上皮细胞间质化在胃癌发生发展中的作用

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摘要：胃癌是世界范围内最常见的肿瘤之一。因为其复杂的发生发展机制，早期发现与有效治疗尤为困难。上皮细胞间质化 (epithelial–mesenchymal transition，EMT) 是胚胎发育、伤口愈合、纤维疾病发展中的重要过程。最近有研究表明，胃癌的发生与 EMT 的异常激活有密切关系。EMT 的激活使得胃癌上皮细胞具有间质细胞的特征，上皮极性减少，而且间质细胞获得干细胞侵袭、转移、抗凋亡、耐药等特征。至今发现多种分子与 EMT 有关，如 E– 钙黏蛋白等。也有研究发现 EMT 可能与表观遗传机制有关。现已发现的与 EMT 有关分子可以作为胃癌早期诊断的标志，而 EMT 的发现也会为胃癌靶向治疗提供新的思路。本文就其研究进展做一综述。

关键词：上皮细胞间质化；胃癌；E– 钙黏蛋白
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Role of epithelial-mesenchymal transition in gastric cancer initiation and progression

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Abstract: Gastric cancer is one of the most common malignant tumors worldwide. Due to its intricate initiation and progression mechanisms, early detection and effective treatment of gastric cancer become difficult. The epithelial-mesenchymal transition (EMT) is characterized as a fundamental process that is critical for embryonic development, wound healing and fibrotic disease. Recent evidence shows that aberrant EMT activation in the human stomach is closely associated with gastric carcinogenesis and tumor progression. EMT activation endows gastric epithelial cells with increased characteristics of mesenchymal cells and reduces their epithelial features. Moreover, mesenchymal cells tend to acquire stem cell or tumorigenic phenotypes such as invasion, metastasis and apoptosis resistance as well as drug resistance during EMT progression. There are a number of molecules that indicate the stage of EMT (e.g. E-cadherin cell biomarker). In addition, EMT regulation may be associated with certain epigenetic mechanisms. The molecules can be used as early diagnostic markers for gastric cancer, and EMT regulation can provide potential targets for gastric cancer therapy. Here, we review the role of these aspects of EMT in gastric cancer initiation and development.
Keywords: epithelial-mesenchymal transition; gastric cancer; E-cadherin

胃癌是全球第4大常见肿瘤，占肿瘤病死率的第2位[1]。在中国，胃癌的发病率仅次于肺癌居恶性肿瘤的第2位[2]。虽然近年来内镜技术的发展使得胃癌的发病率呈现下降趋势，但早期诊断与有效诊治还是现阶段治疗中面临的挑战。胃癌的5年生存率仅为20%，复发转移及化疗耐药是预后差的主要原因。因此，研究胃癌的发生发展对于胃癌的治疗至关重要。研究发现，上皮细胞间质化(epithelial–mesenchymal transition，EMT)在胃癌的发生发展中起着举足轻重的作用，深入研究胃癌细胞的EMT进程并积极探索有效的治疗措施成为当前胃癌诊治中亟待解决的问题。本文从EMT的基本特征、EMT在胃癌发生发展中的作用对EMT的功能给予总结和综述。

1 上皮细胞间质化的基本特征

上皮细胞间质化被认为是肿瘤细胞转移的起始及关键环节而成为近年研究的热点[3–4]。上皮细胞与间质细胞彼此间的转换可以描述为上皮细胞间质化和间质细胞上皮化(mesenchymal–epithelial transition，MET)。EMT在形态上主要表现为上皮细胞失去分化特征，获得了间质细胞特征：上皮标记物E–钙黏蛋白的缺失，间质标记物N–钙黏蛋白和波形蛋白等表型的获得。同时还表现为细胞极性丧失、细胞间连接疏松并伴随细胞迁移和运动能力增强，导致肿瘤易于离开原有位置发生转移[1]。研究表明，EMT与干细胞表型、肿瘤细胞侵袭性增强及多种治疗抵抗密切相关[2,5–6]。

根据转化细胞的不同，EMT分为3种类型[7]。1型EMT由上皮细胞转化来的间质细胞组成身体整体框架，是多种细胞胚胎发育过程中的基础环节。如在原肠胚、神经嵴、心脏和肌肉骨骼形成过程中都有EMT的参与[8]。2型EMT，上

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皮细胞转化为成纤维细胞，其与伤口愈合、组织修复、器官纤维化密切相关[7]。3型EMT在肿瘤的发生发展过程中可促使肿瘤离开原有位置，迁移到新的组织而形成第2个瘤结节，其赋予细胞侵袭与转移的特性，导致治疗的失败[9-10]。

EMT涉及重要形态变化，所以有许多分子可以作为其标记物。CDH1编码的E-钙黏蛋白是表达于上皮细胞的一种跨膜糖蛋白，其对于维持细胞连接和结构的完整性至关重要[8]。E-钙黏蛋白的缺失及表达下调被认为是EMT的重要标记物[11]。EMT发生时，E-钙黏蛋白转化为在间质细胞中表达的N-钙黏蛋白。因此，随着EMT的发生，可以看到E-钙黏蛋白的表达下调和N-钙黏蛋白的表达上调，而二者也被认为是EMT的分子标记物。其他细胞表皮蛋白，基质(extracellular matrix，ECM)蛋白质和细胞骨架标记物如FSP1，β-catenin和α-SMA也被用来描述EMT[7]。另外，特定的参加EMT调控的转录因子和microRNA也可以被看做EMT的分子标志。

2 上皮细胞间质化在胃癌发生中的作用

EMT发生过程中，上皮细胞获得间质细胞及干细胞特性。EMT诱导的干细胞对于胃癌的发生起着关键作用。曾有观点认为每个细胞都可以变为癌细胞，事实上只有一小部分细胞能引起癌症的发生，如肿瘤干细胞(cancer stem cells，CSCs)。

CSCs侵袭性广泛，自我更新能力强，可以分化为多种癌细胞。胃CSCs的存在已经被证实。Takaishi等[12]发现，CD44阳性的胃癌具有CSCs的特性，如引起肿瘤的发生、促使治疗后的肿瘤进展。还有研究显示，胃CSCs的标记物CD44与EMT的转录因子密切相关，提示胃CSCs与EMT相关[13]。Ryu等[13]对276例原发性胃癌患者(含54例淋巴结转移)进行了免疫组化染色，染色的分子为与EMT相关的蛋白质，如Snail-1、ZEB-1、E-cadherin、Vimentin、β-catenin和CSC的分子标记物CD44。结果显示，CD44的表达与Snail-1、ZEB-1、E-cadherin密切相关。在胃上皮细胞，位于幽门腺底部的干细胞通过Wnt通路激活EMT通路[14-15]。

近年有研究证实，EGFR/Ras在体内和体外对胃的干细胞都有稳定作用，参与了EMT诱导肿瘤发生的过程[16]。研究者还发现在表达Runx3(-/-)p53(-/-)的胃癌细胞系GIF-14中，TGF-β和EGFR通路共同促使肿瘤的发生[16]。另一个研究显示癌症相关的纤维化可以激活WNT5A，其可诱导EMT突变，保持CSCs在胃癌细胞中的特性。因此，WNT5A可能为GC的进展提供有利的微环境[17]。

3 上皮细胞间质化在胃癌进展中的作用

EMT不仅参与肿瘤的发生，对肿瘤的进展也起着重要作用。EMT赋予肿瘤侵袭与迁移、干细胞的特性，阻止肿瘤凋亡，使机体处于免疫抑制状态。肿瘤的侵袭性包括细胞间的连接、细胞与基质的连接消失、周围基质蛋白水解[18]。EMT完成了侵袭，便开始远处转移。肿瘤转移是个多步骤的过程，包括局部侵入、内渗、转运、外渗、局部定植[19]。

较多研究证实，E-钙黏蛋白的突变与和胃癌的发生及其恶性行为密切相关[20]。而N-黏蛋白被认为比E-钙黏蛋白的作用更强。EMT诱导的CSCs不仅赋予了细胞自我更新的能力，还使耐药基因过度表达，阻止细胞凋亡，这也是临床治疗中出现多药耐药(multi-drug resistance，MDR)的原因。化疗是胃癌治疗的重要手段，化疗主要诱导癌细胞的凋亡。EMT导致的MDR在其他肿瘤中已有验证[21-22]，在胃癌中鲜有报道。越来越多的证据表明，奥沙利铂(oxaliplatin，OXA)耐药的结肠癌[23]，阿霉素(adriamycin，ADM)耐药的乳腺癌[24]，紫杉醇(paclitaxel，PTX)耐药的卵巢癌[25]，顺铂耐药的肺癌[26]，放疗抵抗的前列腺癌[27]及吉非替尼耐药的肺癌[28]，拉帕替尼耐药的HER2阳性的胃癌[29]等治疗抵抗的细胞系均呈现EMT表型，且伴随细胞侵袭能力的增强。而抑制EMT的相关转录因子Snail、Twist、ZEB等，可增加肿瘤细胞对化疗药物的敏感性[30-31]。提示EMT参与了肿瘤获得性耐药过程，或许是肿瘤耐药的普遍现象，研究EMT相关信号通路可能为逆转肿瘤耐药提供新的治疗思路。然而对于EMT与胃癌化疗耐药的研究却少见报道。HGF/c-MET信号通路是人体重要的信号传导通路，参与肿瘤转移、侵袭、增殖和血管发生[32]。已有文献证实c-MET高表达与乳腺癌[33]、结直肠癌[34]、非小细胞肺癌[35]等发生发展密切相关。近年来，许多研究发现MET扩增、HGF(MET的配体)高表达及MET通路的活化与非小细胞肺癌、胃癌、食管胃交界癌的预后较差有关[36-38]。随着对c-MET的深入研究，更多的证据表明，HGF/c-MET信号通路可能在对以致癌激酶为靶点的靶向药物以及部分化疗药物的固有性和获得性耐药性中具有关键作用[39]。李进等发现MET、HER3和IGF-1R等通路的异常活化介导了HER2阳性胃癌对拉帕替尼无应答[40]。另有部分研究也发现c-MET的表达与EMT有密切相关。有文献报道胃癌中c-MET表达与结肠癌转移相关因子1(metastasis-associated in colon cancer-1，MACC1)表达呈正相关，且与腹膜转移及淋巴结转移相关[41]；而MACC1可诱导EMT的发生[42]。而HGF和c-MET的共表达可诱导胃癌细胞发生EMT及促进腹膜转移[43]。

4 结语

EMT在胃癌的形成、侵袭和转移方面发挥了重要作用。E-钙黏蛋白的缺失是EMT进程中的关键步骤。E-钙黏蛋白转录抑制因子如Snail、ZEB和Twist也显得尤为重要。这些因子促进胃癌的发展，也为胃癌的研究提供了新的视角。其他参与胚胎发育与EMT进展的因子也应该成为我们今后研究的方向。此外，EMT也为干细胞的研究和其他相关领域提供了新观点。但其机制还尚不明朗，需要我们去继续探索。

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