治疗方案制定，关系患者生命健康，因此临床产品必须具备全流程、可追溯、标准化的质量控制体系。实验室原型芯片仅需满足科研实验的基础质控要求，无需适配临床严苛的质控标准，存在质控体系碎片化、关键质控环节缺失、无统一质控标准等问题，这也是技术难以跨越转化鸿沟的重要原因。完善分析前、分析中、分析后全链条质量控制策略，是实现生物芯片临床合规化、标准化应用的核心前提。

分析前质量控制是规避检测误差的第一道防线，核心覆盖样本采集、转运、保存、预处理全环节。生物芯片对生物样本的完整性、活性、纯度敏感度极高，血液、组织液、细胞样本的采集时间、抗凝方式、保存温度、转运时长、预处理工艺均会直接影响检测结果。目前，实验室原型的样本处理标准仅适用于科研小样本实验，缺乏临床大样本场景的标准化质控规范。临床场景中，不同采集人员的操作差异、样本转运过程的环境波动、大批量样本预处理的流程差异，均会导致样本活性下降、杂质干扰、靶点降解等问题，最终造成芯片检测结果偏差。因此，分析前需建立统一的临床样本质控标准：明确不同检测场景的样本采集规范、转运时效、低温保存条件，制定标准化的样本离心、提纯、稀释预处理 SOP，配套样本质量筛查机制，剔除溶血、脂血、降解等不合格样本，从源头规避样本误差。

分析中质量控制聚焦芯片检测过程的实时质控，覆盖设备运行、环境参数、反应过程、批次质控等核心环节。芯片检测过程对温度、湿度、振动、光照等环境参数高度敏感，微小环境波动即可影响生物探针结合效率、微流体流动稳定性，导致检测信号异常。同时，批量检测过程中，芯片批次差异、设备运行参数漂移、加样误差、孵育偏差等，均会引发系统误差。针对该环节，需建立常态化过程质控体系：一方面，制定芯片产品出厂批次质控标准，每批次产品需完成精度、重复性、特异性抽样检测，确保批次一致性；另一方面，规范临床检测环境参数标准，实现检测设备实时参数监控、定期校准，增设室内质控品同步检测机制，每批次临床样本检测均搭配高低值质控品，实时监测检测体系的稳定性，及时排查设备、试剂、芯片带来的系统误差。

分析后质量控制聚焦结果判读、数据溯源、误差分析与产品迭代。实验室科研检测对结果容错、数据溯源要求较低，而临床检测结果需具备 100%可追溯性，且结果判读标准需符合临床诊疗规范。当前，多数原型芯片的数据分析算法、结果判读阈值为科研定制化，缺乏临床大样本验证，存在假阳性和假阴性率偏高、判读标准不统一等问题。分析后质控需完善三大体系：一是标准化结果判读体系，依托大规模临床样本数据校准检测阈值，建立适配不同人群、不同疾病场景的判读标准，降低误诊、漏诊风险；

二是全数据溯源体系，实现芯片生产批次、样本信息、检测参数、结果数据、操作人员的全链条记录，满足临床合规溯源要求；三是误差复盘与迭代机制，针对异常检测结果、临床不符案例进行复盘分析，定位材料、工艺、操作、算法层面的问题，反向优化芯片设计、制造工艺与质控流程，持续提升产品临床适配性与可靠性。

5. 趋势与展望

智能化与自动化集成：结合人工智能(AI)与微流控技术，通过机器学习优化芯片结构设计、自动识别CTCs荧光图像、精准分析光电化学信号，实现“进样－分离－检测－分析”全流程自动化，降低人工操作误差。

单细胞多组学分析：将微流控分选与单细胞测序、质谱、荧光成像等技术结合，实现CTCs单细胞分离、基因组突变检测、蛋白表达分析，全面解析癌症转移机制与药物靶点，指导个体化治疗。

便携化即时检测(POCT)：研发低成本、易加工的纸基/塑料微流控芯片，结合便携式光电化学检测仪，构建床旁检测系统，实现基层医疗机构与家庭场景的癌症早期快速筛查。

6. 结论

癌症早期精准诊断是降低死亡率的关键，CTCs作为液体活检核心标志物，其高效富集与高灵敏检测是临床应用的核心难题。微流控技术凭借微型化、集成化、低损伤等优势，为CTCs分离检测提供了全新解决方案。被动式与主动式微流控分离技术各有优劣，物理－生物亲和协同、多物理场耦合是提升富集效率的核心方向；荧光、电化学、光电化学等检测技术中，光电化学－荧光双模态检测可实现灵敏度与可视化的协同，是最优检测策略。

当前，微流控技术在临床样本适配、间充质CTCs捕获、通量－灵敏度平衡、临床转化等方面仍面临挑战，未来需向智能化、单细胞多组学、便携化POCT、多标志物联合检测方向发展。随着技术不断优化与临床验证推进，微流控CTCs检测技术将成为肿瘤早期诊断、预后监测、疗效评估的重要工具，为全球肿瘤防控提供有力支撑。

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