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Hans汉斯

染色体不稳定性调控肿瘤免疫微环境：从基础机制到结直肠癌治疗突破

边孜力，潘运龙*

暨南大学附属第一医院胃肠外科，广东 广州

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摘　要

染色体不稳定性(Chromosomal instability, CIN)作为实体瘤的主要特征之一，通过驱动基因组异质性、微核形成及细胞质双链DNA (dsDNA)累积等多种复杂的机制对肿瘤免疫微环境(TME)的形成及其对免疫应答造成一定的影响。近年来研究揭示了CIN的“两面性”：即中等水平的CIN能使肿瘤更好地适应肿瘤微环境的变化，而过度的CIN会导致遗传灾难和细胞死亡，触发细胞焦亡并释放损伤相关分子模式(DAMPs)，提高抗肿瘤免疫识别。然而，CIN与免疫微环境之间的关系目前仍然是一个复杂的网络，特别是在结直肠癌(CRC)中，CIN相关分子机制(如YY2/BUB1B轴)通过释放肿瘤新抗原和促炎因子(IL-1、IFNγ)，重塑TME并克服微卫星稳定(MSS)型CRC的免疫治疗抵抗。此外，联合丝氨酸/苏氨酸激酶(AURK)抑制剂与免疫检查点阻断、或通过代谢重编程靶向糖酵解和DNA修复通路，为克服CRC治疗耐药提供了新策略。本文整合基础机制与临床转化视角，提出靶向CIN-TME交互网络的联合治疗策略，为优化结直肠癌免疫治疗及拓展适应症提供理论依据和应用前景。

关键词

染色体不稳定性(CIN)，肿瘤免疫微环境(TME)，结直肠癌，免疫治疗

Chromosomal Instability Regulates the Tumor Immune Microenvironment: From Fundamental Mechanisms to Therapeutic Breakthroughs in Colorectal Cancer Treatment

Zili Bian, Yunlong Pan*

*通讯作者。

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Department of Gastrointestinal Surgery, The First Affiliated Hospital of Jinan University, Guangzhou Guangdong

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Abstract

Chromosomal instability (CIN), as one of the main features of solid tumors, affects the formation of tumor immune microenvironment (TME) and its impact on immune response through various complex mechanisms, such as driving genomic heterogeneity, micronucleus formation and cytoplasmic double-stranded DNA (dsDNA) accumulation. Recent studies have revealed the "two sides" of CIN, *i.e.*, moderate levels of CIN enable tumors to better adapt to changes in the tumor microenvironment, whereas excessive CIN leads to genetic catastrophe and cell death, triggers cellular paralysis and releases damage-associated molecular patterns (DAMPs), and enhances anti-tumor immune recognition. However, the relationship between CIN and the immune microenvironment currently remains a complex network, especially in colorectal cancer (CRC), where CIN-associated molecular mechanisms (e.g., the YY2/BUB1B axis) remodel the TME and overcome immunotherapeutic resistance in microsatellite-stabilized (MSS)-type CRC through the release of tumor neoantigens and pro-inflammatory factors (IL-1, IFNγ). In addition, combining serine/threonine kinase (AURK) inhibitors with immune checkpoint blockade, or targeting glycolytic and DNA repair pathways through metabolic reprogramming, provides new strategies to overcome CRC treatment resistance. In this review, we integrate basic mechanisms and clinical translational perspectives to propose a combination therapy strategy targeting the CIN-TME interaction network, which provides a theoretical basis and application prospect for optimizing colorectal cancer immunotherapy and expanding indications.

Keywords

Chromosomal Instability (CIN), Tumor Immune Microenvironment (TME), Colorectal Cancer, Immunotherapy

1. 引言

染色体不稳定性(Chromosomal instability, CIN)是肿瘤细胞的典型特征之一[1]，广泛存在于结直肠癌、乳腺癌等多种恶性肿瘤中，其在肿瘤发生、发展以及肿瘤免疫微环境中起重要作用[2]-[5]。CIN 通过持续产生亚克隆多样性，以促进肿瘤的适应性[6]-[8]，但同时 CIN 具有抗增殖作用[9]-[12]、诱导细胞死亡[13] [14]、衰老[12] [15]-[17]以及抗肿瘤免疫反应[18]-[24]。近年来，随着单细胞技术的不断发展，CIN 对肿瘤免疫微环境(Tumor Microenvironment, TME)的调控机制逐渐成为研究热点。一方面，微核来源的胞质 DNA (dsDNA)能够上调免疫细胞的迁移和促进抗原呈递，从而发挥抗肿瘤免疫过程[24]；另一方面，CIN 诱导的 cGAS-STING 慢性激活可使下游信号通路重编程，形成免疫抑制性微环境，促进肿瘤转移[25]。这种双向调控机制在结直肠癌中亦有突破性研究——微卫星稳定(MSS)型肿瘤因低肿瘤突变负荷和免疫“冷”表型对 PD-1/PD-L1 抑制剂耐药，而 CIN 相关信号可能通过重塑抗原呈递和 T 细胞功能克服这一局限。此外，有丝分裂调控蛋白(如 Aurora 激酶家族)的异常表达不仅加剧 CIN，还可通过代谢重编程或 DNA 损

伤应答(DDR)间接调控免疫细胞功能。这些发现提示，靶向 CIN 相关通路与免疫治疗的协同作用或能逆转 MSS 型 CRC 的免疫耐受。

2. CIN 的分子机制及其免疫调控的双重性

CIN 的分子机制复杂，主要包括致癌信号传导、有丝分裂前复制应激和中心体复制缺陷、姐妹染色单体黏连、纺锤体组装检查点信号传导或着丝粒－微管附着异常[26]。CIN 有数个关键的标志物，其中包括染色体滞后、微核、非整体倍、多倍体[2] [27]-[34]。其中微核包含具有非典型表观遗传修饰的受损染色体片段，导致异常的转录调控。这种转录机制的失调可能会导致内源性 dsRNA 的产生，从而在基因毒性治疗期间激活抗肿瘤免疫反应。微核在其膜破裂后释放染色体片段(dsDNA)可激活细胞质 DNA 感应通路(如 cGAS-STING)，诱导 I 型干扰素(IFNα/β)分泌，进而促进抗原呈递细胞(APC)的成熟和 $CD8^+$ T 细胞的活化[35]。其在免疫微环境中的调控的双重性主要表现为：

促免疫效应：在正常细胞中，通常不存在 dsDNA，但当发生染色体错误分离时，其释放的 dsDNA 通过激活 STING-TBK1-IRF3 轴，增加 I 型干扰素(IFN)和 MHC I 分子的上调，触发免疫原性细胞死亡(如焦亡)，释放损伤相关分子模式(DAMPs)，激活免疫系统，从而增强抗肿瘤免疫反应[36]。此外，CIN 驱动的基因组异质性可增加肿瘤新抗原的多样性，提升免疫系统对肿瘤的识别效率[37]。近日，日本癌症研究基金会的 Shunsuke Kitajima 团队发现通过染色体错误分离形成微核后，微核的破裂不仅导致胞质 dsDNA 的增加，而且导致胞质 dsRNA 的积累，激活线粒体抗病毒信号转导(MAVS)介导的 dsRNA 感知通路和 cGAS/STING 通路：在 NSCLC 细胞系中过表达 MAVS 显著增加 MPS1 (纺锤体组装检查点的重要调控因子)抑制剂诱导的天然免疫反应，包括信号通路分子 TBK1 和 STAT1 的激活增加，以及 CXCL10 和 IFN-β 的分泌增加，二者的协同作用上调免疫细胞的迁移和抗原递呈过程[24]。

免疫抑制风险：然而，高水平 CIN 引发的肿瘤细胞内 cGAS-STING 通路长期激活，引发细胞对干扰素信号的脱敏及 TME 的重编程，转而促进免疫抑制性微环境的形成。例如，慢性 STING 激活通过内质网应激(ER stress)诱导 CCL2、CXCL1 等免疫抑制性细胞因子的分泌，招募调节性 T 细胞(Treg)和髓源性抑制细胞(MDSCs)，同时下调干扰素刺激基因(ISG)的表达，削弱抗肿瘤免疫应答[25]。

3. CIN 重塑结直肠癌免疫微环境的独特模式

CIN 在结直肠癌中广泛存在[2]，但在结直肠癌中，为了逃避 dsDNA 介导的 STING 激活并逃避免疫监测，cGAS/STING 通路在结肠癌细胞中经常受到抑制，这就导致肿瘤免疫原性降低，从而导致内在免疫检查点阻断(ICB)的耐药性[24]。在结直肠癌(CRC)中，CIN 与微卫星状态(MSI/MSS)的交互显著影响免疫治疗响应：

MSI-H 型 CRC：微卫星高度不稳定(MSI-H)型 CRC 由错配修复缺陷(dMMR)驱动，其特征为高肿瘤突变负荷(TMB)和新抗原丰度，使其对 PD-1/PD-L1 抑制剂敏感[38]。然而，目前研究发现 MSI-H 型肿瘤的 CIN 程度通常较低，其免疫激活主要依赖新抗原-MHC 复合物介导的 T 细胞识别，而非 CIN 相关的固有免疫信号。

MSS 型 CRC：约占 CRC 病例的 85%，传统上对免疫治疗耐药，被称作为“冷”肿瘤。近期研究发现，YY2 过表达与抗 PD-L1 治疗相结合，分别将 MSI 和 MSS CRC 肿瘤的生长抑制降低了不到 4 倍和 6 倍。此外，过表达的 YY2 通过增强 BUB1B 表达导致染色体错配率升高，进一步增加了抗 PD-L1 抗体治疗诱导的细胞毒性 T 淋巴细胞(CTL)向由 MSI 或 MSS CRC 细胞形成的肿瘤病灶的浸润。同样，这种组合增加了 Ki67 + $CD8^+$、TNFα + $CD8^+$和 IFNγ + $CD8^+$ T (T 细胞增值的标志物)细胞的比例；同时降低了 PD-1 + $CD8^+$和 TIM-3 + $CD8^+$ T (T 细胞衰竭的标志物)细胞的比例。在过表达 YY2 并联合抗 PD-L1 抗体

治疗的 MSI 和 MSS 肿瘤病灶中，白介素 1 (IL-1) (焦亡的标志物)表达和细胞死亡显著增加。这些结果表明，YY2 过表达/抗 PD-L1 联合治疗可诱导染色体错配、细胞焦亡以及肿瘤病灶内免疫微环境的形成，从而促进 CTL 的增殖和活化，同时防止其耗竭。因此，细胞毒性 T 淋巴细胞(CTLs)在微卫星不稳定性高(MSI)和微卫星稳定(MSS)的肿瘤中均增强了其杀伤肿瘤的效果[39]。

纺锤体组装检查点(SAC)是有丝分裂保真度的重要保障机制，其受损可导致 CIN，过表达 YY2/BUB3 能够通过调控 SAC 有助于诱导 CIN，过量的 CIN 使 CRC 细胞对奥沙利铂和紫杉醇显着敏感，降低耐药性[40]。细胞分裂过程中起重要作用的另一种蛋白质：丝氨酸/苏氨酸激酶(Aurora 激酶，AURK)，其基因的扩增(过表达)可存在于结直肠癌中，与更具侵袭性的转移性肿瘤和化疗耐药性(如顺铂)有关[41]。AURKA (Aurora 激酶 A)的表达和活性在细胞内被严格的调控，可通过 AURKA-BOD1L1-PP2A 轴在维持染色体分离“保真度”起重要作用[42]，一旦失调将会导致 CIN、AURKA 在大多数肿瘤中异常高表达，与患者不良预后及更短的生存期相关，其高表达导致肿瘤细胞恶性增殖、上皮间质转化、转移、肿瘤干细胞的自我更新等，AURKA 的抑制会诱导多种肿瘤细胞的生长抑制和凋亡。研究发现 AURKA 抑制剂可提高肿瘤细胞和骨髓细胞中 PD-L1 的表达，降低抗肿瘤免疫治疗[43]。AURKB (Aurora 激酶 B)通过靶向 AURKB-MAD2L2 轴调节糖酵解和 DNA 损伤应答(DDR)，从而调节结直肠癌的进展[44]，此外，抑制 AURKB 可增加结直肠癌对 5-氟尿嘧啶的反应性[45]。

4. 靶向 CIN-TME 交互网络的联合治疗策略

染色体不稳定性(CIN)与肿瘤免疫微环境(TME)的交互作用为联合治疗提供了多维度干预窗口。基于 CIN 的免疫调控特性，以下策略在未来或许可以推动临床转化突破：

(1) CIN 诱导与免疫检查点阻断协同

靶向有丝分裂调控蛋白(如 AURK、BUB1B)可人为增强 CIN，促进微核形成和免疫原性信号释放。例如，Alisertib (AURKA 抑制剂)与抗 PD-L1 联用在未来有广阔的前景，不仅解决了 Alisertib 耐药的问题，还显著提高 PD-1 免疫治疗的敏感性。此外，通过靶向 AURKB-MAD2L2 轴从而破坏 CRC 中基本代谢和 DNA 修复机制或许也是一种有前景的治疗策略。通过 YY2 的过表达诱导的染色体错配分离引发细胞焦亡，可使 MSS 型 CRC 对 PD-1 抗体治疗响应率提升，为改善结直肠癌中 ICI 治疗效果提供了一种新策略。

(2) 代谢重编程与免疫调控协同

为了满足自身生存的能量供应，肿瘤细胞会通过代谢重编程调整能量供应和消耗途径，比如采用糖酵解等呼吸方式，肿瘤细胞的这些异常代谢会对免疫细胞造成影响，从而影响免疫治疗效果。在结直肠癌细胞中靶向 AURKB 基因会导致氧化应激增强、细胞损伤以及脂质过氧化加剧，从而抑制结直肠癌的进展[44]。微生物存在于多种肿瘤中，通过其多样的代谢产物间接调控肿瘤细胞的生存、转移和耐药。比如微生物代谢物短链脂肪酸、胆汁酸和肌苷，可以通过血液进行不同微生物群落的交换，进而调控肿瘤微环境中细胞的生命活动[46]；此外，微生物还能通过多种方式直接或间接对肿瘤微环境和肿瘤细胞产生积极的影响，其中就包括直接引起双链 DNA 的损伤，对免疫细胞产生不同的影响，从而影响免疫治疗的效果[47]。

5. 挑战与展望

尽管靶向染色体不稳定性(CIN)与肿瘤免疫微环境(TME)的交互网络为结直肠癌(CRC)治疗提供了新方向，但其临床转化仍面临多重挑战。**首先**，CIN 的异质性及其动态调控机制尚未完全解析。不同肿瘤中 CIN 程度、驱动基因(如 AURK、BUB1B、BUB3)的突变谱以及微环境因子(如细胞因子、微生物群)的协同作用可能显著影响治疗效果，但目前缺乏精准的分子分型工具以指导个体化治疗。**其次**，CIN 诱导

的免疫激活与抑制的平衡难以把控。例如，靶向 AURK 虽可增强微核形成并激活 cGAS-STING 通路，但长期抑制可能加剧基因组不稳定性，甚至通过代谢重编程(如糖酵解上调)或 DNA 损伤应答(DDR)异常间接促进免疫逃逸。此外，联合治疗策略(如 AURK 抑制剂与 PD-L1 阻断)的临床前模型与人体试验结果存在差异，部分归因于肿瘤微环境中免疫细胞亚群(如 Treg、MDSCs)的动态变化未被充分纳入评估体系。

未来研究需聚焦以下方向：

1、精准解析 CIN-TME 交互的动态图谱：结合单细胞多组学与空间转录组技术，解析 CIN 程度、微核释放频率与免疫细胞浸润特征的关联，明确关键节点分子(如 YY2、MAVS)的调控阈值，以规避免疫抑制风险。

2、优化联合治疗策略的靶向性与安全性：开发选择性 AURK 变构抑制剂或基因编辑工具(如 CRISPR-Cas9)，在增强 CIN 诱导的免疫原性同时，避免非特异性基因组损伤；探索代谢干预(如靶向糖酵解、改善肿瘤内缺氧环境)与免疫检查点阻断的协同效应，以逆转“冷肿瘤”微环境。

3、构建临床转化的多维预测模型：开发并能常规用于临床整合患者 CIN 评分工具、微生物组特征及免疫细胞耗竭标志物(如 PD-1+、TIM-3+、$CD8^+$ T 细胞)，建立预后分层系统，筛选潜在获益人群。此外，利用类器官与人源化小鼠模型模拟 MSS 型 CRC 的免疫抑制微环境，开发新型治疗药物并进行临床研究，为患者提供更精准的治疗方案，改善患者的预后。

总之，CIN-TME 交互网络的研究为突破 CRC 免疫治疗瓶颈提供了全新视角，但其复杂性要求跨学科协作与技术创新。通过精准调控 CIN 的“免疫双刃剑”效应，未来有望实现从基础机制到临床应用的跨越，为 MSS CRC 患者带来生存获益。

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