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基质细胞调节的EMT在肿瘤浸润转移中作用的研究进展

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摘　要：恶性肿瘤的浸润转移是肿瘤恶变的主要表现形式之一，而上皮间质转化(epithelial-mesenchymal transition, EMT)是造成肿瘤浸润转移的重要机制。肿瘤细胞通过EMT获得迁移性，进而从原发灶脱离进入血液，随血液循环流动，然后从血管溢出并定植，形成转移灶。EMT的发生与分布在肿瘤周围的基质细胞有密切的关系，受到基质细胞分泌的多种细胞因子的调节。该文就近年来基质细胞调节的EMT在肿瘤浸润转移中作用的研究加以综述，讨论各种基质细胞对EMT诱导的影响，重点讨论肿瘤微环境中对EMT影响较大的几类基质细胞与EMT之间的关系。

关键词：肿瘤微环境；上皮间质转化；基质细胞；细胞因子
中图分类号：R734.2　　**文献标志码**：A

Research progress on the role of stromal cell-regulated EMT in tumor invasion and metastasis

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Abstract: Invasion and metastasis of malignant tumor is one of the main manifestations of malignant transformation, and epithelial-mesenchymal transition (EMT) is an important mechanism that causes tumor infiltration and metastasis. After acquiring migration through EMT, tumor cells can detach from the primary foci into the blood and flow with the blood circulation. By overflowing from the blood vessels, the tumor cells finally colonize the distant organs and form new metastases. The occurrence of EMT is closely related to the stromal cells distributed around the tumor and is regulated by various cytokines secreted by the stromal cells. In this article, recent studies on the role of stromal cell-regulated EMT in tumor invasion and metastasis are reviewed and the effects of various stromal cells on EMT induction were discussed. Our discussions mainly focused on the relationship between EMT and the types of stromal cells that have a greater impact on EMT process in the tumor microenvironment.

Key words: tumor microenvironment; epithelial-mesenchymal transition; stromal cells; cytokines

上皮间质转化(epithelial-mesenchymal transition, EMT)这一概念首先是由Greenberg和Hay[1]提出的，是指上皮细胞在某些细胞因子的作用下失去上皮特征而获得间质特征的过程[2]。EMT在正常组织中是胚胎发育、组织纤维化以及伤口愈合等生理过程的关键驱动因素[3-4]。体内EMT实验证明，EMT的激活对于在正常组织中神经嵴细胞从神经管迁移等过程至关重要[5]。EMT也是肿瘤发生与转移的重要机制[3-4]。研究表明，早期的肿瘤细胞明显处于上皮样状态，随着肿瘤的进展，逐渐获得更多的间质特性[6]。间质特性的获得使肿瘤细胞更具运动性和侵袭性，而这一过程正是肿瘤细胞通过EMT实现的。大量证据表明，EMT是所有类型癌症恶性演进的重要环节[7-9]。近年来，EMT在肿瘤演化等领域的相关

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研究取得了重要的进展。

1 EMT与肿瘤细胞

细胞在发生EMT时，会导致上皮特性丧失和间质特性获得。一方面，上皮特性的丧失表现为细胞失去细胞间黏附性和细胞极性，进而造成细胞间连接的缺失。该过程伴随着上皮标志物E-钙黏蛋白(E-cadherin)的减少[10]。正常情况下，上皮表型的细胞表现为顶端-基底端极性，并通过紧密连接、黏附连接和桥粒的结构连接在一起。其中黏附连接由细胞表面E-钙黏蛋白分子实现[11]。这种连接方式对上皮组织结构的完整性是至关重要的。在EMT激活后，由于E-钙黏蛋白的表达被抑制，上皮细胞典型的多角形、鹅卵石样形态丧失[12]，导致细胞更容易从上皮组织中脱离。另一方面，间质特性的获得表现为细胞获得纺锤形的间质形态[12]，并伴随着间质标志物N-钙黏蛋白(N-cadherin)、波形蛋白(vimentin)的增加[10](图1)。间质标志物的存在和细胞形态的改变使得间质细胞具有运动和迁移能力。又由于间质细胞是非极性的，且细胞间的连接缺乏，所以单个间质细胞可以在细胞外基质迁移。E-钙黏蛋白表达的下调和N-钙黏蛋白的上调降低了细胞的黏附能力，同时增强了细胞的移动性，使细胞可以迁移和侵袭，这是EMT的典型特征[11]。不难看出，EMT使细胞表型实现转化从本质上来看是通过改变上皮和间质表型相关标志物的表达来实现的。

在肿瘤细胞EMT过程中，调节标志物表达的一个主要机制是EMT诱导转录因子(EMT-TFs)的激活。这些转录因子主要包括锌指转录因子Snail和slug、锌指E盒结合同源框ZEB1和ZEB2以及碱性螺旋-环-螺旋转录因子Twist1和Twist2[13-14]。细胞从上皮向间质状态的转化是由这些关键转录因子介导的，这些转录因子是细胞黏附、细胞极性和活性的主要调节因子。它们抑制与上皮表型相关的基因的表达并诱导间质基因的表达，最终导致细胞EMT样特征[6]。E-钙黏蛋白的下调和N-钙黏蛋白、波形蛋白的上调就是EMT-TFs协同诱导的结果。

上皮间质转化是一种可逆的细胞生物学过程。一方面，上皮细胞可快速转变为准间质细胞状态[4]；另一方面，获得间质特性的细胞也可以恢复到上皮状态。EMT的逆过程称为间质上皮转化(mesenchymal-epithelial transformation, MET)。这些转化与肿瘤的分化密切相关[15]。发生EMT时，原发性癌细胞会丧失细胞黏附性，通过抑制E-钙黏蛋白的表达获得间质特性，从而转化为迁移性和浸润性癌细胞。这些癌细胞会穿过基膜，通过血管渗入血液，到达转移部位附近后再从血液中溢出，在目标器官表面形成微转移[16]。一旦到达转移部位，肿瘤细胞则要经历MET，恢复到原来的上皮表型，形成恶性继发性肿瘤[17]。这是肿瘤细胞通过EMT迁移的完整过程(图2)。

上皮间质转化(EMT)离不开特定的微环境，微环境对EMT有着重要的影响。事实上，在肿瘤微环境(tumor microenviroment, TME)中，大量存在的基质细胞在各种肿瘤的发生和发展中起着关键的作用[18-19]，尤其是在EMT过程中。常见的基质细胞包括肿瘤相关成纤维细胞(tumor-associated fibroblast,

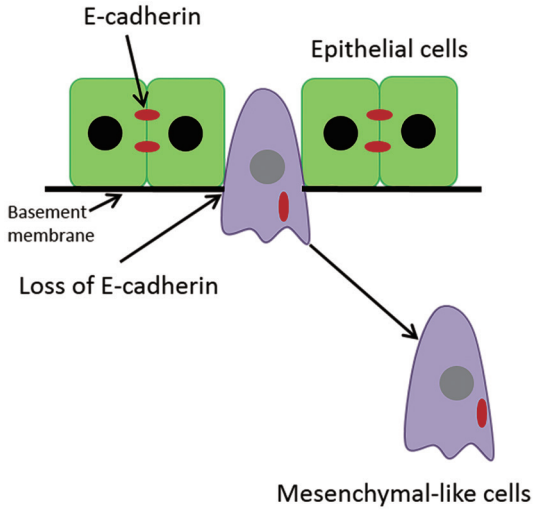

图1 细胞发生EMT从上皮组织中脱离的过程

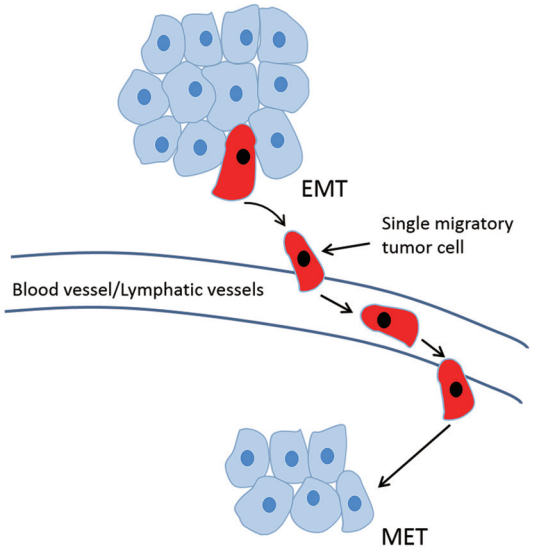

图2 肿瘤细胞通过EMT发生迁移的过程

TAFs)、肿瘤相关的巨噬细胞(tumor-associated macrophages, TAMs)、骨髓来源的抑制细胞(myeloid-derived suppressor cells, MDSCs)和T淋巴细胞等。各种基质细胞能够分泌多种细胞因子和趋化因子，这些因子以旁分泌的方式作用于附近的癌细胞。旁分泌信号联合作用促进Snail等转录因子的激活[10]，可诱导EMT的发生[11]。研究基质细胞如何诱导对肿瘤细胞迁移和浸润过程至关重要的EMT是非常重要的，可以为临床上寻找有效遏制肿瘤转移的治疗手段提供借鉴。

2　肿瘤相关成纤维细胞对肿瘤EMT的促进

肿瘤相关成纤维细胞TAFs作为一种重要的基质细胞，是TME的重要组成部分，在细胞外基质的重塑、肿瘤的恶性转化和转移等方面起着重要作用[11,20]。TAFs来源于多种不同类型的细胞，这些细胞包括间质成纤维细胞、上皮间质转化细胞、血管内皮细胞、骨髓分化间质细胞、脂肪细胞和星状细胞[21]。其中，骨髓分化间质细胞和间质成纤维细胞是TAFs的主要来源。在肿瘤发展期间，这些不同来源的TAFs会不断被招募到肿瘤周围，并发挥调控作用。

TAFs调控肿瘤演进有多种途径。首先，TAFs能够分泌肿瘤生长因子，促进肿瘤细胞生长。其次，TAFs可以将内皮祖细胞诱导到肿瘤组织中，促进肿瘤内血管的形成[22]。另外，人们发现TAFs对于肿瘤原位生长及癌细胞转移扩散等方面也有重要作用。

大量研究结果表明，在TAFs调控肿瘤演进的众多机制中，EMT调节机制是最主要的[23]。TAFs实现癌细胞中EMT诱导的一个重要途径就是通过其所分泌的一系列细胞因子和生长因子的协同作用[24-26]。这些因子主要包括TGF-β、IL-6、VEGF和HGF等，它们均由TAFs以旁分泌的方式产生。TAFs通过旁分泌方式诱导癌细胞发生EMT的这一机制正在被人们所认识[11]。

2.1　转化生长因子

TAFs所释放的细胞因子之中研究最广泛的是各种肿瘤发展进程中至关重要的转化生长因子-β (transforming growth factor-β, TGF-β)[27]。间质成纤维细胞能够分泌TGF-β和间质细胞源性因子1 (stromal cell-derived factor-1, SDF1)，这两种因子通过特定的信号通路共同作用，在癌症演进过程中维持着间质成纤维细胞向肌成纤维细胞的分化[28]。而肌成纤维细胞比正常基质成纤维细胞分泌更高水平的TGF-β。

由TAFs所分泌的TGF-β对EMT的影响是通过一些特定的信号通路调控细胞核中的基因转录来实现。在众多信号通路中，TGF-β-Smads信号通路在调控癌细胞表达EMT相关基因过程中起着重要的作用。TGF-β有I型(TβRI)和II型(TβRII)两个重要受体。TGF-β (配体)在起作用时，先结合细胞表面具有丝氨酸苏氨酸激酶活性的受体(I型和II型)，配体先磷酸化激活II型受体，再通过II型受体激酶诱导I型受体的磷酸化。活化的I型受体使Smad2/3 (R-Smads)磷酸化，这些受体活化的Smads (R-Smads)与通用型Smad4 (Co-Smad)形成蛋白复合物。活化的Smad复合物移位到细胞核中，通过与其他转录因子的合作来共同调节靶基因的转录[29](图3)。此外，TGF-β还能够通过非经典信号通路调控MAPK和PI3K/Akt等其他与癌症相关的信号通路实现其功能[30]。Zhuang等[31]发现，TGF-β在TAFs条件培养基中大量存在，通过活化Smad2激活经典的TGF-β信号转导，可以在膀胱癌细胞中诱导EMT。在该模型中，TGF-β诱导EMT造成Snail1、ZEB1和ZEB2等相关基因的过度表达，使上皮标志物E-钙黏蛋白表达下调，间质标志物波形蛋白、N-钙黏蛋白的表达上调，并最终实现EMT转化。

2.2　白细胞介素-6

TAFs分泌的诱导肿瘤细胞EMT的另一种重要的细胞因子是白细胞介素-6 (IL-6)。TAFs通过分泌IL-6诱导EMT，增强癌细胞的迁移[25,32]。IL-6作为一种重要的炎症因子，与细胞膜上的IL-6R受体结合，可以激活JAK2/STAT3和PI3K/AKT等多种信号通路。JAK2/STAT3通路是从细胞膜到细胞核的信号转导通路。JAK2蛋白激酶的激活可以催化STAT3蛋白磷酸化并进入细胞核，从而调节EMT相关基因和其他基因的表达[33]。Xiao等[34]发现，IL-6在体外可使人腹膜间皮细胞(human peritoneal mesothelial cells, HPMCs)表型由典型的鹅卵石样转变为成纤维细胞样，这正是细胞EMT的典型特征。Wu等[32]发现，TAFs分泌的IL-6通过JAK2/STAT3信号通路促进了胃癌的EMT和转移。Shintani等[35]的研究表明，TAFs衍生的IL-6可通过诱导EMT在非小细胞肺癌(NSCLC)中引起顺铂耐药性。2018年的一项研究表明，TAFs通过JAK2/STAT3途径高水平表达IL-6，促进了TGF-β介导的卵巢癌EMT，进而抑制细胞凋亡并导致紫杉醇耐药性提高[36]。从这些研究

中不难看出，TAFs分泌IL-6诱导肿瘤演进过程中EMT的机制不仅可以促进肿瘤的发生和转移，也可以促进肿瘤的耐药性。可以预期，近期将会有更多的TAFs所分泌的IL-6增强癌细胞的迁移和EMT方面的具体工作。

2.3 其他生长因子及趋化因子

还有一些其他由TAFs分泌的生长因子及趋化因子能够诱导EMT。(1) TAFs 分泌的血管内皮生长因子(VEGF)通过诱导 Snail 和 Twist 等EMT相关基因在胰腺癌和乳腺癌中的表达，诱导EMT的发生[37-38]；(2) TAFs 可分泌 CCL2、 CCL7及 CXCL16 等细胞因子，激活肝癌细胞的TGF-β途径和 Hedgehog途径，从而促进肝癌细胞 EMT 过程，增强其转移能力；(3) TAFs产生的MMP2、MMP3、MMP9等基质金属蛋白酶通过Rac1b/ROS途径来降解 E-cadherin，降低肝癌细胞的黏附性，并促进β-catenin进入细胞核，调控Snail和slug的表达，诱导EMT的发生，进而增强肝癌细胞的运动性[39]；(4) TAFs衍生的肝细胞生长因子(hepatocyte growth factor, HGF)通过激活HGF/c-MET (HGF受体)途径也能够促进癌细胞的转移[40]。TAFs所释放的HGF在未经MET扩增的胃癌细胞中可以促进癌细胞的增殖、迁移和侵袭。HGF配体通过结合c-MET受体，激活大量的细胞内信号通路，诱导肿瘤细胞EMT[41]。

3 肿瘤相关巨噬细胞与EMT

3.1 TAMs对肿瘤EMT的诱导作用

上皮间质转化过程实现的另外一个重要途径是肿瘤相关巨噬细胞的诱导作用。巨噬细胞作为一种免疫细胞具有很高的可塑性，是免疫代谢、慢性炎症和组织稳态的关键[42]。迁移到肿瘤基质中的巨噬细胞称为肿瘤相关巨噬细胞TAMs[43]。TAMs通常是肿瘤微环境中最丰富的浸润免疫细胞，在许多恶性肿瘤中都参与了癌症的演进、耐药性的产生和免疫逃逸，并且与不良预后有关[44-45]。TAMs通过促进基质重塑、抑制适应性免疫、促进血管生成和EMT来促进癌症演进[44,46]。其中EMT的诱导是TAMs分泌不同种类的细胞因子和趋化因子协同作用的结果，这种机制已被广泛研究[11]。

TAMs在不同癌症中有不同的表型，通常表现为抗炎和促肿瘤表型的极化[47-48]，即 M1型和M2型两种亚型。M1型巨噬细胞对肿瘤的演进过程有阻碍作用；而M2型巨噬细胞分泌一系列细胞因子，能够通过多种信号途径促进EMT和免疫抑制[49]。这些细胞因子包括TGF-β[50]、IL-8、COX-2/STAT3[51]、EGFR/ERK1/2[52]、Smad/Snail[53]、AKT/mTOR[54]、CCL-18[55]和HIF-1α[56]。这些细胞因子在诱导EMT的过程中可以抑制适应性免疫。与由上皮细胞系中产生的肿瘤相比，M2型巨噬细胞和调节性T细胞(regulatory T cells, Treg)更广泛地存在于间质细胞系衍生的肿瘤基质中[57]。HIF-1α促进低氧条件下的间质癌细胞分泌CCL-20，CCL-20随后上调TAMs中吲哚胺2、3-二加氧酶(IDO)的表达，从而抑制肝细胞癌中$CD4^+$T和$CD8^+$T细胞的功能[58]。Zhang等[59]发现，mTORC1/mTORC2抑制剂可抑制EMT并下调TAMs募集和PD-L1表达，从而提高对肺癌的免疫力；Li等[60]首次发现了胃癌衍生的间质基质细胞(gastric cancer-derived mesenchymal stromal cells, GC-MSC)通过JAK2/STAT3信号通路分泌IL-6和IL-8，诱导巨噬细胞极化为M2亚型。随后，在这些由GC-MSC引发的M2型巨噬细胞的作用下，波形蛋白、纤连蛋白和slug这三个主要的间质标志物基因的表达水平显著上调。相比之下，关键的上皮相关标志物E-钙黏蛋白基因的表达水平大大降低了。因此，GC-MSC诱导的巨噬细胞可以促进胃癌细胞EMT的进程，从而促进肿瘤转移。不难看出，M2型巨噬细胞是TAMs对肿瘤演进中的EMT的诱导及免疫抑制的主导因素。抑制M1型向M2型巨噬细胞的转化及诱导其逆转化过程可能会减弱恶性肿瘤演进过程中的EMT。

3.2 TAMs诱导EMT的其他细胞因子途径

TAMs分泌细胞因子促进肿瘤EMT还有其他多种途径。(1)与TAFs分泌TGF-β的过程类似， TAMs以旁分泌的方式在乳腺、肝细胞和F9畸胎性癌细胞中分泌TGF-β，进而诱导EMT[61-62]；(2) TAM还能够分泌肿瘤坏死因子(tumor necrosis factor, TNF)，TNF与TGF-β协同作用可以促进结肠癌中的EMT[63]；(3)间质癌细胞通过分泌粒细胞-巨噬细胞集落刺激因子(granulocyte-macrophage colony stimulating factor, GM-CSF)招募TAMs，被招募至肿瘤细胞周围的TAMs会分泌CCL18，诱导EMT，进而促进乳腺癌转移[55]；(4) TAMs分泌的IL-6作用于COX-2/PGE_2信号通路，通过激活β-catenin从细胞质向细胞核的转移，也可以导致EMT[64]。

4 骨髓来源的抑制细胞

上皮间质转化过程的实现还可以通过骨髓来源抑制细胞MDSCs来诱导。MDSCs是一种不成熟的

骨髓细胞群，研究发现这些细胞能够诱导EMT，具有免疫抑制能力[65]。MDSCs可以被所分泌的髓系特异性化学引诱剂招募到原发肿瘤中[66]。一旦被招募，MDSCs就会聚集在原发性肿瘤的周围诱导EMT，促进癌症干细胞样细胞的生成，并通过分泌TGF-β和激活COX2、EGF和HGF促进癌细胞的扩散[66-67]。

MDSCs作为髓样细胞的异质表型能够通过EMT促进TME中的免疫抑制[68]。MDSCs能够抑制T细胞、自然杀伤细胞(natural killer cells, NK)和树突状细胞(dendritic cells, DCs)的各种功能[47,68]。MDSCs执行渗透和抑制功能有赖于诱导酶CXCL2和COX-2的作用[69]。在此过程中，Snail通过NF-κB信号上调CXCL2的表达，诱导MDSCs募集进入肿瘤微环境，从而抑制$CD8^+$T细胞并促进卵巢肿瘤生长[69]。 TME中渗透的MDSCs也可诱导EMT促进肿瘤生长和转移[67]。例如，β-catenin/TCF4和COX-2的上调可以促进MDSCs介导的鼻咽癌EMT。此外，COX-2还可以介导癌细胞与MDSCs之间的相互作用以促进转移[70]。

可以看出，由MDSCs诱导的EMT不仅参与了肿瘤细胞的迁移过程，还减弱了免疫细胞对肿瘤的杀伤效果，协助了肿瘤的免疫逃逸。这与TAFs诱导的EMT在肿瘤演进过程中的作用相似。

5　T淋巴细胞

免疫细胞也在诱导EMT和促进肿瘤转移方面发挥作用。积聚在肿瘤基质中的各种免疫细胞通过与邻近的癌细胞相互影响，以激活先前潜伏的处于休眠状态的EMT进程。

作为在癌症的免疫监视和免疫编辑中具有代表性的免疫细胞，$CD8^+$T细胞可以诱导EMT并促进肿瘤转移。研究表明，在体外与活化的效应T细胞共培养后，胰腺导管上皮细胞中的E-钙黏蛋白表达缺失，上皮细胞获得纺锤形的间质形态，同时有波形蛋白和ZEB1的表达[71]。研究还发现，$CD8^+$T细胞通过在体内诱导EMT，导致具有干细胞样特性的间质乳腺癌细胞的产生[72-73]。

除了$CD8^+$T细胞以外，$CD4^+$T细胞也能诱导EMT过程。人们发现被$CD4^+$T细胞紧密包围的胰腺腺管内上皮瘤(pancreatic intraepithelial neoplasia, PanIN)中E-钙黏蛋白的分泌减少，而波形蛋白表达增加，这与未被T细胞包围的PanINs不同。对透明细胞肾癌研究也发现，作为IL-6主要来源的$CD4^+$T细胞诱导了EMT过程[74]。

尽管T细胞介导的EMT产生的机制尚需进一步明确，但活化的效应T细胞释放的细胞因子(例如IL-6、TNF和TGF-β)的确促进了EMT的发生。

6　总结与展望

综上所述，在肿瘤微环境中，基质细胞以旁分泌的方式诱导EMT，进而促进肿瘤的演进。由基质细胞分泌的各种细胞因子可以激活EMT相关的信号通路，调节EMT-TFs的产生。细胞因子与信号通路协同作用组成一个复杂的EMT信号网络。结合本文以上阐述内容，该网络中部分重要调控机制由图3和图4呈现。图3为重要的细胞因子与信号通路协同作用调节EMT-TFs的机制示意图；图4为本文中涉及的基质细胞分泌多种细胞因子调节EMT的示意图。利用基质细胞与EMT 的关系来干预肿瘤的发生发展才刚刚起步，进一步开展对基质细胞的深入研究有助于阐明肿瘤发生和演进的机制，为肿瘤的早期诊断提供新的特异性标记，并为肿瘤的治疗提供新的靶点。目前对于基质细胞与肿瘤细胞EMT之间关系的研究还存在许多问题：(1)TAFs等部分基质细胞的来源和活化机制尚不清楚；(2)基质细胞诱导EMT的具体信号分子和信号通路协同作用的生物学网络仍需进一步完善；(3)基质细胞与EMT相关的诊治特异标记尚未明确；(4)各种由基质细胞诱导的EMT-TFs调控EMT程序的分子作用机制尚不明确。

EMT是上皮细胞与间质细胞相互转化的高度动态过程，间质细胞样特性赋予了肿瘤细胞较强的运动和侵袭能力、对治疗的抵抗力以及免疫逃避能力。尽管减弱基质细胞对EMT的诱导强度是否能抑制癌细胞的侵袭转移以及能否削弱肿瘤的耐药性尚不完全清楚，但是基质细胞分泌的细胞因子诱导的EMT的确增强了上皮癌细胞侵袭和转移、对免疫的抵抗以及获得间质细胞样特性的能力。

虽然作用机制还有待进一步明确，但是肿瘤微环境中的基质细胞在诱导EMT中的作用已经被很好地证实。我们有理由期待在不远的将来，通过探讨基质细胞免疫抑制作用的机制，以肿瘤周围的基质细胞为靶点抑制肿瘤转移的药物开发将会有重要的进展。

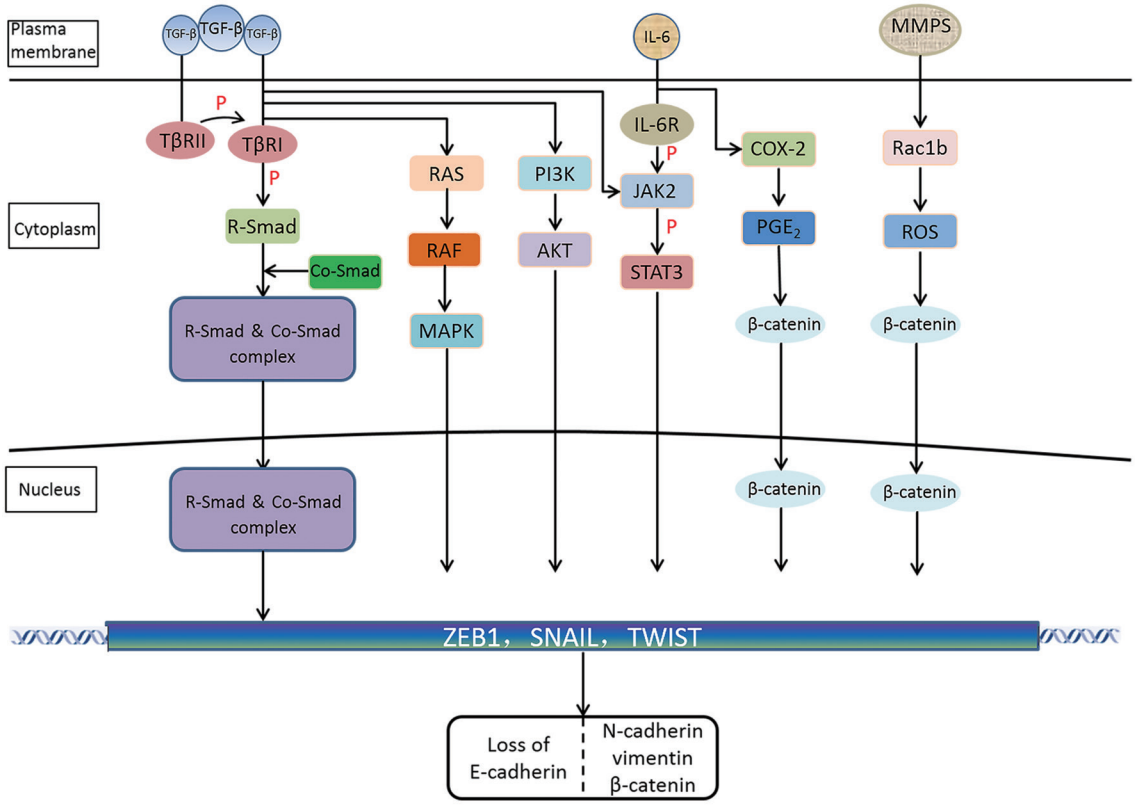

图3 部分重要细胞因子与信号通路协同调节EMT的机制

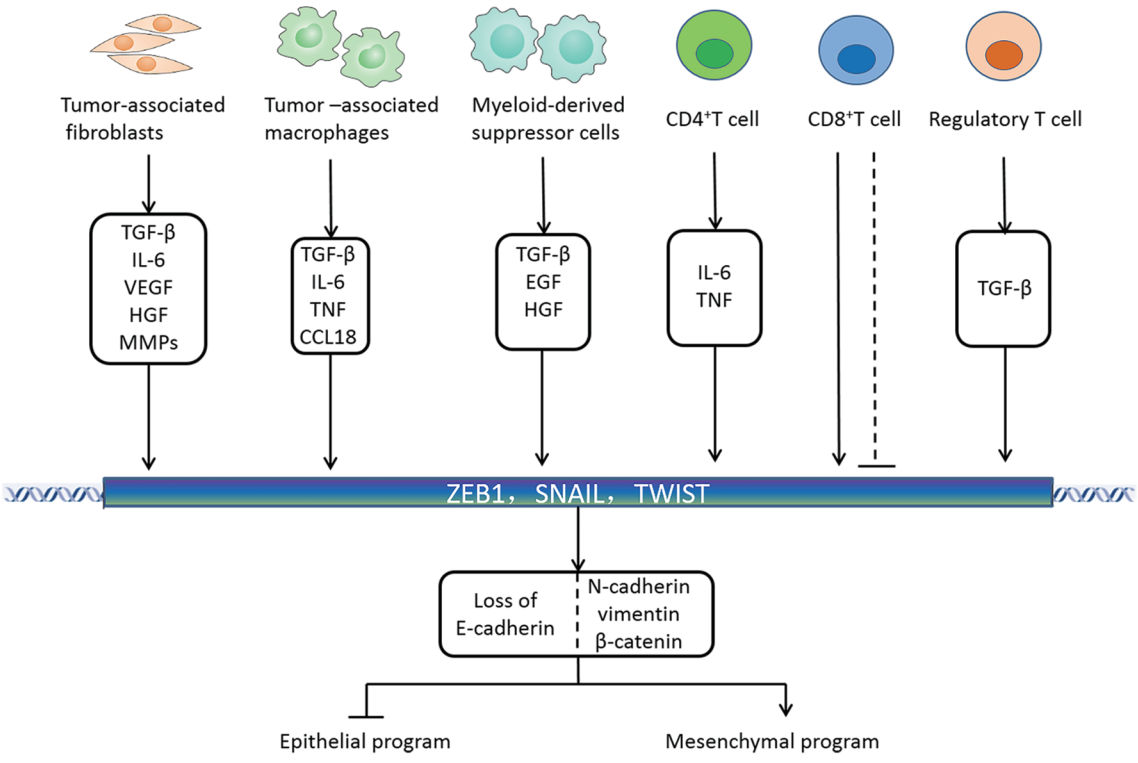

图4 基质细胞分泌多种细胞因子调节EMT的机制

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