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分子机制到治疗靶点：RUNX2在肿瘤中的研究进展

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摘　要

RUNX2是一种关键的转录因子，其在多种癌症的发生和发展中起着重要作用。由于RUNX2在多种癌症类型中对预后具有显著的影响，其作为癌症生物标志物的潜力引起了广泛关注。RUNX2通过与核心结合因子β (CBFβ)结合，增强对靶基因的调控，促进癌细胞的增殖、迁移和侵袭。RUNX2与PI3K/AKT信号通路互作，激活肿瘤进展的关键途径。抑制RUNX2的表达和功能已显示出抑制肿瘤生长和迁移、促进癌细胞凋亡的潜力，使其成为癌症治疗中的有意义靶标。近年研究还发现，RUNX2影响肿瘤微环境和化疗耐药性，针对RUNX2的小分子抑制剂和靶向疗法的开发，为提高治疗效果和减少耐药现象提供了新的策略。

关键词

RUNX2，癌症，分子机制，治疗靶点

From Molecular Mechanisms to Therapeutic Targets: Research Progress of RUNX2 in Cancer

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Abstract

RUNX2 is a critical transcription factor that plays an important role in the initiation and progression

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of various cancers. Due to its significant impact on prognosis across multiple cancer types, RUNX2 has garnered widespread attention as a potential biomarker for cancer. By interacting with core-binding factor *β* (CBF*β*), RUNX2 enhances the regulation of target genes, promoting cancer cell proliferation, migration, and invasion. RUNX2 also interacts with the PI3K/AKT signaling pathway, activating key pathways involved in tumor progression. Inhibiting RUNX2 expression and function has demonstrated potential in suppressing tumor growth and migration, as well as inducing apoptosis in cancer cells, making it a meaningful therapeutic target in cancer treatment. Recent studies have also revealed that RUNX2 influences the tumor microenvironment and chemotherapy resistance. The development of small molecule inhibitors and targeted therapies against RUNX2 offers novel strategies to improve therapeutic efficacy and reduce resistance.

Keywords

RUNX2, Cancer, Molecular Mechanisms, Therapeutic Targets

1. 引言

在哺乳动物中，RUNX (Runt-related transcription factor)代表一个由三个转录因子组成的家族，它们共享一个共同的DNA结合结构域——Runt结构域，与果蝇的Runt基因同源。RUNX家族成员(包括RUNX1、RUNX2和RUNX3)与核心结合因子*β* (CBF-*β*)结合形成异源二聚体，增强其与DNA结合的能力，并参与随后的转录调控[1] [2]。转录因子(transcription factors, TFs)约占人类基因组的8%，并在真核细胞的多条信号通路中发挥着关键的调控作用。研究表明，约20%的转录因子与至少一种人类表型相关[3]。转录因子的调控过程具有高度的动态性，单个转录因子可以在不同的细胞类型中调控多个基因的转录。转录因子通过与其他蛋白质如共激活因子、共抑制因子、染色质重塑因子等相互作用，形成复杂的调控网络，共同决定着基因的表达模式和细胞的命运。这使得转录因子在基因工程、疾病治疗、生物技术等领域具有广泛的应用前景。因此，转录因子的失调与多种疾病的发生机制密切相关，包括心血管疾病、炎症性疾病以及各种类型的癌症[4]，这也进一步凸显了转录因子介导的基因调控机制在生理中的重要性[5]。

RUNX2是一种众所周知的成骨细胞、软骨细胞分化[6] [7]和器官形态发生[8] [9]的主要调节因子。与许多其他对胚胎发生至关重要的因素一样，RUNX2在癌症中经常被异常地重新激活。新的研究发现它参与了癌症的进展和肿瘤的发生。许多研究揭示了RUNX2介导的下游轴在调节癌症转移、增殖、血管生成、癌症干细胞和耐药等方面的功能[10] [11]。先前的报道证实，RUNX2在大多数人类肿瘤中高表达，并且RUNX2的高表达与肿瘤患者的不良预后相关[1]。多篇报道表明，抑制RUNX2的表达和功能，能够有效抑制肿瘤生长、迁移、耐药，促进肿瘤细胞凋亡。因此，RUNX2可能是癌症治疗中的一个有意义的靶标[1] [5] [11] [12]。

2. RUNX2的分子结构

RUNX2基因位于人类的6p21.1位点，编码多种亚型，共有12种转录变体。RUNX2包括其Runt结构域、转录激活域、抑制域、核定位信号和磷酸化位点。RUNX2蛋白的核心是一个高度保守的Runt结构域，这是一种约128个氨基酸的序列，负责DNA结合和异源二聚体形成[2]。这个结构域使RUNX2能够结合到特定的DNA序列上，调节目标基因的表达。RUNX2包含转录激活域与转录抑制域，这些域通

过与其他蛋白如共激活因子或转录抑制因子相互作用，增强或抑制转录过程。RUNX2 通过核定位信号，使其能够被运输到细胞核中，发挥转录调控功能。RUNX2 的活性和稳定性可以通过磷酸化调控。磷酸化通常影响 RUNX2 与其他蛋白的相互作用，以及其对靶基因的调控能力。

3. RUNX2 在人类癌症中的表达及作用

3.1. RUNX2 在癌症中的表达

先前的研究证实，RUNX2 在包括胶质瘤在内[13]的多种癌症中过度表达，如乳腺癌[14]、肺癌[15]、骨肉瘤[16]、前列腺癌[17]、肝癌[18]、胰腺癌[12]、白血病[19]等。且高表达的 RUNX2 与癌症患者的不良预后相关[20]。

3.2. RUNX2 的致癌途径

先前的报道证实，RUNX2 能够通过多种途径来促进致癌作用。CBFβ(核心结合因子 β，core-binding factor subunit beta)是一个关键的调节蛋白，是一个转录因子的非 DNA 结合亚基，主要功能是它与 CBFα(如 RUNX1、RUNX2 和 RUNX3 等家族成员)结合形成核心结合因子，稳定与其结合的 RUNX 家族转录因子，并增强这些因子与 DNA 的亲和力。这种非 DNA 结合蛋白通过与 RUNX1、RUNX2 和 RUNX3 等蛋白形成复合体，发挥其功能，调节下游基因的表达。有研究表明，CBFβ 与 RUNX2 复合体促进结直肠癌细胞的增殖、迁移、侵袭和抑制细胞凋亡[21]。白血病中，RUNX1 或其辅因子 CBFβ 的敲除导致细胞死亡[22]。在癌症发生中，CBFβ 的异常可能导致 RUNX 蛋白的稳定性和功能受损，从而影响细胞增殖与凋亡的调控，进一步促进肿瘤形成和发展[23]。

PI3K/AKT 信号通路是细胞内一条重要的信号传导途径，广泛参与细胞生长、存活、代谢和增殖等多种生物过程。而 PI3K 的突变或过表达可以导致 AKT 持续激活，促进肿瘤细胞的生存和抗凋亡能力。有研究表明，RUNX2 和 PI3K/AKT 轴相互激活作为肿瘤进展的驱动力[24]。RUNX2 基因过表达和 PTEN 基因单拷贝失活共同促进 AKT 信号通路过度激活以及前列腺肿瘤形成[25]。RUNX2 通过促进钙粘蛋白转换、向 I 型胶原的侵袭和 AKT 的激活来加速前列腺癌的侵袭性[26]。核内 HDAC4 介导 RUNX2 去乙酰化，从而抑制胍苷乙酸 n-甲基转移酶(GAMT)的表达。通过 AMPK-AKT-Bad 信号通路诱导 PC 细胞凋亡[12]。

RUNX2 可以通过负调控肿瘤抑制因子从而引起致癌途径的失调及癌症的发展。WWOX (WW domain containing oxidoreductase)被认为是一个肿瘤抑制基因，其突变、缺失或表达下调与多种类型的癌症相关。WWOX 在细胞周期、凋亡、DNA 修复和信号转导等过程中发挥重要作用，尤其在抑制细胞增殖和促进凋亡方面起着关键作用。有研究表明，骨肉瘤中 WWOX 肿瘤抑制因子的频繁衰减与致瘤性增加和 RUNX2 异常表达相关[27]。转化生长因子 β (TGF-β)家族成员骨形态发生蛋白 3b (BMP-3B/GDF10)被认为是肿瘤生长抑制剂和肺癌中沉默的基因，RUNX2 在肺癌中沉默 BMP-3B 引起肿瘤进展[15]。RUNX2 也与 TEAD 竞争 YAP1 关联，独立于 RASSF1A 和 p73，联合敲低会加剧 YAP1-TEAD 水平，将 YAP1 从肿瘤抑制基因转变为癌基因[28]。

MYC 是一系列调节基因和原癌基因的家族，它在细胞周期进程、凋亡和细胞转化中扮演着关键角色，在各种类型的癌症中常见表达上调。有研究表明，RUNX2 在体内发挥了一种新的肿瘤保护作用，RUNX2 和 MYC 通过抑制细胞凋亡和生长停滞共同参与淋巴瘤的发展[29] [30]。特异性 RUNX2 超级增强子能够激活 MYC，促进细胞浆细胞样树突状细胞肿瘤的发展[31]。

3.3. RUNX2 在细胞增殖中的作用

先前的研究已经证明 RUNX2 与细胞增殖密切相关[32]-[34]。有研究表明，降低 RUNX2 能通过抑制

PI3K/Akt 通路的激活从而抑制癌细胞的增殖[33]。RUNX2 通过调控应激信号途径中的细胞周期来发挥作用，当 RUNX2 功能丧失时，细胞显示出 S-G2-M 周期蛋白和相关蛋白激酶活性的异常升高。S-G2-M 阶段是细胞周期中 DNA 复制和细胞分裂发生的阶段，正常情况下这些阶段被严格调控。周期蛋白和蛋白激酶是推动细胞周期进程的重要蛋白，它们的活性升高意味着细胞可能会无视存在的生长抑制信号，继续进入分裂阶段。这种信号缺陷和周期蛋白活性的异常提高可能导致细胞免疫过于正常的生长控制机制，如老化和程序性细胞死亡，增加细胞癌变的风险。因此，RUNX2 的缺失打破了细胞生长的正常调控，使细胞更容易不受控制地增殖，从而可能促进肿瘤的形成[35]。

3.4. RUNX2 在细胞迁移、侵袭中的作用

RUNX2 在维持细胞增殖能力的同时，还能激活与细胞侵袭和迁移相关的信号通路。有研究表明，RUNX2 上调基质金属蛋白酶(MMPs)等因子的表达，这些蛋白酶在细胞外基质降解中起关键作用，为细胞穿越基质屏障提供了条件[36]。RUNX2 的表达支持多发性骨髓瘤 MM 的侵袭性表型，并与不良预后相关，作为 MM 进展的主要调节因子[37]。RUNX2 是促进结直肠癌转移的关键转录因子，维持去乙酰化组蛋白 H3K27 状态，抑制 RUNX2 能抑制肿瘤细胞迁移、侵袭[38]。体内高侵袭性转移性乳腺癌细胞中，RUNX2 的缺失限制了乳腺中肿瘤的形成，并在体外将癌细胞聚集恢复为更正常的腺泡蛋白样结构[14]。RUNX2 介导人转移性乳腺癌细胞骨涎蛋白的表达[39]。前列腺癌细胞中 PTEN 的频繁缺失导致 FOXO1 失活，导致 RUNX2 的致癌活性不受抑制，从而导致肿瘤细胞的迁移和侵袭[17]。RUNX2 的刺激可能与分泌机制有关，促进细胞间和细胞－基质相互作用，从而促进肿瘤转移[40]。RUNX2 通过转录激活 ITGBL1 靶点，通过激活 TGF-β 信号通路促进乳腺癌骨转移[41]。

3.5. RUNX2 对 EMT 的调控

有研究表明，利用全基因组表达阵列进行转录组分析和计算机分析，RUNX2 上调了许多具有突变癌症相关功能的基因。它们包括分泌因子(CSF2, SDF-1)、蛋白水解酶(MMP9, CST7)、细胞骨架调节剂(SDC2, Twinfilin, SH3PXD2A)、细胞内信号分子(DUSP1, SPHK1, RASD1)和转录因子(Sox9, SNAI2, SMAD3)，这些因子在上皮到间质转化(EMT)、组织侵袭以及归巢和附着到骨骼中起作用。诱导 RUNX2 增强了肿瘤侵袭性。它还通过阻断细胞周期进程中的 G1/S 相变促进细胞静止[42]。RUNX2 招募转移相关的 1 (MTA1)/NuRD 和 Cullin 4B (CUL4B)-Ring E3 连接酶(CRL4B)复合物，形成转录抑制复合物，催化组蛋白去乙酰化和泛素化，与乳腺癌 EMT 密切相关[11]。下调 RUNX2 的表达能通过调控半乳糖凝集素-3 抑制肝癌细胞的 EMT [43]。直肠癌肿瘤干细胞中 RUNX2 可能通过激活 CD44 介导 EMT [44]。RUNX2 的过表达可以在正常乳腺上皮细胞中诱导类上皮间质转化(EMT)的变化[45]。

3.6. RUNX2 对肿瘤微环境的调控

肿瘤微环境(tumor microenvironment, TME)是指肿瘤细胞周围的局部环境，包括各种细胞类型、细胞外基质(ECM)、细胞因子和化学信号等，这些组成部分共同影响肿瘤的发展、进展和对治疗的响应。有研究表明，RUNX2 杂合缺失阻止了 PTEN 敲除引起的恶性上皮细胞外多层 SMA 阳性基质的形成，而癌细胞向周围基质生态位的侵袭是发生远处转移的必要步骤，这说明 RUNX2 异常激活在 PTEN 缺失诱导的 IAS 和 TME 重塑中起着关键作用[46]。成骨细胞中 RUNX2 缺乏通过改变新骨部位的骨微环境来促进骨髓瘤的进展[47]。沉默骨髓瘤细胞中的 RUNX2 抑制了骨桥蛋白 mRNA 和蛋白的表达，参与 MM 诱导的血管生成的病理生理[48]。肿瘤微环境的这些特征共同作用，形成一个复杂的生物学系统，不仅支持肿瘤的生长和发展，还使肿瘤对许多传统疗法表现出抵抗性。

3.7. RUNX2 在细胞耐药性中的作用

RUNX2 在肿瘤化疗耐药中被广泛研究。其中 RUNX2 依赖性 DNA 修复调控在化疗耐药中可能起着关键作用。RUNX2 通过调节多种 DNA 修复途径对肿瘤细胞的化疗药物反应产生影响，包括基础切除修复(BER)、同源重组修复(HR)和非同源末端连接(NHEJ)。RUNX2 的表达可以降低某些关键 DNA 修复基因的活性，使细胞对 DNA 损伤更敏感。通过 RNA 干扰技术沉默 RUNX2 表达的细胞，其对多种化疗药物(如阿霉素和顺铂)的敏感性有所增加。这表明通过靶向 RUNX2 可能改善某些癌症治疗的效果[49] [50]。

有研究表明，RUNX2 通过直接与 TGF-β 结合调控肿瘤干细胞的干细胞性来影响化疗耐药。肿瘤干细胞高表达 RUNX2，且沉默 RUNX2 可以通过激活 p53 家族依赖性细胞死亡途径，减弱 DNA 修复，从而增强肿瘤对 DNA 损伤诱导的抗癌药物的疗效[49]。通过全基因组多组学方法发现，筛选药物抑制 RUNX2 通路，结合基于替莫唑胺的 GBM 标准治疗，会导致胶质瘤细胞生长明显受损[51]。RUNX2 在胃癌耐药细胞和组织中显著表达，同时 RUNX2 负向调控 p53 凋亡通路，降低胃癌化疗效果[52]。RUNX2 在骨肉瘤中的过表达与化疗反应差异有关[16]。

4. RUNX2 作为治疗靶点

RUNX2 似乎是许多癌症类型的预后生物标志物。通过使用特定的小分子抑制剂来阻断 RUNX2 的活性，或是通过小分子 RNA 技术降低 RUNX2 的表达，有望增强化疗的效果，减少癌症治疗中的耐药现象。有研究表明，miR-135 和 miR-203 靶向 RUNX2 抑制乳腺癌和转移性骨病的进展[53]。环状 RNA-CGNL1 通过 NUDT4-HDAC4-RUNX2-GAMT 介导的细胞凋亡调控胰腺癌进展[12]。

CADD522 是一种双氯苯胺类衍生化合物，它作为线粒体 ATP 合酶抑制剂，能够抑制 RUNX2 与 DNA 的结合，并显示出抗肿瘤活性。在对 RUNX2 的影响中，CADD522 还能调节 RUNX2 靶基因的转录，例如降低基质金属蛋白酶-13、血管内皮生长因子和葡萄糖转运蛋白-1 的表达，同时通过增加 RUNX2 的稳定性来提高 RUNX2 的表达量[54]。CADD522 通过多种机制发挥其对 RUNX2-DNA 结合的抑制作用，包括与 RUNX2 竞争 DNA 结合位点、抑制葡萄糖摄取导致细胞周期阻滞、降低 CBF-β 的表达和减少 RUNX2 在 S451 位点的磷酸化。CADD522 通过抑制线粒体 ATP 合成来减少 ATP 的产生，从而抑制癌细胞的能量代谢。此外，CADD522 还能增加线粒体产生的活性氧种(ROS)，进一步诱导癌细胞死亡[55]。这些发现表明 CADD522 具有作为抗肿瘤药物的潜力。

HDAC (组蛋白去乙酰化酶，histone deacetylases)是一类重要的酶，它们的主要功能是去除染色质上组蛋白尾部赖氨酸残基的乙酰基。这种去乙酰化作用导致染色质结构更为紧密，从而抑制基因的转录活性。HDAC 抑制剂通过增加组蛋白的乙酰化水平，放松染色质结构，从而激活被抑制的基因表达，具有促进细胞死亡、抑制炎症和阻止肿瘤生长的潜力。有研究表明，抑制遗传调控因子 HDAC 的活性显著抑制 RUNX2 的表达[56]。组蛋白去乙酰化酶抑制剂(HDACi)抑制了 RUNX2 的肿瘤表达[57]。HDAC 抑制剂 PXD-101 能抑制骨肉瘤细胞的增殖，诱导凋亡[58]。

综上所述，RUNX2 是一种在多种癌症中发挥关键作用的转录因子，它通过影响细胞的增殖、分化和生存途径，参与癌症的发生和发展。RUNX2 的异常表达与肿瘤的侵袭性、转移以及化疗抗性密切相关[10]。RUNX2 的深入研究将有助于揭示其在肿瘤发展中的分子机制，为开发针对 RUNX2 的靶向治疗策略提供新的思路和依据。此外，作为癌症治疗的潜在新靶点，RUNX2 的抑制剂正在被积极开发，但仍需要更多的研究以合成更具有特异性、效力更高和药代动力学特性更优的新化合物。随着研究的深入，针对 RUNX2 的新型靶向药物有望为治疗癌症提供更有效的治疗方案。

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