

神经内分泌前列腺癌的研究进展

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摘要

神经内分泌前列腺癌(Neuroendocrine Prostate Cancer, NEPC)是前列腺癌中一类具有高度侵袭性且致死率极高的特殊亚型, 其临床特征主要表现为疾病进展迅速、对常规雄激素受体(Androgen Receptor, AR)靶向治疗存在原发性耐药或继发性耐药, 且患者预后极差。尽管少数情况下NEPC可原发发生, 但更多病例源自前列腺癌在长期接受雄激素剥夺治疗(Androgen Deprivation Therapy, ADT)或雄激素受体通路抑制剂(Androgen Receptor Pathway Inhibitor, ARPI)治疗的压力下, 发生转分化而形成。然而, 该转分化机制的分子基础迄今仍存在较大争议。NEPC患者整体生存率极低, 且目前有效的治疗手段十分有限, 其临床管理面临重大挑战。本文系统综述了NEPC的最新研究进展, 旨在为NEPC的基础研究转化与临床治疗优化提供参考。

关键词

神经内分泌, 前列腺癌, 分子靶向治疗

Research Advances in Neuroendocrine Prostate Cancer

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Abstract

Neuroendocrine Prostate Cancer (NEPC) is a rare but highly aggressive subtype of prostate cancer with an exceptionally high mortality rate. Clinically, NEPC is characterized by rapid disease progression, primary resistance or acquired resistance to conventional Androgen Receptor (AR)—targeted therapies, and extremely poor prognosis. Although NEPC can arise de novo in a minority of cases, it

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more commonly develops through transdifferentiation of prostate adenocarcinoma under the selective pressure of long-term Androgen Deprivation Therapy (ADT) or Androgen Receptor Pathway Inhibitor (ARPI). However, the molecular mechanisms underlying this transdifferentiation remain highly controversial. NEPC patients exhibit very low overall survival, and effective therapeutic options are currently limited, posing major challenges to clinical management. This review provides a comprehensive overview of recent advances in NEPC research, aiming to inform future translational studies and the optimization of clinical treatment strategies.

Keywords

Neuroendocrine, Prostate Cancer, Molecular Targeted Therapy

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1. 引言

近年来,随着基因组学和转录组学研究的深入,越来越多的证据表明多种关键分子驱动因子在神经内分泌型前列腺癌(Neuroendocrine Prostate Cancer, NEPC)的发生和进展中发挥动态作用,不同阶段的分子改变共同塑造了其独特的生物学特征[1]-[3]。这些研究不仅揭示了 NEPC 的复杂演化机制,也为新型靶向治疗和免疫治疗的开发提供了理论依据。因此,系统总结 NEPC 的临床表现、病理学与分子特征,以及现有和新兴治疗策略,对于推动该领域的研究进展并改善患者预后具有重要意义。本文将重点阐述 NEPC 的分子生物学特征,临床病理特征,同时探讨其治疗现状及潜在的治疗新方向,以期对未来 NEPC 的诊断与临床管理工作提供参考。

2. 分子生物学特征

随着多组学技术的快速发展,研究者对 NEPC 的分子生物学特征有了更深入的认识。大量证据表明,NEPC 的发生与进展并非依赖单一机制,而是基因组学异常、表观遗传学重塑及转录因子调控等多层次分子事件共同作用的结果。

2.1. 基因组层面特征

NEPC 亚型呈现出多种特征性基因组改变,这些改变与疾病发生机制及起源密切相关。其一,ERG 与 TMPRSS2 融合基因在 NEPC 中的发生频率约为 50%,与前列腺腺癌相当,但在正常神经内分泌细胞中并未观察到该融合事件[4][5]。此外,在腺癌与 NEPC 混合型肿瘤中,研究发现腺癌灶与邻近神经内分泌灶往往共享 TMPRSS2-ERG 融合事件,这一证据提示 NEPC 可能源自腺癌前体,该假说亦得到基因组研究及谱系追踪临床前实验的支持[6][7]。其二,NEPC 的另一显著基因组特征是 TP53 与 RB1 基因的缺失,且该缺失多发生于去势治疗产生耐药的过程中。大量临床前研究证实,TP53 与 RB1 的联合缺失是驱动肿瘤细胞获得神经内分泌样表型的关键分子基础[8]-[12]。

2.2. 表观遗传学层面特征

表观遗传的改变被认为是驱动 NEPC 细胞谱系可塑性及干细胞样特性的核心机制,主要涉及 DNA 甲基化、组蛋白修饰及染色质可及性的动态变化,这些变化共同调控转录过程与细胞分化状态[13][14]。研

究显示, NEPC 的全基因组 DNA 甲基化模式与去势抵抗性前列腺癌(Castration-Resistant Prostate Cancer, CRPC)存在显著差异, 且该甲基化模式与细胞分化、发育及细胞黏附相关通路密切关联[15]。值得注意的是, 这些特征性甲基化改变可在细胞游离 DNA (cell-free DNA, cfDNA)中检测到, 提示其具有作为无创生物标志物的潜在价值[16]。与此同时, 组蛋白修饰异常在 NEPC 细胞谱系重编程中亦发挥关键作用。EZH2 作为 Polycomb 抑制复合物 2 (Polycomb Repressive Complex 2, PRC2)的核心组分, 在 NEPC 中呈显著高表达状态, 其通过介导组蛋白 H3 第 27 位赖氨酸三甲基化(H3K27me3)促进靶基因沉默, 进而破坏细胞分化稳态[17]。临床前证据表明, 抑制 EZH2 不仅可恢复雄激素受体(Androgen Receptor, AR)的表达, 还能增强肿瘤细胞对 AR 靶向治疗的敏感性, 因此 EZH2 被视为具有药物开发潜力的重要靶点[11] [18] [19]。

2.3. 转录因子调控特征

NEPC 亚型常伴随转录因子的异常活化或抑制, 这些改变直接影响神经内分泌表型的形成与维持。REST 作为神经元特异性基因的关键抑制因子, 在前列腺腺癌中通常高表达, 而在 NEPC 中则显著下调[20] [21]。REST 的缺失不仅可诱导神经内分泌标志物(如嗜铬粒蛋白 A、突触素)的表达, 还能解除对细胞周期相关基因(如 AURKA)的抑制, 从而促进肿瘤细胞增殖[22] [23]。在 AR 抑制治疗的压力下, RNA 剪接因子 SRRM4 可将 REST 剪接为无功能的同源物, 进一步削弱其转录抑制作用, 这些发现提示 REST 下调是 NEPC 神经内分泌表型形成的关键分子事件[24] [26]。另一重要转录因子为 ONECUT2, 其在内胚层来源组织的分化调控及神经系统发育中发挥核心作用。临床样本分析显示, NEPC 的 ONECUT2 表达水平显著高于良性前列腺组织、原发性前列腺腺癌及 CRPC (Spearman 等级相关系数 = 0.54, $P = 7.96 \times 10^{-35}$) [27]。机制上, REST 可通过结合 ONECUT2 启动子区域抑制其表达; 而在 NEPC 中, REST 功能缺失导致 ONECUT2 持续去抑制, 进而通过调控下游靶基因推动神经内分泌表型的建立与维持[28]。

3. 临床病理特征

NEPC 的发病模式具有显著异质性, 既可原发发生, 也可在治疗压力下诱导形成。其中, 原发性 NEPC (de novo NEPC)在前列腺癌初诊病例中十分罕见, 占比不足 2% [29] [30]。相比之下, 治疗诱导型 NEPC (treatment emergent NEPC, t-NEPC)更为常见, 在 CRPC 患者中的发生率可达 10%~17%, 其主要起源是腺癌细胞在雄激素剥夺治疗(Androgen Deprivation Therapy, ADT)或雄激素受体通路抑制剂(Androgen Receptor Pathway Inhibitor, ARPI)的选择压力下, 发生表型转分化而形成[2] [3] [31]。从特征关联性来看, t-NEPC 在临床表型、遗传学改变及病理学特征上, 与小细胞型 NEPC (Small Cell-NEPC, SC-NEPC)及小细胞肺癌 (Small Cell Lung Cancer, SCLC)存在显著相似性[32]。

t-NEPC 是一类高度异质性的肿瘤。活检结果显示, t-NEPC 患者既可能表现为纯小细胞神经内分泌癌, 更常见的则是肿瘤组织中同时存在神经内分泌癌成分与典型前列腺腺癌成分, 这一现象直接体现了其显著的异质性[3] [33] [34]。从疾病演化轨迹来看, t-NEPC 的谱系可从 AR 依赖性的腺癌, 逐渐演变为 AR 非依赖性的小细胞神经内分泌癌。因此, 与原发性 NEPC 相比, t-NEPC 在临床表现与基因组特征上均呈现出更明显的异质性: 原发性 NEPC 多为 AR 阴性表型, 常伴随血清前列腺特异性抗原 (Prostate-Specific Antigen, PSA)水平偏低、内脏转移频发、对 AR 靶向治疗不敏感及预后不良; 而 t-NEPC 中, 具有纯小细胞癌组织学形态的病例同样对 AR 靶向治疗无应答, PSA 水平与肿瘤负荷明显不匹配, 疾病进展迅速且预后极差[3] [34]; 与之不同, 混合型组织学的 t-NEPC 患者往往表现为 PSA 水平较高, 免疫组化(Immunohistochemistry, IHC)检测可观察到一定程度的 AR 表达, 且对 AR 靶向治疗仍保留部分敏感性[35]。

3.1. 组织学特征

在组织学层面, NEPC 通常表现为低分化神经内分泌肿瘤, 其形态学特征与其他器官来源的神经内分泌肿瘤高度相似, 典型表现为 AR 表达缺失, 同时伴随多种神经内分泌标志物的上调。值得注意的是, NEPC 还常伴随血管生成显著增强, 这一特征可能与其高度侵袭性的生物学行为密切相关。根据世界卫生组织的组织学分类标准, NEPC 可进一步分为五个主要亚型: 小细胞癌(Small Cell Carcinoma, SCPC 为最常见亚型)、大细胞 NEPC、伴 Paneth 细胞的腺癌(Adenocarcinoma with Paneth Cells, APC)、分化良好的类癌肿瘤(Carcinoid Tumor, CT-NEPC)、伴神经内分泌分化的腺癌(adenocarcinoma with neuroendocrine differentiation) [36]-[39]。其中, APC 与 CT-NEPC 属于罕见表型, 目前临床报道极为有限。此外, 还存在一种混合型亚型, 神经内分泌癌 - 腺泡状腺癌(mixed NE carcinoma-acinar adenocarcinoma), 该亚型被认为是特殊的过渡性或复合性组织学类型, 进一步凸显了 NEPC 在组织学水平上的显著异质性[33] [36]。

3.2. 免疫组化诊断特征

IHC 在 NEPC 的诊断中具有重要辅助价值, 临床常用的经典神经内分泌标志物包括 INSM1、CgA、SYP 及 CD56 [3] [36] [40]。此外, 还发现 FOXA2、CXCR2 等潜在候选标志物。但需特别注意, 若肿瘤组织学形态仍呈典型腺泡或导管腺癌特征, 仅凭神经内分泌标志物阳性表达, 不足以确立 NEPC 的诊断 [41], 这主要是由于转移性前列腺癌中, 完整组织学评估的获取往往存在困难, 从而限制了基于解剖病理学定义的诊断准确性。

目前, 临床并不推荐在前列腺癌中常规开展神经内分泌特征的 IHC 检测, 且腺泡状腺癌中局灶性神经内分泌分化的临床意义尚未明确。同时, IHC 检测结果可能存在不一致性, 少数 NEPC 病例甚至可能缺乏典型神经内分泌标志物, 仅表现为极低的 PSA 水平[42]。现有研究认为, 从传统前列腺腺癌向高级别 NEPC 的转化是一个连续过程, 由复杂分子机制相互作用驱动, 最终导致形态学亚型的多样化。在此过程中, 部分病例可能呈现中间型表型作为过渡阶段, 从而进一步增加了诊断复杂性[43]。

在诊断实践中, 联合检测 AR 及其信号通路相关基因、前列腺谱系标志物(如 AR、NKX3.1、PSA)与神经内分泌标志物(如 INSM1、SYP、CgA、CD56), 可为 NEPC 的判定提供重要参考。此外, 腺癌向高级别 NEPC 转化过程中, 常伴随细胞增殖率显著升高, 因此通过 IHC 检测 Ki-67 指数, 可辅助神经内分泌肿瘤的评估与分级[44] [45]。

4. NEPC 的治疗进展

尽管近年来研究人员对 NEPC 的分子机制已有一定认识, 但临床可用的治疗手段仍十分有限。目前, 无论是原发性 NEPC 还是治疗诱导型 NEPC, 一线治疗方案仍以铂类化疗为主, 这一策略主要借鉴 SCLC 等其他小细胞神经内分泌癌的治疗模式。随着研究的深入, 越来越多针对 NEPC 的新型治疗策略已进入临床前或临床试验阶段, 为改善患者预后带来新希望。

4.1. 化疗

当前 NEPC 尚未形成统一的标准化治疗方案, 但在临床实践中, 以铂类为基础的联合化疗是应用最广泛的策略, 其中顺铂(Cisplatin)联合依托泊苷(Etoposide)是最常用的方案[46]。NEPC (尤其是分化不良的小细胞型 NEPC)在组织学特征、疾病进展模式及治疗反应上与 SCLC 高度相似, 因此其临床治疗策略多参考 SCLC 的化疗经验[47]-[49]。从作用机制来看, 顺铂通过与 DNA 嘌呤碱基形成交联结构导致 DNA 损伤, 依托泊苷则通过抑制 DNA 拓扑异构酶 II 活性阻断 DNA 复制过程, 二者协同作用可有效诱导肿瘤细胞凋亡。但该方案的不良反应较为明显, 主要包括肾脏毒性、心血管毒性及恶心呕吐等[50]-[52]。鉴于

NEPC 具有高度增殖的生物学特性, 顺铂联合依托泊苷方案可通过协同效应抑制肿瘤生长, 并在一定程度上延缓耐药发生。

另有一项II期临床试验探索了卡铂(Carboplatin)联合卡巴他赛(Cabazitaxel)方案的疗效。从作用机制来看, 卡铂通过与肿瘤细胞中的 DNA 发生交联反应, 干扰 DNA 的复制和修复, 从而阻止肿瘤细胞的增殖和生长。卡巴他赛作用机制为抑制癌细胞微管蛋白聚合, 干扰其有丝分裂过程。该研究共纳入 160 例转移性去势抵抗性前列腺癌(metastatic Castration-Resistant Prostate Cancer, mCRPC)患者, 其中包含 6 例小细胞前列腺癌患者。结果显示, 与单用卡巴他赛相比, 该联合治疗将患者的中位无进展生存期从 4.5 个月(95% CI 3.5~5.7)延长至 7.3 个月(95% CI 5.5~8.2), 风险比为 0.69 (95% CI 0.50~0.95, $P=0.018$)。但由于该研究中纳入的小细胞前列腺癌患者样本量有限, 目前尚无法明确该方案在 NEPC 人群中的具体生存获益[53]。

总体而言, NEPC 对化疗通常表现出较高的初始敏感性, 但疗效维持时间较短, 获得性耐药的快速出现极大限制了化疗的长期疗效。此外需特别指出, 尽管 NEPC 对传统 AR 靶向治疗高度耐药, 且免疫组化检测多显示 AR 表达下调, 但转录组分析提示部分 t-NEPC 仍保留一定程度的 AR 信号活性, 其分子特征与前列腺腺癌及经典 NEPC 存在重叠[3][15]。在临床中, t-NEPC 转移灶也常观察到小细胞成分与腺癌成分共存的混合组织学特征, 因此对于此类患者, 临床推荐在持续 ADT 的基础上, 选择紫杉类药物/铂类药物联合的治疗方案。

4.2. 针对表观遗传调控因子的药物研究

NEPC 的发生发展涉及多种基因组改变及表观遗传调控机制, 这为开发新型靶向治疗药物提供了潜在方向, 目前已有多个表观遗传调控因子被列为 NEPC 的候选治疗靶点。其中, 赖氨酸特异性去甲基化酶 1 (Lysine-Specific Demethylase 1, LSD1)可催化组蛋白 H3 第 4 位赖氨酸的去甲基化, 在维持肿瘤细胞干性及调控细胞分化过程中发挥关键作用。研究发现, LSD1 可与结合蛋白 ZNF217 相互作用, 激活与致命性前列腺腺癌相关的分子网络[54]。同时, LSD1 已被证实是 SCLC 的潜在治疗靶点[55], 这提示其在 NEPC 治疗中也可能具有应用前景。

N-myc/Aurora 激酶 A (AURKA)信号轴是 NEPC 中另一个重要的调控通路。AURKA 抑制剂 Alisertib 可通过抑制 N-myc 和它的稳定因子 Aurora-A 之间的相互作用, 从而抑制 N-myc 信号, 抑制肿瘤的生长。一项II期临床试验纳入 60 例转移性前列腺癌患者, 对 Alisertib 的疗效进行评估。结果显示, 该研究未达到预设的主要终点(6 个月无进展生存率仅 13.4%), 但部分患者仍表现出显著疗效: 其中 AURKA 扩增的患者与生存延长相关, 而具有 N-myc 相关分子特征的患者也提示存在潜在获益[56]。这些研究结果表明, 靶向表观遗传调控因子或 N-Myc/AURKA 信号通路的治疗策略, 有望为 NEPC 患者提供新的治疗选择。

4.3. 新型免疫治疗

免疫检查点抑制剂(Immune Checkpoint Inhibitors, ICIs)通过阻断 T 细胞表面的抑制性通路(即免疫检查点), 使 T 细胞重新获得识别和杀伤肿瘤的能力, 从而实现抗肿瘤免疫应答。尽管 ICIs 在尿路上皮癌、肾癌等泌尿生殖系统肿瘤中已取得较好疗效[57]-[59], 但在 CRPC 中单独使用时效果有限, 这与前列腺癌肿瘤微环境的强免疫抑制特性密切相关[60]-[64]。近年来, 免疫联合治疗策略在 NEPC 中逐渐显示出潜力。由于 NEPC 与 SCLC 在生物学特征上高度相似, 部分在 SCLC 中证实有效的免疫治疗策略被逐步引入 NEPC 的研究中[65]。

SCLC 患者通常具有较高的肿瘤突变负荷(Tumor Mutation Burden, TMB), 而高 TMB 往往提示肿瘤细胞更易被免疫系统识别, 因此理论上对免疫治疗更敏感[66]。在一项临床研究中, 一线应用 PD-L1 免疫

检查点抑制剂阿替利珠单抗(Atezolizumab)联合化疗, 相较于单纯化疗, 显著延长了 SCLC 患者的总生存期和无进展生存期, 该方案已获 FDA 批准[67]。在前列腺癌中, 对临床样本进行的免疫组化染色和 RNA-seq 数据分析显示, NEPC 的 PD-L1 表达水平高于 CRPC 样本, 这提示 NEPC 患者可能较腺癌型 CRPC 更易从 ICI 治疗中获益[68][69]。但目前针对 NEPC 的 ICI 临床研究证据仍较为有限, 临床应用主要参考 SCLC 的治疗经验。

此外, 多个探索 ICI 联合治疗的临床试验正在开展, 包括 ICI 与 PARP 抑制剂、酪氨酸激酶抑制剂或放疗的联合方案。例如, 帕博利珠单抗(Pembrolizumab)联合仑伐替尼(Lenvatinib)、阿替利珠单抗(Atezolizumab)联合替沃扎尼(Tivozanib)等组合已进入 II 期临床试验阶段[70]-[72]; 双重免疫检查点阻断方案在多种实体瘤中已显示出协同抗肿瘤效应, 目前也在 NEPC 中积极探索。同时, 免疫激活剂 BXCL701 联合 ICI, 以及 DLL3 靶向双特异性抗体等新型免疫治疗策略, 在临床前研究中亦展现出潜在应用价值[73]-[75]。总体而言, 尽管当前 NEPC 免疫治疗的相关临床证据仍有限, 但免疫治疗(尤其是联合治疗策略)未来有望成为 NEPC 治疗领域的重要发展方向。

5. 结论与展望

神经内分泌前列腺癌是一种恶性程度极高的前列腺癌亚型, 致死率高, 近年来已成为研究重点。其发生机制复杂且伴随高度异质性, 加之组织学评估受限, 使得临床诊断仍面临挑战。在治疗方面, 目前一线方案主要依赖铂类为基础的化疗, 可获得一定的初始疗效, 但普遍存在耐药问题, 长期预后仍不理想。随着分子机制研究的深入, 靶向表观遗传因子以及免疫检查点抑制剂联合策略逐渐展现出应用潜力。总体而言, 未来研究亟需进一步阐明 NEPC 转分化的分子基础, 建立更为精准的生物标志物体系, 并探索联合靶向与免疫治疗的新模式, 以期改善患者的临床结局。

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