电子、语音版

·综述·

上皮间质转化与胶质瘤侵袭迁移的研究进展

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摘　要：胶质瘤是一种恶性程度高、浸润性生长的颅内原发性肿瘤。肿瘤的侵袭和转移是导致患者预后差的主要原因。上皮细胞-间质细胞转换(EMT)是胶质瘤细胞获得高度迁移和侵入表型特征的关键过程。EMT是一个进化上保守的细胞发育程序，和致癌效应密切相关。该文就EMT与胶质瘤侵袭迁移相关作用机制和靶向治疗进行综述，为胶质瘤的诊疗研究提供理论依据。

[国际神经病学神经外科学杂志, 2023, 50(1): 75-80]

关键词：胶质瘤；上皮间质转化；侵袭迁移；分子机制；靶向治疗

中图分类号：R739.41　　**DOI:**10.16636/j.cnki.jinn.1673-2642.2023.01.015

Research advances in epithelial-mesenchymal transition and the invasion and migration of glioma

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Abstract: Glioma is a highly malignant and invasive intracranial primary tumor, and tumor invasion and metastasis is the main cause of poor prognosis. Epithelial-mesenchymal transition (EMT) is the key process for glioma cells to obtain the phenotypic characteristics of strong migration and invasion abilities. As an evolutionarily conserved cellular development process, EMT is closely associated with carcinogenic effect. This article reviews the mechanism of action of EMT in the invasion and migration of glioma and related targeted therapy, so as to provide a theoretical basis for the diagnosis and treatment of glioma.

[Journal of International Neurology and Neurosurgery, 2023, 50(1): 75-80]

Keywords: glioma; epithelial-mesenchymal transition; invasion and migration; molecular mechanism; targeted therapy

神经胶质瘤是脑和脊髓最常见的原发性肿瘤[1]，具有高侵袭性、高复发率和高致死率特点[2]。根据世界卫生组织（World Health Organization，WHO）最新分类标准，胶质瘤可以分为4级，其中1和2级表示低级别胶质瘤，3和4级表示高级别胶质瘤[3]。

上皮间质转化（epithelial-mesenchymal transition，EMT）是上皮细胞获得间质特征并获得主动侵袭迁移能力的过程[4]。Greenburg和Hay[5]通过使用胶原凝胶培养系统在三维条件下培养胚胎和成人前晶状体上皮细胞，观察到上皮细胞会失去极性并获得间充质特性，他们将此现象称为“上皮间充质”转化。EMT与肿瘤发生、恶性进展、肿瘤干细胞、肿瘤细胞迁移、血管内浸润、转移和治疗抵抗等密切相关[6]。因此，探索EMT在神经胶质瘤侵袭迁移中的作用机制对于制定新的有效临床治疗策略具有重要意义。

1　EMT概述

1.1　EMT概念

EMT是控制多种细胞生物形态发生的基本过程，这

收稿日期：2022-04-29；**修回日期：**2023-02-06

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一过程也在包括纤维化和癌症进展在内的多种过程中被重新激活[7]。EMT可能与癌细胞抗凋亡、获得组织侵袭性、癌症干细胞特征和癌症治疗抵抗性有关。更重要的是,EMT过程的病理再激活在器官纤维化或癌症进展转移中发挥着重要作用[8]。转录因子(例如Snail、TWIST、ZEB)、表观遗传修饰、microRNA(例如miRNA-200家族)以及长链非编码RNA(lncRNA)等多种因素与EMT发生密切相关[9]。

EMT的过程可以划分为几个步骤,一旦上皮细胞能够对EMT诱导信号作出反应,这些信号就会促进细胞间黏附复合物的破坏和上皮细胞特征性顶端-基底极性的丧失[10-12],同时蛋白酶活性导致基底膜破裂和细胞侵入[13]。经历EMT后,细胞获得迁移和侵入特性,使它们能够通过细胞外基质迁移[14]。EMT关键上皮标志物包括E-cadherin、Mucin-1、细胞角蛋白(如CK19、CK18、CK8)、Occludin和Desmoplakin。相反,在此过程中获得间质标志物包括N-cadherin、波形蛋白、平滑肌肌动蛋白(αSMA)、基质金属蛋白酶(matrix metalloproteinase, MMP)2和MMP9[15]。

1.2　EMT分类

根据生物学特性不同,EMT分为3种类型[16]:Ⅰ型EMT与胚胎和器官的发育有关;Ⅱ型EMT与伤口愈合、组织再生和器官纤维化有关;Ⅲ型EMT与肿瘤的发生发展、恶性肿瘤的进展和癌症干细胞的特征有关,是肿瘤侵袭和转移的重要机制[17]。获得EMT表型的癌细胞更具攻击性行为,包括对药物、压力和细胞凋亡的抗性,衰老抑制,免疫逃逸和获得干细胞样特征。肿瘤细胞的这些显著变化使它们能够浸润周围组织,发生远处转移并促进癌症进展[18]。

2　EMT与肿瘤的侵袭转移

大量研究证实,恶性肿瘤临床治疗效果欠佳的最常见原因是复发和转移,而绝大多数肿瘤在肿瘤进展中都经历EMT,使得肿瘤细胞在进展期间获得浸润和转移特性,加速形成恶性肿瘤并使得侵袭转移能力增强。Hao等[19]研究证实,miRNA-190通过抑制EMT表型,减弱肝癌细胞的迁移和侵袭能力,并抑制肿瘤血管生成。Wang等[20]利用结肠癌HCT116细胞建立裸鼠原位异种移植模型,证实Cinobufacini通过抑制Wnt/β-连环蛋白信号通路和EMT抑制结肠癌侵袭和转移。有研究[21]表明,瑞戈非尼通过靶向分化抑制剂1(ID1)抑制肝细胞癌(hepatocellular carcinoma, HCC)中的EMT,从而抑制肿瘤细胞迁移、侵袭和血管形成。这些发现表明,瑞戈非尼可能被开发成为HCC转移的抑制剂。Zheng等[22]通过对Snail或TWIST(EMT的2个关键转录因子)缺失的胰腺导管腺癌(PDAC)基因工程小鼠模型进行研究,发现Snail或TWIST诱导的EMT不会限制侵袭转移的速率,但会抑制癌细胞增殖,肿瘤中核苷转运蛋白的表达增强,这有助于增强化疗药物吉西他滨治疗的敏感性。因此EMT抑制剂与化疗药物相结合在胰腺癌的治疗中发挥重要作用。

3　EMT与胶质瘤的侵袭迁移

EMT是一个高度复杂和动态的过程,受诱导因子、转录因子家族和一系列信号通路基因的调控,并与胶质瘤侵袭迁移相关[23]。

3.1　胶质瘤侵袭转移的EMT相关生长因子

EMT是由各种诱导因子触发的,多种生长因子也与触发EMT程序有关。诱导因子包括表皮生长因子(EGF)、成纤维细胞生长因子(FGF)、缺氧诱导因子(HIF)、转化生长因子(TGF)超家族和胰岛素生长因子1(IGF1)等[24-25]。当生长因子与受体酪氨酸激酶(receptor tyrosine kinase, RTK)相互作用时,磷酸化RTK自身的酪氨酸残基,从而激活下游的PI3K/AKT通路、MAPK通路、SRC通路等,进而在细胞内诱导EMT。其中转化生长因子-β(transforming growth factor-β, TGF-β)是常见且有效的EMT诱导剂。TGF-β通过经典的Smad途径,Smads通过直接激活EMT转录因子的表达来诱导基因重编程,与这些转录因子协同控制靶基因[26]。

3.2　胶质瘤侵袭转移的EMT相关转录因子

在胶质瘤细胞中,不同的信号转导通路通过激活集中在相对低分子量的转录因子来协调与EMT相关基因表达,这些转录因子统称为"EMT诱导转录因子(EMT-inducing transcription factors, EMT-TFs)"[27]。激活EMT-TFs的不同组合可以赋予癌细胞迁移和侵袭能力,从而使EMT反应细胞具有转移潜力[28]。根据结构的不同,EEMT-TFs通常可分为3个不同的蛋白质家族:即Snail(包括Snail和Slug)、ZEB(包括ZEB1和ZEB2)和基本螺旋-环-螺旋(包括TWIST1、TWIST2和TCF3)家族[27]。一些研究表明,在具有不同分化的胶质瘤中Snail同源因子-1(SNAI-1)表达不同,因此SNAI-1被认为与细胞增殖和浸润有关[29]。ZEB1可以通过募集CDH1启动子和抑制E-cadherin的表达来促进胶质瘤的转移[30]。TWIST过表达是促进胶质瘤细胞系侵袭能力增强的重要因素[31]。EMT调节因子STAT3在促进肿瘤侵袭和生长方面也很重要[32-33]。最新研究发现性别决定区Y-box-2(SOX-2)在结直肠癌中促进化疗耐药,并赋予癌症干细胞特性,进而促进EMT[34]。见表1。

3.3　胶质瘤侵袭转移的EMT相关信号通路

3.3.1　TGF-β/Smad信号通路　TGF-β是细胞生长、凋亡、分化和迁移的多功能调节剂,在肿瘤进展中TGF-β具有双重作用。在肿瘤早期通过诱导生长停滞和促进细胞凋亡来抑制肿瘤发生,在晚期癌症中,TGF-β通过诱导EMT促进肿瘤发生、侵袭和迁移[35-36]。TGF-β与其受体结合后激活Smad 2和Smad 3,然后再与胞质内的Smad 4

表1　EMT中的关键分子及其作用

EMT-TFs	分子类型	作用
TGF-β	转化生长因子	激活各种下游通路
Snail	EMT诱导转录因子	促进细胞增殖和浸润
ZEB	EMT诱导转录因子	促进传递性和抑制E-钙粘蛋白的表达
TWIST	EMT诱导转录因子	增强肿瘤侵袭
STAT3	EMT调节因子	促进肿瘤的浸润和生长
SOX2	干性相关标记	维持可塑性以实现转换
β-Catenin	Wnt信号通路关键蛋白	启动EMT相关基因的转录

结合。Smad三聚体复合物进入细胞核内,可以直接激活EMT转录因子Snail和Slug、ZEB1和ZEB2以及TWIST的表达来促进从而增强EMT进展和细胞侵袭转移[37](见图1)。在肿瘤细胞中,TGF-β通过致癌和抗致癌信号诱导调节EMT,从而促进癌症侵袭和转移。TGF-β也可通过其他机制促进癌症的侵袭和转移,例如调节细胞周期、血管生成和血管完整性,以及与肿瘤微环境的相互作用[38]。已有研究[39]证实:TGF-β诱导胶质母细胞瘤(Glioblastoma, GBM)细胞系发生EMT。经TGF处理的U87和U251胶质瘤细胞可通过Smad 2信号通路发生EMT,胶质瘤细胞侵袭迁移增强。

3.3.2　Wnt/β-Catenin信号通路　Wnt信号转导是EMT发生发展的主要信号通路,起到监管作用[40]。迄今为止,Wnt信号通路有3条,包括经典的Wnt/β-Catenin、Wnt/Ca^{2+}和Wnt细胞极性(PCP)信号通路[41]。大量研究[42]表明,Wnt/β-Catenin信号通路的失调会导致EMT,其特征是β-Catenin的核转位和E-cadherin抑制。β-Catenin被认为是Wnt信号转导中的关键蛋白,β-Catenin在细胞质中的积累导致其在细胞核中的易位和激活[43],进一步启动了EMT相关基因的转录[44]。β-Catenin易位至细胞核并与T细胞因子/淋巴增强因子(TCF/LEF)形成复合物,促进包括TWIST、Snail和其他癌基因(如Cyclin D1)在内的Wnt靶基因的转录,进而促进EMT[45]。当没有Wnt配体的情况下,糖原合成激酶-3β(GSK-3β)使得β-Catenin磷酸化并将其降解。Wnt配体与其受体结合可以抑制GSK-3β,进而阻止β-Catenin磷酸化,减少其在细胞质内降解积聚,使其进入细胞核并调节靶基因的转录[46](见图1)。而从而将细胞质β-Catenin维持在低水平。研究发现[47],Wnt/β-Catenin信号通路的激活使β-Catenin在胶质母细胞瘤干细胞(glioblastoma stem cells,GSC)中的表达增加14倍以上,提示Wnt/β-Catenin信号通路可调控GSC的活性。Wnt/β-Catenin信号通路的激活可促进GMB内ZEB1的表达和EMT的发生,加剧GMB的迁移和侵袭[48]。

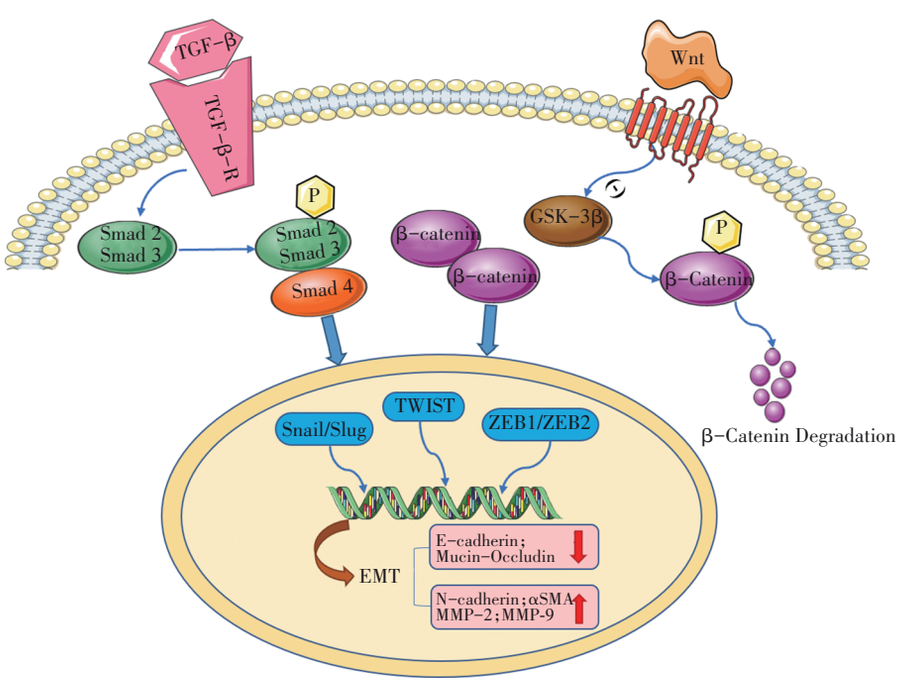

图1　胶质瘤侵袭转移的EMT相关信号通路

3.4　胶质瘤侵袭转移的EMT相关微小RNA(miRNA)

近年来,愈来愈多的研究报道miRNA在胶质瘤起始、进展和侵袭中发挥着至关重要的作用[49]。miRNA是具有19~25个核苷酸的小型非编码分子,调节转录后水平的基因表达[50-51]。据报道,人体10%~40%的mRNA受miRNA的调节[52],而miRNA的失调可能导致肿瘤转移[53]。已有研究显示在几种癌症中启动的EMT与miRNA-200家族的低表达相关,例如膀胱癌[54]、乳腺癌[55]、卵巢癌[56]、胃

癌[57]等。研究越来越关注miRNA和EMT之间的相互作用,大量研究报道,miRNA可通过靶向Wnt信号通路或其下游转录因子发挥EMT抑制剂的作用[42]。

4　靶向治疗

EMT受诱导因子、转录因子家族和一系列信号通路基因的调控,与胶质瘤的侵袭和进展有关。目前靶向抑制EMT主要有以下几个方面策略:①靶向EMT诱导转录因子,研究证明,EMT激活转录因子,包括Snail、Slug、TWIST1和ZEB1,可增强胶质瘤的增殖、侵袭和迁移[58]。因此抑制EMT相关诱导转录因子表达,可能阻止EMT发生。②靶向EMT信号通路,EMT的调控是一个由多种分子调控的调控网络,在肿瘤发展的初始过程中发挥着重要作用。研究[59]证实黄芪甲苷(AS-IV)可以抑制胶质瘤细胞中EMT相关的Wnt/β-Catenin信号转导,进而影响胶质瘤侵袭迁移能力。因此,深入探究EMT信号通路调控网络和反馈机制,将为胶质瘤高精度靶向治疗的发展提供更可靠的证据。③EMT相关的miRNA可被用作胶质瘤的潜在治疗靶点,有研究显示使用miRNA-223-3p类似物治疗GBM可抑制癌细胞的增殖和迁移,这表明miRNA-223-3p可能作为GBM的抑制因子和潜在的治疗靶点[60]。Nan等[61]验证miRNA-451通过激活胶质瘤中的钙结合蛋白39(CAB39)阻断PI3K/Akt/Snail信号通路来抑制EMT和肿瘤转移。

因此,了解驱动EMT的机制对于寻找胶质瘤中肿瘤细胞扩散浸润的新靶点非常重要。针对这种特点,靶向胶质瘤EMT途径已经形成了一个有效治疗策略。

综上所述,脑胶质瘤的EMT是由一系列调节系统组成的复杂调节网络,这依赖于组织和信号转导的环境。研究胶质瘤中EMT发生的相关信号通路,为研制针对EMT过程中的主要信号转导通路阻断剂和各种转录因子抑制剂提供理论基础,可为恶性肿瘤的发病机制研究和临床诊治提供新的思路。

参　考　文　献

[1] CHEN R, SMITH-COHN M, COHEN AL, et al. Glioma subclassifications and their clinical significance[J]. Neurotherapeutics, 2017, 14(2): 284-297.

[2] 李德培, 陈忠平. 脑胶质瘤临床诊疗新进展[J]. 国际神经病学神经外科学杂志, 2020, 47(1): 87-90.

[3] WEN PY, PACKER RJ. The 2021 WHO classification of tumors of the central nervous system: clinical implications[J]. Neuro Oncol, 2021, 23(8): 1215-1217.

[4] CANO CE, MOTOO Y, IOVANNA JL. Epithelial-to-mesenchymal transition in pancreatic adenocarcinoma[J]. ScientificWorldJournal, 2010, 10: 1947-1957.

[5] GREENBURG G, HAY ED. Epithelia suspended in collagen gels can lose polarity and express characteristics of migrating mesenchymal cells[J]. J Cell Biol, 1982, 95(1): 333-339.

[6] PASTUSHENKO I, BLANPAIN C. EMT transition states during tumor progression and metastasis[J]. Trends Cell Biol, 2019, 29(3): 212-226.

[7] ORTIZ MA, MIKHAILOVA T, LI X, et al. Src family kinases, adaptor proteins and the actin cytoskeleton in epithelial-to-mesenchymal transition[J]. Cell Commun Signal, 2021, 19(1): 67.

[8] BRABLETZ S, SCHUHWERK H, BRABLETZ T, et al. Dynamic EMT: a multi-tool for tumor progression[J]. EMBO J, 2021, 40(18): e108647.

[9] GEORGAKOPOULOS-SOARES I, CHARTOUMPEKIS DV, KYRIAZOPOULOU V, et al. EMT factors and metabolic pathways in cancer[J]. Front Oncol, 2020, 10: 499.

[10] IMODOYE SO, ADEDOKUN KA, MUHAMMED AO, et al. Understanding the complex milieu of epithelial-mesenchymal transition in cancer metastasis: new insight into the roles of transcription factors[J]. Front Oncol, 2021, 11: 762817.

[11] DONG B, WU YD. Epigenetic regulation and post-translational modifications of SNAI1 in cancer metastasis[J]. Int J Mol Sci, 2021, 22(20): 11062.

[12] LAVIN DP, ABASSI L, INAYATULLAH M, et al. Mnt represses epithelial identity to promote epithelial-to-mesenchymal transition[J]. Mol Cell Biol, 2021, 41(11): e0018321.

[13] DATTA A, DENG S, GOPAL V, et al. Cytoskeletal dynamics in epithelial-mesenchymal transition: insights into therapeutic targets for cancer metastasis[J]. Cancers (Basel), 2021, 13(8): 1882.

[14] ACLOQUE H, ADAMS MS, FISHWICK K, et al. Epithelial-mesenchymal transitions: the importance of changing cell state in development and disease[J]. J Clin Invest, 2009, 119(6): 1438-1449.

[15] SERRANO-GOMEZ SJ, MAZIVEYI M, ALAHARI SK. Regulation of epithelial-mesenchymal transition through epigenetic and post-translational modifications[J]. Mol Cancer, 2016, 15: 18.

[16] DAS V, BHATTACHARYA S, CHIKKAPUTTAIAH C, et al. The basics of epithelial-mesenchymal transition (EMT): a study from a structure, dynamics, and functional perspective[J]. J Cell Physiol, 2019, 234(9): 14535-14555.

[17] 张彦璐, 陈影, 应国清. 上皮间质转化在肿瘤侵袭转移中的研究进展[J]. 浙江化工, 2019, 50(7): 11-15.

[18] KANG E, SEO J, YOON H, et al. The post-translational regulation of epithelial-mesenchymal transition-inducing transcription factors in cancer metastasis[J]. Int J Mol Sci, 2021, 22(7): 3591.

[19] HAO Y, YANG JY, YIN SY, et al. The synergistic regulation of VEGF-mediated angiogenesis through miR-190 and target genes[J]. RNA, 2014, 20(8): 1328-1336.

[20] WANG J, CAI H, LIU QL, et al. Cinobufacini inhibits colon cancer invasion and metastasis via suppressing Wnt/β-Catenin signaling pathway and EMT[J]. Am J Chin Med, 2020, 48(3): 703-718.

[21] ZHANG N, ZHANG SQ, WU WD, et al. Regorafenib inhibits migration, invasion, and vasculogenic mimicry of hepatocellular

carcinoma via targeting ID1-mediated EMT[J]. Mol Carcinog, 2021, 60(2): 151-163.

[22] ZHENG XF, CARSTENS JL, KIM J, et al. Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer[J]. Nature, 2015, 527(7579): 525-530.

[23] TAO CM, HUANG K, SHI J, et al. Genomics and prognosis analysis of epithelial-mesenchymal transition in glioma[J]. Front Oncol, 2020, 10: 183.

[24] ISER IC, PEREIRA MB, LENZ G, et al. The epithelial-to-mesenchymal transition-like process in glioblastoma: an updated systematic review and *in silico* investigation[J]. Med Res Rev, 2017, 37(2): 271-313.

[25] LINDSEY S, LANGHANS SA. Crosstalk of oncogenic signaling pathways during epithelial-mesenchymal transition[J]. Front Oncol, 2014, 4: 358.

[26] LIU SJ, REN J, DIJKE PTEN. Targeting TGFβ signal transduction for cancer therapy[J]. Signal Transduct Target Ther, 2021, 6(1): 8.

[27] SHIBUE T, WEINBERG RA. EMT, CSCs, and drug resistance: the mechanistic link and clinical implications[J]. Nat Rev Clin Oncol, 2017, 14(10): 611-629.

[28] CHAFFER CL, JUAN BPSAN, LIM E, et al. EMT, cell plasticity and metastasis[J]. Cancer Metastasis Rev, 2016, 35(4): 645-654.

[29] DEEP G, JAIN AK, RAMTEKE A, et al. SNAI1 is critical for the aggressiveness of prostate cancer cells with low E-cadherin [J]. Mol Cancer, 2014, 13: 37.

[30] PEREZ-OQUENDO M, GIBBONS DL. Regulation of ZEB1 function and molecular associations in tumor progression and metastasis[J]. Cancers (Basel), 2022, 14(8): 1864.

[31] MIKHEEVA SA, MIKHEEV AM, PETIT A, et al. TWIST1 promotes invasion through mesenchymal change in human glioblastoma[J]. Mol Cancer, 2010, 9: 194.

[32] GIANNOPOULOU AI, KANAKOGLOU DS, PIPERI C. Transcription factors with targeting potential in gliomas[J]. Int J Mol Sci, 2022, 23(7): 3720.

[33] LU YB, SUN TJ, CHEN YT, et al. Targeting the epithelial-to-mesenchymal transition in cancer stem cells for a better clinical outcome of glioma[J]. Technol Cancer Res Treat, 2020, 19: 1533033820948053.

[34] ZHU Y, HUANG SM, CHEN SY, et al. *SOX2* promotes chemoresistance, cancer stem cells properties, and epithelial-mesenchymal transition by β-catenin and Beclin1/autophagy signaling in colorectal cancer[J]. Cell Death Dis, 2021, 12(5): 449.

[35] KIM BN, AHN DH, KANG N, et al. TGF-β induced EMT and stemness characteristics are associated with epigenetic regulation in lung cancer[J]. Sci Rep, 2020, 10(1): 10597.

[36] PALLASCH FB, SCHUMACHER U. Angiotensin inhibition, TGF-β and EMT in cancer[J]. Cancers (Basel), 2020, 12(10): 2785.

[37] TRELFORD CB, NG E, CAMPBELL CI, et al. p62/Sequestosome 1 regulates transforming growth factor beta signaling and epithelial to mesenchymal transition in A549 cells[J]. Cell Signal, 2021, 85: 110040.

[38] HAO Y, BAKER D, DIJKE PTEN. TGF-β-mediated epithelial-mesenchymal transition and cancer metastasis[J]. Int J Mol Sci, 2019, 20(11): 2767.

[39] NIE XH, OU-YANG J, XING Y, et al. Calycosin inhibits migration and invasion through modulation of transforming growth factor beta-mediated mesenchymal properties in U87 and U251 cells[J]. Drug Des Devel Ther, 2016, 10: 767-779.

[40] WANG Q, LU WJ, YIN T, et al. Calycosin suppresses TGF-β-induced epithelial-to-mesenchymal transition and migration by upregulating BATF2 to target PAI-1 via the Wnt and PI3K/Akt signaling pathways in colorectal cancer cells[J]. J Exp Clin Cancer Res, 2019, 38(1): 240.

[41] 王舒, 高毅, 师伟. 基于Wnt/β联蛋白信号通路探讨中医药防治骨质疏松症的研究进展[J]. 山西医药杂志, 2019, 48(2): 160-162.

[42] LEI YH, CHEN L, ZHANG G, et al. MicroRNAs target the Wnt/β-catenin signaling pathway to regulate epithelial-mesenchymal transition in cancer (review)[J]. Oncol Rep, 2020, 44(4): 1299-1313.

[43] CAI JC, GUAN HY, FANG LS, et al. MicroRNA-374a activates Wnt/β-catenin signaling to promote breast cancer metastasis[J]. J Clin Invest, 2013, 123(2): 566-579.

[44] RAO TP, KÜHL M. An updated overview on Wnt signaling pathways: a prelude for more[J]. Circ Res, 2010, 106(12): 1798-1806.

[45] DI GREGORIO J, ROBUFFO I, SPALLETTA S, et al. The epithelial-to-mesenchymal transition as a possible therapeutic target in fibrotic disorders[J]. Front Cell Dev Biol, 2020, 8: 607483.

[46] LIU XY, GAO Q, ZHAO N, et al. Sohlh1 suppresses glioblastoma cell proliferation, migration, and invasion by inhibition of Wnt/β-catenin signaling[J]. Mol Carcinog, 2018, 57(4): 494-502.

[47] SHEVCHENKO V, ARNOTSKAYA N, ZAITSEV S, et al. Proteins of Wnt signaling pathway in cancer stem cells of human glioblastoma[J]. Int Rev Neurobiol, 2020, 151: 185-200.

[48] ROSMANINHO P, MÜKUSCH S, PISCOPO V, et al. Zeb1 potentiates genome-wide gene transcription with Lef1 to promote glioblastoma cell invasion[J]. EMBO J, 2018, 37(15): e97115.

[49] HUANG YL, QI L, KOGISO M, et al. Spatial dissection of invasive front from tumor mass enables discovery of novel microRNA drivers of glioblastoma invasion[J]. Adv Sci (Weinh), 2021, 8(23): e2101923.

[50] NOMAN A, FAHAD S, AQEEL M, et al. miRNAs: major modulators for crop growth and development under abiotic stresses[J]. Biotechnol Lett, 2017, 39(5): 685-700.

[51] 袁洁, 费智敏. miRNA-21—治疗神经胶质瘤的新靶标[J]. 国际神经病学神经外科学杂志, 2018, 45(2): 211-214.

[52] LI C, HONG ZT, OU ML, et al. Integrated miRNA-mRNA expression profiles revealing key molecules in ovarian cancer based on bioinformatics analysis[J]. Biomed Res Int, 2021,

2021: 6673655.

[53] RAUE R, FRANK AC, SYED SN, et al. Therapeutic targeting of MicroRNAs in the tumor microenvironment[J]. Int J Mol Sci, 2021, 22(4): 2210.

[54] CAVALLARI I, CICCARESE F, SHAROVA E, et al. The miR-200 family of microRNAs: fine tuners of epithelial-mesenchymal transition and circulating cancer biomarkers[J]. Cancers (Basel), 2021, 13(23): 5874.

[55] ABDALLA F, SINGH B, BHAT HK. MicroRNAs and gene regulation in breast cancer[J]. J Biochem Mol Toxicol, 2020, 34(11): e22567.

[56] DWIVEDI SKD, RAO G, DEY A, et al. Small non-coding-RNA in gynecological malignancies[J]. Cancers (Basel), 2021, 13(5): 1085.

[57] GUO CM, LIU SQ, SUN MZ. miR-429 as biomarker for diagnosis, treatment and prognosis of cancers and its potential action mechanisms: a systematic literature review[J]. Neoplasma, 2020, 67(2): 215-228.

[58] OH SJ, AHN EJ, KIM O, et al. The role played by SLUG, an epithelial-mesenchymal transition factor, in invasion and therapeutic resistance of malignant glioma[J]. Cell Mol Neurobiol, 2019, 39(6): 769-782.

[59] HAN JM, SHEN XH, ZHANG Y, et al. Astragaloside IV suppresses transforming growth factor-β1-induced epithelial - mesenchymal transition through inhibition of Wnt/β-catenin pathway in glioma U251 cells[J]. Biosci Biotechnol Biochem, 2020, 84(7): 1345-1352.

[60] DING QP, SHEN L, NIE XH, et al. MiR-223-3p overexpression inhibits cell proliferation and migration by regulating inflammation-associated cytokines in glioblastomas[J]. Pathol Res Pract, 2018, 214(9): 1330-1339.

[61] NAN Y, GUO LY, LU YL, et al. miR-451 suppresses EMT and metastasis in glioma cells[J]. Cell Cycle, 2021, 20(13): 1270-1278.

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