

二甲双胍通过调控肿瘤微环境抑制 上皮 - 间质转化的研究进展

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摘要

上皮 - 间质转化(EMT)是肿瘤细胞获得侵袭转移能力、增强耐药性等生物学特性的核心过程, 其发生发展与肿瘤微环境的动态调控密切相关。肿瘤微环境中的肿瘤相关成纤维细胞、肿瘤相关巨噬细胞、免疫抑制细胞及可溶性细胞因子等成分, 共同构成“促EMT”的微环境稳态。二甲双胍作为临床一线降糖药物, 近年被证实具有抗肿瘤活性, 其作用机制除直接调节肿瘤细胞代谢外, 还可通过重塑肿瘤微环境间接抑制EMT进程, 为肿瘤转移的防治提供了新的靶点。本文系统综述二甲双胍对肿瘤微环境核心成分的调控作用, 及其与EMT抑制的分子机制关联, 总结当前研究争议, 并展望未来, 旨在为深入理解二甲双胍的非代谢依赖抗肿瘤效应提供参考。

关键词

二甲双胍, 肿瘤微环境, 上皮 - 间质转化

Research Progress on the Inhibition of Epithelial-Mesenchymal Transition by Metformin through Regulation of the Tumor Microenvironment

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Abstract

Epithelial-mesenchymal transition (EMT) is a core process by which tumor cells acquire invasive and metastatic abilities, as well as enhanced drug resistance, and it is closely related to the dynamic regulation of the tumor microenvironment. The components of the tumor microenvironment, such as tumor-associated fibroblasts, tumor-associated macrophages, immunosuppressive cells, and soluble cytokines, collectively form a “promoting EMT” microenvironmental homeostasis. Metformin, as a first-line hypoglycemic drug in clinical practice, has recently been proven to have anti-tumor activity. Its mechanism of action not only directly regulates the metabolism of tumor cells but also can indirectly inhibit the EMT process by reshaping the tumor microenvironment, providing a new target for the prevention and treatment of tumor metastasis. This article systematically reviews the regulatory effects of metformin on the core components of the tumor microenvironment and their molecular mechanisms associated with EMT inhibition, summarizes current research controversies, and looks forward to the future, aiming to provide a reference for in-depth understanding of the non-metabolic-dependent anti-tumor effect of metformin.

Keywords

Metformin, Tumor Microenvironment, Epithelial-Mesenchymal Transition

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1. 引言

肿瘤转移是导致癌症患者死亡的首要原因，而 EMT 是肿瘤转移启动阶段的关键步骤，在 EMT 过程中，上皮细胞丧失了顶端 - 基底极性和稳定的细胞 - 细胞接触，同时转变为了更具有侵袭性的纺锤形的间质样的形态，这一形态的变化与上皮细胞标志物(如 E-cadherin、claudins、ZO-1)表达的抑制和间充质细胞标志物(如 Ncadherin、Vimentin、Fn)表达的增强有关，同时细胞迁移和侵袭的能力以及对细胞凋亡抵抗的能力增强[1] [2]。EMT 的发生并非肿瘤细胞自主行为，而是受肿瘤微环境(Tumor Microenvironment, TME)的精密调控，TME 作为肿瘤细胞生存的“土壤”，其成分异常可通过激活 TGF- β /Smad、Wnt/ β -catenin 等信号通路，直接驱动 EMT 进程[3] [4]。二甲双胍作为典型的降糖药，已在 2 型糖尿病治疗中应用数十年。近年流行病学研究发现，长期服用二甲双胍的糖尿病患者肿瘤发生率显著降低，且肿瘤患者的转移风险与预后改善相关[5]-[7]。后续机制研究证实，二甲双胍可直接抑制肿瘤细胞增殖，但更重要的是通过“改造” TME，切断其对 EMT 的支持[8]-[10]，这一非代谢依赖效应逐渐成为研究热点。目前，关于二甲双胍调控 TME 或抑制 EMT 的单一方向综述较多，但聚焦“TME 调控 EMT 抑制”协同机制的系统总结仍较缺乏。本文围绕二甲双胍对 TME 核心成分的调控作用，及其与 EMT 抑制的分子关联展开综述，为其临床转化提供理论依据。

2. TME 与 EMT 的相互作用：机制基础

TME 是指肿瘤中呈现的非癌细胞和成分，包括它们产生和释放的细胞因子，肿瘤细胞与 TME 之间的持续相互作用在肿瘤的发生、进展、转移和对治疗的反应中起着决定性的作用。肿瘤微环境是由肿瘤

细胞、基质细胞、细胞外基质及可溶性因子构成的复杂生态系统，其稳态失衡是 EMT 启动的核心诱因[11]，理解二者的相互作用，是解析二甲双胍作用机制的前提。

2.1. 基质细胞对 EMT 的驱动作用

肿瘤相关成纤维细胞(CAFs)是 TME 中最丰富的间质细胞，它们不是单一的群体，而是具有多种亚型(如炎症性 CAF、肌成纤维细胞性 CAF 等)，功能各异。CAF 通过分泌 TGF- β 、成纤维细胞生长因子(FGF)等细胞因子激活 EMT 通路[12]。当 TGF- β 配体与细胞膜表面的 II 型及 I 型受体结合后，会激活受体胞内区的丝氨酸/苏氨酸激酶结构域，随后，下游的胞质信号蛋白 Smad2 和 Smad3 被特异性磷酸化，磷酸化的 Smad2/3 与 Smad4 形成异源三聚体复合物，并易位至细胞核内，在核内，该复合物作为转录调控因子，直接或间接地启动 EMT 核心转录因子(如 SNAIL、SLUG、TWIST 等)的表达，这些转录因子进而特异性结合到 E-钙粘蛋白基因的启动子区域，抑制其转录，最终导致细胞粘附功能丧失，驱动 EMT 进程[13]。与此同时，在 TME 中，CAF 分泌的多种基质金属蛋白酶(如 MMP-2、MMP-9)通过降解胶原、纤连蛋白等细胞外基质成分，不仅为癌细胞的迁移开辟了物理路径，更关键的是能切割并释放锚定于 ECM 中的潜伏生长因子，例如 EGF，这些被释放的生长因子随后激活其位于上皮细胞膜上的受体，通过 MAPK/PI3K 等下游信号通路，与 TGF- β 信号协同作用，正反馈式地进一步增强 EMT 进程[14]。

2.2. 白细胞介素家族 EMT 的调控

白细胞介素是一种由多种细胞产生和分泌的细胞因子或信号蛋白，它们主要的功能是作为“信使”在细胞间传递信息，从而调节免疫细胞的活化、增殖、分化、趋化和功能，是免疫系统精确调控、协调作战的关键。有研究表明，在胃癌中[15]，IL-6 与受体结合激活 JAK/STAT3 信号通路后，STAT3 二聚体进入细胞核，作为转录因子直接上调 SNAIL、TWIST 等的表达。在卵巢癌中[16]，IL-8 通过与细胞膜上的特异性 G 蛋白偶联受体 CXCR1 或 CXCR2 结合，激活下游 Wnt/ β -catenin 通路，这一活化过程使得糖原合成酶激酶-3 β (GSK-3 β)失活，GSK-3 β 的失活导致 β -catenin 免受磷酸化降解，从而在胞质中稳定积累并易位入核，在细胞核内， β -catenin 作为转录共激活因子，与 TCF/LEF 家族转录因子结合，进而启动一系列与 EMT、细胞增殖相关的靶基因表达。IL-10 作为一种强效的抗炎和免疫抑制分子，主要通过“重编程”肿瘤微环境中的免疫细胞(尤其是巨噬细胞)，使其分泌一系列其他因子，从而间接激活癌细胞的 EMT 程序。IL-10 通过 JAK2/STAT3 信号通路促进 TAM 的募集和 M2 极化，极化的 M2 型 TAMs 又可分泌 TGF- β 激活 Smad 通路启动 EMT 核心转录因子[17]。综上所述，IL-6、IL-8 及 IL-10 通过激活 JAK/STAT、Wnt/ β -catenin、TGF- β /Smad 等关键信号通路，在肿瘤微环境中构成一个复杂的调控网络，协同驱动上皮-间质转化程序。这些因子作为连接慢性炎症与肿瘤恶性演进的核心桥梁，其作用机制为我们深入理解肿瘤的侵袭与转移提供了重要理论基础。

3. 二甲双胍对肿瘤微环境核心成分的调控作用

二甲双胍不仅通过直接抑制肿瘤细胞增殖，还通过“重塑”肿瘤微环境间接抑制 EMT 进程。特别地，二甲双胍通过多靶点、多维度的作用，显著改变肿瘤微环境中基质细胞之间的相互作用，并进一步调节免疫微环境的酸性状态。这些改变为癌细胞的侵袭性转化提供了新的抑制靶点。

3.1. 基质细胞间相互作用的调控

在 TME 中，CAF、TAMs 以及其他免疫细胞通过复杂的细胞因子和代谢物信号网络相互作用，共同促进或抑制 EMT 过程[18] [19]。而二甲双胍在这方面的作用尤为突出，研究表明，二甲双胍可以通过抑制 CAF 的活化，减少其分泌的促肿瘤因子(如 TGF- β 、IL-6)，从而减少对 EMT 的支持[20] [21]。同时，

二甲双胍通过激活 AMPK 通路,减少乳酸等代谢产物的分泌,这不仅改变了 TME 的代谢状态,还通过改变免疫微环境的酸性条件,抑制了 EMT 过程[22] [23]。

3.2. 代谢改变与免疫微环境的酸性状态

代谢改变,尤其是乳酸分泌减少,在二甲双胍治疗下显著影响 TME 中的酸性环境。乳酸是肿瘤细胞通过糖酵解途径产生的主要代谢产物,它在 TME 中积累,导致局部酸性环境的形成,这种酸性环境进一步促进了 CAFs、TAMs 等基质细胞的活化,并通过细胞因子的分泌加剧了 EMT 的进程[24]-[26]。二甲双胍通过抑制糖酵解,减少乳酸的产生,从而改变了 TME 的代谢状态,降低了免疫微环境的酸性,间接抑制了 EMT 的发生。具体而言,二甲双胍通过 AMPK/mTOR 通路的调节,减轻了乳酸在肿瘤微环境中的积累,这一过程抑制了 TAMs 的 M2 型极化,进而减少了其分泌的 TGF- β 等促 EMT 因子,进一步减缓了 EMT 的进程[27]-[30]。

3.3. CAFs 和免疫细胞的互作

在二甲双胍的作用下,CAFs 与免疫细胞之间的互作也发生了显著变化。二甲双胍不仅抑制了 CAFs 的激活和其分泌的免疫抑制因子(如 TGF- β),同时也通过调节乳酸水平,影响免疫细胞(如 TAMs 和 Tregs)的功能[31]-[34]。例如,减少乳酸积累能够提高免疫细胞对肿瘤细胞的识别能力,并减少免疫细胞的抑制作用。这种代谢与免疫细胞功能的相互影响,进一步减少了 TME 中的 EMT 促进信号[35] [36]。

4. 二甲双胍调控肿瘤微环境抑制 EMT 的分子机制:核心通路关联

二甲双胍通过调控 TME 抑制 EMT,并非单一通路作用,而是通过多通路协同,将 TME 的“促 EMT 信号”转化为“抑 EMT 信号”,以下总结其核心分子机制关联。

4.1. 调节 AMPK 信号

AMP 活化蛋白激酶(AMPK)是一种异源三聚体丝氨酸/苏氨酸蛋白激酶,由催化 α 亚基与两个调节亚基 β 和 γ 复合物组成,作为重要的能量传感器和调节剂,AMPK 的激活通过磷酸化下游底物在各种细胞过程中发挥多种作用,包括代谢、自噬、衰老、细胞运动和细胞抗应激性[37]。据报道[38],AMPK 可以磷酸化 EZH2 (一种 H3K27me3 甲基转移酶)以抑制肿瘤发生,丙酮酸脱氢酶的亚基 PDHA 也被发现是 AMPK 的直接底物,用于调节乳腺癌转移。在一项结直肠癌异种移植小鼠的实验中发现[39],二甲双胍可通过激活 AMPK 抑制 mTOR 通路,进而使得小鼠的肝转移率和肝转移结节数量显著降低,肿瘤增殖和 EMT 减少。另外一项关于胰腺导管腺癌的研究中发现[9],二甲双胍通过减少包括 IL-1 β 在内的炎症细胞因子的表达以及 TAM 在体外和体内的浸润和 M2 极化来缓解肿瘤炎症,进而减轻结缔组织增生与 ECM 重塑、EMT 和最终全身转移,这些对体外巨噬细胞的影响与二甲双胍对 AMPK/STAT3 通路的调节有关。而在子宫内膜腺癌细胞中[40],二甲双胍可通过子宫内膜腺癌细胞中 AMPK 信号传导抑制 17 β -雌二醇诱导的上皮间质转化。

4.2. 抑制 TGF- β /Smad 通路:切断核心促 EMT 信号

TGF- β /Smad 信号通路,是细胞中一条高度保守的信号转导途径,它广泛参与调控细胞的增殖、分化、迁移、凋亡以及细胞外基质的生成,该通路在胚胎发育、组织修复、免疫调节和维持成体组织稳态中发挥着至关重要的作用。在癌症中,TGF- β 扮演着双重角色,在早期作为肿瘤抑制因子,在晚期则转变为促进肿瘤侵袭和转移的因子,随着肿瘤进展,细胞可能对 TGF- β 的生长抑制效应产生抵抗,此时,癌细胞会利用 TGF- β 信号来促进上皮-间质转化、增强侵袭能力、诱导血管生成和抑制免疫应答,从而促进

肿瘤的转移和免疫逃逸[41]。已知 TGF- β 信号传导可刺激转录因子的表达,包括 SNAIL、TWIST 和 ZEB,而这些转录因子是 EMT 过程的关键调节因子[42]。研究表明,在胰腺癌中,二甲双胍通过下调 PANC-1 细胞中的 Smad 通路和下调 BxPC-3 细胞中 Akt/mTOR 通路来抑制 TGF- β_1 诱导的 EMT [2]。TGF- β_1 信号传导的改变和 STAT3 的异常激活与各类肿瘤的进展密切相关,活跃的 STAT3 可信号作为调节转录因子,通过直接与 SNAIL 的启动子区域结合,STAT3 的表达和随后诱导 EMT [43]-[45]。在前列腺癌研究中发现单独使用恩杂鲁胺治疗可上调间充质生物标志物(N-钙粘蛋白、波形蛋白)的水平,并下调上皮标志物(E-钙粘蛋白),而二甲双胍可以减弱这种诱导作用,这一发现与作者先前研究的体外前列腺癌细胞模型和体内 CWR22Rv1 异种移植小鼠模型高度一致,这一作用机制通过抑制 TGF- β_1 表达和 STAT3 激活来实现的[46]。通过另有研究表明,在直肠癌中,二甲双胍可抑制直肠癌细胞中 TGF- β_2 介导的 SNAIL 和 TWIST 表达来抑制细胞迁移和侵袭[47]。

4.3. 调控非编码 RNA: 表观遗传层面的 EMT 抑制

miRNA 是一类非编码 RNA (Non-Coding RNA, ncRNA)分子[48],含有 18~23 个氨基酸,通过与靶信使 RNA (mRNA)结合,促使靶 mRNA 降解或抑制其向蛋白质的翻译,从而发挥其在细胞增殖、分化、凋亡、代谢以及机体发育和疾病发生等的作用[49]。越来越多的研究揭示了 miRNA 在癌症转移中的关键调控作用[50],转录因子与 miRNA 组成的嵌合体——[SNAIL/miR-34]:[ZEB/miR-200]是 EMT 过程的核心调控系统[51] [52],在用 TGF- β 诱导的人结直肠癌细胞系 SW480 和 HCT116EMT 模型中发现[53],对于 [SNAIL/miR-34]:[ZEB/miR-200]系统,在 TGF- β 诱导的 EMT 模型中,二甲双胍增加 miR200a、miR-200c 和 miR-429 的水平,降低 miR-34a、SNAIL-1 和 ZEB1 的水平,表明二甲双胍可以在结直肠癌的 EMT 过程中执行[SNAIL/miR-34]:[ZEB/miR-200]系统的双向调节,这种调节总体上反映了 EMT 抑制效应,在细胞群体水平上,这种抑制表现为 EMT 过程中 E/M 杂交细胞亚群的增加。在黑色素瘤中[54],miR-5100 靶向 SPINK5 激活 STAT3 磷酸化促进 EMT 增强瘤细胞转移,而二甲双胍可显著抑制 miR-5100/SPINK5/STAT3 通路,并减少了 C57 小鼠模块中 B16-F10 细胞向肺的转移。另有研究证明二甲双胍通过调节 miR-663 的 DNA 甲基化逆转 EMT,增加了胰腺癌细胞对吉西他滨的化学敏感性[55]。

5. 研究现状与争议

5.1. 二甲双胍浓度问题: 体外实验 vs 生理相关浓度

大量体外研究为了探讨二甲双胍的抗肿瘤机制,使用的药物浓度通常处于 mM 级别(如 2~50 mM),远高于临床常规给药后体内可达到的血药浓度;而常规口服剂量(2500 mg/天)在肝脏内的浓度约为 50~100 $\mu\text{mol/L}$,在外周血中则更低(约 10~40 $\mu\text{mol/L}$) [23] [56] [57]。这一浓度差异表明:许多体外实验的抗肿瘤效应可能只在非生理相关条件下出现,从而可能高估了二甲双胍的临床价值。相比之下,一些研究开始采用更接近“生理相关浓度”的实验设计。例如某些低剂量二甲双胍(≈ 250 mg/日)在食管鳞癌临床 II 期试验中观察到了对肿瘤免疫微环境的重编程作用(如影响 B 细胞、T 细胞、巨噬细胞浸润) [58] [59]。这类研究更接近临床使用情境,为后续转化研究提供了更可靠的依据。因此,未来体外实验设计和机制研究推荐更多使用逼近临床血药浓度范围的条件,以减少体内/体外差异对机制解释和效果判断的干扰。

5.2. TME 成分调控的优先级

TME 成分复杂,二甲双胍对 CAFs、TAMs、细胞因子的调控并非同步,其作用优先级尚不明确。例如,在肺癌模型中,二甲双胍对 TAMs 的调控作用更显著,而在乳腺癌中对 CAFs 的调控更关键[60] [61],这种差异是否与癌种特性相关,仍需深入研究。

5.3. 个体差异与联合用药

糖尿病患者与非糖尿病患者的 TME 结构存在差异,二甲双胍的作用是否受血糖水平影响?此外,二甲双胍与化疗、免疫治疗的联合应用,是否会增强其调控 TME 抑制 EMT 的效应?目前相关研究较少,需进一步探索。

6. 结论与展望

综上所述,二甲双胍调控肿瘤微环境以抑制上皮-间质转化的机制,已成为其抗肿瘤效应的重要一环。该药物能够直接抑制癌相关成纤维细胞的活化、重塑免疫微环境——包括阻碍 M2 型肿瘤相关巨噬细胞的极化、减少调节性 T 细胞的浸润,同时纠正促肿瘤的细胞因子失衡,从而多维度切断肿瘤微环境中驱动 EMT 的关键信号网络,这一系统性作用机制不仅深化了对二甲双胍抗癌潜力的理解,也为基于肿瘤微环境调控的联合治疗策略提供了新的理论依据与干预思路。在未来可构建更贴近临床的模型如采用人源化小鼠模型(如 PBMC 人源化、PDX 模型),验证二甲双胍在“人类 TME”中的作用,为机制研究提供更精准的方向。

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