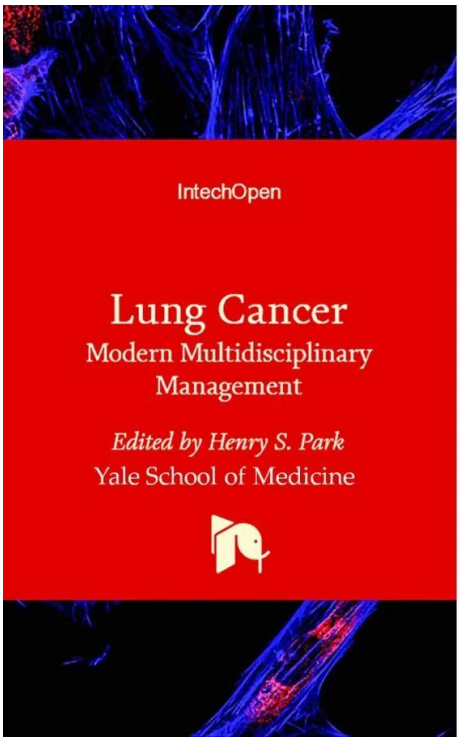
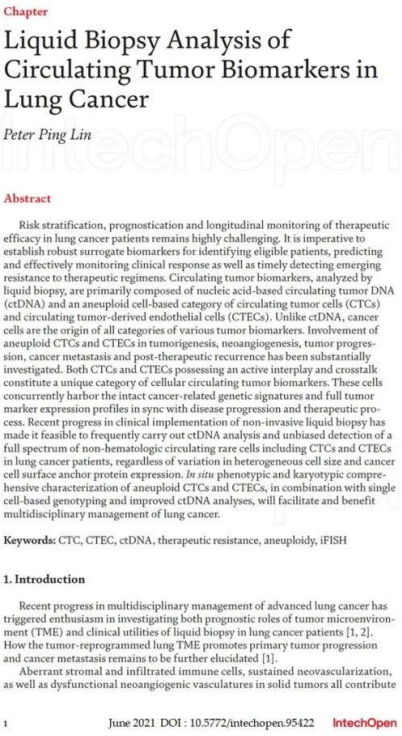
SE-iFISH 检测肺癌 CTC、CTEC 写入耶鲁大学新书





Chapter

Liquid Biopsy Analysis of Circulating Tumor Biomarkers in Lung Cancer

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Abstract

Risk stratification, prognostication and longitudinal monitoring of therapeutic efficacy in lung cancer patients remains highly challenging. It is imperative to establish robust surrogate biomarkers for identifying eligible patients, predicting and effectively monitoring clinical response as well as timely detecting emerging resistance to therapeutic regimens. Circulating tumor biomarkers, analyzed by liquid biopsy, are primarily composed of nucleic acid-based circulating tumor DNA (ctDNA) and an aneuploid cell-based category of circulating tumor cells (CTCs) and circulating tumor-derived endothelial cells (CTECs). Unlike ctDNA, cancer cells are the origin of all categories of various tumor biomarkers. Involvement of aneuploid CTCs and CTECs in tumorigenesis, neoangiogenesis, tumor progression, cancer metastasis and post-therapeutic recurrence has been substantially investigated. Both CTCs and CTECs possessing an active interplay and crosstalk constitute a unique category of cellular circulating tumor biomarkers. These cells concurrently harbor the intact cancer-related genetic signatures and full tumor marker expression profiles in sync with disease progression and therapeutic process. Recent progress in clinical implementation of non-invasive liquid biopsy has made it feasible to frequently carry out ctDNA analysis and unbiased detection of a full spectrum of non-hematologic circulating rare cells including CTCs and CTECs in lung cancer patients, regardless of variation in heterogeneous cell size and cancer cell surface anchor protein expression. *In situ* phenotypic and karyotypic comprehensive characterization of aneuploid CTCs and CTECs, in combination with single cell-based genotyping and improved ctDNA analyses, will facilitate and benefit multidisciplinary management of lung cancer.

Keywords: CTC, CTEC, ctDNA, therapeutic resistance, aneuploidy, iFISH

1. Introduction

Recent progress in multidisciplinary management of advanced lung cancer has triggered enthusiasm in investigating both prognostic roles of tumor microenvironment (TME) and clinical utilities of liquid biopsy in lung cancer patients [1, 2]. How the tumor-reprogrammed lung TME promotes primary tumor progression and cancer metastasis remains to be further elucidated [1].

Aberrant stromal and infiltrated immune cells, sustained neovascularization, as well as dysfunctional neoangiogenic vasculatures in solid tumors all contribute

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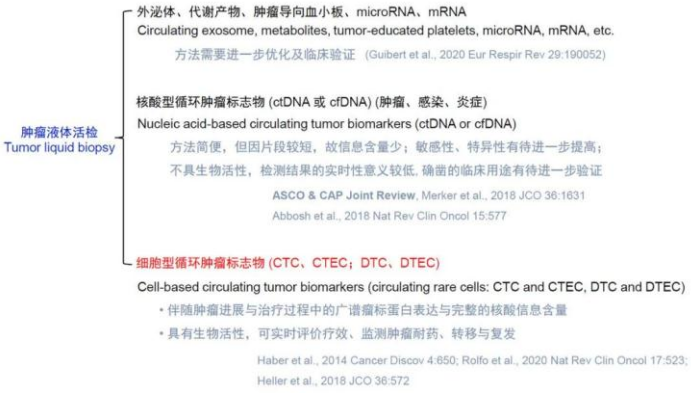
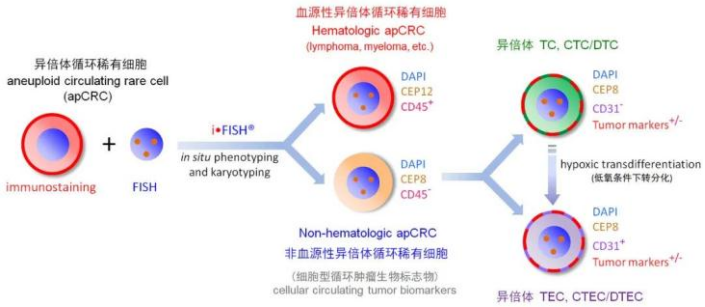
应美国耶鲁大学医学中心 Dr. Henry Park 邀请，赛特生物林平博士在最新出版、由 Dr. Park 主编的《肺癌 - 现代多学科综合诊治方法》(Lung Cancer - Modern Multidisciplinary Management) 一书中，对肺癌领域的液体活检，包括核酸型 (ctDNA) 及细胞型循环肿瘤生物标志物 (CTC、CTEC) 的最新研究进展与临床应用做了详细介绍。此外，本书还对目前国际上有关肺癌多学科诊疗的最新进展做了系统性论述，包括肺癌寡转移、基于气态等离子及纳米粒子成像技术的肺癌治疗手段、放化疗、联合免疫治疗、EGFR 靶向治疗、外粒子束治疗、联合物理治疗、肺癌机器人手术等。Dr. Park 在美国哈佛医学院及耶鲁大学医学院学习、工作多年，在肿瘤临床治疗与基础研究领域颇有建树，迄今已发表 100 多篇文章。

相对于常规病理活检手段易对肺癌患者造成侵入性伤害，液体活检近年来在肿瘤诊疗过程中无创、有效检测、分析肿瘤细胞及相关分子，具有特殊的重要意义。肿瘤液体活检的主要技术组成、检测范围及相关特点[1-5]汇总如下图：



肿瘤液体活检技术发展迅速，目前经过大量临床验证、具有代表性的液体活检技术为 ctDNA 和 CTC 检测。相对于小片段、信息含量有限、不具生物活性的 ctDNA，存在于外周血液中的循环肿瘤细胞 (CTC) 、循环肿瘤血管内皮细胞 (CTEC) 及人体其它体液组分（如骨髓、胸腹水、尿液、脑脊液等）中的播散性肿瘤细胞 (disseminated tumor cell, DTC) 和播散性肿瘤血管内皮细胞 (DTEC) 具有染色体异倍体的特性，并在肿瘤治疗及进展过程中表达各种不同的肿瘤标志物蛋白。动态检测循环稀有细胞在肿瘤诊断与防治过程中的特殊优势已开始受到人们日益广泛的密切关注。肿瘤细胞在体内肿瘤微环境或体外低氧条件下可转化为表达了 CD31 的肿瘤血管内皮细胞 CTEC，所以 CTC 与 CTEC 并不是两类完全不相干的细胞。与异倍体 CTC 相比，异倍体 CTEC 同时兼具了恶性肿瘤细胞特性及造血管功能[6]。通过赛特生物 SE-i•FISH® 整合技术，可对 CTC 与 CTEC 进行同步、联合检测，以更加客观、全面评估不同 CTC、CTEC 亚类细胞的特殊临床意义。



目前有关 CTC、CTEC 的检测，已从以往的单一细胞计数转向细胞分子层面，其中染色体异倍体最具代表特征。染色体异倍体可引起肿瘤细胞携带的成百上千基因的扩增或缺失，进而引起大规模的细胞蛋白表型变化，从而进一步促进肿瘤的进展、耐药及高异质性演变[7, 8]。染色体异倍体拷贝数目的增多与肿瘤的恶性度密切相关[9]，高拷贝数预示 KRAS 及 TP53 基因的高频突变，导致肿瘤的恶性度增高及肿瘤患者的较差预后[10, 11]。此外，对肿瘤细胞的 DNA 拷贝数异常分析 (copy number aberrations, CNAs) 也及揭示了小细胞肺癌 (SCLC) CTC 的药敏与耐药机制[12]。除了对患者的 CTC 进行直接分析外，利用 CTC 建立的肿瘤动物模型(CTC-derived xenograft, CDX) 结合单细胞 DNA[13]或 RNA 测序[14]则代表了有关肿瘤耐药研究的最新进展。有关肺癌 CTC 及 CTEC 检测及临床意义汇总如下：

Table 1. Clinical utilities of detecting aneuploid CTCs and CTECs in lung cancer diagnosis and therapy

肺癌诊疗过程中 CTC 与 CTEC 的临床意义

Clinical values of lung cancer CTCs and CTECs	References
Early diagnosis 早期诊断	[17], [39], [65], [83], [85]
Pathological staging 病理分期	[77], [86]
Identification of eligible patients (TKIs, *ALK* crizotinib) 筛选适于靶向治疗的患者	[13], [104], [106]
In vitro therapeutic drug screening 体外筛药	[110, 111]
Under treatment	
Risk assessment for distant metastasis 远端转移风险评估	[64], [87]
Prognosis 预后	[63], [64], [75], [77], [88-90], [102]
Surgery (prognostic value) 术后疗效评估	[92-95]
Timely monitoring therapeutic resistance 实时监测肿瘤细胞产生耐药	[31], [36], [100], [107, 108]
Early detection of recurrence 早期监测肿瘤复发	[37], [65], [96-98]
Advanced molecular characterization 相关先进分子实验技术应用	
Aneuploidy and *ALK* rearrangement 异倍体及 *ALK* 重排	[13], [102-104]
Co-detection of aneuploidy and tumor marker expression in CTCs and CTECs (iFISH) iFISH 联合检测肿瘤标志物表达及染色体异倍体	[8], [36], [52]
CTC-derived xenograft (CDX) CTC 肿瘤动物模型	[28, 29], [31]
Single cell-based DNA sequencing 肺癌 CTC 单细胞 DNA 测序	[28, 29], [100], [106], [108]
Single cell-based RNA sequencing 肺癌 CTC 单细胞 RNA 测序	[31]

与核酸型循环肿瘤生物标志物 ctDNA 相比，细胞型标志物 CTC、CTEC 具有伴随肿瘤进展的完整核酸信息与广谱的肿瘤蛋白表达，可用于实时评估疗效、监测肿瘤耐药及预测肿瘤复发风险。此外，分离后具有生物活性的肿瘤细胞还可用于 CTC 动物模型的建立。CTC 与 CTEC 虽功能各异，但两者相辅相成，共同构成了血液中一对特殊的表达多种肿瘤标志物的“细胞型循环肿瘤标志物”。对两者进行有效联合检测，结合单细胞测序，能更加客观、全面地评估不同 CTC、CTEC 亚类细胞在肿瘤形成、进展、转移、耐药及复发过程中的特殊临床意义。

原文链接：
http://mts.intechopen.com/articles/show/title/liquid-biopsy-analysis-of-circulating-tumor-biomarkers-in-lung-cancer

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