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Pin1与膀胱癌发生的相关性

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摘　要

Pin1是一种肽基－脯氨酰顺式/反式异构酶，属于PPIase家族，可特异性催化有丝分裂磷蛋白中磷酸丝氨酸－脯氨酸或苏氨酸－脯氨酸的酰胺键异构化，诱导其相互作用蛋白质的构象和功能变化。通过脯氨酰异构化，Pin1微调了关键磷蛋白的功能，影响了细胞生长周期调节、免疫反应、生殖细胞发育、神经元分化和存活以及癌症发生。已发现Pin1在许多癌症中过度表达。我们还通过分析Pin1参与Ras突变、Notch1通路和NF-KB通路等相互作用来检查Pin1在膀胱癌发生中的作用。本文主要就Pin1结构及功能进行简单介绍，对Pin1不同系统肿瘤中的表达及调控作用进行总结。最后，探索和讨论了Pin1与膀胱癌的相关性及其作用机制，为膀胱癌的治疗提供新思路、新靶点。

关键词

Pin1，膀胱癌，综述

Correlation between Pin1 and Bladder Cancer

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Abstract

Pin1 peptide is a kind of base-preserved ammonia acyl cis/trans isomerase, belongs to the PPIase family, can specifically catalyze the isomerization of phosphoserine-proline or threonine-proline

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amide bonds in mitotic phosphoproteins, and induces conformational and functional changes in the interacting proteins. Through prolyl isomerization, Pin1 fine-tuned the function of key phosphoproteins, affecting cell growth cycle regulation, immune response, germ cell development, neuronal differentiation and survival, and carcinogenesis. Pin1 has been found to be overexpressed in many cancers. We also examined the role of Pin1 in bladder cancer development by analyzing the interactions of Pin1 in RAS mutation, Notch1 pathway, and NF-KB pathway. In this paper, the structure and function of Pin1 were briefly introduced, and the expression and regulation of Pin1 in different tumor systems were summarized. Finally, the correlation between Pin1 and bladder cancer and its mechanism of action were explored and discussed, providing new ideas and new targets for the treatment of bladder cancer.

Keywords

Pin1, Bladder Cancer, Review

1. 介绍

膀胱癌是泌尿系统常见的恶性肿瘤，2020 年全球膀胱癌新发病例约 57.33 万例，罹患膀胱癌所致的死亡人数约 21.25 万例，男性膀胱癌的发病率和死亡率均为女性的 3~4 倍，新发病例数相较于 2018 年仍在增长[1]。年龄和吸烟是膀胱癌的主要危险因素[2]。膀胱癌的突变率最高，仅次于黑色素瘤和肺癌[3]，它是一种异质性很高的疾病，一旦发生侵袭或转移预后极差[4]。由克里克、富兰克林和沃森在 1953 年精确描述脱氧核糖核酸结构后开创的生物分子时代，极大地扩展了我们对疾病分子基础的理解以及随后生物标志物在临床实践中的应用[5]。到目前为止，在膀胱癌中已经报道了多种预后相关的分子病理，但只有少数被验证，没有被常规使用或指南推荐[6]。

蛋白质磷酸化是一种翻译后修饰，在信号通路的调控中起重要作用[7]。脯氨酸指导的丝氨酸/苏氨酸磷酸化是许多信号通路的普遍调控方式之一，磷酸化后的构象变化是一种新的细胞信号传导的主要机制[8] [9]，参与这一过程的激酶被称为脯氨酸指导的激酶，包括丝裂原活化蛋白激酶(Mitogen-activated protein kinases, MAPKs)、c-Jun 氨基末端激酶(c-Jun N-terminal kinase, JNKs)、周期素依赖性激酶(Cyclin-dependent kinases, CDKs)以及糖原合成酶激酶-3 (Glycogen synthase kinase-3β, GSK-3β)等[10]。Pin1 是一种必需且保守的有丝分裂肽基脯氨酰异构酶(PPIase)，主要定位于细胞核中[7] [11]。Pin1 可特异性催化有丝分裂磷蛋白中磷酸丝氨酸－脯氨酸或苏氨酸－脯氨酸的酰胺键异构化，从而诱导构象变化[12]。新出现的数据表明，这种构象变化对催化活性、去磷酸化、蛋白质－蛋白质相互作用、亚细胞定位、周转具有深远的影响[13]，对不同细胞过程中的许多关键调节因子也具有深远的影响，包括细胞生长周期的调节、应激反应、免疫反应、生殖细胞发育、神经元分化和存活等[14]。

在本文中，我们讨论了 Pin1 的结构和在癌症中表达失调的可能机制、Pin1 在膀胱癌发生中的可能致癌作用以及 Pin1 抑制剂作为抗癌剂的潜力。

2. Pin1 的结构与表达

Pin1 是 1996 年由卢坤平教授在酵母双杂交过程中发现的一种高度保守的小分子蛋白[9] [15] [16]，是

一种肽基－脯氨酰顺式/反式异构酶，是 PPIase 家族的一员[17]，此外还有 FK506 结合蛋白(FKBPs)、亲环蛋白和细小蛋白(parvulins)等。Pin1 拥有三个结构域即 N 端的 WW 结构域、C 端的肽基－脯氨酰顺式/反式异构酶(PPIase)结构域和中间的柔性区域[18]。WW 结构域跨越 Pin1 蛋白的前 39 个氨基酸残基[19]，介导 Pin1 与磷酸化的蛋白质结合，是特异性 pSer/Thr-Pro 的连接区；PPIase 结构域：由 45~163 个氨基酸组成羧基末端的多肽脯氨酰基异构酶区，可以催化前一个脯氨酸肽键的旋转，从而导致蛋白结构的顺反异构[15]。蛋白质中的 pSer/Thr-Pro 基序以两种不同的顺式和反式存在构象，其转化率通常在磷酸化时降低，但由脯氨酰异构酶 Pin1 特异性催化[20]。

在正常细胞中，Pin1 的表达通常非常低，并且受到视网膜母细胞瘤蛋白(Rb)-E2F 通路的严格调控，Rb 和 E2F 蛋白之间的结合由 Rb 的磷酸化控制[7]。Pin1 使许多致癌和细胞信号通路重要的分子键异构化，包括 Bcl-2、p53、c-Jun、*β*-连环蛋白、NF-kappaB、细胞周期蛋白 D1、c-Myc 和 Raf-1 等[21]。Pin1 增强了 cyclin D1，NF-KB，-catenin，c-myc 和 Tax 等多种癌基因的功能，同时阻止或减弱了 Runx3、Bax、RB1 和 Ampk 等肿瘤抑制因子的功能[22]。在细胞周期通路中，Pin1 增加细胞周期蛋白 D1 的表达，从而促进细胞周期进程[23]。在所有癌症中，Rb-E2F 通路都被破坏[24]。Ryo A [25]等人文献表明 Pin1 表达由转录因子 E2F 介导，并由 c-Neu 和 Ha-Ras 通过 E2F 增强，Pin1 是对 Neu/Ras 至关重要的 E2F 靶基因-通过激活细胞周期蛋白 D1 诱导乳腺上皮细胞的转化。抑制 Pin1 会抑制 Neu-和 Ras-诱导的转化表型，可以通过对 Pin1 抑制无效的组成型活性细胞周期蛋白 D1 突变体的过表达来完全挽救[25]。有文献表明，转录因子(NF-kappaB)功能也受 Pin1 介导的脯氨酰异构化的调节[26]。除此以外，Pin1 增强 Notch1 转录和致瘤活性，在人类乳腺癌中，观察到 Pin1 过表达与高水平的激活 Notch1 之间存在很强的相关性[27]。Pin1 催化的调控机制还可能为人类某些疾病的发病机制和治疗提供新的见解，近期研究已获得证据表明 Pin1 与多种疾病有关，例如糖尿病、非酒精性脂肪性肝炎(NASH)、肥胖症、骨质疏松症和心脏肥大[28]，尤其在癌症、哮喘和阿尔茨海默中格外重要[9] [14]。

3. Pin1 在多种肿瘤中过表达

肿瘤发生是一个多步骤和多因素的过程，在遗传和表观遗传水平上都会导致不受控制的细胞增殖、转化和细胞死亡，细胞内外信号调控着细胞增殖[29] [30]，但是肿瘤细胞能够通过多种通路维持增殖信号[31]。细胞增殖和转化的一种主要调节机制是各种前导蛋白激酶(例如 MAP 激酶、细胞周期蛋白依赖性激酶等)磷酸化脯氨酸之前的丝氨酸或苏氨酸残基(pSer/Thr-Pro)上的蛋白质[20]。在细胞周期进程中，Pin1 通过介导的异构化参与调节其相互作用蛋白的不同功能[32]，这种信号机制的失调可导致细胞转化和肿瘤发生[33]。不同的转录、翻译和翻译后因子导致癌细胞中 Pin1 的失调[34]。据报道，Pin1 影响癌症中的各种信号通路[35]，Pin1 过表达诱导染色体不稳定和肿瘤发生，可激活 56 个致癌基因和/或促进生长的调节剂[36]。

Wulf GM 等人[37]首次发现 Pin1 在许多人类乳腺癌组织和细胞系中过表达，其水平与肿瘤分级相关，Pin1 的过表达可能促进肿瘤生长。在肝脏疾病方面，Pin1 最早在肝癌中被发现[23]。有研究表明 Pin1 在超过 50%的肝细胞癌(HCC)中过度表达，其表达是肝癌发生的重要步骤[38]。目前，Pin1 表达与肿瘤发生呈正相关在脑、乳腺癌、宫颈癌、结肠癌、肝癌和前列腺癌在内的各种类型的人类癌症中得到进一步验证[20] [37] [38] [39]。肿瘤患者预后差和死亡的重要原因之一就是发生转移，研究表明 Pin1 表达在转移性灶中显着增加[40]，这提示 Pin1 高表达与肿瘤侵袭转移密切相关[21]。并而 Pin1 过表达与根治性前列腺切除术后肿瘤复发的概率更高和时间更短呈正相关[39]，Ayala G [41]等人研究表明 Pin1 表达作为前列腺癌中潜在的优秀预后标志物的作用，并表明 Pin1 也可能作为前列腺癌的新治疗靶点，以上研究都表明 Pin1 表达与癌症预后有关。

4. Pin1 与膀胱癌

膀胱癌的发病率和死亡率在全球范围内迅速增长，膀胱癌的诊断和治疗难度较大，核分级和肿瘤分期是肿瘤的重要预后因素，但相似分期和分级的肿瘤在生物学行为和临床结果方面可能表现出很大差异[42] [43]。膀胱镜检查是检测膀胱癌的金标准，但是对于早期微小癌的诊断具有局限性，现阶段膀胱镜取活检联合分子病理在膀胱癌的诊断中具有重要价值，膀胱癌早期诊断的分子病理并作为治疗靶点尤为重要[44]。

Ras 致癌基因在人类膀胱癌的发生和发展中起关键作用[7]，Ahmad I 等人研究发现 Ras 激活驱动了膀胱癌的形成[45]，突变 Ras 基因在低拷贝数下诱导尿路上皮增生，在高拷贝数下诱导乳头状肿瘤[46]，Wulf G 等人研究发现 Pin1 消融在预防致癌 Neu 或 Ras 在小鼠中诱导细胞周期蛋白 D1 方面非常有效，文献表明 Pin1 作为 Ras 下游靶标，在细胞转化中起重要作用[47]，这也说明 Pin1 抑制剂在 Ras 驱动的膀胱癌中是有作用的。其次特殊的 NF-KB 通路被认为是膀胱癌细胞增殖和 EMT 的关键参与者，阻断 NF-KB 通路可以抑制肿瘤发生和恶性肿瘤的进展[48]。核因子-KB (NF-kB)家族是炎症、免疫、细胞存活和肿瘤发生的标志[49] [50]，先前的研究证明 Pin1 使许多致癌和细胞信号通路重要的分子键异构化，包括 NF-kappaB 通路[46]，因此抑制 Pin1 可能会通过抑制 NF-KB 通路来减少膀胱癌的而发生。另外 NOTCH1 信号通路可通过调节细胞增殖、分化和凋亡在肿瘤发生中发挥关键作用[7] [51]。Lu N 等人发现异氟醚可以通过 Notch1 通路加速了原位膀胱肿瘤的形成并促进了膀胱癌的肝转移[52]，研究表明膀胱癌中的 NOTCH1 拷贝数和表达减少，膀胱癌细胞系中的 NOTCH1 激活减少了增殖，这表明 NOTCH1 充当肿瘤抑制因子[53]，然而 Pin1 可以增强 Notch1 转录和致瘤活性[27]，导致膀胱癌的发生。Bao L [20]等人也在研究中发现，Pin1 在膀胱移行细胞癌中是过表达的。所以抑制 Pin1 可能会一定程度 Notch1 通路，通过此来减少膀胱癌的发生。

5. Pin1 作为膀胱癌治疗的新药物靶点

膀胱内化疗与经尿道膀胱切除术在减少疾病复发方面是相当有效的，晚期尿路上皮癌患者最有效的一线全身治疗是吉西他滨－顺铂，丝裂霉素 C、表柔比星、硫替帕、吉西他滨和阿霉素是为此目的最常用的药物，研究表明放疗联合化疗可以改善局部控制，虽然它们是有效的，但仍有改进的余地[54] [55] [56]。目前，卡介苗膀胱内治疗是非肌肉浸润性膀胱癌治疗的标准做法，包括原位癌、高级别乳头状肿瘤和浸润性斑块固有肿瘤，卡介苗已用于治疗膀胱癌数十年，但其作用机制尚未完全了解[57]。Atezolizumab 用于接受铂基化疗后疾病进展后或 12 个月内的局部晚期或转移性尿路上皮癌患者，这是自卡介苗以来首次批准用于膀胱癌的免疫疗法[56]。作为单一免疫疗法药物在晚期膀胱癌患者中的益处有限，应进一步评估免疫检查点抑制剂与其他药物联合用于膀胱癌的治疗。

已有研究报道 Pin1 在肺癌、宫颈癌、食管癌、前列腺癌、乳腺癌中高表达[47]，且伴随 Pin1 高表达的肿瘤患者预后更差，它是一个有吸引力的抗癌治疗靶点。大多数开发的 Pin1 抑制剂都是小分子，通过与其催化活性位点结合来抑制其异构酶活性[58]。Pin1 抑制剂现在临床已有少部分应用，其效果良好。Koikawa K 等人使用临床可用药物靶向 Pin1 与免疫化学疗法的协同，使胰腺癌得以根除[47]。Pu W 等人也通过抑制剂 API-1 靶向 Pin1 调节抑制了肝细胞癌的发展[59]。Wei S 等人研究发现全反式维甲酸可抑制 Pin1 活性来抑制乳腺癌和急性早幼粒细胞白血病的细胞增殖[60]。以上充分证明 Pin1 抑制剂可能是潜在的抗癌药物，Pin1 的致癌作用可能成为开发抗癌药物的新方向。但目前尚不确定 Pin1 抑制剂是否会对膀胱正常组织产生任何不利影响，临床前或临床研究对于检验 Pin1 抑制剂在膀胱癌治疗中的安全性和有效性是必要的。

6. 结论

膀胱癌是一种与预后不良相关的侵袭性癌症，可用于晚期或者复发转移性膀胱癌患者的常规治疗选择非常有限。通过磷酸化依赖性脯氨酰异构化，Pin1 发挥作用，以增强其相互作用蛋白在膀胱癌发生中的致癌活性。一些研究已经证明，抑制 Pin1 活性会导致细胞生长和肿瘤发展的抑制。Pin1 表达可以作为膀胱癌中潜在的优秀预后标志物，Pin1 在膀胱癌中过表达可能产生的多种致癌作用使其成为一种有吸引力的治疗靶点。

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