

CTEC 可作为乳腺癌筛查及预后的有效指标

循环肿瘤血管内皮细胞 (CD31⁺ CTEC) 自 2017 年首次被报道以来^[1], 其在乳腺癌新辅助化疗^[2]、区分良恶性肺小结节与肺癌早诊^[3]、胰腺癌术前预后^[4]、NSCLC 免疫治疗^[5]及抗血管生成治疗^[6]等方面的重要临床价值已引起人们的密切关注。此外, MRD 高比值 CTEC/CTC 与肿瘤复发或发生的相关性也已被证实^[7]。最近, 西安交大医学院附属医院、福建医科大学附属泉州第一医院、上海张江转化医学中心及上海宝藤医学检验所利用赛特 SE-iFISH[®] 技术, 系统性研究并进一步揭示了乳腺癌 CD31⁺CTEC 的重要意义 (Han et al. 2022 J Oncol ID 5247423)。

- 初诊未经治疗、手术后未经治疗或术后辅助化疗的乳腺癌患者, 其体内检测出的循环异倍体细胞中, CD31⁺CTECs 始终占据主要部分, CD31⁻CTCs 只占一小部分
- 伴有淋巴转移 (LMN) 的乳腺癌患者体内 CTEC 含量显著高于未见淋巴转移的患者, 而 CD31⁻CTCs 无显著差异
- 治疗前 (基线) CD31⁺CTEC 数目及治疗后 CD31⁻CTC 数目与患者 PFS 密切相关
- 四倍体 CTC、三倍体及四倍体 CTEC 对辅助化疗敏感, 但多倍体 (≥5 倍体) CTC 及 CTEC 对辅助化疗内源性耐药
- 本实验证实了区分性联合检测 CD31⁻CTC 及 CD31⁺CTEC 的必要性, 并揭示了这两类细胞分别具有不同的重要临床意义

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Research Article

Circulating Tumor-Derived Endothelial Cells: An Effective Biomarker for Breast Cancer Screening and Prognosis Prediction

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Background: Circulating tumor-derived endothelial cell (CTEC) is a new potential tumor biomarker to be associated with cancer development and treatment efficacy. However, few evidences are available for breast cancer. **Aims:** To study the relationship between CTCs and CTECs in breast cancer patients. **Methods:** 20 breast cancer patients were recruited, and preoperative and postoperative blood samples were collected. Besides, 20 healthy persons were enrolled as controls. An improved subtraction enrichment and immunostaining-fluorescence in situ hybridization (SE-iFISH) method was adopted to collect CTCs as single CTC, and CD31⁺ (circulating tumor cell) (CTC). Then, the clinical significance of CTCs and CTECs on breast cancer screening and prognosis prediction was evaluated and compared. **Results:** The positive rate of CTCs and CTECs in newly diagnosed breast cancer patients was 68.75% and 71.88%, respectively. Among detected circulating tumor cells, CTECs accounts for a greater proportion than CTCs in breast cancer patients. CTECs positive rate and level were significantly higher in breast cancer patients with lymph node metastasis (LNM) than those without LNM ($P = 0.043$), while there was no significant difference in CTCs. CTECs (area under the curve, AUC = 0.859) had better performance than CTCs (AUC = 0.795) to distinguish breast cancer patients from controls by receiver operator characteristic curve analysis. Preoperative CTECs count ≥ 2 was a significant risk factor for reducing PFS of breast cancer patients. **Conclusions:** CTECs may function as a reliable supplementary biomarker to breast cancer screening and prognosis prediction.

CTC 与 CTEC 量化分析

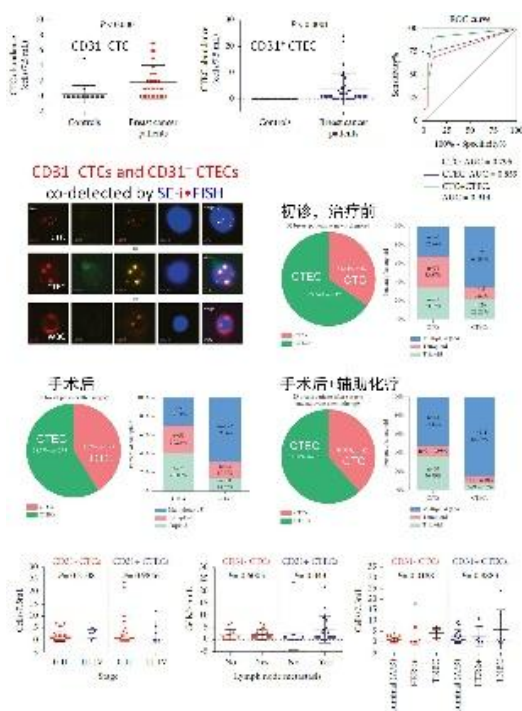
与正常人相比, 乳腺癌患者的 CTC 和 CTEC 数量均显著升高。ROC 曲线分析显示, 与 CD31⁻CTC 相比 (AUC=0.795), CD31⁺CTEC 能够更加有效区分正常人与乳腺癌患者 (AUC=0.859)。

量化分析显示, 患者治疗前及治疗后 (术后、术后+辅助化疗) CTEC 高占比维持不变 (59-65%), 且手术前、后 CTC 及 CTEC 中不同倍体的各亚类细胞比例也基本维持不变。但患者接受辅助化疗后, 相比治疗前, 三倍体 CTC (CTC^{tri}) 比例基本不变, 四倍体 CTC (CTC^{tetra}) 比例显著下降 (34% 至 11%), 而多倍体 CTC (CTC^{multi}) 比例显著升高 (32% 至 52%)。CTEC 亦呈现相似的变化, 三倍体、四倍体 CTEC 比例下降 (其中, CTEC^{tri} 22% 至

文章要点

- 109 位受检者入组, 含 89 例乳腺癌患者及 20 例正常人。相对于 CD31⁻CTCs, CD31⁺CTECs 可以更加有效地区分肿瘤患者与健康人

10%)，多倍体 CTEC (CTEC^{multi}) 比例上升 (65%至 85%)。结果提示，四倍体 CTC、三倍体及四倍体 CTEC 对辅助化疗敏感，多倍体 CTC 及 CTEC 对辅助化疗内源性耐药。

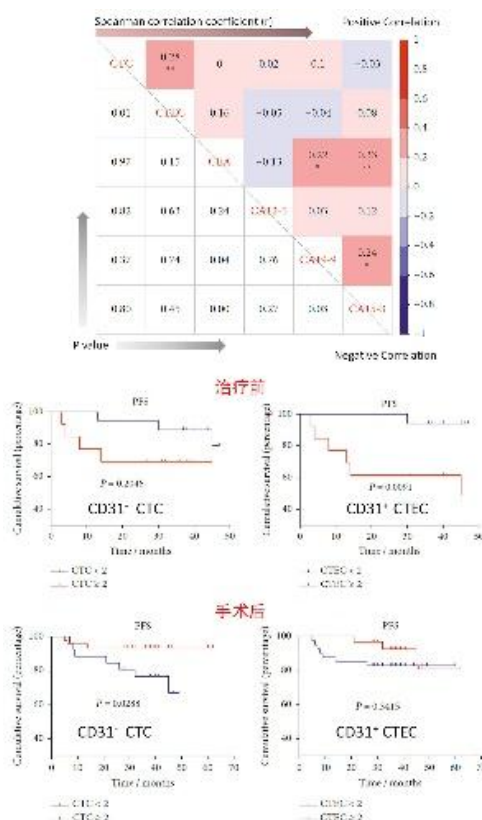


进一步的分析显示，伴有淋巴结转移的患者，CD31⁺ CTEC 数量显著升高，而 CD31⁻ CTC 数量无明显变化。比较各种分子分型 (Luminal A/B, HER2, TNBC 三阴) 乳腺癌患者的检测结果，只有 CD31⁻ CTC 在这些不同分型患者中的数目变化有统计学意义。

治疗前 CD31⁺ CTEC 数目有效预测乳腺癌患者预后

本研究通过 Sperman's Rank Correlation Coefficient 计算显示，CTC 与 CTEC 数目呈正相关，但两者与 CEA、

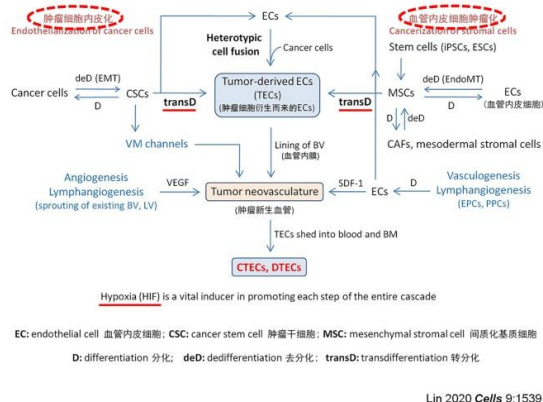
CA12-5、CA19-9、CA15-3 含量无明显相关性，提示乳腺癌 CTC、CTEC 可作为独立于传统肿瘤标志物的另一类生物标志物 (biomarker)。患者预后分析显示，乳腺癌患者治疗前的基线 CD31⁺ CTEC 数目可有效预测患者预后 (PFS)，而手术后 CD31⁻ CTC 数目与 PFS 密切相关。



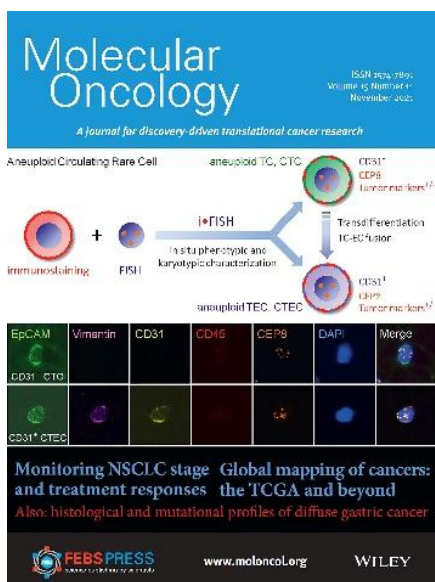
讨论

本研究再次证实了有效区分、联合检测 CD31⁻ CTC 及 CD31⁺ CTEC 的必要性。CTC 与 CTEC 并不是毫不相关的两类细胞。美国哈佛大学 Dr. Klagsbrun 科研组 2004 年就已报道，肿瘤血管由 CD31⁺ 异倍体肿瘤血管内皮细胞 (TEC) 构成^[8]，TEC 脱落入血形成 CTEC^[1]。这些被喻为披着 CD31 (羊皮) 的 CTEC 来源于肿瘤细胞 (狼)，

CTEC 通过肿瘤细胞内皮化及内皮细胞肿瘤化形成，其中涉及了肿瘤细胞与内皮细胞的融合或肿瘤细胞低氧转分化的过程^[9, 10]。



CTC 与 CTEC 共同构成了外周血中一对“细胞型循环肿瘤标志物”，它们当中的各种亚类细胞在肿瘤生成、进展、转移、耐药、复发等过程中相辅相成，有着重要临床价值。SE-i•FISH® 有效检测 CD31⁻ CTC 及 CD31⁺ CTEC 的成果已被不断报道，有关 CTEC 更多、更重要的临床意义仍有待于人们进一步去揭示。



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