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·综述·

上皮间质转化与肿瘤转移的研究进展

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上皮细胞间质转化(epithelial-mesenchymal transition,EMT)是指具有极性的上皮细胞通过特定程序转化为具有活动能力的间质细胞的过程,其公认的标志有上皮细胞标志物 E 钙黏蛋白(E-cadherin)、角蛋白等表达下调,间质细胞标志物波形蛋白(vimentin)表达上调,进而细胞获得迁移和侵袭能力。EMT 在多种生理病理过程中发挥重要作用,其在肿瘤转移中的作用是近年的研究热点。

1 EMT 的概论

Greenburg 等[1]于 1982 年首次提出 EMT 的概念,EMT 最初被认为是胚胎发生的一个特征,EMT 与胚胎的组织和器官发育有密切联系,对原肠胚形成、神经嵴的形成、心脏瓣膜的形成、肌细胞形成等过程有重要影响[2]。2002 年,Theiry[3]提出恶性肿瘤细胞发生转移前,通过 EMT 获得侵袭和转移能力,自此 EMT 成为解释肿瘤转移的重要理论。EMT 是多步骤的动态过程,第一阶段为桥粒破裂、细胞分散、部分细胞间边界分离,第二阶段为抑制细胞角蛋白的表达、激活波形蛋白的表达、破坏基底膜、重排细胞骨架,第三阶段为迁移至间质成分中,最后原本的上皮细胞发生表型转换,变成间质细胞。EMT 过程中细胞表现为 3 种表型:上皮细胞表型(E state),上皮细胞向间质细胞过渡表型(P state)和间质细胞表型(M state)。部分上皮细胞来源的恶性肿瘤在其发生和发展过程中发生 EMT,进而促进肿瘤细胞的侵袭和转移[4]。以生物学环境为依据,EMT 被分为 3 种亚型,与胚胎植入、发育和器官形成相关的 EMT 为 1 型 EMT,与损伤修复、组织再生和器官纤维化相关的 EMT 为 2 型 EMT,与上皮源性恶性肿瘤相关的 EMT 为 3 型 EMT[5]。

2 EMT 的发生

2.1 生长因子

肝细胞生长因子(hepatocyte growth factor,HGF)、转化生长因子(transforming growth factor-β,TGF-β)、胰岛素样生长因子(insulin-like growth factor Ⅱ,IGF-Ⅱ)、表皮生长因子(epidermal rowth factor,EGF)、血管内皮生长因子(vascular endothelial growth factor,VEGF)等均参与 EMT。HGF 作为原癌基因 C-met 的配体,可以改变肿瘤细胞表面 E-cad 的分布并活化 PI3K 与 ERK1/2 信号通路,从而促进 EMT[6]。TGF-β1 诱导的 EMT 现象最早发现于鼠类细胞中,之后研究发现其广泛存在于人类细胞中[7]。TGF-β1 与其受体(TGFβRI 或 TGF-βII)结合,激活下游信号分子,导致下游蛋白 Smad2/Smad3 磷酸化,磷酸化的 Smad2/Smad3 与 Smad4 结合形成复合体转移到细胞核内,调节转录因子表达,从而抑制上皮细胞标志蛋白如 E-cad 等的转录活性,导致细胞 EMT 形成及侵袭转移[8]。TGF-β 的靶基因整联蛋白可通过加强 17 个基因的表达,进而引发 EMT[9]。免疫细胞(如 T 细胞、B 细胞及树突细胞)、缺氧等可协同 TGF-β 来诱导 EMT,其作用机制可能在于上述因素可增强肿瘤细胞对 TGF-β 修饰作用的敏感性[10]。IGF-Ⅱ可以诱导 β-连环素从上皮细胞表面转移到核内,并下调胞内 E-cad 的表达,从而促使 EMT 快速发生[11]。

2.2 酪氨酸蛋白激酶

酪氨酸蛋白激酶(tyrosine-protein kinase,TPK),包括 Ras、Rab、ARF、Ran、Rho、RGK 等,在肿瘤组织中高表达,能与蛋白质的酪氨酸残基特异性结合并

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将其磷酸化,调控肿瘤的发生发展。Ras 的效应物通过抑制 TGF-β 诱导的细胞程序性死亡,增强 TGF-β 的致浸润效应,从而促进肿瘤细胞发生 EMT[12]。在多种恶性肿瘤中均发现 RhoA、RhoB、RhoC、RhoE、RhoG、RhoH、Rac1、Rac2、Rac3 和 Cdc42 的过度表达。Ellenbroek 等[13]提出了 Rho 在癌细胞激活过程中的多种影响,包括抑制细胞凋亡、使细胞丧失极性、下调黏附蛋白表达等。Rho 可改变细胞骨架、细胞黏附能力、细胞能动性并诱导张力纤维形成,从而改变细胞表型[14]。RhoA 失活,会致使微管结构不稳甚至丧失,进而基膜水解,细胞发生 EMT[15]。

2.3 转录因子

E-cad 表达的下调或缺失是 EMT 的基本特征,许多转录因子都可抑制 E-cad 的表达。Snail1、Snail2(又称 Slug)、ZEB1、ZEB2、E47 和 KLF8 均能与 E-cad 的启动子结合,从而直接抑制其表达,而 Twist、Goosecoid、E2.2、SIX1、FOXC2 间接抑制其表达[16-17]。Slug 被激活后可使桥粒破裂、细胞分散,引发 EMT 的第一阶段[18]。转录因子 p63 对上皮结构的正常发育是必需的,Snail 和 Slug 可调控 p63 异构体的表达[19],从而减少细胞间黏附,增加肿瘤细胞的迁移性,促使肿瘤细胞发生 EMT 改变[20]。Snail 一方面以其锌指区域与 E-cad 启动子中 Epal 元件(-178 ~ +92bp)E 盒结构主链上的 CANNTG 序列结合,从而下调 E-cad 的表达[21];另一方面还可下调闭合蛋白和细胞角蛋白等上皮细胞标志物的表达,并上调纤连蛋白和黏连蛋白等间质细胞表面标志物的表达[22]。转录因子 FOXA1 和 FOXA2 可调控 E-cad 的表达和维持上皮表型,在胰腺癌细胞中沉默 FOXA1 和 FOXA2 的表达可促使细胞发生 EMT[23]。Twist 是肿瘤细胞发生 EMT,进而侵袭转移的重要因素之一[24]。Twist 以 Twist/Mi2/NuRD 蛋白质复合物与上皮钙黏蛋白的启动子结合,从而下调上皮细胞钙黏蛋白的表达,上调纤维连接蛋白及神经钙黏蛋白的表达,进而破坏细胞间连接,诱导细胞发生 EMT[25-27]。

2.4 miRNA

miR-200 家族和 miR-205 对 EMT 有重要影响[28],SNAIL1/miR-34 复合物是细胞从 E 状态转变至 P 状态的双稳态开关,而 ZEB1/miR-200 复合物是细胞从 P 状态转变至 M 状态的双稳态开关[29]。而 p53 作为肿瘤的抑制因子,能激活 miR-200 和 miR-34 的表达,进而抑制蛋白 ZEB 和 SNAIL,阻止 EMT 的发生,维持上皮表型[30]。miR-155 作为 TGF-β 和 SMAD4 的下游效应分子,参与降解细胞间的紧密连接,因而促进细胞的侵袭和转移[31]。miR-27 可激活 Wnt 信号通路,上调 ZEB1、ZEB2、Slug 和波形蛋白的表达,下调 E-cad 的表达,从而促进 EMT,是 Twist1 诱导 EMT 过程中必需的因子[32]。miR-106b ~ 25 通过与 Smad7 蛋白抑制剂结合,促使 EMT 的发生[33]。下调 miR-7 表达后肿瘤细胞的侵袭转移能力明显增强,而 miR-7 表达增加可抑制 Snail,从而上调 E-cad 的表达,并部分逆转 EMT[34]。目前对 miR-200 家族、miR-34 家族的研究最透彻,miR-200 家族对 EMT 的作用在乳腺癌、结肠癌、前列腺癌、胰腺癌、胃癌中有确凿证据。miRNA 的研究还存在很大空白。

3 EMT 与肿瘤转移

转移是肿瘤患者死亡的主要原因,90% 恶性实体肿瘤的死因为远处转移[35]。恶性肿瘤的侵袭转移是一个复杂的、多步骤、多因素、序贯的过程,包括从肿瘤原发部位脱离,进入周围基质,进入循环或淋巴系统,粘附在血管或淋巴管内皮细胞壁并向脉管外迁移,浸润到转移部位,血管增生,形成新的转移灶。其中肿瘤从原发部位游离是肿瘤转移最初始步骤,也是肿瘤转移发生的先决条件[36]。EMT 是使肿瘤细胞获得浸润能力的重要机制,发生 EMT 改变后肿瘤细胞间粘附能力下降,浸润能力增强,突破基底膜,进入血液循环,然后循环肿瘤细胞在种植部位形成转移瘤[37]。E-cad 表达降低或缺失是 EMT 最显著的特征,同时也是多种肿瘤不良预后及转移的临床预后指标[38-39]。当 TGF-β 信号作用于表达 Ras 的乳腺上皮细胞时,细胞倾向于发生 EMT,并且细胞凋亡受到抑制[40]。但这一反应能被上皮分化的诱导因子逆转,比如 GATA-3[41]。EMT 抑制因子 miR-200 抑制 PD-L1,但 EMT 活化因子 ZEB1 抑制 miR-200 的转录,从而解除 miR-200 对肿瘤细胞 PD-L1 的抑制,导致 CD8(+)T 细胞免疫抑制及转移[42]。p53 活化因子 ASPP2 通过形成 ASPP2-β-连环蛋白-E-cad 三元复合物,抑制 β-连环蛋白反式激活 ZEB1,从而抑制 EMT 和肿瘤细胞转移[43]。肿瘤细胞重编程代谢过程以利于增殖,转录因子 Snail1 介导 TGFβ1 引发 EMT,其抑制脂肪酸合酶,进而抑制脂肪生成,在体外实验中增加肿瘤细胞转移能力[44]。

Wnt 信号通路在肿瘤发生发展过程中起重要作用,并参与 EMT 的发生[45]。在乳腺癌细胞中激活

Wnt 信号通路后,Snail 的表达明显减少,而间质细胞标志物波形蛋白的表达增加。乳腺癌骨转移可激活 TGF-β 信号,进而促进病灶的形成[46]。经由经典和非经典途径,Wnt 信号可分别激活基质金属蛋白酶(matrix metalloproteinases, MMPs)中的 MMP-2、MMP-3、MMP-7、MMP-9 等亚型,而 MMP 能降解细胞外基质,促进肿瘤侵袭和转移[47-50]。EMT 复杂的信号通路级联中研究透彻的是 Wnt 信号通路、Hedgehog 信号通路和 TGF-β 介导的信号通路,另外已经明确 Notch 信号通路在乳腺癌和胰腺癌中的作用。

近年来提出肿瘤干细胞(cancer stem cells, CSC)学说,CSC 的远处迁移是肿瘤转移的关键问题[51]。Snail 和 Twist 协同激活 EMT 的重要调控因子 ZEB1,通过抑制 miRNA,从而调控 CSC[52]。另外,ZEB1 能够把非干性细胞转变为干细胞,并能维持乳腺癌细胞和胰腺癌细胞的干性[53]。EMT 与 CSC 之间的分子机制仍不清楚,研究已知其与 AR 信号通路、生长因子受体酪氨酸激酶介导的通路、Pten 相关通路、STAT3 相关通路、Wnt、Notch 和 Hedgehog 信号通路有关[54-59]。发生 EMT 的细胞能获得某些类似干细胞的特性,这进一步说明 EMT 与恶性肿瘤侵袭转移关系密切[60]。CSC 与 EMT 之间关联的研究从 90 年代中期开始,目前在乳腺癌、非小细胞性肺癌、膀胱癌、头颈癌、胰腺癌、结肠直肠癌中有确切证据。

90% 的头颈鳞癌中上皮生长因子受体(epidermal growth factor receptor, EGFR)过度表达[61],且倾向于不良预后[62],活化的 EGFR 通过诱导 EMT[63]使肿瘤细胞侵袭转移能力增加[64]。在初期表现出明显 EMT 特征的头颈鳞癌病灶的转移距离(E-cad 表达下调和波形蛋白表达上调)是初期不具备 EMT 特征的头颈鳞癌病灶转移距离的三倍[65],E-cad 表达的缺失也与口咽肿瘤的复发率和口咽肿瘤、下咽骨肿瘤的存活率密切相关[66]。非瑟酮(3,3′,4′,7-四羟基黄酮)抑制 EMT 相关的分子改变,上调上皮细胞标志物 E-cad,下调间质细胞标志物波形蛋白,并使 EMT 调控因子 Twist 显著减少,因此非瑟酮抑制 LMP1 阳性的鼻咽癌细胞的侵袭转移[67]。EBV-miR-BART7-3p 与鼻咽癌的淋巴道转移密切相关,其抑制人类肿瘤抑制因子 PTEN,进而使 Snail 和 β-连环蛋白表达上调,引发 EMT[68]。FOXC1 下调 E-cad 表达,促进鼻咽癌细胞发生 EMT[69]。而 FOXQ1 通过上调 TGF-β1 表达而引发 EMT[70]。异黏蛋白(MTDH)通过 AKT 信号通路促进 EMT,从而促进头颈鳞癌的转移[71]。EGCG(epigallocatechin-3-gallate)显著抑制头颈鳞癌中由 TGF-β1 介导的 EMT[72],而 TGF-β1 通过 TGF-β/Smad 信号通路引发头颈鳞癌发生 EMT[73]。

4 结语

EMT 在肿瘤侵袭和转移中有重要作用,EMT 的分子发生机制十分复杂,仍有待充分阐明,其也是近年来的研究热点,许多方面的研究面临着挑战。EMT 的短暂特性、分子和表型异质性、复杂的信号通路级联等等,国际上对 EMT 的含义和分级缺乏统一的定义;对 EMT 进行抗癌治疗方面:目前大多数 EMT 研究基于体外实验,其成果未必能应用于体内,针对 EMT 的抗癌治疗在体内的疗效尚无确凿证据。深入研究 EMT 的发生机制将有助于我们深刻理解肿瘤的发生和发展机制,为阻止肿瘤进展、治疗肿瘤侵袭和转移提供新的思路和方向。

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