【Nature Cancer】：CTC 可塑性构成乳腺癌对 HER2 类药物耐药的决定性因素

肿瘤细胞可塑性指的是肿瘤细胞为了应对外在的治疗药物压力而在细胞内产生一系列变化的过程，最终导致肿瘤细胞对治疗药物产生耐受，成为“杀不死的小强”。

HER2+ CTCs 广泛存在于免疫组化 IHC 鉴定的肿瘤组织 HER2 低表达、甚至不表达的患者体内[1-3]。HER2 靶向抑制剂可有效延长 HER2low 乳腺癌患者疾病无进展生存期 (PFS)，该具有里程碑意义的结论最近已被证实[4]，相似的 HER2 靶向抑制剂在胃癌领域的重要发现在几年前同样被北京大学肿瘤中心沈琳主任团队及赛特生物联合报道[1]。CTC 在体内的存活时长是肿瘤转移过程中最为关键的影响因素，与 CTC 存活密切相关的细胞内信号传导通路对于阻断肿瘤转移具有不可估量的临床意义。CTC 中的 HER2 通过与携带有神经调节蛋白-1 (neuregulin-1, NRG1) 结合位点的 HER3 偶联成 HER2-HER3 二聚体，进而通过 PI3K-PKT、MAPK、JAK-STAT 等通路激活下游一系列与致瘤 (oncogenic) 相关的信号传导通路。HER3 及其配体 NRG1 在 HER2+ CTC 中起着关键作用，与 HER2+ CTC 生存密切相关。

最近，德国多所著名院校共同深入研究并进一步揭示了 NRG1-HER3 通路在乳腺癌 CTC 中的重要作用。该通路与其代偿性的其它通路共同构成了 CTC 因应外部压力所形成的细胞可塑性 (plasticity)，从而导致 CTC 的耐药及可持续生长。该研究对于今后优化肿瘤精准治疗奠定了坚实基础。相关文章刚刚得到发表 (Wurth et al., 2025 ***Nat Cancer*** doi: 10.1038/s43018-024-00882-2)。

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Circulating tumor cell plasticity determines breast cancer therapy resistance via neuregulin 1–HER3 signaling

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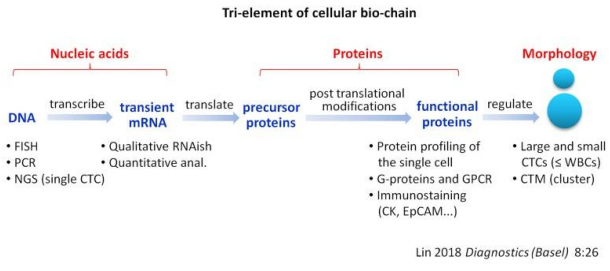
Circulating tumor cells (CTCs) drive metastasis, the leading cause of death in individuals with breast cancer. Due to their low abundance in the circulation, robust CTC expansion protocols are urgently needed to effectively study disease progression and therapy responses. Here we present the establishment of long-term CTC-derived organoids from female individuals with metastatic breast cancer. Multiomics analysis of CTC-derived organoids along with preclinical modeling with xenografts identified neuregulin 1 (NRG1)–ERBB2 receptor tyrosine kinase 3 (*ERBB3*/HER3) signaling as a key pathway required for CTC survival, growth and dissemination. Genome-wide CRISPR activation screens revealed that fibroblast growth factor receptor 1 (FGFR1) signaling serves a compensatory function to the NRG1–HER3 axis and rescues NRG1 deficiency in CTCs. Conversely, NRG1–HER3 activation induced resistance to FGFR1 inhibition, whereas combinatorial blockade impaired CTC growth. The dynamic interplay between NRG1–HER3 and FGFR1 signaling reveals the molecular basis of cancer cell plasticity and clinically relevant strategies to target it. Our CTC organoid platform enables the identification and validation of patient-specific vulnerabilities and represents an innovative tool for precision medicine.

本文作者首先富集乳腺癌患者 CTCs 及胸水 (pleural effusion) 或腹水中的脱落肿瘤细胞，并以此制备成 CTC-derived xenograft (CDX) 及 effusion-derived xenograft (EDX) 异体移植动物模型用以增殖肿瘤细胞。增殖的肿瘤细胞再经体外特殊培养后形成

具有 3D 结构的类器官 (CTC-derived organoids, CDOs)，用于后续包括全基因组 CRISPR 激活筛选 (genome-wide CRISPR activation screens)等一系列多组学分析(multiomics analyses)。

本文要点：

- CTC 上的 HER2 表达及其信号传导通路与 HER2 抑制剂疗效密切相关，但**组织病理常规使用的 IHC 分值评估 HER2 表达并不能反映 CTC 上的 HER2 表达情况，两者并无关联**
- 成功建立了 CTC/胸腹水肿瘤细胞-CDX/EDX-CDOs (CTC 类器官) 培养体系：绝大部分 CDX/EDX 的细胞分裂、生长 20 代依然与原代细胞的基因突变保持一致；由 CDX/EDX 扩增细胞制备的源自 10 位乳腺癌患者的 11 个 CDOs 也与肿瘤患者检测出的 *TP53*、*PIK3CA*、*APC*、*CDH1* 高频基因突变及染色体异倍体相一致
- NRG1-HER3 是 CTC 存活、生长及播散的关键通路；其中，必不可少的关键因子 NRG1 可促进 $HER3^+$ CTCs 的耐药性生存及其参与的肿瘤转移
- 乳腺癌患者一旦对 anti-HER2/HER3 开始耐药，其 CTC 中的成纤维细胞生长因子受体-1 (*fibroblast growth factor receptor-1, FGFR1*) 基因呈现高表达；FGFR1 通路的激活构成了 CTC 对 anti-HER2/HER3 的逃逸机制
- FGFR1 参与的 FGF-FGR1 传导通路具有对 NRG1-HER3 通路的代偿性功能 (compensatory function)：在 NRG1 缺失时，FGFR1 可有效维持 CTC 的耐药性生存与生长，这两条不断动态变化且相辅相成、相互作用的不同通路在分子水平上共同构成了 CTC 因应外界压力而得以存活的细胞可塑性
- 同时联合阻断 NRG1-HER3 及 FGF-FGR1 信号传导通路可有效破坏 CTC 的可塑性并抑制其生长与增殖



Lin 2018 *Diagnostics (Basel)* 8:26

相对于单一研究染色体、瘤标、ctDNA、mRNA、外泌体、代谢产物等，肿瘤细胞 (包括 CTC) 作为万物之源，汇集了肿瘤核酸、肿瘤标志物蛋白及肿瘤细胞形态三要素于一身，以其一系列独特的生物学特征，包括生物活性、可实时反映伴随肿瘤不断进展与变化的核酸和瘤标表达，以及与之相关的肿瘤耐药与药敏的动态演变，近年来已受到人们日益广泛的密切关注，其在肿瘤检测、诊疗及临床研究中为人们提供了眼见为实的可靠依据。在对可视性肿瘤细胞 CTC **统筹考虑其细胞三要素**的基础上开展深入研究[5]，并结合由其生成的类器官研究，将会为进一步优化肿瘤患者的个体化精准治疗提供新的有力依据。

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