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E-Cadherin在泌尿系统恶性肿瘤中的研究进展

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摘 要

近年来，泌尿系统肿瘤发病率呈显著上升，如最常见的前列腺癌、膀胱癌和肾细胞癌，占据了恶性肿瘤总发病率相当大的比例。目前认为，导致泌尿系统恶性肿瘤患者死亡的主要原因是肿瘤发生远处器官转移，最终导致器官功能衰竭，转移的潜在机制仍尚未十分明确，有待进一步阐明。据了解，E-cadherin是一种钙依赖性细胞间黏附分子，在细胞黏附和维持细胞表型以及分化中起关键作用。同时，它也参与细胞的运动，在上皮间充质转化(EMT)过程中起重要作用，是EMT过程的标志，确认与肿瘤进展密切相关。E-cadherin表达的缺失能够介导肿瘤进展，引发严重不良后果。在本综述中，我们简要概述了E-cadherin的结构和功能，并系统阐述其在泌尿系统恶性肿瘤的研究进展。

关键词

E-Cadherin，前列腺癌，膀胱癌，肾癌，上皮间充质转化

Advances in the Study of E-Cadherin in Urological Malignancies

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Abstract

In recent years, the incidence of urological malignancies has shown a significant increase. The most

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common types, such as prostate cancer, bladder cancer, and renal cell carcinoma, account for a considerable proportion of the total incidence of malignant tumors. Currently, the primary cause of death in patients with urological malignancies is distant organ metastasis, which ultimately leads to organ failure. The underlying mechanisms of metastasis are still not fully understood and require further elucidation. E-cadherin is a calcium-dependent cell adhesion molecule that plays a crucial role in cell adhesion, maintaining cell phenotype and differentiation. It is also involved in cell motility and is a key factor in the epithelial-mesenchymal transition (EMT) process, which is a hallmark of tumor progression. Loss of E-cadherin expression is associated with adverse outcomes in various cancers, including urological malignancies. In this review, we briefly summarize the structure and function of E-cadherin and systematically discuss the recent advances in its role in urological malignancies.

Keywords

E-Cadherin, Prostate Cancer, Bladder Cancer, Renal Cell Carcinoma, Epithelial-Mesenchymal Transition

1. 引言

癌症是导致全球人口死亡的主要因素之一，据 2022 年全球癌症统计数据显示，全球新发癌症病例数接近 2000 万人，死亡病例数 970 万人。前列腺癌是男性中最为常见的恶性肿瘤之一，在全球新发病例排名第 4，膀胱癌和肾癌也非常常见，分别排在第 9 和第 14 [1]。目前，这些疾病最为有效的治疗方法是外科手术，尽管在一定程度上取得了效果，但这些疾病复发率较高，结局往往不够令人满意[2]-[4]。目前，前列腺癌治疗面临的挑战主要是绝大部分患者最终会进入去势抵抗期(CRPC)，导致患者晚期治疗效果和预后不佳[5]。据称，泌尿系统恶性肿瘤最终会发生远处器官转移，导致多器官功能衰竭，它是癌症患者死亡的主要原因[6]。因此，深入了解肿瘤的转移机制对疾病的治疗和延长患者的有效生存期至关重要。

E-cadherin 是研究最为广泛的钙粘蛋白之一，隶属于经典钙粘蛋白家族，主要分布于上皮细胞的细胞膜上，通过 NH2-末端胞外域的同质相互作用介导钙依赖性的细胞－细胞黏附过程[7]。研究表明，E-cadherin 在胚胎发育、维持上皮组织形态和极性中发挥至关重要的作用，它可通过与连环蛋白形成稳定的复合物来实现其在细胞膜上的稳定性和功能的准确性。同时，E-cadherin 还可通过接触抑制细胞增殖，涉及 Wnt、Hippo 等信号通路[8] [9]。在恶性肿瘤中，E-cadherin 表达的缺失与疾病的进展和转移有关。在 E-cadherin 缺陷的癌细胞中，通过对 E-cadherin 再表达后可以观察到肿瘤的进展和转移受到了一定程度的限制[10]。实际上，E-cadherin 被理解为一种抑癌因子，因而表达下调促进癌症进展，这在恶性上皮癌中得到了证实[11]-[13]。

截至目前，关于 E-cadherin 的研究越来越多，人们对其功能作用的理解也不断深刻。可以发现，E-cadherin 在不同疾病中发挥的功能特点不同，导致其在不同疾病中充当着不一样的角色。本文中，我们将深入探讨 E-cadherin 与泌尿系统几种常见肿瘤的关系和作用。

2. E-Cadherin 的概述

钙粘蛋白家族至少有五个亚家族，共拥有 23 个成员。E-cadherin 是经典的 I 型钙粘蛋白家族的成员

之一，由 CDH1 基因编码，该基因定位于染色体 16q22.1，含有 16 个外显子和 15 个内含子。E-cadherin 有两种存在形式，一种是最为常见的分布于细胞膜上的单跨膜蛋白分子，分子大小约为 120 KD，由一个较大的胞外域、一个跨膜区和一个保守的胞内域构成，另外一种是可溶性 E-cadherin，分子量约为 80 Kda，由另外一种形式切割形成[14]。E-cadherin 胞外域由 5 个钙粘蛋白胞外重复结构域 EC1~EC5 构成，它们能够与 Ca^{2+}结合形成刚性线性分子，而胞内域则由近膜结构域(JMD)和连环蛋白结合结构域两个子结构域组成(CBD)，能够与连环蛋白特异性结合，间接与肌动蛋白细胞骨架连接[15]。

E-cadherin 是粘附连接的组成部分，在 AJ 结构和功能的维持中起主导作用，对抑制单个上皮细胞的运动和维持组织结构稳定至关重要，其表达的降低通常与肿瘤的发生、侵袭和转移密切相关[16]。E-cadherin 的胞内域结构可与连环蛋白相互作用，能够介导钙粘蛋白－连环蛋白复合物锚定于肌动蛋白细胞骨架上，对调节细胞黏附的稳定性和传递细胞内信号至关重要[17]。生理状态下，与 E-cadherin 相互作用的 β-catenin 还参与 Wnt 信号通路，影响基因转录和细胞增殖[18]。E-cadherin 还通过调节 cyclin D1 和 c-myc 的表达影响上皮细胞的增殖。在癌症相关疾病中，除了参与 Wnt 信号通路外，E-cadherin 还参与 Hippo 信号通路实现对细胞增殖的调控[8] [9]。此外，E-cadherin 还起到促血管生成因子的作用，可溶性 E-cadherin 通过与 VE-cadherin 相互作用形成异二聚体促进血管生成[19]。同时，E-cadherin 还参与 Rho 家族小 GTPases 和 PI3K/AKT 信号通路，调控肌动蛋白聚合、细胞黏附和运动，与 EMT 有关[20] [21]，在肿瘤的发生、进展和远处转移中的重要性受到了广泛关注。

3. E-Cadherin 与常见的泌尿系统肿瘤的关系

现有的研究证据表明，E-cadherin 表达异常与泌尿系统肿瘤的进展及不良预后密切相关。E-cadherin 的三种构成成分分别发挥不同功能。例如，细胞外结构域主要负责与细胞间和细胞外基质的相互作用，参与维持上皮组织结构稳定性和各种信号通路的传导过程，而细胞内结构域则与细胞骨架相关蛋白相互作用并影响细胞的迁移能力，与此同时，还参与多条信号通路的传导过程影响细胞的增殖、侵袭和血管生成，而跨膜结构部分则起到稳定分子和传递细胞内外信号的作用[15]-[21]。以下简要归纳了 E-cadherin 在几种常见泌尿系统肿瘤中的作用。

3.1. 前列腺癌

在前列腺癌中，E-cadherin 表达异常与 EMT 过程、疾病进展和转移之间密切相关[22]-[24]。截止目前，已经有不少文献报道 E-cadherin 在前列腺癌组织中表达降低，并且通常涉及前列腺癌组织分化、PSA 水平变化、细胞增殖和转移等方面[25] [26]。前列腺上皮组织结构的完整性依赖于 E-cadherin 参与的细胞间黏附链接和维持的细胞极性，E-cadherin 水平下降或缺失可能导致前列腺增生并最终发展为浸润性腺癌[16] [27]，涉及组织分化过程。一项研究显示，通过使用 PB-Cre4 去除前列腺上皮细胞中的 E-cadherin，能够诱导小鼠前列腺上皮内瘤变(PIN)，与此同时，E-cadherin 的缺失还提高了胞质和胞核中的 β-catenin 水平，有效提高雄激素诱导的转录水平和细胞生长[27]。另外一项实验显示，当 E-cadherin 和 PKD1 (蛋白激酶 1)联合失调时，能够抑制前列腺癌细胞的增殖，并且对细胞增殖的抑制效应可通过共表达 β-catenin 进行消除，这表明 E-cadherin 对细胞增殖的影响是通过调控 β-catenin 来实现[28]，该过程又可能是通过 β-catenin 与 Wnt 信号通路相互作用完成[29]。除此之外，E-cadherin 可能还通过 Hippo 信号通路介导细胞的增殖接触抑制，从而发挥抑癌效应，该机制可能是 E-cadherin/catenin 复合物作为 Hippo 信号通路的上游调节因子对 Hippo 信号通路进行调控[30]。

已经明确，E-cadherin 是前列腺癌转移和侵袭的重要因素。Epi-miR-22 是一种表观遗传学 microRNA，它能够直接靶向 E-cadherin 的 3’-非翻译区，其过表达能够降低 E-cadherin 的水平，进而促进前列腺癌的

细胞侵袭和转移[31]。此外，在骨转移性前列腺癌细胞中检测出 E-cadherin 表达异常，提示骨转移患者体内的 E-cadherin 水平异常对前列腺癌骨转移至关重要[32]，但有关机制尚不明确。一种称为 *Teucrium polium* 的天然植物提取物可以通过恢复细胞内 E-cadherin/*β*-catenin 复合物的水平来抑制前列腺癌细胞运动和侵袭[33]，未来可能被应用于临床治疗。前列腺特异性抗原(PSA)当前仍然是预测前列腺癌可靠的标志物，前列腺癌患者血浆中的 E-cadherin 与 PSA 具有相关性，其能够协助 PSA 用于前列腺癌的诊断和预后[34]。综上所述，E-cadherin 参与前列腺癌的进展过程，其在癌细胞中的表达水平下降是影响癌症增殖和转移的重要因素。然而，在前列腺癌中，E-cadherin 在表达缺失层面可能并不局限于充当促癌因子的角色。一项研究显示，E-cadherin 的缺失可能引发前列腺上皮细胞的癌性转化，但与此同时，它也能够诱导细胞凋亡以阻止非典型前列腺上皮内瘤变细胞转化为癌细胞[35]。这提示 E-cadherin 在前列腺癌中的作用可能并非局限于单一层面，而是一个复杂的过程。

3.2. 膀胱癌

据最新统计数据显示，膀胱癌仍然是当前最为常见的泌尿系统癌症之一，是威胁人类健康的重要因素。同样地，E-cadherin 也和膀胱癌密切相关，参与膀胱癌进展和侵袭过程。E-cadherin 在膀胱癌中似乎更多扮演着标志物的角色，多项研究提示 E-cadherin 在膀胱癌的预测、分期和预后方面具有重要地位[36]-[39]。CDH1 是 E-cadherin 的编码基因，研究显示其在膀胱癌早期阶段水平开始上升，并且与免疫细胞的浸润呈负相关，对膀胱癌的早期预测有帮助[40]。Wentao 等人表明，E-cadherin 在癌旁组织的表达显著高于癌组织，并且进一步通过 logistic 回归分析发现，E-cadherin 是尿路上皮癌复发的危险因素[41]。特别是在非肌层浸润性膀胱癌中，E-cadherin 的作用似乎更为显著，多项研究认为 E-cadherin 是非肌层浸润性膀胱癌新的预测因子，不论是在新发肿瘤还是术后肿瘤复发[42]-[44]。E-cadherin 参与膀胱癌的肿瘤的分期将有助于临床治疗方案的制定。

3.3. 肾癌

肾癌近年来发病率呈不断上升趋势。研究表明，E-cadherin 与肾癌的发生和进展有关，并且似乎具有重要作用。在肾透明细胞癌中，E-cadherin 的表达降低[45]，促进了肾癌的生长和转移过程。E-cadherin 促进肾癌的迁移和侵袭通常涉及多条信号通路的激活。肝细胞核因子-4*α* (HNF-4*α*)在肝脏的分化中起重要作用，Yaohui 等人进一步研究了该因子在肾癌中的作用，结果显示 HNF-4*α* 表达下调与肾癌患者的肿瘤分期、复发和转移等有关，并且发现该作用是通过转录调节肾癌中的 E-cadherin 促进细胞的迁移和侵袭来实现的[46]。MicroRNA 与调节癌症的进展和转移有关，miR-720 的表达与肾细胞癌呈正相关，在肾癌中表达升高，miR-720 缺失时能够抑制肾癌细胞的增殖、迁移和侵袭等。该作用可能是 miR-720 通过对 *α*E-catenin-E-cadherin 复合物直接靶向实现[47]。此外，环状 RNA Circ-AKT3 还可以通过改变 miR-296-3p/E-cadherin 信号通路影响肾癌的转移。总之，E-cadherin 发挥促瘤效应受多条信号通路的调节。

4. 总结

泌尿系统恶性肿瘤是全球范围内重要的健康问题，而肿瘤转移是导致患者死亡的主要原因。E-cadherin 作为一种重要的细胞间黏附分子，其表达异常通常与肿瘤的进展和转移密切相关。本综述系统阐述了 E-cadherin 在前列腺癌、膀胱癌和肾细胞癌中的研究进展和意义。在泌尿系统肿瘤中，E-cadherin 的表达下调或功能丧失普遍存在，通过促进 EMT、增强细胞迁移和侵袭能力，驱动肿瘤转移。例如，前列腺癌中 E-cadherin 缺失与骨转移和去势抵抗性发展相关；膀胱癌中其低表达提示预后不良；肾癌中 E-cadherin 下调通过 miRNA 或环状 RNA 调控加速转移等。E-cadherin 不仅是预后标志物(如与非肌层浸润

性膀胱癌复发相关)，还可能成为治疗靶点。例如，天然化合物 *Teucrium polium* 通过恢复 E-cadherin/*β*-catenin 复合物抑制前列腺癌转移，表观遗传药物(如去甲基化剂)在恢复 E-cadherin 表达中展现出潜力。E-cadherin 在泌尿系统肿瘤中扮演着“双刃剑”角色，其功能复杂性为研究带来挑战，同时也为诊断和治疗提供了新机遇。未来需通过基础与临床研究的深度融合，推动 E-cadherin 从机制研究向临床应用的转化，最终改善患者预后。

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