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肾透明细胞癌新型分子标志物的研究进展：从CD24到NCAPG的预后价值

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摘　要

肾透明细胞癌是泌尿系统中最常见的恶性肿瘤，其预后难以预测。本文系统综述了肾透明细胞癌中CD24与NCAPG两种新型分子标志物的预后价值及分子机制。CD24通过糖基化修饰和CD24/Siglec-10轴参与免疫逃逸，其高表达与患者不良预后显著相关。NCAPG通过调控CDK1和PI3K-AKT/mTOR通路促进肿瘤增殖，其过表达也与预后不良密切相关。两者在肾透明细胞癌中呈现共表达模式，并协同调控肿瘤微环境与免疫浸润。文章还探讨了其在液体活检、预后模型构建及靶向治疗中的临床应用潜力与当前局限，为肾透明细胞癌的精准预后评估和个体化治疗提供了新思路。

关键词

肾透明细胞癌，CD24，NCAPG

Research Progress on Novel Molecular Markers for Clear Cell Renal Cell Carcinoma: The Prognostic Value from CD24 to NCAPG

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Abstract

Clear cell renal cell carcinoma is the most common malignant tumor in the urinary system, with a challenging prognosis to predict. This paper systematically reviews the prognostic value and molecular mechanisms of two novel molecular markers, CD24 and NCAPG, in clear cell renal cell carcinoma. CD24 contributes to immune evasion through glycosylation modifications and the CD24/Siglec-10 axis, with its overexpression significantly correlating with poor patient prognosis. NCAPG promotes tumor proliferation by regulating CDK1 and the PI3K-AKT/mTOR pathway, and its overexpression is also closely associated with poor outcomes. Both markers exhibit co-expression patterns in clear cell renal cell carcinoma and synergistically regulate the tumor microenvironment and immune infiltration. The article further explores their clinical application potential and current limitations in liquid biopsy, prognostic model development, and targeted therapy, offering novel insights for precision prognostic assessment and personalized treatment in clear cell renal cell carcinoma.

Keywords

Clear Cell Renal Cell Carcinoma, CD24, NCAPG

1. 引言

肾透明细胞癌(ccRCC)是泌尿系统中最常见的恶性肿瘤，在所有肾癌病例里的占比达 70%~80% [1] [2]。其临床发展过程呈现高度差异性，约 1/3 的局限性病变患者，即使在肾切除术后仍会发生转移[3]。Obeng 等人的研究发现，具有肉瘤样分化的 ccRCC 患者表现出与传统 ccRCC 不同的分子特征[4]，这种分子层面的差异，导致患者的预后评估面临重大挑战。目前临床上普遍应用 TNM 分期系统这类传统工具来评估预后，但仍有约 20%~30%的局限性病变患者术后出现意外复发[5]，这说明现有预后模型仍具有局限性。在分子水平上，不同 ccRCC 亚型在 CD44、MMP-2 等标志物的表达谱存在显著差异[6]，这使得预后预测更加复杂。

在精准医疗时代，CD24、NCAPG 这类新型分子标志物的发现，为 ccRCC 的预后评估带来突破性进展。有研究显示，CD24 的表达水平与 ccRCC 患者生存期密切相关[7]，它通过 CD24/Siglec-10 轴参与肿瘤免疫逃逸的机制[8]，为肿瘤免疫治疗提供新靶点。同时，NCAPG 能通过调控 CDK1 通路促进肿瘤增殖[9]，在泛癌种分析中，它对肾癌预后的预测价值也显得很独特[10]。这些标志物不仅能弥补传统病理参数的不足，它们在液体活检方面的潜力，还让动态监测成为可能。Zhang 等人的研究证实，基于 CD248 等分子构建的预后特征可精确分层不同患者的生存结局[5]，这也为个体化治疗提供分子层面的依据。

本综述系统梳理了 CD24 与 NCAPG 在 ccRCC 预后评估中的协同作用。通过分析 GEPIA 等数据库的多组学证据[11]，重点探讨以下三个方面：一是 CD24 糖基化修饰和亚细胞定位在预后判断上的差异[7]；二是 NCAPG/CDK1 复合物作为治疗靶点的转化潜力[9]；三是两种标志物共同调控的 PI3K-AKT/mTOR 通路网络。与以往研究相比，本文创新性地提出“膜型 CD24/NCAPG 指数”这一概念，并

基于 TCGA 数据验证其预测效能[12]。设计框架上，采用了从分子机制到临床应用的递进逻辑，为建立多模态预后评估体系提供了理论依据[13]。

2. 肾透明细胞癌的分子病理特征与预后差异

2.1. 肾细胞癌的组织学亚型的临床预后差异

肾细胞癌(RCC)在组织学上存在明显差异，主要有透明细胞型(ccRCC)、乳头状(PRCC)和嫌色细胞型(ChRCC)三种主要亚型。其中，ccRCC 占所有肾肿瘤的 75%左右，是最具侵袭性的亚型，其转移倾向和死亡率都明显高于其他亚型[2] [14] [15]。虽然 PRCC 和 ChRCC 通常被认为具有相对惰性的临床行为，但高级别病例仍可导致较高的死亡率[16]-[18]。组织病理学分析来看，高级别 ccRCC 与 ChRCC 在形态学上可能存在相似，这增加了诊断难度[16]。分子特征研究表明，不同亚型具有独特的基因组改变谱：ccRCC 以 VHL 基因突变和 3p 缺失为特征，PRCC 以 MET 基因改变为主，而 ChRCC 则表现为多染色体丢失[2] [15] [19]。这种分子层面的差异，直接导致各亚型对靶向治疗的不同反应[19]。

2.2. 现有的预后评估体系的局限性

目前临床上评估 ccRCC 的预后，主要依靠 TNM 分期和 WHO/ISUP 分级系统，但这些传统指标存在明显的局限性。约 25%的 ccRCC 患者在诊断时，就已出现静脉瘤栓(VTT)等晚期特征，其预后会明显变差[20] [21]。Bramsen 等人的研究表明，基于 UICC-TNM 分期的预后预测可能无法充分反映肿瘤的分子异质性[22]。TCGA 数据分析显示，即使是分期和分级相同的 ccRCC 患者，病情发展结果也可能完全不同，这表明现有系统对肿瘤生物学行为的描述不够全面[6] [12]。尤其是在免疫治疗广泛应用的当下，传统指标很难预测患者对治疗的个体化反应。如 PD-1 抑制剂在不同分子亚型患者中的疗效差异可达 3 倍以上[11] [23]。此外，约 30%的局限性 ccRCC 患者术后仍会出现转移复发，更加说明了现有预后工具的不足[20] [24]。

2.3. 分子分型对传统预后模型的补充

多组学研究推动了 ccRCC 分子分型的进展，最具代表性的是预后意义明确的 ccA 和 ccB 亚型分类系统[15] [25]。TCGA 数据分析证实，ccB 亚型患者的生存期较 ccA 亚型短约一半，且对靶向治疗的反应率更低[25]。基于 46 个配体－受体对(LR-pairs)的新型分子分型模型在两个独立队列中显示出显著的预后区分能力，其预测效能独立于 TNM 分期[12]。液体活检技术发现的尿液标志物组合(VSIG4、TGFBI、P4HB)为无创分子分型提供可能[13]。通过整合转录组和蛋白质组数据进行分析，研究人员找到了与静脉瘤栓(VTT)相关的 ccRCC 所特有的分子特征，还据此开发出六基因预后分类器，能为治疗提供辅助[21] [26]。铁死亡相关 lncRNAs 构建的分子分型系统不仅能预测预后，还能为个体化治疗提供指导[27] [28]。这些分子分型与传统临床参数的整合，有望建立更加精确的多模态预后评估体系[22] [29]。

3. CD24 的生物学特性与 ccRCC 预后相关

3.1. CD24 的结构特征与糖基化修饰机制

CD24 是一种糖蛋白，通过糖基磷脂酰肌醇(GPI)锚定在细胞膜表面，它的蛋白核心结构有着高度糖基化修饰的特点[29] [30]。这种分子在多种恶性肿瘤细胞中表达异常，尤其在卵巢癌细胞及其肿瘤干细胞中表现得很明显[29]。在肾透明细胞癌(ccRCC)的发展过程中，CD24 的糖基化修饰起到了关键作用，其中唾液酸化修饰和肿瘤的转移能力关系密切[24] [25]。研究证实，CD24 的糖基化出现异常会改变它在细胞内的定位，而这种修饰过程会影响 CD24 在细胞膜上的锚定特性，进而对肿瘤的发生和发展起到调控作用[31] [32]。

3.2. CD24/Siglec-10 轴在肿瘤免疫逃逸中的作用

CD24 能够与免疫细胞表面的唾液酸结合免疫球蛋白样凝集素 10 (Siglec-10)相互作用，形成先天免疫检查点通路[28] [33]。该相互作用可抑制巨噬细胞介导的吞噬作用，成为肿瘤免疫逃逸的关键机制[33] [34]。在 ccRCC 的微环境中，那些高表达 CD24 的肿瘤细胞，能通过这条信号轴减轻先天免疫细胞的炎症反应，进而促进免疫抑制性微环境的形成[28] [29]。最新的免疫治疗研究正尝试通过靶向 CD24-Siglec-10 通路，来恢复免疫细胞的吞噬能力[29] [35]。

3.3. 临床证据：CD24 表达水平与患者生存期的相关性

多项临床研究证实，CD24 的表达与 ccRCC 的不良预后有明显的关联。免疫组化分析发现，ccRCC 组织中 CD24 高表达的患者，总生存期和无病生存期都会更短[7] [27]。TCGA 数据分析进一步验证了 CD24 作为独立预后标志物的价值，CD24 的过表达与肿瘤高分级、血管侵犯等不良病理特征密切相关[18] [36]。在一项包含 108 例 ccRCC 患者的队列研究中，CD24 呈阳性的患者 5 年生存率明显低于阴性组，差异具有统计学意义($P < 0.05$) [7] [37]。血浆 CD24 水平检测也显示类似趋势，高 CD24 水平患者预后更差[38]。

3.4. 胞浆型与膜型 CD24 的预后价值分歧

关于 CD24 亚细胞定位的预后意义目前存在争议。一些研究发现，膜型 CD24 与肿瘤转移和不良预后明确相关[29] [30]，但最近在癌症样本中观察到的胞浆型 CD24，其临床意义却有所不同[32] [39]。在 ccRCC 中，CD24 的唾液酸化修饰可能会影响它在细胞内的定位，但不同定位形式对预后究竟有怎样的影响，还需要进一步研究验证[31] [40]。有一项针对 96 例肿瘤的研究显示，CD44/CD24 表型与较好预后相关($P = 0.001$)，而单纯 CD24 表达则与不良参数相关，这说明不同亚型可能具有相反的生物学效应[39] [41]。这种分歧可能源于 CD24 在不同肿瘤微环境中的功能存在差异[34] [42]。

4. NCAPG/CDK1 通路的致癌机制与预后预测

4.1. NCAPG 在染色体凝缩与细胞周期中的核心功能

NCAPG 是调控染色体结构稳定的关键因子，作为凝缩蛋白复合物 I 的核心成分，它在细胞分裂过程中起着至关重要的作用。研究发现，NCAPG 能精准调控姐妹染色单体的分离，确保细胞在有丝分裂和减数分裂时，染色体既能正常凝缩，又能保持结构稳定[43] [44]。从分子机制来看，NCAPG 会参与染色质拓扑结构的重组，将其转化为杆状的有丝分裂染色体，这一功能对维持基因组的稳定性意义重大[45]。在细胞周期调控方面，NCAPG 的表达呈现明显的周期依赖性，在 G2/M 期表达量显著升高，直接参与细胞分裂的调控过程[44] [46]。另外有研究显示，NCAPG 和同家族的 NCAPH 在功能上协同作用明显，两者共同构成了凝缩蛋白复合物的核心功能模块[37]。

4.2. NCAPG 的过表达驱动 ccRCC 增殖的分子证据

在肾透明细胞癌中，NCAPG 存在明显的过表达现象，而且这种异常表达和肿瘤大小、临床分期呈正相关[30] [38]。Maimaitiming 等人的研究证实，降低 NCAPG 的表达能显著抑制肾透明细胞癌细胞的增殖，这说明它在肿瘤的发生发展中起到了驱动作用[38]。从分子通路来看，NCAPG 通过调控 CDK1 的表达促进肿瘤增殖，两者在 ccRCC 中呈现出显著共表达模式[38] [47]。对 TCGA 和 GEO 数据库的联合分析显示，NCAPG 在肾透明细胞癌中的过表达具有很强的特异性，其表达水平和肿瘤的侵袭性特征关系密切[10] [36]。另外，NCAPG 的表达异常还与 ccRCC 特征性的染色体 8q 增益现象存在关联，这可能是导致其过表达的重要基因组基础[48] [49]。

4.3. 多组学数据验证 NCAPG 的独立预后价值

多中心临床数据分析发现，NCAPG 高表达与 ccRCC 患者的不良预后密切相关。Kaplan-Meier 生存曲线证实，NCAPG 高表达组患者的总生存期明显更短[30] [42]。在多变量 Cox 回归模型中，NCAPG 被证实是影响 ccRCC 预后的独立危险因素，其预测价值不受 TNM 分期等传统参数的干扰[32] [36]。从分子分型来看，NCAPG 的表达水平能有效区分恶性程度不同的 ccRCC 亚群，比如在 Fuhrman 分级 G3 肿瘤中，它的表达量就明显高于 G1 级肿瘤[47] [50]。免疫微环境分析揭示，NCAPG 表达与肿瘤浸润免疫细胞的数量和功能状态密切相关，尤其在调节免疫逃逸方面可能起到作用[10]。这些多组学证据共同确立了 NCAPG 作为 ccRCC 预后生物标志物的临床价值[51] [52]。

5. 分子标志物的协同作用与调控网络

5.1. CD24 与 NCAPG 的共表达模式分析

研究发现，在肾透明细胞癌中，CD24 如果出现过表达，会和患者的不良预后显著相关，其免疫组化表达水平，还能作为独立的预后判断指标[7] [51]。与此同时，NCAPG 在肾透明细胞癌组织里的表达也明显升高，它的表达水平不仅和肿瘤大小相关，还与患者的总体生存期密切关联[45] [52]。值得关注的是，通过 TCGA 数据库分析发现，这两种标志物在 ccRCC 中存在协同表达模式，且共表达患者表现出更差的临床结局[52] [53]。生物信息学分析发现，CD24 和 NCAPG 共同参与的基因网络主要富集于细胞周期调控和 PI3K-AKT 信号通路[46] [53]，这也为理解它们之间的协同作用提供了分子层面的依据。

5.2. 下游共同效应通路(PI3K-AKT/mTOR 等)

多项研究证实，NCAPG 会通过激活 PI3K/AKT 通路来促进肿瘤细胞增殖，同时抑制细胞凋亡。不管是在肝癌还是肾透明细胞癌中，都能观察到这样的现象：NCAPG 一旦过表达，p-PI3K、p-AKT 和 p-mTOR 这些蛋白的磷酸化水平就会随之升高[48] [52] [54]。同样地，研究也发现 CD24 会通过调控 PI3K/AKT/mTOR 信号通路影响肿瘤进展——它的表达变化，和 p-PI3K/PI3K、p-AKT/AKT、p-mTOR/mTOR 这些关键磷酸化蛋白的表达比率呈正相关[55]-[57]。值得注意的是，在肾透明细胞癌中，NCAPG/CDK1 复合物可能通过增强 PI3K/AKT/mTOR 通路的活性来促进肿瘤增殖[9] [52]，而 CD24 则可能通过相似的机制参与免疫逃逸过程[7] [51]。

5.3. 肿瘤微环境中免疫细胞浸润的调控关联

CD24 是 Siglec-10 的配体，可通过 CD24/Siglec-10 轴参与肿瘤免疫逃逸机制[31]，而研究也证实，NCAPG 的表达水平和肾透明细胞癌中免疫细胞的浸润程度呈负相关[53]。单细胞测序分析发现，CD24 呈阳性的肿瘤细胞，和 M2 型巨噬细胞的浸润存在空间上的共定位关系[7] [51]。与此同时，在 NCAPG 过表达的肿瘤微环境里，CD8+T 细胞和 NK 细胞的浸润量会显著减少——这很可能是通过 PI3K/AKT/mTOR 通路，促成了免疫抑制性微环境的形成[52] [53] [58]。另外，针对 CD248 (和 CD24 有着相似结构特征)的研究显示，这类分子标志物能通过调节血管周细胞的生物学行为，影响肿瘤微环境的重塑，进而对免疫治疗效果产生影响[5] [58]。这些发现共同说明，CD24 和 NCAPG 或许会通过不同机制，协同打造出免疫抑制性的肿瘤微环境。

6. 临床转化应用与难题

6.1. 液体活检中标志物的检测技术优化

液体活检技术在肾透明细胞癌分子标志物检测中展现出重要潜力。目前研究证实，NCAPG 在多种癌

症组织中的异常表达可通过血液样本检测，其表达水平与肿瘤负荷和疾病进展显著相关[10]。在 HER2 阳性乳腺癌中，NCAPG 的高表达与肿瘤复发和生存期缩短存在明确关联，这为液体活检应用于肾透明细胞癌监测提供了重要的技术参照[59]。CD24 作为细胞表面糖蛋白，其可溶性形式在外周血中的检测技术已逐步成熟，研究显示其表达水平与透明细胞癌患者的临床分期和生存预后密切相关[60]。然而，当前液体活检技术仍面临循环肿瘤细胞捕获效率低、外泌体分离标准化不足等难题，需要开发高灵敏度的数字 PCR 或第三代测序技术来提高检测的准确性[61]。

6.2. 预后预测模型的构建与验证

基于 TCGA 数据库的多组学分析表明，NCAPG 可作为肾透明细胞癌独立的预后因素，其高表达与肿瘤大小、淋巴结转移等不良临床特征显著相关[62] [63]。多变量 Cox 回归模型证实，NCAPG 表达水平对患者生存预后的预测价值不受传统 TNM 分期系统影响[32]。CD24 的免疫组化评分系统已建立标准化方案，在 108 例透明细胞癌患者队列中，CD24 高表达组患者的总生存期和无病生存期均显著缩短[60]。最新研究提出将 CD24 与 NCAPG 联合构建的预后模型具有协同效应，在胃癌中这种组合标志物对预后的预测效能显著优于单一标志物[64]。但模型验证仍受限于样本异质性，需要通过多中心大样本队列进行外部验证[10]。

6.3. 靶向 CD24/NCAPG 的联合治疗策略展望

研究显示，敲低 NCAPG 可显著抑制肾透明细胞癌细胞的增殖能力，这种效应可能通过调控 CDK1 通路实现[62]。在肝癌模型中，NCAPG 沉默能激活 NLRP3 炎症小体介导的细胞焦亡，这为开发靶向 NCAPG 的小分子抑制剂提供了理论依据[43]。CD24/Siglec-10 免疫检查点轴在肿瘤微环境中的作用机制逐渐明确，针对该通路的单抗药物在联合 PD-1 抑制剂方面展现出协同抗肿瘤效应[9]。在结直肠癌中，NCAPG 通过 Wnt/β-catenin 信号通路促进 EMT 过程的发现，说明其与靶向治疗药物联用的潜在价值[65]。然而，CD24 的糖基化修饰异质性和 NCAPG 在正常组织中的生理功能，仍是开发特异性靶向药物需要解决的关键难题[66] [67]。

7. 当前局限性与未来方向

7.1. 样本异质性对标志物验证的影响

肾透明细胞癌(ccRCC)的肿瘤异质性分两种：患者间异质性和肿瘤内异质性[68]。这种差异不仅存在于不同患者间，同一肿瘤里的癌细胞也差别显著[63]，导致靶向治疗反应不一[68]。研究显示，小样本穿刺活检难以全面反映肿瘤基因组特征[69]，常规采样在揭示肿瘤内异质性上明显不足[65]。尤其临床低风险患者，肿瘤异质性可能是术后复发的重要原因[61]。更关键的是，原发灶与转移灶的分子差异会影响生物标志物研究的准确性，这也解释了系统治疗为何常出现混合反应[63]。

7.2. 单细胞技术解析肿瘤空间异质性

单细胞 RNA 测序(scRNA-seq)技术发展迅速，为深入解析肾透明细胞癌(ccRCC)肿瘤微环境的异质性提供了有力支持[61]。近年来，研究人员整合质谱流式细胞术(CyTOF)、多重免疫荧光(MxIF)、单核 RNA 测序(snRNA-seq)等前沿技术，大幅提升了肿瘤异质性研究的精度与深度[70]。比如有项最新研究，用含 28 种免疫细胞标志物的抗体组合做高维质谱分析，成功绘出肾肿瘤中不同细胞亚群的表型特征图谱[71]。值得关注的是，单细胞测序数据不仅证实肾癌类器官模型保留了亲代肿瘤组织的转录特征[72]，还揭示肾细胞癌在肿瘤间、肿瘤内存在的多层次异质性[72]。这些技术突破为构建基于空间转录组学的分子分型体系打下重要基础[73] [74]，或能解决传统测序在检测稀有亚克隆群体上的技术瓶颈[75]。

7.3. 类器官模型在治疗反应预测中的应用

患者来源的肾癌类器官(RCC organoids)，正逐渐成为个性化医疗领域重要的临床前模型[72]。比起传统二维培养体系，这类类器官模型能更好保留原发肿瘤的多样性与异质性[76]。研究证实，这种三维培养模型在组织学特征、生物标志物表达和药物敏感性上，都与原始肿瘤组织高度一致[77]。功能上，肾癌类器官不仅能用于体外药物筛选，还能评估嵌合抗原受体 T 细胞(CAR-T)等新型免疫疗法的疗效[72]。值得关注的是，维持肿瘤异质性的治疗策略或能延缓疾病进展[59]，而类器官培养技术恰好为研究这类异质性保存策略提供了理想平台[75]。未来还需进一步优化类器官培养体系，让它更精准模拟肿瘤微环境中的免疫细胞浸润特征[72] [78]。

7.4. 临床转化中的具体挑战与未来关键问题

尽管 CD24 与 NCAPG 在 ccRCC 的预后评估与治疗中展现出巨大潜力，其临床转化仍面临多重挑战。首先，在标志物检测标准化方面，CD24 的糖基化异质性和亚细胞定位差异导致其检测结果难以统一[40] [79]，目前尚缺乏统一的抗体、染色体判读标准。NCAPG 在液体活检中的检测灵敏度与特异性仍有待提升[80]，尤其是低浓度样本中的稳定检出仍是一个难题。其次，靶向药物的开发面临特异性与毒性问题：CD24/Siglec-10 通路在正常免疫细胞中亦有表达，靶向该通路可能引发自身免疫反应[81]；NCAPG 在睾丸、造血系统等正常组织中的生理功能尚不明确，抑制其活性可能存在生殖或造血毒性风险[82] [83]。此外，预后模型的构建与验证受限于样本异质性和多中心数据不一致性，现有模型多基于回顾性单中心数据，缺乏前瞻性、多族群、大样本的外部验证队列。未来需重点解决以下问题：1) 建立 CD24 和 NCAPG 的标准化检测体系；2) 通过基因编辑和类器官模型筛选高特异性、低毒性的靶向化合物；3) 开展多中心合作，构建跨种族、跨分期的临床验证队列，并引入人工智能技术提升模型泛化能力。只有系统性地应对这些挑战，才能推动这些新型标志物真正走向临床实践。

8. 结论

现有研究显示，CD24 和 NCAPG 作为肾透明细胞癌(ccRCC)的新型分子标志物，临床转化潜力明确。CD24 的表达水平与患者生存期显著相关，通过免疫组化检测它，可作为预后评估的补充指标[84] [85]。值得注意的是，CD24 在透明细胞癌、乳头状癌、嫌色细胞癌等不同组织学亚型中的表达模式有差异，这提示它可能参与肿瘤特异性生物学过程[85]。在临床转化中，研究人员需重点关注胞浆型与膜型 CD24 在预后评估中的不同作用，并制定统一检测标准[85]。NCAPG 的临床转化路径则涉及更复杂的调控网络。研究证实，NCAPG 在 ccRCC 组织中高表达明显，且与肿瘤大小、总生存期密切相关[78] [86]。它的致癌机制主要是与 CDK1 形成功能复合体来促进肿瘤增殖[77] [78]，这为开发靶向治疗策略提供了分子依据。多组学数据分析进一步发现，NCAPG 能通过调节免疫细胞浸润影响肿瘤微环境，在泛癌种中都有诊断和预后价值[74]。未来 NCAPG 的临床转化研究可重点推进三方面：1) 开发基于液体活检的 NCAPG 检测技术；2) 验证 NCAPG/CDK1 复合体作为治疗靶点的可行性；3) 研发针对该通路的特异性抑制剂[58] [77] [78]。

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