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microRNA-378 与肿瘤血管生成的研究进展 *

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摘要：微小 RNA（MicroRNAs，miRNAs）是真核生物中一类长度约为 21 到 23 个核苷酸的非编码小分子单链 RNA。miRNA 通过与靶 mRNA 3′ UTR（3′ -untranslated region，3′ 非编码区）完全或不完全结合，抑制翻译或直接诱导其降解，发挥转录后负调控作用。miRNA 参与机体多种生理和病理过程，且可通过调控其靶标基因参与各种信号通路，影响血管生成。miR-378 属于诸多 miRNAs 中的一种。目前已知 miR-378 的研究主要集中在肿瘤发生及血管生成、心血管疾病和脑缺血等病理过程，其中与肿瘤发生及血管生成相关研究居多。miR-378 在不同肿瘤中的发挥的作用也不一样，在脑胶质瘤，肺癌，横纹肌肉瘤等肿瘤中发挥促癌基因的作用，在卵巢癌，胃癌，大肠癌等肿瘤中发挥抑癌基因的作用。但是，miR-378 调节肿瘤血管生成的作用机制还有待于深入研究。本文主要对 miR-378 在四种肿瘤（脑胶质瘤、肺腺癌、卵巢癌和横纹肌肉瘤）中调控血管生成的相关性研究进展进行综述，以期为这些疾病的治疗和预防提供一种新的思路。

关键词：miR-378；肿瘤；血管生成

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Research Progress of microRNA-378 and Tumor Angiogenesis*

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ABSTRACT: MicroRNAs (miRNAs) are non-coding small-molecule single-stranded RNAs of approximately 21 to 23 nucleotides in length in eukaryotes. The miRNA inhibits translation or directly induces degradation by completely or incompletely binding to the target mRNA 3'UTR (3'-untranslated region, 3' non-coding region), and exerts a negative post-transcriptional regulation. Numerous studies have shown that miRNAs participate in a variety of physiological and pathological processes in the body, and can affect angiogenesis by regulating their target genes to participate in signaling pathways. MiR-378 is one of the families of miRNAs. At present, miR-378 is mainly studied in the pathogenesis of tumorigenesis and angiogenesis, cardiovascular disease and cerebral ischemia, and most of the studies related to tumorigenesis and angiogenesis. MiR-378 plays a different role in different tumor tissues, and plays a role as a tumor-promoting gene in glioma, lung cancer, rhabdomyosarcoma, etc., and acts as a tumor suppressor gene in tumors such as ovarian cancer, gastric cancer, colorectal cancer. However, the mechanism by which miR-378 regulates tumor angiogenesis remains to be further studied. This study mainly introduces the progress of miR-378 in the regulation of angiogenesis in four tumors (glioma, lung adenocarcinoma, ovarian cancer and rhabdomyosarcoma), providing a new idea for the treatment and prevention of these diseases.

Key words: miR-378; Tumor; Angiogenesis

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前言

早在一个多世纪前，人类已经发现肿瘤生长会伴随血管的生成[1]，丰富的血管可以为肿瘤的生长提供充足的养分[2]。血管生成（Angiogenesis）是指从原有的毛细血管或毛细血管后静脉基础上通过激活内皮细胞后，促进其增殖、迁移，以芽生或非芽生的形式生成新的血管和血管网的复杂过程[2-4]。血管生成由很多促血管生成因子和抑血管生成因子共同调控，机体正常水平时，二者处于平衡状态；一旦正调节因子增多或者负调节因子减少，血管生成开关被开启，血管生成增多；反之，则血管生成减少[5-7]。正常的血管生成是进行伤口愈合和组织再生必不可少的环节；然而病理性血管生成却会促进疾病发生发展，如肿瘤血管生成等[8-12]。肿瘤血管生成包括肿瘤细胞通过分泌促血管生成因子激活静息状态的内皮细胞，降解基底膜和细胞外基质

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ECM,使内皮细胞增殖,迁移至肿瘤附近,并形成毛细血管网包绕或侵入肿瘤的复杂过程[13,14]。肿瘤启动肿瘤血管生成开关的信号非常多,例如机械压力、代谢变化(如 pH、PO_2、低血糖等)、基因突变或者免疫炎症反应等,肿瘤的种类、恶性程度、生长位置也会影响信号之间的相互作用[15-18]。

MicroRNAs 是一类内源性的非编码小分子 RNA，最早由 Lee 等人[19]于 1993 年对秀丽隐杆线虫进行突变体遗传分析时发现。随着分子生物学的发展，发现 miRNA 普遍存在于机体中,且参与多种生理和病理过程[20-23]。其中,miR-378 在肿瘤发生[24-26]、心血管疾病[27,28]和脑缺血[29-31]等疾病中的作用日益受到关注,已有研究提示 miR-378 可通过调控其靶基因参与的信号通路,影响血管生成。

本文主要总结近年来有关 miR-378 在四种肿瘤（脑胶质瘤、肺腺癌、卵巢癌和横纹肌肉瘤)中调控血管生成的相关性研究的进展，为我们研究 miR-378 的调控机制提供新的视角,并为肿瘤的治疗研究提供新的可能。

1 miRNA 的生物合成及其作用机制

miRNA 来自一些从 DNA 转录而来，但无法进一步翻译成蛋白质的 RNA。成熟 miRNA 由原始 miRNA 转录本(Primary transcrips miRNA, Pri-miRNA)经核糖核蛋白酶 Ⅲ Drosha 剪切形成 60 到 70 个核苷酸组成的具有茎环结构的 pre-miRNA，然后由 Exportin 5 等转运至细胞质。核糖核酸酶Ⅲ Dicer 再将 pre-miRNA 切割成约 21 到 23 个核苷酸长度的 miRNA 双链,双链 miRNA 降解形成单链的成熟 miRNA。成熟单链 miRNA 还需要与 Argonaute 蛋白等组装形成 RNA 诱导沉默复合体（RNA-induced silencing complex, RISC),RISC 作用于特异 mRNA 的 3'UTR,从而抑制翻译过程或者直接降解 mRNA [32-34]。

2 肿瘤血管生成

2.1 肿瘤生长具有血管依赖性

肿瘤新生血管为肿瘤提供营养物质和氧气,同时也可通过血管将肿瘤细胞转移至宿主其他部位,进而增强肿瘤灶的远处转移能力[35,36]。肿瘤生长可分为两个时期:无血管期以及血管期。肿瘤发生前期处于无血管期,而当肿瘤体积达到 1 mm^3～2 mm^3 时,肿瘤生长进入血管期,肿瘤通过新生成的血管获得生长所需营养和及时排出代谢产物[37];若无新生成血管长入瘤体内,可判断肿瘤进入休眠期或已直接退化[37]。Folkman 等[38]研究表明,生长于鸡胚绒毛膜囊上的肿瘤,体积大于 1 mm^3 之后三天内若有毛细血管深入瘤体,表现为肿瘤细胞增殖加快,肿瘤生长加速,反之肿瘤细胞发生坏死甚至自溶;Bauer 等[39]进行裸鼠皮下移植瘤接种实验发现,肿瘤在血管期呈指数生长,而在无血管期只呈线性生长。

2.2 肿瘤血管生成主要调控因子

肿瘤细胞分泌多种促血管生成因子后可激活静息状态的内皮细胞进而促进新生血管的生成 [2]。促血管生成因子包括:(1)肿瘤细胞在缺氧条件下会产生缺氧诱导因子(Hif1-α),且其能直接激活血管内皮生长因子 VEGF 的表达[40];诱导基质金属蛋白酶 MMPs 产生[41-43];趋化血管内皮组细胞 EPC 的浸润[44]等,故已被认为是促进血管形成的始动因子[45]。(2)血管内皮生长因子 VEGF 为最主要的促血管生成因子。肿瘤细胞产生 VEGF 后与靶细胞即血管内皮细胞膜上的 VEGF 受体(VEGFR)结合,激活下游信号的级联反应,从而发挥 VEGF 效应,即增加血管通透性、促进内皮细胞迁移和增殖、初级内皮细胞存活和抗凋亡等,最终促进肿瘤血管生成[46]。研究发现几乎所有的肿瘤组织中 VEGF 的表达都升高,且在临床上以 VEGF 为靶向的抗肿瘤血管治疗也取得了良好效果[47,48]。(3)其他促进血管生成分子,如:血小板转化因子(Platelet derived growth factor, PDGF)、转化生长因子(Transforming growth factor-β, TFG-β)、成纤维生长因子（Fibroblast growth factor, FGF)、血管紧张素 I/II(Angiotensin I/ II, Ang I/ II)等。(4)基质金属蛋白酶 MMPs 家族,虽然 MMPs 不直接促进血管生成,但能降解基底膜和细胞外基质 ECM 促进内皮细胞向肿瘤迁移。多种恶性肿瘤血管生成都伴有 MMPs 表达水平和活性的增高[49]。其中有研究表明 MMP-9 能使与基质结合的 VEGF 释放，增强其促血管生成的作用[50]。

3 miR-378 对血管生成的影响

目前只有少数研究表明肿瘤细胞中 miR-378 表达失调可能会影响其分泌促血管生成因子，并且在不同的肿瘤中 miR-378 发挥不同的调节作用,既可充当促癌基因,也可充当抑癌基因[51-54]。这意味着 miR-378 参与调控肿瘤血管生成的作用网络和机理的复杂程度远远超出现有的认识水平,有待深入研究。下面将总结 miR-378 在四种肿瘤(脑胶质瘤、肺腺癌、卵巢癌和横纹肌肉瘤)中调控血管生成的相关研究结果。

3.1 miR-378 与脑胶质瘤

脑胶质瘤是人类中枢神经系统最常见的原发性肿瘤,呈侵袭性强、复发率高、预后差的特点,可能与缺少肿瘤标志物有关[55,56]。近年来,人们逐渐认识到脑胶质瘤的实质是一种多基因异常疾病,其分子机制可能是由于抑癌基因的突变缺失及原癌基因的过表达,导致胶质瘤细胞逃避了正常的调控机制,故胶质瘤相关的异常基因及其作用机制仍为当前的研究热点[57-59]。

miR-378 对肿瘤发生及肿瘤血管生成作用首次是在神经胶质瘤细胞 U87 中发现的。Yang 等[60]团队报道,miR-378 促进胶质瘤细胞 U87 体内成瘤的体积增长，且肿瘤血管管径明显变粗；通过生物信息学和体外实验发现,miR-378 可通过下调靶基因 SuFu,从而促进肿瘤细胞的存活。但是 miR-378 影响小鼠肿瘤血管管径的分子机制尚不清楚。Li 等[61]的放疗实验,更是发现 miR-378 并没有改变 U87 细胞株自身的放疗敏感性,但能通过促进肿瘤血管生成增加肿瘤的血氧供应从而显著提高放疗效果,延长小鼠存活时间。已有研究证实 SHH 信号通路可以上调血管内皮生长因子 VEGF-A 以及血管生成中其他的调控因子 Ang-1(血管生成素 -1)、Ang-2(血管生成素 -2)的表达[62-64]。此外,人 miR-378 可以通过与人 miR-125a 竞争性结合到血管内皮生长因子 VEGF-A 3'UTR 后直接上调血管内皮生长因子 VEGF-A 的表达[65]。因此,可推测 miR-378 是通过间接调控血管生成相关因子 VEGF-A、Ang-1、Ang-2 来促进胶质瘤血管生成。

3.2 miR-378 与肺癌

肺癌是一种恶性肿瘤，在中国和其他亚洲国家，已成为男性癌症死亡的主要原因。根据世界卫生组织报告，全球癌症死亡人数到 2030 年将超过 1310 万 / 年，全球每年死于肺癌的患者达 137 万以上[66-69]。

Chen 等 [70] 用蛋白印迹 WB 研究发现高表达 miR-378 的 A549 肺腺癌细胞会促进血管内皮生长因子 VEGF、基质金属蛋白酶 MMP-2 和 MMP-9 的表达上调；体内研究也发现 miR-378 促进成瘤，且生成肿瘤血管数量更多；IHC 免疫组化实验也验证了 miR-378 明显上调 MMP-2、MMP-9 和 VEGF 的表达。因此认为 miR-378 可以通过上调 A549 肺腺癌细胞中 VEGF、MMP-2、MMP-9 的表达，从而促进体内肿瘤生长及肿瘤血管生成。

Ho 等[71]研究发现，在斑马鱼胚胎模型中，使用 miR-378 抑制剂处理 A549 肺腺癌细胞后注射到斑马鱼胚胎卵黄囊区域的中间，发现血管生成能力大大抑制，可能与 miR-378 通过靶向 RBX1 后抑制 A549 侵袭有关。Skrzypek 等[72]认为 miR-378 可直接抑制血红素氧合酶 -1（HO-1，HMOX1）的表达，进而促进 Ang-1（血管生成素 -1）、Ang-2（血管生成素 -2）和 MUC5AC（黏蛋白 -5AC）的表达。培养过过表达 miR-378 的 NCI-H292 肺腺癌细胞的条件性培养基可增强 HMEC-1 内皮细胞系形成血管的能力；将过表达 miR-378 的 NCI-H292 肺腺癌细胞皮下接种形成移植瘤后发现，miR-378 促进肿瘤生长，分化群聚也显示 miR-378 促进更多的肿瘤血管生成。

这些研究均表明：肺癌细胞中 miR-378 高表达后会促进肺癌的发生及肿瘤血管生长，提示 miR-378 可以促进血管生成，为肺癌新型治疗提供新思路和靶点。

3.3 miR-378 与横纹肌肉瘤

横纹肌肉瘤是一类具有骨骼肌发生特征的异质性软组织恶性肿瘤。属于心脏第二常见的原发性肉瘤，恶性程度高，易转移，常见于 15 岁以下儿童[73-76]。横纹肌肉瘤主要包括肺泡型横纹肌肉瘤和胚胎型横纹肌肉瘤。目前，尽管有新的药剂和强化治疗，但其复发率仍达 17%，发生肿瘤迁移的患者 5 年存活率仅 30%[77]。

Skrzypek 等[78]研究发现：SMS-CTR 胚胎横纹肌肉瘤细胞中 MET 信号传导促进了肿瘤内毛细血管的生长；将低表达 MET 的 RH30 ARMS 细胞（RH30 shMET）与正常 RH30 ARMS 细胞接种于 NOD-SCID 小鼠皮下后发现，RH30 shMET 组形成的肿瘤中的毛细血管数量与 RH30 ARMS 细胞组比明显减少；IHC 免疫组化实验发现过表达 TPR-MET 的 SMS-CTR 肿瘤组的 CD31（新生血管标志物）的表达与 SMS-CTR 细胞组相比显著增加；将过表达 TPR-MET 的 SMS-CTR 细胞的条件培养基培养 HUVEC 内皮细胞，在基质胶中发现血管网和血管生成形成的连接节点数量明显增多。因此，推测所有促血管生成现象可能是因为在过表达 TPR-MET 的 SMS-CTR 细胞中，miR-378，MMP9 和 VEGF 为高表达，而低表达 MET 的 ARMS 细胞表现出抗血管生成作用则可能为通过降低上述因子表达所致。此外，使用 miR-378 抑制剂后，可逆转 TPR-MET 促进 VEGF mRNA 和蛋白质水平的调控作用。所有结果都表明，miR-378 可能为 MET 促血管生成的介质之一。因此可认为 miR-378 在横纹肌肉瘤的发生、发展、血管生成中具有重要的调控作用，但具体作用机制尚有待进一步研究。

3.4 miR-378 与卵巢癌

卵巢癌是女性生殖系统中死亡率最高的恶性肿瘤。大部分患者因在早期缺乏典型症状和有效诊断方法，故在确诊时已为中晚期，且 5 年总生存率仅为 30%[79-81]。近年来，虽然手术治疗和辅助化疗已经大大提高卵巢癌患者的生存率，但仍面临着卵巢癌的复发和化疗耐药等问题，这些都大大增加了卵巢癌的临床治疗难度。

Chan 等[82]表明 miR-378 在卵巢癌细胞和人类卵巢癌肿瘤组织中的表达比正常卵巢上皮细胞表达都高。用 miR-378 模拟物转染 SKOV3 卵巢癌细胞后发现，高表达 miR-378 的 SKOV3 卵巢癌细胞中，与血管生成相关的基因（ALCAM，EHD1，ELK3，TLN1）的表达均降低；使用抗血管生成药物贝伐珠单抗治疗复发性卵巢癌患者时发现，低表达 miR-378 的卵巢癌患者会有较长的生存时间，分析可能是 miR-378 抑制血管生成所致。因此可认为卵巢癌细胞和组织中 miR-378 表达模式可能与正常卵巢癌不同，miR-378 可以作为预测卵巢癌中抗血管生成治疗反应的生物标志物。

4 总结与展望

肿瘤细胞中 miR-378 异常表达后可影响肿瘤血管的生成。在胶质瘤、肺腺癌、胚胎横纹肌肉瘤细胞中高表达 miR-378 后可发现其促进肿瘤血管生成；但却会抑制卵巢癌的血管生成。因此，miR-378 在不同肿瘤中调控血管生成存在差异，但导致差异原因仍不清楚。此外，miR-378 调控血管生成的信号通路及作用机制已进行研究，但更多的集中在 miR-378 与相关肿瘤细胞靶基因的研究。且肿瘤血管生成也会受到肿瘤微环境、免疫系统等影响，调控机制可能涉及多种分子靶向细胞增殖或凋亡、迁移、侵袭、粘附、管腔形成等复杂的血管生成相关的生物学过程调节，从而影响肿瘤的血管生成。随着对 miR-378 研究的深入，发现 miR-378 不仅能够调控肿瘤中血管生成，而且与心血管等疾病也密切相关，但作用机制尚不清楚。若将具体作用网络通路及分子机制进一步深入研究，则可为这些疾病的治疗提供新的思路，最终也为我们全面研究 miR-378 的调控网络提供新的视角。

参 考 文 献(References)

[1] Folkman J. Angiogenesis [J]. Journal of Biological Chemistry, 1992, 267(16): 1-18

[2] Xu Y, Yuan FE, Chen QX, et al. Molecular mechanisms involved in angiogenesis and potential target of antiangiogenesis in human glioblastomas[J]. Glioma, 2018, 1(2): 35

[3] Ofek P, Tiram G, Satchifainaro R. Angiogenesis regulation by nanocarriers bearing RNA interference [J]. Advanced Drug Delivery Reviews, 2017, 119: 3-19

[4] Meiyu LU, Zhong W, Chunfeng SI, et al. Tumor angiogenesis and tumor vascular-targeted drug: research advances[J]. Anhui Medical & Pharmaceutical Journal, 2018

[5] Marmé D. Tumor angiogenesis: a key target for cancer therapy [J]. Oncology Research & Treatment, 2018, 41(4)

[6] Moreirasoares M, Coimbra R, Rebelo L, et al. Angiogenic Factors produced by Hypoxic Cells are a leading driver of Anastomoses in Sprouting Angiogenesis-a computational study[J]. Scientific Reports, 2018, 8(1)

[7] Xie Y, Qi Y, Zhang Y, et al. Regulation of angiogenic factors by the PI3K/Akt pathway in A549 lung cancer cells under hypoxic conditions[J]. Oncology Letters, 2017, 13(5): 2909-2914

[8] Kareva I. Chapter 4-Blood vessel formation and pathological angiogenesis as mitigated by competing angiogenesis regulators [J]. Understanding Cancer from A Systems Biology Point of View, 2018: 45-60

[9] Pauty J, Usuba R, Cheng IG, et al. A vascular endothelial growth factor-dependent sprouting angiogenesis assay based on an in vitro human blood vessel model for the study of anti-angiogenic drugs[J]. Ebiomedicine, 2018, 27: 225-236

[10] Khalil S, Yendala R, D'Cunha N, et al. Giant-cell tumor of bone with pathological evidence of blood vessel invasion [J]. Hematology oncology & Stem Cell Therapy, 2017, 10(3): 161

[11] Ronca R, Benkheil M, Mitola S, et al. Tumor angiogenesis revisited: regulators and clinical implications [J]. Medicinal Research Reviews, 2017, 37

[12] Stylianopoulos T, Munn LL, Jain RK. Reengineering the tumor vasculature: improving drug delivery and efficacy [J]. Trends in Cancer, 2018, 4(4): 258

[13] Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases[J]. Nature, 2000, 407(6801): 249

[14] You WK, Stallcup WB. Localization of VEGF to vascular ECM is an important aspect of tumor angiogenesis[J]. Cancers, 2017, 9(8): 97

[15] Kang EB, Lee GB, In I, et al. PH-sensitive fluorescent hyaluronic acid nanogels for tumor-targeting and controlled delivery of doxorubicin and nitric oxide[J]. European Polymer Journal, 2018, 101

[16] Rasheduzzaman M, Moon JH, Lee JH, et al. Telmisartan generates ROS-dependent upregulation of death receptor 5 to sensitize TRAIL in lung cancer via inhibition of autophagy flux [J]. International Journal of Biochemistry & Cell Biology, 2018

[17] Rabender CS, Bruno N, Alam A, et al. Sepiapterin enhances tumor radio and chemosensitivities by promoting vascular normalization[J]. Journal of Pharmacology & Experimental Therapeutics, 2018, 365(3): jpet. 117. 245258

[18] Wang F, Xia X, Yang C, et al. SMAD4 gene mutation renders pancreatic cancer resistance to radiotherapy through promotion of autophagy[J]. Clin Cancer Res, 2018, 24(13): 3176-3185

[19] Croce CM. Causes and consequences of microRNA dysregulation in cancer[J]. Cancer Journal, 2012, 48(3): 215-222

[20] Wu W. MicroRNA, noise, and gene expression regulation [J]. Methods Mol Biol, 2018: 91-96

[21] Zhao H, Kuang L, Wang L, et al. Prediction of microRNA-disease associations based on distance correlation set[J]. Bmc Bioinformatics, 2018, 19(1): 141

[22] Liu Q, Zhang L, Li H. New Insights: microRNA function in CNS development and psychiatric diseases [J]. Current Pharmacology Reports, 2018, 4(7006): 1-13

[23] Motti ML, D'Angelo S, Meccariello R. MicroRNA, cancer and diet: facts and new exciting perspectives[J]. Curr Mol Pharmacol, 2018, 10

[24] Krist B, Florczyk U, Pietraszek-Gremplewicz K, et al. The role of miR-378a in metabolism, angiogenesis, and muscle biology [J]. International Journal of Endocrinology, 2015, (2015-12-29), 2015, 2015(2, part 1): 1-13

[25] Molinapinelo S, Gutiérrez G, Pastor MD, et al. MicroRNA-dependent regulation of transcription in non-small cell lung cancer[J]. Plos One, 2014, 9(3): e90524

[26] Naixin D, Xin JS, Ting TW, et al. miR-378a-3p exerts tumor suppressive function on the tumorigenesis of esophageal squamous cell carcinoma by targeting Rab10 [J]. International Journal of Molecular Medicine, 2018, 42: 381-391

[27] 张秀敏, 于波, 李学渊. 过表达 miR-378 骨髓间充质干细胞移植治疗心肌梗死[J]. 中国组织工程研究, 2017, 21(9): 1390-1396

[28] Yuan J, Liu H, Gao W, et al. MicroRNA-378 suppresses myocardial fibrosis through a paracrine mechanism at the early stage of cardiac hypertrophy following mechanical stress[J]. Theranostics, 2018, 8(9): 2565-2582

[29] Sun M, Yamashita T, Shang J, et al. Time-dependent profiles of microRNA expression induced by ischemic preconditioning in the gerbil hippocampus[J]. Cell Transplantation, 2015, 24(3): 367-376

[30] 钟洁, 李洁霏, 郭颖, 等. miR-378 负性调节 caspase-3 蛋白表达减轻氧 - 糖剥夺致小鼠 N2A 细胞缺血损伤 [J]. 基础医学与临床, 2013, 33(11): 1446-1451

[31] Zhang N, Zhong J, Han S, et al. MicroRNA-378 alleviates cerebral ischemic injury by negatively regulating apoptosis executioner caspase-3 [J]. International Journal of Molecular Sciences, 2016, 17 (9): 1427

[32] Ambros V. The functions of animal microRNAs [J]. Nature, 2004, 431(7006): 350-355

[33] Zielaksteciwko AE, Browne JA. How to explore the function and importance of microRNAs: microRNAs expression profile and their target/pathway prediction in bovine ovarian cells [J]. Methods in Molecular Biology, 2018, 1733: 93

[34] Zhang Y, Yun Z, Gong L, et al. Comparison of miRNA evolution and function in plants and animals[J]. Microrna, 2018, 7(1): 4

[35] Fabbri M. MicroRNAs and mi-rceptors: a new mechanism of action for intercellular communication [J]. Philos Trans R Soc Lond B Biol Sci, 2018, 373(1737): 20160486

[36] Xu Y, Yuan FE, Chen QX, et al. Molecular mechanisms involved in angiogenesis and potential target of antiangiogenesis in human glioblastomas[J]. Glioma, 2018, 1(2): 35-42

[37] Li LY. Targeting tumor vasculature for anti-cancer therapy [J]. Clinical Journal of Cancer Biotherm, 2001, 8(3): 163-3167

[38] Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease[J]. Nature Medicine, 1995, 1(1): 27-31

[39] Bauer AJ, Terrell R, Doniparthi NK, et al. Vascular endothelial growth factor monoclonal antibody inhibits growth of anaplastic thyroid cancer xenografts in nude mice[J]. Thyroid Official Journal of the American Thyroid Association, 2002, 12(11): 953

[40] Yaguang Hu, Xi Lu, Yue Xu, et al. Salubrinal attenuated retinal neovascularization by inhibiting CHOP-HIF-1α-VEGF pathways [J]. Oncotarget, 2017, 8(44): 77219-77232

[41] Tang J, Xia J, Zhang X. The relationship between the level of serum HIF-1α, MMP-2 and VEGF and clinical features in patients with non-small cell lung cancer [J]. Chinese Journal of Clinical Rational Drug Use, 2018

[42] Ai P, Shen B, Pan H, et al. MiR-411 suppressed vein wall fibrosis by downregulating MMP-2 via targeting HIF-1α [J]. Journal of Thrombosis & Thrombolysis, 2018, 45(2): 264-273

[43] Liu G, Liu L, Pathology DO. Expression of HIF-1α and MMP-2 in gastric cancer and their clinicopathological significance [J]. Contemporary Medicine, 2018

[44] Lam Y, Lecce L, Ng M. Androgens enhance ischaemia-mediated neovascularisation by stimulation of HIF-1α and endothelial progenitor cell (EPC) mobilisation [J]. Heart Lung & Circulation, 2013, 22(Suppl 1): S12-S12

[45] Lee YA, Choi HM, Lee SH, et al. Hypoxia differentially affects IL-β-stimulated MMP-1 and MMP-13 expression of fibroblast-like synoviocytes in an HIF-1α-dependent manner [J]. Rheumatology, 2012, 51(3): 443-450

[46] 朱振浩, 陈家乐, 伍丽青, 等. miRNA 参与的血管内皮生长因子及其信号通路调控在肿瘤血管生成中作用的研究进展[J]. 广东医学, 2016, 37(1): 136-139

[47] Banys-Paluchowski M, Witzel I, Riethdorf S, et al. The clinical relevance of serum vascular endothelial growth factor (VEGF) in correlation to circulating tumor cells and other serum biomarkers in patients with metastatic breast cancer [J]. Breast Cancer Research & Treatment, 2018, 15(02): 1-12

[48] Bagheri A, Kumar P, Kamath A, et al. Association of angiogenic cytokines (VEGF-A and VEGF-C) and clinical characteristic in women with unexplained recurrent miscarriage [J]. Bratislavske Lekarske Listy, 2017, 118(5): 258

[49] 左慧, 李丽. 在恶性肿瘤中检测 MMPs、TIMPs 的研究进展 [J]. 中国临床医学, 2003, 10(1): 95-97

[50] Belotti D, Paganoni P, Manenti L, et al. Matrix metalloproteinases (MMP9 and MMP2) induce the release of vascular endothelial growth factor (VEGF) by ovarian carcinoma cells: implications for ascites formation[J]. Cancer Research, 2003, 63(17): 5224-5229

[51] 钟思思, 辛柳燕, 郑永亮, 等. miR-378 与肿瘤的研究进展 [J]. 中国老年学, 2015(24): 7253-7256

[52] Velazqueztorres G, Shoshan E, Ivan C, et al. A-to-I miR-378a-3p editing can prevent melanoma progression via regulation of PARVA expression[J]. Nature Communications, 2018, 9(1): 461

[53] Tang X, Zhou J, Zhang J, et al. Low expression of FUS1 is negatively correlated with miR-378 and may predict adverse prognoses in acute myeloid leukemia[J]. Acta Haematologica, 2018, 139(2): 89

[54] Ji KX, Cui F, Qu D, et al. MiR-378 promotes the cell proliferation of non-small cell lung cancer by inhibiting FOXG1[J]. European Review for Medical & Pharmacological Sciences, 2018, 22(4): 1011

[55] 尤永平. 我国脑胶质瘤基础研究与转化现状与进展 [J]. 南京医科大学学报(自然科学版), 2018, (1): 1

[56] Shalijiangaierken, Cai L, Neurosurgery DO. Research progress of microRNA in gliomas[J]. Systems Medicine, 2018

[57] Shi C, Lamba N, Zheng LJ, et al. Depression and survival of glioma patients: a systematic review and meta-analysis[J]. Clinical Neurology & Neurosurgery, 2018, 172: 8

[58] Guishard AF, Yakisich JS, Azad N, et al. Translational gap in ongoing clinical trials for glioma[J]. Journal of Clinical Neuroscience Official Journal of the Neurosurgical Society of Australasia, 2018, 47: 28

[59] Van AW, Senders JT, Martin E, et al. Clinical challenges of glioma and pregnancy: a systematic review [J]. Journal of Neuro-Oncology, 2018, (6): 1-11

[60] Lee DY, Deng Z, Wang CH, et al. MicroRNA-378 promotes cell survival, tumor growth, and angiogenesis by targeting SuFu and Fus-1 expression [J]. Proceedings of the National Academy of Sciences of the United States of America, 2007, 104(51): 20350

[61] Li W, Liu Y, Yang W, et al. MicroRNA-378 enhances radiation response in ectopic and orthotopic implantation models of glioblastoma[J]. Journal of Neuro-Oncology, 2017, 136(Suppl 4): 1-9

[62] Nagase T, Nagase M, Yoshimura K, et al. Angiogenesis within the developing mouse neural tube is dependent on sonic hedgehog signaling: possible roles of motor neurons[J]. Genes to Cells, 2005, 10 (6): 595-604

[63] Pola R, Ling LE, Silver M, et al. The morphogen Sonic hedgehog is an indirect angiogenic agent upregulating two families of angiogenic growth factors[J]. Nature Medicine, 2001, 7(6): 706-711

[64] Lavine KJ, White AC, Park C, et al. Fibroblast growth factor signals regulate a wave of Hedgehog activation that is essential for coronary vascular development[J]. Genes Dev, 2006, 20(12): 1651-1666

[65] Hua Z, Lv Q, Ye W, et al. MiRNA-directed regulation of VEGF and other angiogenic factors under hypoxia[J]. Plos One, 2006, 1(1): e116

[66] 杨丽颖, 陈平. 肺癌死亡率增加冬季雾霾不容小觑 [J]. 家庭医学(下半月), 2018(1): 50-51

[67] Wang Y. Clinical study of compound kushen injection combined with chemotherapy on advancednon-small cell lung cancer [J]. China Journal of Chinese Medicine, 2015

[68] Toriyama M, Tagaya E, Yamamoto T, et al. Lung cancer development in the patient with granulomatosis with polyangiitis during long term treatment with cyclophosphamide: first documented case[J]. Respirology Case Reports, 2018, 6(2): e00284

[69] Wang S, Lian X, Sun M, et al. Efficacy of compound Kushen injection plus radiotherapy on nonsmall-cell lungcancer: A systematic review and meta-analysis [J]. Journal of Cancer Research & Therapeutics, 2016, 12(4): 1298

[70] Chen LT, Xu SD, Xu H, et al. MicroRNA-378 is associated with non-small cell lung cancer brain metastasis by promoting cell migration, invasion and tumor angiogenesis [J]. Medical Oncology, 2012, 29(3): 1673-1680

[71] Chai SH, Noor SM, Nagoor NH. MiR-378 and miR-1827 regulate tumor invasion, migration and angiogenesis in human lung adenocarcinoma by targeting RBX1 and CRKL, respectively [J]. Journal of Cancer, 2018, 9(2): 331

[72] Skrzypek K, Tertil M, Golda S, et al. HO-1 and miR-378 regulate tumor microenvironment and angiogenic potential of human lung cancer[J]. Vascular Pharmacology, 2012, 56(5-6): 369-369

[73] Wasti AT, Mandeville H, Gatz S, et al. Rhabdomyosarcoma [J]. Paediatrics & Child Health, 2018, 28(4) （下转第 1586 页）

Sulfated Polysaccharide Fucoidan Rescues Senescence of Endothelial Colony Forming Cells for Ischemic Repair [J]. Stem Cells, 2015, 33 (6): 1939-1951

[23] Bennis Y, Sarlon-Bartoli G, Guillet B, et al. Priming of late endothelial progenitor cells with erythropoietin before transplantation requires the CD131 receptor subunit and enhances their angiogenic potential[J]. J Thromb Haemost, 2012, 10(9): 1914-1928

[24] Sang Hun Lee J H L, Yong-Seok Han, Jung Min Ryu, et al. Hypoxia accelerates vascular repair of endothelial colony-forming cells on ischemic injury via STAT3-BCL3 axis [J]. Stem Cell Research & Therapy, 2015, 6(1): 139

[25] Mena H A, Zubiry P R, Dizier B, et al. Acidic preconditioning of endothelial colony-forming cells (ECFC) promote vasculogenesis under proinflammatory and high glucose conditions in vitro and in vivo[J]. Stem Cell Res Ther, 2018, 9(1): 120

[26] Lee S H, Lee K B, Lee J H, et al. Selective Interference Targeting of Lnk in Umbilical Cord-Derived Late Endothelial Progenitor Cells Improves Vascular Repair, Following Hind Limb Ischemic Injury, via Regulation of JAK2/STAT3 Signaling [J]. Stem Cells, 2015, 33(5): 1490-500

[27] Falabella Af S L, Valencia Ic, Eaglstein Wh. The use of tissue-engineered skin (Apligraf) to treat a newborn with epidermolysis bullosa[J]. Arch Dermatol, 1999, 135(10): 1219-1222

[28] Ando W, Tateishi K, Hart D A, et al. Cartilage repair using an in vitro generated scaffold-free tissue-engineered construct derived from porcine synovial mesenchymal stem cells [J].Biomaterials, 2007, 28 (36): 5462-5470

[29] Fu J, Wang D A. In Situ Organ-Specific Vascularization in Tissue Engineering[J]. Trends Biotechnol, 2018, 36(8): 834-849

[30] Jung H S, Kim M J, Hong S H, et al. The potential of endothelial colony-forming cells to improve early graft loss after intraportal islet transplantation[J]. Cell Transplant, 2014, 23(3): 273-783

[31] Traktuev D O, Prater D N, Merfeld-Clauss S, et al. Robust functional vascular network formation in vivo by cooperation of adipose progenitor and endothelial cells[J]. Circ Res, 2009, 104(12): 1410-1420

[32] Goerke Sm O J, Plaha J, Stark Gb, et al. Endothelial progenitor cells from peripheral blood support bone regeneration by provoking an angiogenic response[J]. Microvasc Res, 2015, 98: 40-47

[33] Laurenzana A B A, D'alessio S, Bianchini F, et al. Melanoma cell therapy: Endothelial progenitor cells as shuttle of the MMP12 uPAR-degrading enzyme[J]. Oncotarget, 2014, 5(11): 3711-3727

[34] Margheri G Z A, Olmi R , Trigari S, et al.Tumor-tropic endothelial colony forming cells (ECFCs) loaded with near-infrared sensitive Au nanoparticles: A "cellular stove" approach to the photoablation of melanoma[J]. Oncotarget, 2016, 7(26): 39846-39860

[35] Bodempudi V O J, Terai K, Zamora Ea, et al.Blood outgrowth endothelial cell-based systemic delivery of antiangiogenic gene therapy for solid tumors[J]. Cancer Gene Ther, 2010, 17(12): 855-863

[36] Wei J W J, Nakamura T, Stiller D, et al. Targeted release of oncolytic measles virus by blood outgrowth endothelial cells in situ inhibits orthotopic gliomas[J]. Gene Ther, 2007, 14(22): 1573-1586

[37] Melero-Martin Jm D O M, Allen P, Dudley Ac, et al. Host Myeloid Cells Are Necessary for Creating Bioengineered Human Vascular Networks *in Vivo*[J]. Tissue Eng Part A, 2010, 16(8): 2457-2466

[38] Naima Souidi M S, Juliane Rudeck, Dirk Strunk, et al. Stromal Cells Act as Guardians for Endothelial Progenitors by Reducing their Immunogenicity after Cotransplantation [J]. STEM CELLS, 2017, 35 (5): 1233-1245

[39] Burnouf T, Strunk D, Koh M B, et al. Human platelet lysate: Replacing fetal bovine serum as a gold standard for human cell propagation?[J]. Biomaterials, 2016, 76: 371-387

[40] Reinisch A H N, Obenauf Ac, Kashofer K,et al.Humanized large-scale expanded endothelial colony-forming cells function in vitro and in vivo[J]. Blood Cells Mol Dis, 2009, 113(26): 6716-6725

[41] Huang L C P, Grimes Br, Yoder Mc. Human umbilical cord blood plasma can replace fetal bovine serum for in vitro expansion of functional human endothelial colony-forming cells [J]. Cytotherapy, 2011, 13(6): 712-721

[42] Prasain N, Lee M R, Vemula S, et al. Differentiation of human pluripotent stem cells to cells similar to cord-blood endothelial colony-forming cells[J]. Nat Biotechnol, 2014, 32(11): 1151-1157

（上接第 1600 页）

[74] El DD, Mcgowan-Jordan J, De NJ, et al. Update on molecular findings in rhabdomyosarcoma[J]. Pathology, 2017, 49(3)

[75] Russo I, Paolo VD, Gurnari C, et al. Congenital rhabdomyosarcoma: a different clinical presentation in two cases[J]. Bmc Pediatrics, 2018, 18(1): 166

[76] Missiaglia E, Shepherd C J, Aladowicz E, et al. MicroRNA and gene co-expression networks characterize biological and clinical behavior of rhabdomyosarcomas[J]. Cancer Letters, 2017, 385: 251-260

[77] 冯晨, 唐锁勤, 黄东生, 等. 儿童横纹肌肉瘤 8 例临床分析[J]. 中国实用儿科杂志, 2005, 20(5): 297-299

[78] Skrzypek K, Kusienicka A, Szewczyk B, et al. Constitutive activation of MET signaling impairs myogenic differentiation of rhabdomyosarcoma and promotes its development and progression[J]. Oncotarget, 2015, 6(31): 31378-31398

[79] 狄文, 胡媛. 卵巢癌的大数据研究 [J]. 中国实用妇科与产科杂志, 2018, 34(1): 18-22

[80] Lorusso D, Tripodi E, Maltese G, et al. Spotlight on olaparib in the treatment of BRCA-mutated ovarian cancer: design, development and place in therapy [J]. Drug Design Development & Therapy, 2018, 12: 1501-1509

[81] Torre LA, Trabert B, Desantis CE, et al. Ovarian cancer statistics, 2018[J]. Histopathology, 2018

[82] Chan JK, Kiet TK, Blansit K, et al. MiR-378 as a biomarker for response to anti-angiogenic treatment in ovarian cancer [J]. Gynecologic Oncology, 2014, 133(3): 568-574