北京协和医院首次发现 CD44+ CTEC 与胰腺癌快速复发密切相关

胰腺癌在全球范围内属最高致死率肿瘤，85%的胰腺癌为胰腺导管腺癌，唯一治疗手段就是手术切除加术后辅助性治疗。大部分胰腺癌患者术前都存在影像学不可见的微转移灶 (micrometastatic foci)，或术后、药物治疗后体内仍有微量残留肿瘤细胞 (minimal residual disease, MRD) [1]，这导致很多患者术后半年内快速复发，5 年以上生存率患者只占 7-8%。如果能在术前对患者的较差预后作出准确评估，并且在术后对 MRD 进行有效检测，从而采取积极治疗手段，将会极大提高胰腺癌等其他肿瘤的治疗效果。因此对胰腺癌微转移灶及 MRD 实施细胞水平的相关检测已成为当务之急[2]。

最近，北京协和医院外科戴梦华主任率领团队利用赛特 SE-i•FISH 技术对 73 例入组的胰腺导管腺癌 (PDAC)患者术前及术后的循环肿瘤细胞 CTC (CD31-) 、循环肿瘤血管内皮细胞 CTEC (CD31+) 开展了深入研究，在国际上首次发现了患者术前干细胞标志物 CD44+ 的 CTEC 与术后远端快速复发具有显著相关性。CD44+ CTEC 可作为独立预后因素，有效判断胰腺癌患者术后的疾病进展情况 (DFS)。该研究先期部分成果已刚刚得到发表(Xing et al., 2021 Cancer Manag Res 13:4417)。

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ORIGINAL RESEARCH

CD44+ Circulating Tumor Endothelial Cells Indicate Poor Prognosis in Pancreatic Ductal Adenocarcinoma After Radical Surgery: A Pilot Study

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Background: Circulating tumor endothelial cells (CTECs) are cells that originate from tumor endothelial cells (TECs) of blood vessels and are shed into peripheral blood. Some studies have shown that CTECs are associated with tumor angiogenesis, growth and indicate prognosis in patients with malignant solid tumor. However, the role of CTECs especially the phenotype of CTECs in pancreatic adenocarcinoma (PDAC) is still not clear. We investigated the relationship between CTECs and patients' prognosis.

Methods: A total of 73 patients with resectable PDAC were enrolled in our research and underwent radical surgery. Peripheral venous blood samples were collected before surgery, on postoperative day (POD) 7 and on postoperative month (POM) 1, respectively. We used integrated subtraction enrichment and immunostaining-fluorescence in situ hybridization (SE-iFISH) platform to identify and enumerate CTECs. Immunofluorescence was used to identify CTECs expressing CD44 and vimentin.

Results: In patients with early tumor recurrence (DFS< 6 months), the preoperative CD44+ CTEC levels showed significantly higher ($P = 0.023$). Univariate and multivariate analysis showed that history of diabetes [HR 2.656 (1.194–5.908), $P = 0.017$], numbers of positive lymph nodes [HR 1.871 (1.388–2.522), $P < 0.001$], preoperative numbers of CD44+ CTECs [HR 1.216 (1.064–1.390), P = 0.004], and POM1 CA19-9 level [HR 1.002 (1.001–1.002), P < 0.001] were independent prognostic factors for DFS.

Conclusion: The detection of CD44+CTECs in patients with resectable PDAC preoperatively could be an independent predictor of shorter DFS after radical surgery.

Keywords: circulating tumor endothelial cells, pancreatic adenocarcinoma, prognostic factor, CD44

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the primary causes of cancer-related mortality worldwide.[1,2] The only potentially curative treatment for PDAC is surgical resection. While patients with localized disease have been treated with integrated therapy based on radical surgery, the 5-year survival rate still remains 7%-8%.[3] Many of these patients developed early postoperative metastatic recurrences due to micrometastatic foci occurred at the time of surgery. Many patients are understaged at diagnosis for the reason that these micrometastatic foci are not identified preoperatively.

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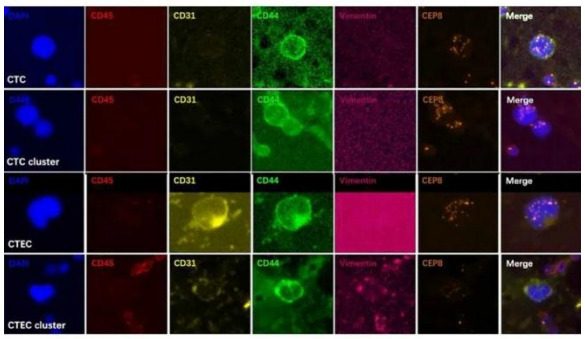

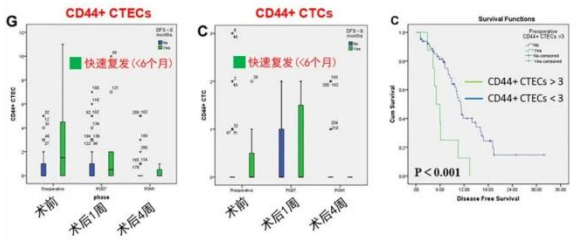

肿瘤细胞 CTC 可以在体内或体外通过转分化直接形成肿瘤血管内皮细胞 CTEC。CTEC 的本质就是细胞表面表达了 CD31 的肿瘤细胞，也被喻为“披着羊皮的狼”[3]。

CD44 作为干细胞的典型标志物之一，与肿瘤的发生及转移密切相关。北京协和医院外科研究团队利用赛特 6-通道 i•FISH 技术对入组患者术前、术后一周及术后四周的异倍体 CTC、CTEC 进行了动态监测，并同步、原位检测了这些 CTC、CTEC 上 CD44 及间质化标志物波形蛋白 Vimentin 的表达。研究发现，患者术前均可查出 CETC，其中，术后快速复发的患者，术前 CTEC 数目显著高于非快速复发患者，CTEC 数目在术后持续降低。患者术前 CTC 数目明显低于 CTEC，但术后一周数目显著升高，一个月后基本清零。生存分析显示，术前 CD44+ CTEC 与患者的较差预后（术后半年内快速复发）高度相关。多变量 Cox 回归分析证实，CD44+ CTEC 可作为独立预后因素，有效预测患者术后是否会快速复发。初步的细胞数目分析显示，与 CD31+ CTEC 相比，CD31- CTC 没有显示明确临床意义。

结论

- 本临床实验进一步证实了同步检测和有效区分 CD31- CTC 、CD31+ CTEC 的必要性，并为在临床上开展对肿瘤微小转移灶及 MRD 的检测、提高肿瘤治疗疗效进行了有意义的开拓性研究
- 对于术后半年内远端快速复发的患者：(a) 术前 CD44+ CTEC 数目是 CD44+ CTC 的 6 倍；(b) 术后一周，CD44+ CTC 反而显著

高于 CD44+ CTEC，两者数量差异高达 8 倍；(c) 术后一个月，CD44+ CTC 迅速回落，CD44+ CTEC 是 CD44+ CTC 的 4 倍

- 手术前检测干性 CD44+ CTEC 可及时判断胰腺癌患者预后；术后一周及四周监测的 CD44+ CTC、CD44+ CTEC 与胰腺癌快速复发密切相关
- 患者伴有糖尿病史、肿瘤转移的淋巴结数目大于 2、升高的 CA19-9 (> 89.6 U/ml) 也与术后快速复发密切相关
- CTC 或 CTEC 的总体数量与预后无明显相关性

这是继 CTEC、PD-L1+ CTEC 在肺癌[4, 5]及乳腺癌[6]中的临床意义被报道之后，再次证明 CTEC 在不同癌种中与肿瘤进展及疗效密切相关。有关胰腺癌 CD44+ CTEC 的后续拓展实验已在积极开展中。

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