

上皮-间质转化: 肿瘤转移的重要调控机制

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摘要 上皮-间质转化(epithelial-mesenchymal transition, EMT)是指上皮细胞在特定生理或病理情况下向间质细胞表型转变的过程。近年来发现, EMT与肿瘤转移密切相关, 已成为当前生命科学研究的热点。研究证明, 激活TGF- β 、Wnt/ β -catenin、Notch、Hedgehog、IL-6/STAT3以及NF- κ B等信号通路, 调控Snail1、Snail2、Twist1、Twist2、ZEB1和ZEB2等转录因子, 可诱导EMT进程。此外, 许多非编码RNA(如microRNA和lncRNA)也参与肿瘤EMT调控。揭示EMT的分子调控机制以及其与恶性肿瘤的关系, 对于预防和治疗癌症具有重要意义。

关键词 上皮-间质转化; EMT; 肿瘤; 转移; 机制

Epithelial-mesenchymal Transition: An Important Mechanism for Regulation of Tumor Metastasis

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Abstract The epithelial-mesenchymal transition (EMT) is a unique process in which cells lose epithelial characteristics and gain mesenchymal properties under special physiological or pathological situations. EMT is proved to be highly relevant to tumor metastasis, and has been a focus of recent biological research. The signaling pathways including TGF- β , Wnt/ β -catenin, Notch, Hedgehog, IL-6/STAT3 and NF- κ B can trigger EMT in tumor cells by inducing Snail1, Snail2, Twist1, Twist2, ZEB1 and ZEB2 expression. In addition, non-coding RNAs (such as microRNAs and lncRNAs) also play critical roles in the regulation of EMT. Thus, the identification of molecular mechanism of EMT in malignant cells might provide a tool to better prevent and treat cancers.

Key words epithelial-mesenchymal transition; EMT; tumor; metastasis; mechanism

肿瘤转移是导致恶性肿瘤患者死亡的主要原因。深入研究肿瘤转移机制, 可为抗肿瘤转移治疗奠定基础。近年来, 上皮-间质转化(epithelial-mesenchymal transition, EMT)在肿瘤转移中的作用受到越来越多的关注。

1 EMT概述

EMT是指上皮型细胞在特定生理或病理情况

下向间质型细胞表型转变的过程^[1]。EMT的主要形态学特征: 上皮细胞失去其典型的胞间连接结构, 重组细胞骨架, 由多边形变为梭形的纤维细胞样形态。细胞发生EMT后变得孤立, 运动能力增强, 耐凋亡。EMT的主要分子特征: E-钙黏蛋白(E-cadherin)、密封蛋白(occludin)等上皮标志物表达和功能缺失, 同时N-钙黏蛋白(N-cadherin)、波形蛋白(vimentin)等间质细胞标志物过量表达(图1)^[2-3]。根据EMT参与

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的不同生物进程, 现将其分为三大类(表1): 胚胎形成和器官发育中的EMT, 创伤修复和器官纤维化中的EMT, 以及肿瘤中的EMT^[4]。

2 EMT与肿瘤转移

转移是恶性肿瘤细胞的基本生物学特征, 是临

床上绝大多数肿瘤患者的致死因素。目前, 虽然对肿瘤转移的机制未完全明了, 但已有的研究表明, 肿瘤转移是一个多因素、多阶段参与的复杂过程, 依赖于肿瘤细胞和促进肿瘤细胞生长、侵袭、转移以及血管形成等内环境因素的相互作用^[5]。E-cadherin是一种依赖Ca²⁺的黏附分子, 具有同种分子亲和

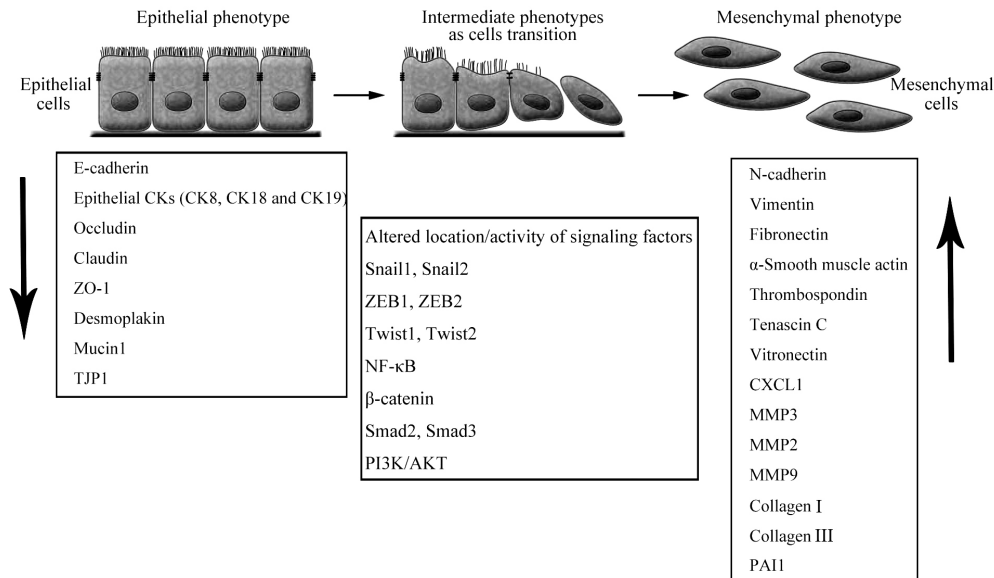


图1 EMT主要特征(根据参考文献[3-4]作适当修改)

Fig.1 The main characteristics of EMT (modified from references [3-4])

表1 EMT分类

Table 1 Classifications of EMT

EMT亚型 EMT subtypes	特征 Characteristics
Type 1	Associated with development, including implantation, gastrulation and neural crest formation
Type 2	Associated with wound healing, tissue regeneration and organ fibrosis
Type 3	Occurring during cancer progression, whereby EMT in epithelial cancer cells produces cells with increased invasive and metastatic capacity

性, 能稳定相邻细胞的连接^[6]。脊椎动物上皮细胞的胞间连接主要依赖于顶端(apical side)的紧密连接(tight junction, TJ)以及外侧的黏附连接(adherens junction, AJ)和桥粒(desmosome)^[7]。紧密连接主要由连接黏附分子(junctional adhesion molecule, JAM) claudin和occludin组成, 它们通过ZO-1、ZO-2和ZO-3与微丝骨架相联系。黏附连接主要由跨膜黏附分子nectin和E-cadherin组成, 它们分别通过afadin和catenin与细胞骨架结合。EMT会导致上皮细胞的E-cadherin、claudin、occludin等连接分子表达缺失, 破坏细胞极性。EMT也会促使一些参与细胞外基质(主要包括胶原、层黏素和纤维结合素等)和基底膜降解和破坏的溶解酶如基质金属蛋白酶(matrix

metalloproteinase, MMP)高表达, 破坏肿瘤细胞侵袭的组织学屏障, 便于细胞从原发肿瘤分离脱落发生侵袭转移。通常认为EMT发生在肿瘤转移的起始阶段。除赋予肿瘤细胞迁移和侵袭能力外, EMT还可使肿瘤细胞获得干细胞特征, 从而促进肿瘤干细胞(cancer stem cells, CSCs)的产生^[8-9]。而CSCs具有迁移性, 是肿瘤浸润、转移和侵袭性生长的基础。由于牵涉一些阻碍细胞生长的转录因子, EMT常会产生许多不易增殖的细胞, 而间质-上皮转化(mesenchymal-epithelial transition, MET)有助于侵入继发组织或器官基质的肿瘤细胞生长增殖形成转移瘤灶。此外, EMT可阻碍肿瘤细胞的早衰和凋亡, 使它们逃脱机体免疫系统的监视, 继而在体内存

活^[10]。目前已发现, 乳腺癌、卵巢癌、宫颈癌、黑色素瘤、胃癌、肝癌以及胰腺癌等恶性肿瘤细胞的转移与EMT密切相关。

3 EMT在肿瘤中的重要调控机制

目前, 对肿瘤EMT的调控机制仍不明确, 根据已有的研究表明, TGF- β 、Wnt/ β -catenin、Notch、Hedgehog、IL-6/STAT3以及NF- κ B等信号通路可诱导EMT进程(图2)。EMT中所涉及的重要转录因子有: Snail1、Snail2、Twist1、Twist2、ZEB1和ZEB2等^[11-12]。此外, 还有许多非编码RNA(non-coding RNA, ncRNA)如微RNA(microRNA或miRNA)和长链非编码RNA(long non-coding RNA, lncRNA), 也参与肿瘤EMT调控^[13]。

3.1 转录因子

E-cadherin表达缺失是EMT最重要的标志性变化。基因突变、表观遗传引起的基因沉默以及负调控的转录因子结合到*CDH1*(编码E-cadherin)启动子上都会导致E-cadherin表达下调。Snail1、Snail2、ZEB1、ZEB2、Twist1和Twist2作为E-cadherin的重要阻遏蛋白是研究肿瘤细胞EMT分子调控机制网络的关键枢纽^[14]。

3.1.1 Snail1和Snail2 Snail是一类重要的转录因子, 依赖C-末端的锌指结构域和N-末端的SNAG(Snail/Gfi)结构域调控靶基因的表达^[15]。脊椎动物体内存在3种Snail蛋白: Snail1(即通常称作的Snail)、Snail2(即Slug)和Snail3。研究表明, Snail1和Snail2异常表达与侵袭型肿瘤密切相关。*CDH1*启动子的E-box(CAGGTG)区上存在Snail结合位点, Snail蛋白结合到该位点后会招募其他蛋白共

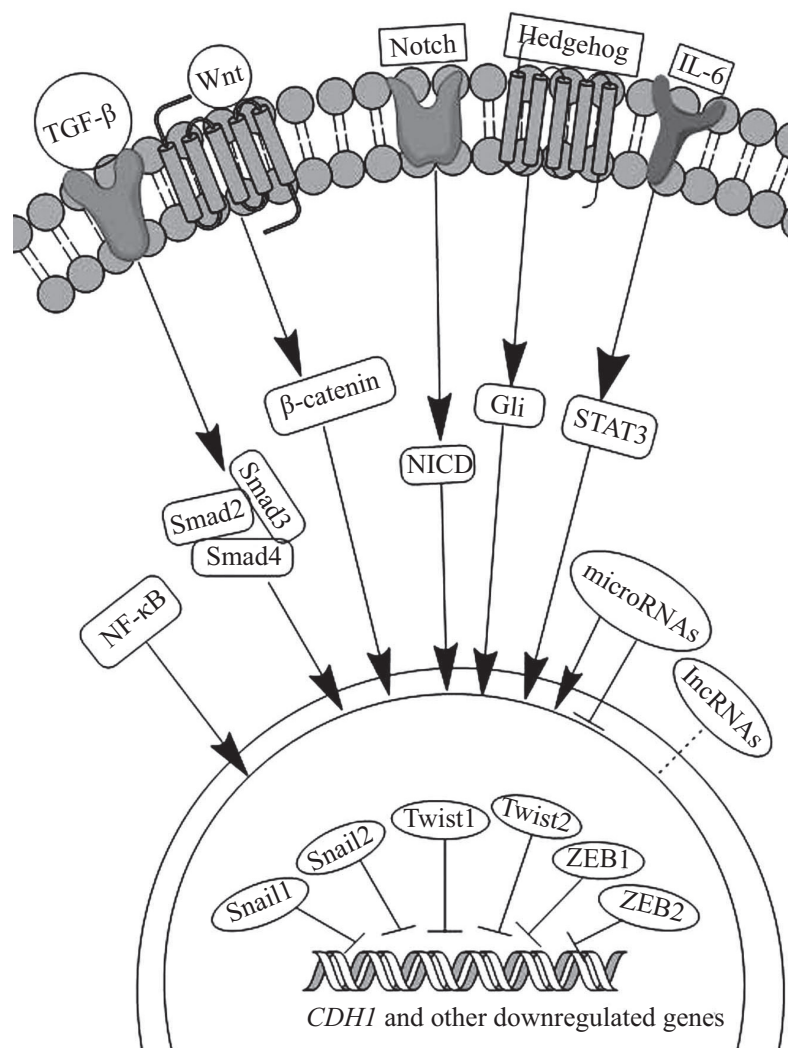


图2 肿瘤EMT的关键调控机制

Fig.2 The critical mechanism for regulation of EMT in cancers

同阻止*CDH1*转录, 导致E-cadherin表达降低。Snail也可抑制*Crumbs3*转录调控细胞极性^[16]。上皮细胞极性(polarity)的建立和维持主要通过PAR(Par3-Par6-aPKC)复合物、CRB(*Crumbs-Pals-Patj*)复合物和SCRIB(*Scribble-Dlg-Lgl*)复合物3个极性复合物之间的相互调节以及它们对细胞骨架和细胞间连接的调节实现的^[17]。前两个复合物负责上皮细胞顶端区域(apical domain)的形成, 第三个负责基底侧部区域(basolateral domain)的形成。胞间连接的建立是上皮细胞极性形成的前提条件, PAR复合物在此过程中起了关键作用, 它会将CRB复合物与紧密连接联系起来, 并一起调控紧密连接的建立。Snail诱导上皮细胞会导致紧密连接处的PAR复合物和CRB复合物减少, 细胞极性丢失, 运动性增强。此外, Snail1也可通过调控*ZEB2*影响细胞的EMT进程。而Snail2具有独特的Slug区域, 这使其有别于Snail蛋白家族的其他成员。研究发现, Snail2能抑制E-cadherin、Claudin-1、Occludin等黏附分子的表达, 进而破坏细胞-细胞的连接, 促使肿瘤细胞发生侵袭、转移^[18-19]。另外, Snail2可提高膜类基质金属蛋白酶MT4-MMP(membrane-type 4 MMP, 即MMP-17)的表达水平^[20]。MMP是一类重要的Zn²⁺和Ca²⁺依赖的内源性蛋白水解酶, 能降解细胞外基质中的各种蛋白成分, 其活性主要受3个水平的调节: 基因转录水平、无活性的酶前体经蛋白水解作用而激活以及相应金属酶组织抑制剂TIMP(tissue inhibitor of metalloproteinases)作用^[21]。研究发现, MMP-3、MMP-7、MMP-9和MMP-13能诱导细胞发生EMT, 使细胞获得更强的侵袭性^[22-24]。Snail和Slug都是不稳定的蛋白, 其半衰期(half-life)<1 h。Snail被糖原合成酶激酶-3β(glycogen synthase kinase-3β, GSK-3β)磷酸化后, 会发生泛素化降解^[25]。启动受体酪氨酸激酶、PI3K/Akt以及Wnt/β-catenin信号通路会抑制GSK-3β的活性, 上调Snail表达, 促使细胞发生EMT。Slug也可通过泛素-蛋白酶体降解途径维持自身在细胞中的平衡状态。在非小细胞肺癌细胞中发现, 野生型的P53和泛素连接酶MDM2可与Slug形成P53-MDM2-Slug复合物, 导致Slug降解, 进而削弱细胞的侵袭能力^[26]。

3.1.2 Twist1和Twist2 Twist家族是胚胎发育中一类高度保守的碱性螺旋-环-螺旋(basic helix-loop-helix, bHLH)转录因子, 和E12或E47形成异源

二聚体与特异性的DNA序列相结合, 具有相对的组织特异性^[27]。研究发现, Twist1-E12二聚体通过招募Mi2/核小体重塑和去乙酰化酶(Mi2/nucleosome remodeling and deacetylase, Mi2/NuRD)蛋白复合物到*CDH1*的启动子上, 共同抑制E-cadherin的表达^[28]。Mi2/NuRD包含Mi2、组氨酸去乙酰化酶2(histone deacetylase 2, HDAC2)、转移相关蛋白2(metastasis-associated protein 2, MTA2)以及Rb相关蛋白46(Rb-associated protein 46, RbAp46)等蛋白。Mi2具有染色质依赖的ATP酶活性, 有助于组蛋白八聚体与DNA发生相对移动, 改变核小体的位置, 同时使核小体的DNA得以暴露, 促使转录因子与相应序列结合。HDAC2使组蛋白去乙酰化, 得以恢复自身的正电荷, 增强了与DNA之间的引力, 使松弛的核小体变得十分紧密, 不利于基因的表达。Mi2和HDAC2同时结合到*CDH1*上, 加强了基因沉默。Twist1也能通过BMI1增强对*CDH1*转录的抑制作用^[29]。BMI1是一种重要的PcG(polycomb group)蛋白, 该类蛋白通过染色质修饰调控靶基因的转录抑制。PcG蛋白在人体细胞内可形成2个重要的核心蛋白复合体: PRC1(polycomb-repressive complex 1)和PRC2。PRC2在转录抑制起始阶段发挥作用, 而PRC1则维持染色质的阻抑状态。根据以上认识推测: Twist1是否招募了PRC1蛋白复合物来维持*CDH1*的转录沉默? Twist1是否在Mi2/NuRD和PRC1的共同作用下直接抑制*CDH1*的转录? 目前仍无法解答上述问题, 需要深入的研究加以证实。另外, Twist1也可通过Snail2调控EMT^[30]。而关于Twist2在肿瘤EMT进程中的分子调控机制目前报道的并不多。研究发现, 乳腺癌细胞Twist2蛋白的定位与E-cadherin的失调表达有关: 细胞质Twist2高表达不会改变细胞形态和E-cadherin表达水平; 而细胞核内Twist2高表达会导致E-cadherin蛋白缺失^[31]。对于Twist2蛋白是什么时候又是通过什么机制由胞质转入细胞核而后启动EMT的, 目前仍不能阐明。

3.1.3 ZEB1和ZEB2 ZEB是胚胎发育和细胞分化过程中的重要转录因子。ZEB1和ZEB2(即SIP1)末端都有锌指簇, 可识别并结合*CDH1*的E-box(CACCTG)序列。ZEB1募集CTBP和BRG1共同抑制*CDH1*的转录, 进而调控EMT进程^[32]。ZEB2通过抑制编码E-cadherin(黏附连接)、ZO-3(紧密连接)、plakophilin 2(桥粒)和connexin 26(间隙连接)等

基因的转录, 进而削弱肿瘤细胞之间的连接作用, 使细胞获得更强的运动性, 发生浸润、转移^[33]。

3.2 信号通路

3.2.1 TGF- β 信号通路 转化生长因子- β (transforming growth factor- β , TGF- β)是一多功能蛋白, 可影响细胞的增殖、分化、凋亡、黏附和迁移。TGF- β 对不同的细胞有不同的效应: 它刺激成纤维细胞分裂, 抑制正常上皮细胞生长, 而其诱导的上皮肿瘤细胞却会发生EMT^[34]。TGF- β 与肿瘤细胞膜上具有丝氨酸/苏氨酸蛋白激酶活性的高亲和性受体T β RI和T β RII相结合, 激活Smad2和Smad3, 并与Smad4形成三聚体一同进入细胞核, 与其他转录因子共同调控靶基因(如Snail1、Snail2、ZEB)的表达, 最终导致细胞E-cadherin低表达, 同时N-cadherin、vimentin等间质细胞标志物高表达, 肿瘤细胞获得较强的运动性^[35]。此外, 还发现TGF- β 可通过激活Erk MAP激酶、Rho GTPases和PI3K/Akt等信号通路, 重组细胞骨架, 调控细胞的生长、转移能力, 经非Smad途径诱导EMT。

3.2.2 Wnt/ β -catenin信号通路 目前认为, β -catenin是Wnt信号通路的枢纽分子, 介导Wnt信号从膜至胞浆进核的传递。正常生理状态下, β -catenin与 α - γ -catenin以及E-cadherin形成E-cadherin/catenin复合体, 桥接细胞骨架肌动蛋白(actin), 维持上皮细胞之间的黏附连接^[36]。而胞质中游离的 β -catenin会被APC(adenomatous polyposis)、GSK-3 β 和Axin形成的复合物磷酸化, 发生泛素化降解^[37]。Wnt配体与膜上的受体Frizzled和LRP5/6结合后会募集胞质中的Dvl(Dishevelled)蛋白, 活化的Dvl可抑制GSK-3 β , 使 β -catenin不被降解。大量游离的 β -catenin进入核内和TCF/Lef转录因子结合, 激活Wnt靶基因, 导致下游与恶性肿瘤相关的基因的转录, 最终影响细胞的生理状态。研究发现, Wnt/ β -catenin信号通路除了上调Twist1、Snail1、Snail2以及ZEB1等转录因子的表达外, β -catenin/TCF/Lef也能促使fibronectin和vimentin基因转录, 诱导肿瘤细胞EMT化^[38-39]。

3.2.3 Notch信号通路 Notch受体激活后, 会发生2次剪切, 其最关键的一步是 γ -secretase蛋白酶剪切受体的胞内区域, 释放Notch细胞内结构域(Notch intracellular domain, NICD)^[40-41]。NICD会转移到核内与CSL(C protein binding factor 1/Suppressor of Hairless/Lag-1)蛋白共同调控靶基因的表达。CSL

是一类重要的DNA结合蛋白, 是Notch信号通路的关键调节因子。NICD未入核时, CSL与多种共抑制因子(corepressor, CoRep)一起阻遏目的基因的表达。一旦NICD与CSL结合, 便会募集共激活因子(coactivator, CoAct), 促进靶基因转录。研究发现, Notch信号通路介导低氧诱导的肿瘤EMT采用2种不同的机制调控Snail1表达: 一是NICD结合到Snail1启动子上直接促进Snail1表达; 二是通过缺氧诱导因子1 α (hypoxia-inducible factor 1 α , HIF1 α)促进赖氨酰氧化酶(lysyl oxidase, LOX)表达, 而LOX能使Snail1稳定表达^[42]。另外, 该途径也可调控Snail2的表达, 进而影响细胞的EMT^[43]。

3.2.4 Hedgehog信号通路 Hedgehog信号通路主要由配体Hedgehog、跨膜蛋白受体Ptc(Patched)和Smo(Smoothened)以及下游的转录因子Gli(Gli1、Gli2和Gli3)级联构成^[44-46]。当Hedgehog缺失时, Ptc可抑制Smo的活性, 使Hedgehog信号通路处于抑制状态; 当Hedgehog激活时, Ptc结合Hedgehog, Smo抑制被解除, Gli从微管上解离, Gli蛋白酶水解被抑制, 以全长的形式进入细胞核, 诱导目的基因的转录。Hedgehog通路主要通过与其他信号通路间的交叉和级联反应, 参与EMT的发展进程: 上调JAG2启动Notch信号通路, 导致Snail1高表达; 上调整合素(Integrin) α v β 6活化TGF- β 信号通路, 增强Snail2、ZEB1和ZEB2的表达^[47]。Hedgehog通路也会促使Twist2高表达, 但其机制还不明确。此外, 该信号通路还可通过调控FOXC2影响细胞的EMT。FOXC2是EMT进程的重要调节分子, 它可直接抑制p120-catenin表达, 间接调控E-cadherin^[48]。p120-catenin是catenin家族的重要成员, 可稳定膜上的E-cadherin, 和其他分子一起介导微管(microtubule)与E-cadherin间的连接^[49]。p120-catenin缺失会导致E-cadherin内化并降解, 进而削弱细胞间的致密黏附, 促使细胞发生浸润、转移。

3.2.5 IL-6/STAT3信号通路 研究显示, EMT与细胞因子如白介素-6(interleukin-6, IL-6)密切相关。IL-6受体由特异性的配体结合蛋白和gp130信号转导蛋白组成^[50]。当IL-6与受体结合后, Janus激酶(Janus kinase, JAK)在gp130的胞质区募集, 引起gp130磷酸化, 激活STAT3(signal transducer and activator of transcription 3)。活化的STAT3形成同源二聚体, 转移到核内与特异性核酸序列结合, 调节

靶基因转录。研究发现, IL-6通过激活STAT3, 促进Twist1转录, 导致乳腺癌细胞发生EMT^[51-52]。此外, IL-6/STAT3信号通路也会调控Snail的表达^[53]。

3.2.6 NF- κ B信号通路 NF- κ B家族是一类高度保守的转录因子, 包括5个亚单位: RELA(p65)、RELB、REL、p50和p52^[54]。RELA、RELB和REL的N端有REL同源区(REL homology domain, RHD), C端均有反式激活结构域(transactivation domain, TAD)。RHD负责与DNA结合、二聚体化以及核易位, 而TAD则与转录活化相关。p50和p52只有RHD缺乏TAD, 因此, p50和p52同源二聚体并不能激活基因转录, 而作为一种抑制分子, 它们在细胞内通常各自以其前体p105和p100的形式存在。在静息的细胞中, NF- κ B二聚体与抑制蛋白I κ B(inhibitor of NF- κ B)结合, 以无活性的形式存在于胞浆中。I κ B包括I κ B α 、I κ B β 和I κ B γ 。当细胞受细胞外信号刺激后, I κ B激酶(I κ B kinase, IKK)复合体活化导致I κ B磷酸化并降解, 促使NF- κ B释放并移位入核, 与特异性的DNA序列结合, 调节相关基因的转录。IKK复合体分为催化亚基(IKK α 和IKK β)和调节亚基(IKK γ)。NF- κ B的活化主要通过经典和非经典2条途径得以实现^[55]。经典的NF- κ B活化依赖于IKK β 和IKK γ 的激酶活性, 它们会使I κ B α 磷酸化, 最终以RELA:p50为主的异源二聚体得以入核发挥其生物学功能。而非经典的NF- κ B活化依赖于IKK α , 此过程中p100降解为p52, 最终RELB:p52二聚体转入细胞核调控靶基因的转录。研究发现, NF- κ B与*vimentin*、*MMP-2*及*MMP-9*等间质细胞相关基因的异常表达密切相关: NF- κ B可结合到*vimentin*和*MMP-9*启动子上进而促进基因转录; NF- κ B也可诱导MT-MMP表达促使MMP-2前体水解, 间接活化*MMP-2*^[56]。另有研究发现, ZEB1和Twist1的启动子上存在NF- κ B结合位点, p65通过该位点可促进靶基因的转录, 进而调控下游基因的表达, 最终使上皮细胞获得间质细胞表型^[57-58]。我们知道IL-6是NF- κ B信号通路的重要产物, 由此推测, NF- κ B可通过激活IL-6/STAT3信号通路间接调控EMT。

3.3 ncRNA的调控

3.3.1 microRNA microRNA是真核生物中一类高度保守的、内源性非编码小分子RNA, 其长度约为22个核苷酸^[59]。miRNA本身不具备编码蛋白质的功能, 但其参与基因的转录后调控。研究发现, miR-

200家族(miR-200a、miR-200b、miR-200c、miR-141和miR-429)、miR-138、miR-205等多种miRNA参与EMT的调控, 这里主要介绍一下miRNA-200和miR-138^[60]。miRNA-200是最早被发现参与EMT调控的miRNA。miR-200a和miR-200b可通过抑制ZEB1和ZEB2的转录, 阻止细胞的EMT^[61-62]。miRNA主要由位于基因间隔区的核苷酸序列编码, 经核苷酸聚合酶(主要是RNA聚合酶II)作用生成RNA初级转录本(primary transcript)即pri-miRNA, 然后转变成具有茎环结构的pre-miRNA, 最后形成成熟的miRNA。miR-200b、miR-200a和miR429拥有相同的pri-miRNA, 而miR-200c和miR-141具有相同的pri-miRNA。ZEB蛋白结合到编码miR-200c~141和miR-200b~a~429基因的启动子上会阻碍它们的pri-miRNA生成^[63-64]。由此可见, 打破miR-200和ZEB之间负反馈回路调节的平衡, 会使ZEB在细胞中异常表达, 进而导致肿瘤的发生。研究发现, *vimentin*、*ZEB2*和*EZH2* (enhancer of zeste homolog 2)的mRNA上存在miR-138的作用靶序列^[65]。因此, miR-138可通过3种不同机制抑制肿瘤EMT: (1)直接对*vimentin*进行转录后调控; (2)通过ZEB2在转录水平调控E-cadherin的表达; (3)通过EZH2从表观遗传学角度调控E-cadherin表达。EZH2是PRC2的重要成员, 参与组蛋白H3的第27位赖氨酸三甲基化(trimethylation of histone H3 lysine 27, H3K27me3)^[66]。EZH2既可直接使*CDH1*启动子处发生H3K27me3, 导致*CDH1*基因沉默; 也可通过Nkd1(Wnt信号通路的拮抗物)启动子处的H3K27me3, 活化Wnt/ β -catenin信号通路, 阻遏E-cadherin的表达。

3.3.2 lncRNA lncRNA是一类长度大于200个核苷酸的非编码RNA^[67]。研究表明, lncRNA主要通过基因印迹(genetic imprinting)、染色质重塑、细胞周期调控、剪接调控、mRNA降解和翻译调控等主要机制发挥生物学功能^[68]。因此, lncRNA异常表达会引发肿瘤。据报道, 膀胱癌细胞内lncRNA-H19高表达, 会促使EZH2表达, 下调E-cadherin, 进而增强细胞的转移性^[69]。据此我们推测, lncRNA可能参与EMT调控。另外, 在Snail1诱导细胞EMT的实验中, ZEB2蛋白增加, 伴随大量ZEB2天然反义转录物(natural antisense transcript, NAT)生成^[70]。NAT是一类重要的lncRNA, 与其互补的RNA通过碱基配对, 形成RNA双链(dsRNA), 导致靶mRNA降解或翻

译抑制^[71]。研究发现, ZEB2蛋白质合成必需的内部核糖体进入位点(internal ribosome entry site, IRES)位于ZEB2 mRNA的5'-非翻译区(UTR)的一个内含子上, 该内含子剪接会使ZEB2翻译受阻。高表达的NAT与ZEB2 mRNA结合, 会覆盖5'-UTR内含子的5'剪接位点, 使IRES不被剪切, 因此, 核糖体可以高效地合成ZEB2蛋白。目前, lncRNA研究正处于起步阶段, 它们在肿瘤中的功能和分子调控机制还不十分清楚。随着科学技术的进步和研究的深入, 人类终会揭开它的神秘面纱。

4 EMT的抗癌价值

外科手术、放疗、化疗和生物靶向治疗是肿瘤治疗的主要策略, 虽然这些治疗可使肿瘤在近期内缩小或移除, 但仍有一部分患者即使已消除肿瘤原发灶, 也会因肿瘤的复发和转移而死亡。肿瘤EMT的研究对于预防和治疗癌症具有重要意义。(1)肿瘤诊断。E-cadherin和vimentin等关键分子可作为肿瘤风险评估、检测和诊断的分子标志物。(2)肿瘤治疗。一是药物治疗。针对信号传导通路中某些特定的靶分子设计药物, 阻断肿瘤细胞的EMT进程。研究发现, T β R I抑制剂SD-208和LY2157299能高效阻遏TGF β 诱导的肿瘤转移^[72-73]。长期服用高效低毒的分子靶向药物, 有可能使恶性肿瘤转化为一种类似于高血压、糖尿病的慢性病。二是生物治疗。目前, 常用的生物治疗策略就是改变基因在肿瘤细胞的表达水平来影响肿瘤的发生与发展。当特定的基因低表达或不表达, 可采用基因治疗方法导入相应的外源基因; 当特定的基因高表达, 可采用多种方法下调或抑制相应基因的表达。但如何使外源性基因靶向导入肿瘤细胞发挥最大药物学效应, 同时不会对机体产生毒副作用, 是临床药物开发所要解决的重大问题。

5 结语

除了生物个体外, 外界环境与肿瘤EMT的形成也密切相关。近期发现, 幽门螺旋杆菌(*Helicobacter pylori*, *H.poly*)可诱导胃癌上皮细胞发生EMT^[74]。虽然最近的十几年来对EMT的认识取得了令人瞩目的进展, 但由于肿瘤的异质性、个体的差异性, EMT的调控机制、生理病理意义乃至生物医学科学中的应用等诸多方面尚有诸多问题有待于进一步阐明和修

正。随着对这些问题认识的不断深入, 将大大推动基于EMT机制的肿瘤治疗策略的快速发展, 使我们在更高的层面及时准确地预测肿瘤的转移和复发, 并采取有效的防治措施。

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