肿瘤寡转移(OMD)过程中的异倍体 CTC 与 CTEC

肿瘤转移与肿瘤患者的死亡率密切相关，很多肿瘤会发生转移。以胃肠道肿瘤为例，大于 70%的胃肠道肿瘤患者或早或晚都会伴有肿瘤转移发生。目前，临床针对肿瘤转移的治疗主要还是以局部淋巴结为主要观察指标，凡是有淋巴结以外的转移，一般都按广泛转移进行非个体化的全身用药（如化疗）。美国芝加哥大学 Hellman 和 Weichselbaum 在 1995 年提出了“肿瘤寡转移”(oligometastasis, OMD)的概念，它是恶性肿瘤转移过程中存在的一种中间状态，是肿瘤生物侵袭性较温和的时期，介于局限性原发灶与广泛性转移之间的过渡阶段。该发现具有非常重要的临床治疗意义。正确认识肿瘤寡转移 OMD 及针对 OMD 患者采取个体化局部精准治疗（如放疗、手术、射频消融等；同时也考虑是否需要联合全身治疗），将改变传统治疗恶性肿瘤的思维观念，也可为部分肿瘤转移患者带来治愈的可能。最近，由德国多家著名医学院校、上海复旦大学肿瘤中心、长海医院及赛特生物联合对多种肿瘤（尤其是胃肠道肿瘤，包括食管癌、胃癌、肝癌、胰腺癌及结直肠癌） OMD 的发生机理、诊断、多重综合治疗(MDT) 等方面研究的最新进展进行了系统性论述，相关文章刚刚发表在 Seminars in Cancer Biology (影响因子 IF=9.658)上。文章第一及通讯作者分别为德国科隆大学医学院赵越及 Christiane J. Bruns。

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Review

Tumor biology and multidisciplinary strategies of oligometastasis in gastrointestinal cancers

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ABSTRACT

More than 70% of gastrointestinal (GI) cancers are diagnosed with metastases, leading to poor prognosis. For some cancer patients with limited sites of metastatic tumors, the term oligometastatic disease (OMD) has been coined as opposed to systemic polymetastasis (PMD) disease. Stephen Paget first described an organ-specific pattern of metastasis in 1889, now known as the "seed and soil" theory where distinct cancer types are found to metastasize to different tumor-specific sites. Our understanding of the biology of tumor metastasis and specifically the molecular mechanisms driving their formation are still limited, in particular, as it relates to the genesis of oligometastasis. In the following review, we discuss recent advances in general understanding of this metastatic behavior including the role of specific signaling pathways, various molecular markers and biomarkers, as well as the interaction of carcinoma cells with their tissue microenvironments (both primary and metastatic niches). The unique features that underlie OMD provide potential targets for localized therapy. As it relates to clinical practice, OMD is emerging as treatable with surgical resection and/or other local therapy options. Strategies currently being applied in the clinical management of OMD will be discussed including surgical, radiation-based therapy, ablation procedures, and the results of emerging clinical trials involving immunotherapy.

1. Introduction

More than 70% of gastrointestinal (GI) cancers are diagnosed with manifest metastasis, either at the time of diagnosis (synchronous), or at later stages (metachronous) [1]. Whereas many primary tumors can be effectively controlled by local therapies (e.g. surgery, radiation or thermoablation), the effective treatment of metastatic disease represents an important clinical challenge. Given our aging populations worldwide, and the increasing incidence of GI cancers, the medical need to more effectively treat metastatic disease is urgent. In a subgroup of patients, metastasis can be limited to an individual lesion, or even a few foci, for a relatively long period of time and thus can be effectively treated using localized strategies for long term tumor control.

In 1995 Hellman and Weichselbaum proposed a new term for situations where limited tumor metastasis is seen that was termed "oligometastatic disease" or OMD. This has eventually led to a paradigm shift in our understanding and treatment of some metastatic diseases [2]. Importantly, current treatments for metastatic cancer are still largely based on the paradigm that metastatic spread beyond local lymph nodes is uniformly a systemic disease. This often results in non-selective, non-individualized systemic treatments which do not take into

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什么是肿瘤寡转移 OMD？

OMD 是肿瘤由局限性原发灶向远端广泛转移(systemic poly-metastasis, PMD) 的一种中间状态，主要是指起源明确的原发肿瘤发生有限的转移（一般不超过 1-3 或 1-5 个转移灶），机体针对肿瘤的相关免疫应答（炎性反应）还没有被完全调动起来，肿瘤组织内白细胞较少，肿瘤亦无快速进展成远端广泛转移。OMD 可分为两种类型：1) synchronous OMD: 原发灶肿瘤确诊时发生的 OMD； 2)metachronous OMD: 治疗后发生的 OMD。相对于肿瘤广泛远端转移的 PMD，OMD 阶段被认为是应用局部治疗手段（外科手术、放疗）治疗肿瘤的宝贵机会(OMD-guided therapy)。OMD 过程中，肝脏及肺是胃肠道肿瘤转移的首要靶向器官，其中肝脏是最主要的转移器官。

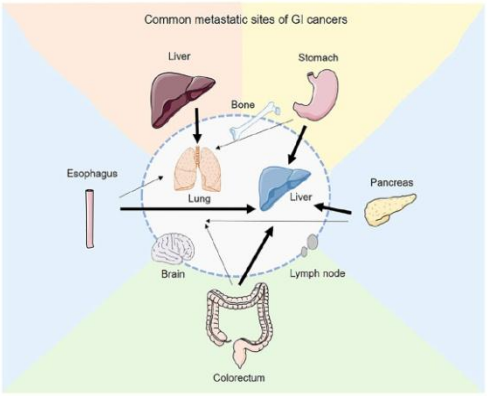

Fig. 1. Common sites of oligometastatic disease in GI cancers. For gastrointestinal cancers (including esophageal cancer, gastric cancer, liver cancer, pancreatic cancer, colorectal cancer *etc.*), liver and lung are relative common organs with localized spread of metastasis. It might be great benefit to achieve the control of oligometastatic disease. (Thickness of black arrows reflects the general frequencies of primary tumor metastasizes to the indicated distant organ site.).

如何区分 OMD 与 PMD？

目前临床确定 OMD 主要基于肿瘤转移灶的数量及无瘤时间间隔的长短，同时人们也更加关注从肿瘤的分子特征(molecular features)及表达标记(expression signature)层面区分 OMD 与 PMD。其中，相关 microRNA (miRNA)检测已被证实可有效区分 OMD 与 PMD。例如，肿瘤细胞高表达 miR-200c 可预测肿瘤通过调节“上皮-间质转化”通路 (EMT pathway) 而诱导产生 PMD。

OMD 与肿瘤微环境

由众多因素构成的肿瘤微环境与 OMD 密切关联。微环境中的“肿瘤相关成纤维细胞”(cancer associated fibroblasts, CAFs) 是高异质性的基质细胞(stromal cells)。CAFs 通过与免疫细胞相互作用，或分泌白细胞介素等淋巴因子从而调节肿瘤的生长、进展、及远端器官的定向转移。此外，本文针对外泌体、ctDNA 的作用也进行了讨论。

OMD 过程中的 CTC 及 CTEC

本文另一亮点是对肿瘤生长及转移过程中起重要作用的异倍体 CTC(CD31-/CD45-)及循环肿瘤血管内皮细胞 (circulating tumor endothelial cell, CTEC) (CD31+/CD45-)进行了详细讨论。

与异倍体肿瘤细胞(tumor cell, TC) 入血形成 CTC 相似，肿瘤组织血管上的异倍体血管内皮细胞 (tumor endothelial cell, TEC) (Hida et al., 2004 Cancer Res 64:8249) 也可以脱落入血形成异倍体循环肿瘤血管内皮细胞 CTEC (Lin et al., 2017 Sci Rep 7:9789)。对异倍体 CTC 与 CTEC 进行有效区别即是高特异性检测 CTC 的首要前提，同时也可帮助人们对这两类细胞进行同步研究。本文首次报道了异倍体 CTEC 和 CTC 一样，也可以表达一系列肿瘤标识物，如 HER2、PD-L1、EpCAM，及干细胞标识物 CD44v6 等。

肿瘤患者体内异倍体 CTEC 表达多种肿瘤标识物

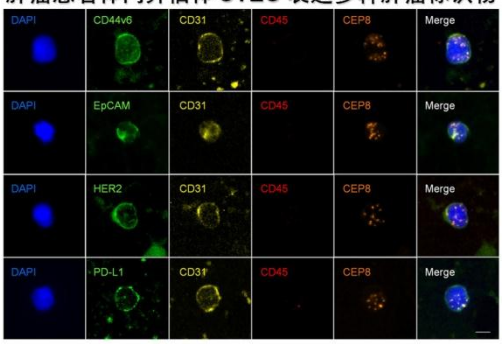

Fig. 2. *In situ* phenotypic and karyotypic characterization of aneuploid CTECs expressing tumor biomarkers. Following subtraction enrichment (SE) of non-hematologic circulating rare cells from variety of carcinoma patients, specimens are subjected to comprehensive characterization performed by immunofluorescence staining-FISH (iFISH) strategy. Several tumor biomarkers, including the stemness marker CD44v6, EpCAM, HER2 and PD-L1, are respectively expressed on the aneuploid CTECs ($CD31^+/CD45^-$, ≥trisomy 8).

与碎片化的小片段“核酸型循环肿瘤标示物 ctDNA”不同，CTC 与 CTEC 共同构成了一对具有生物活性、且富含一系列肿瘤标识物蛋白及完整基因组信息的“细胞型循环肿瘤标识物”(cellular circulating tumor biomarker)。两者功能各异、相辅相成，在肿瘤发生、进展、转移 (包括 OMD 及 PMD)过程中发挥着重要作用。应用赛特 SE-i • FISH®，我们通过一系列临床实验已经证明，CTC 和 CTEC 可分别通过 EMT(epithelial-to-mesenchymal transition) 及 EndoMT(endothelial-to-mesenchymal transition) 形成 Vimentin+间质化细胞。鉴于 EMT/EndoMT 在 OMD 过程中的潜在重要作用，有关 CTC 及 CTEC 表达相关肿瘤标志物的临床意义及研究正在紧锣密鼓地积极开展中。