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MTDH与骨肉瘤的相关研究进展

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摘　要

骨肉瘤是青少年常见的原发性恶性肿瘤，以恶性程度高、预后差、5年生存率低为特点，对患者的生命健康造成严重威胁。如何有效改善骨肉瘤患者的预后，提高治愈率，已成为目前骨肉瘤治疗研究中的热点问题。在许多恶性肿瘤的研究中，异黏蛋白(MTDH)已被证实在肿瘤的发生发展中具有重要作用，参与肿瘤细胞的增殖、侵袭、转移及耐药过程。在骨肉瘤中MTDH基因的作用也得到了部分验证，可将其作为骨肉瘤治疗中的新靶点。本文主要综述了MTDH基因的最新研究现状及其在骨肉瘤中的作用的研究进展。

关键词

异黏蛋白，骨肉瘤，耐药

Research Progress in Correlation between MTDH and Osteosarcoma

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Abstract

Osteosarcoma is a common primary malignant tumor in adolescents, characterized by high malignancy, poor prognosis, and low 5-year survival rate, posing a serious threat to the life and health of patients. How to effectively improve the prognosis of patients with osteosarcoma and increase the cure rate has become a hot topic in current research on the treatment of osteosarcoma.

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In many studies of malignant tumors, it has been proven that metadherin (MTDH) plays an important role in the occurrence and development of tumors, participating in the proliferation, invasion, metastasis, and drug resistance processes of tumor cells. The role of MTDH gene in osteosarcoma has also been partially validated, and it can be used as a new target in the treatment of osteosarcoma. This article mainly reviews the latest research status of MTDH gene and its role in osteosarcoma.

Keywords

MTDH, Osteosarcoma, Drug Resistance

1. 引言

异黏蛋白(metadherin, MTDH)基因，也被称为星形胶质细胞升高基因-1 (AEG-1)或 LYRIC (Lysine Rich CEACAM1)，是近年来发现的一个癌基因，被认为是肿瘤相关抗原[1]。其高表达于多种恶性肿瘤如乳腺癌、肝癌、骨肉瘤黑色素瘤、胶质瘤、神经母细胞瘤、前列腺癌和食道癌，参与并调节增殖、迁移、侵袭、血管生成、化疗耐药性、转移等多种肿瘤生物学过程[2]。因此，MTDH 基因可能可作为肿瘤治疗的新靶点，对未来恶性肿瘤的靶向治疗具有重要价值。本文主要综述了 MTDH 基因的最新研究动态及其在骨肉瘤治疗方面的研究进展。

2. MTDH 基因简介

2.1. MTDH 基因的生物学特征

MTDH 基因于 2002 年作为人类免疫缺陷病毒-1 (human immunodeficiency virus-1, HIV-1)和肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)诱导基因首次在人类初级胎儿星形胶质细胞中被克隆。随后，Brown 和 Ruoslahti 通过体内噬菌体筛选，将小鼠基因克隆为介导乳腺癌细胞向肺转移的蛋白，并命名为 MTDH [2]。MTDH 基因全长 cDNA 包含 3611 个碱基，不包含 poly-A 尾，由 12 个外显子和 11 个内含子组成，位于 8q22 位点[3]。MTDH 编码一种由 582 个氨基酸组成，分子量为 64kD 的 Ib 型单通道跨膜蛋白，主要表达于内质网和核周间隙[4] [5]。MTDH/AEG-1 作为跨膜蛋白出现在细胞质、内质网、核膜和核仁中。该蛋白在哺乳动物中高度保守，在大多数脊椎动物中都能找到，但在非脊椎动物中没有[5]。MTDH 具有 3 个核定位信号区(nuclear localization signals, NLS)，分别位于氨基酸 79~91、432~451、561~580 之间，为 lysine 聚集区域，其中 NLS1 和 NLS3 序列能够介导 MTSH 的细胞核内定位和核转位，发挥调节转录作用，NLS-2 调节并诱导在胞质中的泛素化修饰[6] [7]。

2.2. MTDH 的作用途径

MTDH 被认为是磷脂酰肌醇 3-羟激酶(phosphatidylinositol 3-hydroxy kinase, PI3K)/蛋白激酶 B (protein kinase B，PKB，又称 AKT)、核因子-κB (nuclear factor-κB, NF-κB)、Wnt/β-catenin、促分裂原活化的蛋白激酶(mitogen-activated protein kinase, MAPK)等信号通路的汇聚点，在炎症、血管生成、缺氧、EMT、自噬活性和化疗耐药中发挥重要作用[8]。

2.2.1. PI3K/AKT 通路

原癌基因 Ha-ras 可以激活 PI3K 形成 PIP3 使 PI3K/Akt 信号通路被激活的过程是癌细胞主要生存途径之一[8] [9]。研究表明，MTDH 基因的过表达可激活 PI3K/Akt 信号通路，Akt 被活化后从细胞膜转移至细胞质及细胞核，通过调控 mTOR、磷酸化和失活糖原合酶激酶 3β (GSK3β)、抑制叉头盒 O1 (forkhead box O1, FOXO1)等途径影响骨肉瘤细胞的增殖及凋亡[10] [11]。因此，MTDH 基因与 PI3K/AKT 通路之间高度相关，可作为骨肉瘤治疗的重要靶点。

2.2.2. NF-κB 通路

NF-κB 通路是由 IκBs 组成的经典肿瘤相关调控信号通路。NF-κB 转录因子可在多种肿瘤细胞中表达，当 MTDH 过表达时，IκBs 泛素化降解并释放 p50 和 p65 复合物，这些复合物随后被转运到细胞核中与转移到细胞核中的 MTDH 相互作用，激活基质金属蛋白酶 1 (matrix metalloproteinase 1, MMP1)表达，调控细胞增殖、凋亡、炎性反应及免疫反应等过程[1]。Zhang 等的研究发现锌指转录因子 Miz1 抑制 MTDH 表达后阻止了 NF-κB 通路的激活[12]。Wang 等的研究发现 MTDH 基因可通过 NF-κB 通路诱导含表皮生长因子的纤维蛋白样细胞外基质蛋白 1 (epidermal growth factor-containing fibulin-like extracellular matrix protein 1, EFEMP1)调控基质金属蛋白酶 2 (matrix metalloproteinase 2, MMP-2)的表达，介导骨肉瘤细胞的迁移和侵袭[13]。

2.2.3. Wnt/β-catenin 通路

Wnt/β-catenin 通路也是参与 MTDH 基因介导的肿瘤进展的重要信号通路之一[14]-[20]。Wnts 是一种分泌糖蛋白，在多种细胞过程、胚胎发生、体轴形成、神经发生和癌变中起着关键作用。β-Catenin 是典型 Wnt 信号通路的主要下游效应物。β-catenin 通过酪蛋白激酶 Iα 和糖原合酶激酶 3β (GSK3β)的作用在丝氨酸和苏氨酸残基上磷酸化降解，驱动 β-catenin 核易位，激活 Wnt 通路[14]。在 Li 等人的研究中，证实了抑制 MTDH 基因的表达可抑制 Wnt/β-catenin 信号通路的激活，调控结直肠癌细胞的增殖及侵袭[15]。多项研究表明，通过抑制 Wnt/β-catenin 通路的激活，可抑制骨肉瘤细胞的增殖、转移及侵袭等恶行生物学行为[16] [17] [18] [19] [20]。

2.2.4. MAPK 通路

MTDH 基因也可通过激活 MAPK 通路影响肿瘤的发展。丝裂原活化蛋白激酶(MAPKs)是丝氨酸－苏氨酸蛋白激酶，由生长因子调控的细胞外信号相关激酶(ERKs)、应激激活的 MAPKs、c-jun nh2-末端激酶(JNKs)和 p38 MAPKs 组成，是由 MAPK、MAPK 激酶(MAP2K)和 MAPK 激酶(MAP3K)组成的三激酶信号模块的一部分[21]。在 Xu 等人的研究中 miR-494 高表达可使 p38 MAPK 信号通路失活，促进细胞凋亡，抑制髓母细胞瘤细胞的侵袭、迁移和增殖[22]。Zhu 等人的研究表明，MTDH 基因被敲低后可抑制 p38 MAPK 通路的激活，介导上皮－间充质转化抑制膀胱上皮细胞的纤维化[23]。

3. 骨肉瘤简介

3.1. 骨肉瘤的病因、流行病学及诊断

骨肉瘤是最常见的骨原发性恶性肿瘤，起源于间叶组织，其发病率呈双峰分布，在青少年和大于 60 岁的成年人发病率最高，且在男性中较为常见[24]。病理类型 80%为传统型，其中包括骨母细胞型、软骨母细胞性及纤维母细胞型三种常见亚型。骨肉瘤的好发于四肢长骨干骺端，常见的发病部位依次是股骨、胫骨、肱骨，好发于 10~20 岁青少年[25]。骨肉瘤的病因仍未明确，目前认为其发病是多种因素造成的，主要包括基因因素和环境因素。Li-Fraumeni 综合征、遗传性视网膜母细胞瘤和 Diamond-Blackfan 贫血以及涉及 RECQ 基因家族的原发性 DNA 解旋酶疾病，包括 Rothmund-Thomson 综合征、RAPADILINO

综合征、Bloom 综合征和 Werner 综合征等癌症易感综合征被认为是骨肉瘤发生的风险因素[24]。在老年人群中，Paget 病是一种相当常见的代谢性骨病，约 1%的佩吉特病患者会进展成骨肉瘤[26]。除此之外，曾经接受过放疗或化疗也与儿童骨肉瘤的发生率增加相关[27]。乳糖脱氢酶(LDH)、碱性磷酸酶(ALP)、特异性 AT 序列结合蛋白 2 (Special AT-rich sequence-binding protein 2, SATB 2)以及骨钙素等均为骨肉瘤的敏感标志物，其中碱性磷酸酶在骨肉瘤中具有最重要的诊断意义。使用 X 线、磁共振成像(MRI)、计算机断层扫描(CT)、正电子发射断层扫描(PET)或这些方法的组合也可以辅助诊断骨肉瘤。近些年骨闪烁扫描(BS)经常与 CT 联合使用以识别转移[28]。通过微创穿刺活检方法或开放活检对骨组织活检样本进行病理评估以确定骨肉瘤的分型及分期在骨肉瘤的诊断中也是极为重要的[24]。

3.2. 骨肉瘤的相关调控

骨肉瘤的发生及发展受多种分子生物学机制及其下游信号通路的调控。DNA 的突变、非编码 RNA 的表达改变及表观遗传学的变化通常认为是骨肉瘤发生发展的重要影响因素。

目前普遍认为 TP53 及 RB1 基因的突变在骨肉瘤中是最常见的基因改变。由 TP53 基因编码的 p53 蛋白可调控细胞生长周期、DNA 复制和细胞分裂及激活细胞凋亡等细胞过程[29]。p53 细胞蛋白在正常情况下作为成骨细胞形成的负调控因子，可抑制一些在成骨祖细胞的初始成骨阶段所必需的装炉因子，如 Runx2 等。当 TP53 基因突变时可导致 p53 蛋白失活，使细胞生长失控，驱动肿瘤的发展[30]。RB1 基因为视网膜母细胞肿瘤的抑制基因，现已被确定为骨肉瘤发展的驱动因素之一，有研究表明 RB1 基因对于机体的成骨分化、骨重塑及祖细胞增殖分化的稳定性具有重要意义。Walkley 等发现小鼠成骨细胞中靶向 p53 和 Rb 的突变足以诱导具有人类疾病特征的转移性骨肉瘤[31]。

除此之外，c-Myc 基因在 OS 发病机制中也具有重要作用。c-Myc 基因在 10%以上的病例中过表达，c-Myc 基因涉及细胞增殖、分化和细胞凋亡等细胞生理过程。c-Myc 基因过表达可刺激细胞外信号调节激酶－丝裂原活化蛋白激酶(extracellular signal-regulated kinase-mitogen-activated protein kinase, MEK-ERK)通路的激活，通过抑制 PI3K-AKT 通路的活性增强骨肉瘤细胞的侵袭能力[32]。

非编码 RNA 在骨肉瘤的生物学过程中也发挥着重要的调节功能。MicroRNAs (miRNAs)是一类内源性的非编码小 RNA，在分化、细胞增殖、细胞周期控制、凋亡等多种生物过程中具有重要的调节作用。Meng 等研究证明 miRNA-22 通过下调 PI3K、AKT 及雷帕霉素靶蛋白(mechanistic target of rapamycin kinase, MTOR)的表达，抑制自噬和诱导骨肉瘤细胞及耐药细胞凋亡[33]。环状 RNA (Circular RNAs, circRNAs)，可以充当 miRNA 海绵调节转录或转录后基因表达，并参与多种重要的生物过程的调控。WU 等人研究结果表明 circTADA2A 通过海绵结合 miR-203a-3p 上调环 AMP 反应元件结合蛋白 3 (Cyclic AMP-responsive element-binding protein 3, CREB3)的表达，显著增强了骨肉瘤细胞的增殖、侵袭及肿瘤在体内的生长和转移[34]。

DNA 甲基化、组蛋白修饰以及核小体重塑等表观遗传修饰的改变也可导致骨肉瘤的发生和进展[30]。

4. MTDH 基因与骨肉瘤的恶性生物学行为

MTDH 基因在骨肉瘤的发生及发展中具有重要意义，与骨肉瘤的多种恶性生物学行为有关。多位学者证实了 MTDH 基因在骨肉瘤中高表达，且存在转移的骨肉瘤组织中 MTDH 基因的表达水平高于无转移的组织[35] [36]。

4.1. MTDH 基因与骨肉瘤的增殖、侵袭与转移

MTDH 基因能够参与及调节骨肉瘤细胞的增殖、侵袭及转移过程。通过 MTT 试验及 Transwell 试验，

可观察到过表达 MTDH 基因可明显增强骨肉瘤细胞的增殖及侵袭能力。

有研究表明，MTDH 过表达可介导骨肉瘤的增殖、侵袭过程与基质金属蛋白酶-2 (matrix metallo-proteinase-2, MMP-2)相关，通过转染 MTDH si-RNA 可抑制 MMP-2 的表达，降低骨肉瘤细胞的侵袭性[37]。此外，Wang 等人通过对含表皮生长因子的纤维蛋白样细胞外基质蛋白 1 (epidermal growth factor-containing fibulin-like extracellular matrix protein 1, EFEMP1)的研究发现，MTDH 可通过诱导 EFEMP1 的表达，间接调控 MMP-2 的表达，对骨肉瘤的增殖、侵袭及转移等产生影响。因此，可认为 MTDH 至少部分通过调节 MMP-2 对骨肉瘤的增殖侵袭等进行调控[13]。

MTDH 也可通过受 microRNA 的表达调控骨肉瘤的增殖与侵袭。Guo 等通过检测 microRNA-136 对骨肉瘤增殖侵袭及转移的影响，并验证 MTDH 与 microRNA-136 间的靶向关系后，证明 miR-136 可能通过负向调控其靶基因 MTDH 抑制 OS 细胞的增殖、迁移和侵袭[38]。大量其他类似研究也证明了 miR-22、miR-342-3p、miR-448 等也可通过调控 MTDH 的表达抑制骨肉瘤细胞的增殖及侵袭。因此，MTDH 基因在骨肉瘤的增殖侵袭及庄毅中发挥重要作用，可以此作为骨肉瘤治疗的重要靶点。

4.2. MTDH 基因与新生血管的生成

肿瘤新生血管的生成是维持肿瘤发生发展的重要条件。由血管内皮生长因子(vascular endothelial growth factor, VEGF)、成纤维细胞生长因子(fibroblast growth factor, FGF)、血管生成素(angiopoietin, ANG)、基质金属蛋白酶(matrix metalloproteinase, MMP)等促血管生成因子和血小板应答蛋白 1、血小板因子 4、血管抑制素和内皮抑制素等血管生成抑制剂相互作用，共同调控血管生成过程[39]。在免疫组化分析中，从裸鼠获得的肿瘤注射了克隆的大鼠胚胎成纤维细胞 AEG-1 克隆，结果表明肿瘤具有增加微血管密度和血管生成标志物水平的作用。MTDH 基因可通过调控 NF-κB、PI3K/AKT 通路诱导肿瘤新生血管生成。一项关于三阴乳腺癌标本的分析结果可见 MTDH 与 VEGF 水平与微血管密度(microvessel density, MVD)密切相关，当 MTDH 过表达时，VEGF 水平及 MCD 均增高[40]。在小细胞肺癌、肝细胞癌、头颈部鳞状细胞癌、宫颈癌等多种恶性肿瘤中，MTDH 受 miRNA 的调控，介导肿瘤的新生血管生成[41] [42] [43] [44]。Zhang 等人通过对 miRNA 的研究发现 miRNA 可通过靶向 VEGFA/VEGFR1 途径，抑制骨肉瘤的血管生成[45]。根据上述研究，MTDH 基因可受 miRNA 的调控，调控 VEGF、MMP 等血管生成因子的表达水平，对骨肉瘤中新生血管的生成过程具有极其重要的影响。

4.3. MTDH 基因与上皮－间充质转化

上皮－间充质转化(Epithelial-mesenchymal transition, EMT)是一种可逆的细胞过程，指在某些特定条件下，上皮细胞可短暂地处于准间充质细胞状态，呈现梭形、间充质形态，并可恢复到上皮细胞状态的过程，可使上皮细胞拥有间质细胞的特性[46]。在这一过程中，上皮细胞顶－基底极性等上皮细胞的特征，而获得了前后极性等间质细胞特征，这使上皮细胞获得迁移及侵袭的能力。因此在骨肉瘤等恶性肿瘤中，EMT 可能是肿瘤细胞发生侵袭及转移的重要途径之一[47]。骨肉瘤起源于间叶组织，其细胞表型由 EMT 诱导转录因子(EMT-inducing transcriptions factor, EMT-TF)的功能维持，如 TWIST1、SNAIL、SLUG、ZEB1 和 ZEB2。有研究表明，EMT-TF 在骨肉瘤细胞中过表达时，可促进上皮－间充质转化，促进骨肉瘤细胞的侵袭和转移[48] [49]。在许多恶性肿瘤中，MTDH 通过激活 NF-κB、Wnt/β-catenin、MAPK 等信号通路，调控 EMT 过程，促进肿瘤细胞的转移[23] [50] [51]。TANG 等在验证了在有转移骨肉瘤组织中 MTDH 基因过表达后，通过慢病毒转染敲除骨肉瘤细胞的 MTDH 基因，使用免疫印迹法检测 EMT 及 ERK 信号通路标记物，最终结果显示 MTDH 通过 EMT 促进骨肉瘤细胞的转移。类似的结果在非小细胞肺癌、肝癌、头颈部鳞状细胞癌中也得到验证[52] [53] [54]。

4.4. MTDH 基因与骨肉瘤的耐药

化疗药物的耐药性是导致骨肉瘤治疗失败或发生复发的重要原因之一。MTDH 基因在骨肉瘤的广谱化疗耐药性中也具有重要作用。在对 NCI-60 细胞系的药物基因组分析中，发现 MTDH 基因的表达与化疗药物的耐药有显著的相关性[55]。当 MTDH 基因过表达时，化疗敏感性受影响的药物包括 5-氟尿嘧啶、阿霉素、紫杉醇、顺铂等以及靶向治疗。MTDH 基因通过抑制细胞凋亡、保护性细胞自噬、NF-κB 等信号通路影响肿瘤的化疗敏感性。Zhang 等通过检测转染 MTDH 表达质粒及沉默 MTDH 基因质粒的 Hela 细胞中自噬及凋亡相关蛋白，发现当 MTDH 基因过表达时，可激活 Erk/NF-κB 通路，诱导 Hela 细胞发生自噬，抑制细胞凋亡[56]。在胃癌细胞系中，MTDH 基因过表达时 P-糖蛋白(P-glycoprotein, P-gp)的表达，增强 5-FU 的耐药性[57]。miRNA 可通过调控 MTDH 基因的表达对肿瘤的耐药性产生影响。LI 等使用 5-氟尿嘧啶及顺铂两种化疗药物分别处理沉默 MTDH 的非小细胞肺癌细胞系及对照组，发现当 MTDH 基因被沉默后，肿瘤细胞的化疗敏感性明显增强[58]。类似的结论在乳腺癌、结直肠癌等恶性肿瘤中也得到验证[59] [60]。WANG 等的研究也证实了 miR-22 通过调控 MTDH 基因的表达介导骨肉瘤细胞的自噬，并影响骨肉瘤细胞对顺铂的耐药性[61]。

5. 小结与展望

虽然对骨肉瘤的治疗已由传统的手术及放疗、化疗发展到免疫治疗、光疗法等多种治疗方式，但关于免疫疗法等对骨肉瘤的治疗尚无明确疗效[62]。且骨肉瘤的肺转移及化疗耐药仍是影响骨肉瘤患者预后及 5 年生存率的重要因素。随着对骨肉瘤发病机制与恶性生物学行为的认识不断加深，越来越多的靶点及其对应药物得以研发。本文综述了 MTDH 基因的生物学特征、功能及其在骨肉瘤的发生发展中可能产生的影响。MTDH 基因可通过 PI3K/AKT、NF-κB、WNT/β-catenin、MAPK 等信号通路参与骨肉瘤的增殖、侵袭、转移、新生血管的生成、EMT 等恶性生物学行为过程。在乳腺癌、非小细胞肺癌、结直肠癌、肝癌等恶性肿瘤中，MTDH 基因对其治疗及预后的影响已被证实[63] [64] [65]。因此，可将 MTDH 基因作为骨肉瘤治疗的重要研究靶点，针对 MTDH 及其上下游通路如 circRNA、miRNA 等展开研究，寻找可靠的干预靶点及高效通路，为骨肉瘤的治疗提供更多可能性。这对改善骨肉瘤患者的预后及生存质量具有非常重要的意义和应用前景。

参考文献

[1] Dhiman, G., Srivastava, N., Goyal, M., Rakha, E., Lothion-Roy, J., Mongan, N.P., Miftakhova, R.R., Khaiboullina, S.F., Rizvanov, A.A. and Baranwal, M. (2019) Metadherin: A Therapeutic Target in Multiple Cancers. *Frontiers in Oncology*, **9**, Article No. 349. https://doi.org/10.3389/fonc.2019.00349

[2] Sarkar, D. and Fisher, P.B. (2013) AEG-1/MTDH/LYRIC: Clinical Significance. *Advances in Cancer Research*, **120**, 39-74. https://doi.org/10.1016/B978-0-12-401676-7.00002-4

[3] Shi, X. and Wang, X. (2015) The Role of MTDH/AEG-1 in the Progression of Cancer. *International Journal of Clinical and Experimental Medicine*, **8**, 4795-4807.

[4] Kang, D.C., Su, Z.Z., Sarkar, D., Emdad, L., Volsky, D.J. and Fisher, P.B. (2005) Cloning and Characterization of HIV-1-Inducible Astrocyte Elevated Gene-1, AEG-1. *Gene*, **353**, 8-15. https://doi.org/10.1016/j.gene.2005.04.006

[5] Sutherland, H.G., Lam, Y.W., Briers, S., Lamond, A.I. and Bickmore, W.A. (2004) 3D3/Lyric: A Novel Transmembrane Protein of the Endoplasmic Reticulum and Nuclear Envelope, Which Is Also Present in the Nucleolus. *Experimental Cell Research*, **294**, 94-105. https://doi.org/10.1016/j.yexcr.2003.11.020

[6] Chen, J., Sun, M.X., Hua, Y.Q. and Cai, Z.D. (2014) Prognostic Significance of Serum Lactate Dehydrogenase Level in Osteosarcoma: A Meta-Analysis. *Journal of Cancer Research and Clinical Oncology*, **140**, 1205-1210. https://doi.org/10.1007/s00432-014-1644-0

[7] Thirkettle, H.J., Girling, J., Warren, A.Y., Mills, I.G., Sahadevan, K., Leung, H., Hamdy, F., Whitaker, H.C. and Neal, D.E. (2009) LYRIC/AEG-1 Is Targeted to Different Subcellular Compartments by Ubiquitinylation and Intrinsic Nuc-

lear Localization Signals. *Clinical Cancer Research*, **15**, 3003-3013. https://doi.org/10.1158/1078-0432.CCR-08-2046

[8] Chen, Y., Huang, S., Guo, R. and Chen, D. (2021) Metadherin-Mediated Mechanisms in Human Malignancies. *Biomarkers in Medicine*, **15**, 1769-1783. https://doi.org/10.2217/bmm-2021-0298

[9] Qian, B., Yao, Y., Liu, C., Zhang, J., Chen, H. and Li, H. (2017) SU6668 Modulates Prostate Cancer Progression by Downregulating MTDH/AKT Signaling Pathway. *International Journal of Oncology*, **50**, 1601-1611. https://doi.org/10.3892/ijo.2017.3926

[10] Zhang, J., Yu, X.H., Yan, Y.G., Wang, C. and Wang, W.J. (2015) PI3K/Akt Signaling in Osteosarcoma. *Clinica Chimica Acta*, **444**, 182-192. https://doi.org/10.1016/j.cca.2014.12.041

[11] Sriramulu, S., Sun, X.F., Malayaperumal, S., Ganesan, H., Zhang, H., Ramachandran, M., Banerjee, A. and Pathak, S. (2021) Emerging Role and Clinicopathological Significance of AEG-1 in Different Cancer Types: A Concise Review. *Cells*, **10**, Article No. 1497. https://doi.org/10.3390/cells10061497

[12] Zhang, W., Zhangyuan, G., Wang, F., Jin, K., Shen, H., Zhang, L., Yuan, X., Wang, J., Zhang, H., Yu, W., Huang, R., Xu, X., Yin, Y., Zhong, G., Lin, A. and Sun, B. (2021) The Zinc Finger Protein Miz1 Suppresses Liver Tumorigenesis by Restricting Hepatocyte-Driven Macrophage Activation and Inflammation. *Immunity*, **54**, 1168-1185.E8. https://doi.org/10.1016/j.immuni.2021.04.027

[13] Wang, Z., Cao, C.J., Huang, L.L., Ke, Z.F., Luo, C.J., Lin, Z.W., Wang, F., Zhang, Y.Q. and Wang, L.T. (2015) EFEMP1 Promotes the Migration and Invasion of Osteosarcoma via MMP-2 with Induction by AEG-1 via NF-*κ*B Signaling Pathway. *Oncotarget*, **6**, 14191-14208. https://doi.org/10.18632/oncotarget.3691

[14] Yoo, B.K., Emdad, L., Su, Z.Z., Villanueva, A., Chiang, D.Y., Mukhopadhyay, N.D., Mills, A.S., Waxman, S., Fisher, R.A., Llovet, J.M., Fisher, P.B. and Sarkar, D. (2009) Astrocyte Elevated Gene-1 Regulates Hepatocellular Carcinoma Development and Progression. *Journal of Clinical Investigation*, **119**, 465-477. https://doi.org/10.1172/JCI36460

[15] Li, S., Wu, T., Zhang, D., Sun, X. and Zhang, X. (2020) The Long Non-Coding RNA HCG18 Promotes the Growth and Invasion of Colorectal Cancer Cells through Sponging MiR-1271 and Upregulating MTDH/Wnt/*β*-Catenin. *Clinical and Experimental Pharmacology and Physiology*, **47**, 703-712. https://doi.org/10.1111/1440-1681.13230

[16] Han, Y.L., Luo, D., Habaxi, K., Tayierjiang, J., Zhao, W., Wang, W., Aikebaier, W. and Wang, L. (2022) COL5A2 Inhibits the TGF-*β* and Wnt/*β*-Catenin Signaling Pathways to Inhibit the Invasion and Metastasis of Osteosarcoma. *Frontiers in Oncology*, **12**, Article ID: 813809. https://doi.org/10.3389/fonc.2022.813809

[17] Guo, H., Peng, J., Hu, J., Chang, S., Liu, H., Luo, H., Chen, X., Tang, H. and Chen, Y. (2021) BAIAP2L2 Promotes the Proliferation, Migration and Invasion of Osteosarcoma Associated with the Wnt/*β*-Catenin Pathway. *Journal of Bone Oncology*, **31**, Article ID: 100393. https://doi.org/10.1016/j.jbo.2021.100393

[18] Zhang, D., Han, S., Pan, X., Li, H., Zhao, H., Gao, X. and Wang, S. (2022) EFEMP1 Binds to STEAP1 to Promote Osteosarcoma Proliferation and Invasion via the Wnt/*β*-Catenin and TGF-*β*/Smad2/3 Signal Pathways. *Journal of Bone Oncology*, **37**, Article ID: 100458. https://doi.org/10.1016/j.jbo.2022.100458

[19] Xie, W., Chang, W., Wang, X., Liu, F., Wang, X., Yuan, D. and Zhang, Y. (2022) Allicin Inhibits Osteosarcoma Growth by Promoting Oxidative Stress and Autophagy via the Inactivation of the LncRNA MALAT1-MiR-376a-Wnt/*β*-Catenin Signaling Pathway. *Oxidative Medicine and Cellular Longevity*, **2022**, Article ID: 4857814. https://doi.org/10.1155/2022/4857814

[20] Liang, K., Liao, L., Liu, Q., Ouyang, Q., Jia, L. and Wu, G. (2021) MicroRNA-377-3p Inhibits Osteosarcoma Progression by Targeting CUL1 and Regulating Wnt/*β*-Catenin Signaling Pathway. *Clinical and Translational Oncology*, **23**, 2350-2357. https://doi.org/10.1007/s12094-021-02633-6

[21] Son, Y., Cheong, Y.K., Kim, N.H., Chung, H.T., Kang, D.G. and Pae, H.O. (2011) Mitogen-Activated Protein Kinases and Reactive Oxygen Species: How Can ROS Activate MAPK Pathways? *Journal of Signal Transduction*, **2011**, Article ID: 792639. https://doi.org/10.1155/2011/792639

[22] Xu, X.H., Zhang, S.J., Hu, Q.B., Song, X.Y. and Pan, W. (2019) Retracted: Effects of MicroRNA-494 on Proliferation, Migration, Invasion, and Apoptosis of Medulloblastoma Cells by Mediating C-Myc through the P38 MAPK Signaling Pathway. *Journal of Cellular Biochemistry*, **120**, 2594-2606. https://doi.org/10.1002/jcb.27559

[23] Zhu, Q., Li, K., Li, H., Han, F., Tang, Z. and Wang, Z. (2022) Ketamine Induced Bladder Fibrosis through MTDH/P38 MAPK/EMT Pathway. *Frontiers in Pharmacology*, **12**, Article ID: 743682. https://doi.org/10.3389/fphar.2021.743682

[24] Beird, H.C., Bielack, S.S., Flanagan, A.M., Gill, J., Heymann, D., Janeway, K.A., Livingston, J.A., Roberts, R.D., Strauss, S.J. and Gorlick, R. (2022) Osteosarcoma. *Nature Reviews Disease Primers*, **8**, Article No. 77. https://doi.org/10.1038/s41572-022-00409-y

[25] Ottaviani, G. and Jaffe, N. (2009) The Epidemiology of Osteosarcoma. *Cancer Research and Treatment*, **152**, 3-13. https://doi.org/10.1007/978-1-4419-0284-9_1

[26] Hansen, M.F., Seton, M. and Merchant, A. (2006) Osteosarcoma in Paget's Disease of Bone. *Journal of Bone and Mineral Research*, **21**, 58-63. https://doi.org/10.1359/jbmr.06s211

[27] Tucker, M.A., D'Angio, G.J., Boice, J.D., Strong, L.C., Li, F.P., Stovall, M., Stone, B.J., Green, D.M., Lombardi, F., Newton, W., *et al*. (1987) Bone Sarcomas Linked to Radiotherapy and Chemotherapy in Children. *The New England Journal of Medicine*, **317**, 588-593. https://doi.org/10.1056/NEJM198709033171002

[28] Jafari, F., Javdansirat, S., Sanaie, S., Naseri, A., Shamekh, A., Rostamzadeh, D. and Dolati, S. (2020) Osteosarcoma: A Comprehensive Review of Management and Treatment Strategies. *Annals of Diagnostic Pathology*, **49**, Article ID: 151654. https://doi.org/10.1016/j.anndiagpath.2020.151654

[29] Czarnecka, A.M., Synoradzki, K., Firlej, W., Bartnik, E., Sobczuk, P., Fiedorowicz, M., Grieb, P. and Rutkowski, P. (2020) Molecular Biology of Osteosarcoma. *Cancers* (*Basel*), **12**, Article No. 2130. https://doi.org/10.3390/cancers12082130

[30] De Azevedo, J.W.V., De Medeiros Fernandes, T.A.A., Fernandes, J.V., De Azevedo, J.C.V., Lanza, D.C.F., Bezerra, C.M., Andrade, V.S., De Araújo, J.M.G. and Fernandes, J.V. (2020) Biology and Pathogenesis of Human Osteosarcoma. *Oncology Letters*, **19**, 1099-1116. https://doi.org/10.3892/ol.2019.11229

[31] Walkley, C.R., Qudsi, R., Sankaran, V.G., Perry, J.A., Gostissa, M., Roth, S.I., Rodda, S.J., Snay, E., Dunning, P., Fahey, F.H., Alt, F.W., McMahon, A.P. and Orkin, S.H. (2008) Conditional Mouse Osteosarcoma, Dependent on P53 Loss and Potentiated by Loss of Rb, Mimics the Human Disease. *Genes & Development*, **22**, 1662-1676. https://doi.org/10.1101/gad.1656808

[32] Han, G., Wang, Y. and Bi, W. (2012) C-Myc Overexpression Promotes Osteosarcoma Cell Invasion via Activation of MEK-ERK Pathway. *Oncology Research*, **20**, 149-156. https://doi.org/10.3727/096504012X13522227232237

[33] Meng, C.Y., Zhao, Z.Q., Bai, R., Zhao, W., Wang, Y.X., Xue, H.Q., Sun, L., Sun, C., Feng, W. and Guo, S.B. (2020) MicroRNA-22 Mediates the Cisplatin Resistance of Osteosarcoma Cells by Inhibiting Autophagy via the PI3K/Akt/MTOR Pathway. *Oncology Reports*, **43**, 1169-1186. https://doi.org/10.3892/or.2020.7492

[34] Wu, Y., Xie, Z., Chen, J., Chen, J., Ni, W., Ma, Y., Huang, K., Wang, G., Wang, J., Ma, J., Shen, S. and Fan, S. (2019) Circular RNA CircTADA2A Promotes Osteosarcoma Progression and Metastasis by Sponging MiR-203a-3p and Regulating CREB3 Expression. *Molecular Cancer*, **18**, Article No. 73. https://doi.org/10.1186/s12943-019-1007-1

[35] Orentas, R.J., Yang, J.J., Wen, X., Wei, J.S., Mackall, C.L. and Khan, J. (2012) Identification of Cell Surface Proteins as Potential Immunotherapy Targets in 12 Pediatric Cancers. *Frontiers in Oncology*, **2**, Article No. 194. https://doi.org/10.3389/fonc.2012.00194

[36] Tang, J., Shen, L., Yang, Q. and Zhang, C. (2014) Overexpression of Metadherin Mediates Metastasis of Osteosarcoma by Regulating Epithelial-Mesenchymal Transition. *Cell Proliferation*, **47**, 427-434. https://doi.org/10.1111/cpr.12129

[37] Wang, F., Ke, Z.F., Sun, S.J., Chen, W.F., Yang, S.C., Li, S.H., Mao, X.P. and Wang, L.T. (2011) Oncogenic Roles of Astrocyte Elevated Gene-1 (AEG-1) in Osteosarcoma Progression and Prognosis. *Cancer Biology & Therapy*, **12**, 539-548. https://doi.org/10.4161/cbt.12.6.16301

[38] Guo, T. and Pan, G. (2018) MicroRNA-136 Functions as a Tumor Suppressor in Osteosarcoma via Regulating Metadherin. *Cancer Biomarkers*, **22**, 79-87. https://doi.org/10.3233/CBM-170970

[39] Carmeliet, P. and Jain, R.K. (2000) Angiogenesis in Cancer and Other Diseases. *Nature*, **407**, 249-257. https://doi.org/10.1038/35025220

[40] Li, C., Li, R., Song, H., Wang, D., Feng, T., Yu, X., Zhao, Y., Liu, J., Yu, X., Wang, Y. and Geng, J. (2011) Significance of AEG-1 Expression in Correlation with VEGF, Microvessel Density and Clinicopathological Characteristics in Triple-Negative Breast Cancer. *Journal of Surgical Oncology*, **103**, 184-192. https://doi.org/10.1002/jso.21788

[41] Zhang, S., Li, G., Liu, C., Lu, S., Jing, Q., Chen, X., Zheng, H., Ma, H., Zhang, D., Ren, S., Shen, Z., Wang, Y., Lu, Z., Huang, D., Tan, P., Chen, J., Zhang, X., Qiu, Y. and Liu, Y. (2020) MiR-30e-5p Represses Angiogenesis and Metastasis by Directly Targeting AEG-1 in Squamous Cell Carcinoma of the Head and Neck. *Cancer Science*, **111**, 356-368. https://doi.org/10.1111/cas.14259

[42] Ding, Q., Chen, Y., Dong, S., Xu, X., Liu, J., Song, P., Yu, C. and Ma, Z. (2018) Astrocyte Elevated Gene-1 Is Overexpressed in Non-Small-Cell Lung Cancer and Associated with Increased Tumour Angiogenesis. *Interdisciplinary CardioVascular and Thoracic Surgery*, **26**, 395-401. https://doi.org/10.1093/icvts/ivx340

[43] Yan, J.J., Zhang, Y.N., Liao, J.Z., Ke, K.P., Chang, Y., Li, P.Y., Wang, M., Lin, J.S. and He, X.X. (2015) MiR-497 Suppresses Angiogenesis and Metastasis of Hepatocellular Carcinoma by Inhibiting VEGFA and AEG-1. *Oncotarget*, **6**, 29527-29542. https://doi.org/10.18632/oncotarget.5012

[44] Long, M., Dong, K., Gao, P., Wang, X., Liu, L., Yang, S., Lin, F., Wei, J. and Zhang, H. (2013) Overexpression of Astrocyte-Elevated Gene-1 Is Associated with Cervical Carcinoma Progression and Angiogenesis. *Oncology Reports*, **30**, 1414-1422. https://doi.org/10.3892/or.2013.2598

[45] Zhang, L., Lv, Z., Xu, J., Chen, C., Ge, Q., Li, P., Wei, D., Wu, Z. and Sun, X. (2018) MicroRNA-134 Inhibits Osteosarcoma Angiogenesis and Proliferation by Targeting the VEGFA/VEGFR1 Pathway. *FEBS Journal*, **285**, 1359-1371. https://doi.org/10.1111/febs.14416

[46] Dongre, A. and Weinberg, R.A. (2019) New Insights into the Mechanisms of Epithelial-Mesenchymal Transition and Implications for Cancer. *Nature Reviews Molecular Cell Biology*, **20**, 69-84. https://doi.org/10.1038/s41580-018-0080-4

[47] Lamouille, S., Xu, J. and Derynck, R. (2014) Molecular Mechanisms of Epithelial-Mesenchymal Transition. *Nature Reviews Molecular Cell Biology*, **15**, 178-196. https://doi.org/10.1038/nrm3758

[48] Sharili, A.S., Allen, S., Smith, K., Hargreaves, J., Price, J. and McGonnell, I. (2011) Expression of Snail2 in Long Bone Osteosarcomas Correlates with Tumour Malignancy. *Tumor Biology*, **32**, 515-526. https://doi.org/10.1007/s13277-010-0146-1

[49] Shen, A., Zhang, Y., Yang, H., Xu, R. and Huang, G. (2012) Overexpression of ZEB1 Relates to Metastasis and Invasion in Osteosarcoma. *Journal of Surgical Oncology*, **105**, 830-834. https://doi.org/10.1002/jso.23012

[50] El-Ashmawy, N.E., El-Zamarany, E.A., Khedr, E.G. and Abo-Saif, M.A. (2019) Activation of EMT in Colorectal Cancer by MTDH/NF-*κ*B P65 Pathway. *Molecular and Cellular Biochemistry*, **457**, 83-91. https://doi.org/10.1007/s11010-019-03514-x

[51] He, W., He, S., Wang, Z., Shen, H., Fang, W., Zhang, Y., Qian, W., Lin, M., Yuan, J., Wang, J., Huang, W., Wang, L. and Ke, Z. (2015) Astrocyte Elevated Gene-1(AEG-1) Induces Epithelial-Mesenchymal Transition in Lung Cancer through Activating Wnt/*β*-Catenin Signaling. *BMC Cancer*, **15**, Article No. 107. https://doi.org/10.1186/s12885-015-1124-1

[52] Yin, Q., Han, Y., Zhu, D., Li, Z., Shan, S., Jin, W., Lu, Q. and Ren, T. (2018) MiR-145 and MiR-497 Suppress TGF-*β*-Induced Epithelial-Mesenchymal Transition of Non-Small Cell Lung Cancer by Targeting MTDH. *Cancer Cell International*, **18**, Article No. 105. https://doi.org/10.1186/s12935-018-0601-4

[53] Zhu, K., Dai, Z., Pan, Q., Wang, Z., Yang, G.H., Yu, L., Ding, Z.B., Shi, G.M., Ke, A.W., Yang, X.R., Tao, Z.H., Zhao, Y.M., Qin, Y., Zeng, H.Y., Tang, Z.Y., Fan, J. and Zhou, J. (2011) Metadherin Promotes Hepatocellular Carcinoma Metastasis through Induction of Epithelial-Mesenchymal Transition. *Clinical Cancer Research*, **17**, 7294-7302. https://doi.org/10.1158/1078-0432.CCR-11-1327

[54] Tan, H., Zhu, G., She, L., Wei, M., Wang, Y., Pi, L., Chen, C., Zhang, D., Tan, P., Chen, J., Huang, D., Tian, Y., Liu, Y. and Zhang, X. (2017) MiR-98 Inhibits Malignant Progression via Targeting MTDH in Squamous Cell Carcinoma of the Head and Neck. *American Journal of Cancer Research*, **7**, 2554-2565.

[55] Hu, G., Chong, R.A., Yang, Q., Wei, Y., Blanco, M.A., Li, F., Reiss, M., Au, J.L., Haffty, B.G. and Kang, Y. (2009) MTDH Activation by 8q22 Genomic Gain Promotes Chemoresistance and Metastasis of Poor-Prognosis Breast Cancer. *Cancer Cell*, **15**, 9-20. https://doi.org/10.1016/j.ccr.2008.11.013

[56] Zhang, J., Zhang, Y., Liu, S., Zhang, Q., Wang, Y., Tong, L., Chen, X., Ji, Y., Shang, Q., Xu, B., Chu, M. and Wei, L. (2013) Metadherin Confers Chemoresistance of Cervical Cancer Cells by Inducing Autophagy and Activating ERK/NF-*κ*B Pathway. *Tumor Biology*, **34**, 2433-2440. https://doi.org/10.1007/s13277-013-0794-z

[57] Pei, G., Luo, M., Ni, X., Wu, J., Wang, S., Ma, Y. and Yu, J. (2018) Autophagy Facilitates Metadherin-Induced Chemotherapy Resistance through the AMPK/ATG5 Pathway in Gastric Cancer. *Cellular Physiology and Biochemistry*, **46**, 847-859. https://doi.org/10.1159/000488742

[58] Li, Y.H., Xu, C.L., He, C.J., Pu, H.H., Liu, J.L. and Wang, Y. (2020) CircMTDH.4/MiR-630/AEG-1 Axis Participates in the Regulation of Proliferation, Migration, Invasion, Chemoresistance, and Radioresistance of NSCLC. *Molecular Carcinogenesis*, **59**, 141-153. https://doi.org/10.1002/mc.23135

[59] Li, J., Chen, Y., Zhao, J., Kong, F. and Zhang, Y. (2011) MiR-203 Reverses Chemoresistance in P53-Mutated Colon Cancer Cells through Downregulation of Akt2 Expression. *Cancer Letters*, **304**, 52-59. https://doi.org/10.1016/j.canlet.2011.02.003

[60] Ward, A., Balwierz, A., Zhang, J.D., Küblbeck, M., Pawitan, Y., Hielscher, T., Wiemann, S. and Sahin, Ö. (2013) Re-Expression of MicroRNA-375 Reverses both Tamoxifen Resistance and Accompanying EMT-Like Properties in Breast Cancer. *Oncogene*, **32**, 1173-1182. https://doi.org/10.1038/onc.2012.128

[61] Wang, P., Zhao, Z.Q., Guo, S.B., Yang, T.Y., Chang, Z.Q., Li, D.H., Zhao, W., Wang, Y.X., Sun, C., Wang, Y. and Feng, W. (2019) Roles of MicroRNA-22 in Suppressing Proliferation and Promoting Sensitivity of Osteosarcoma Cells via Metadherin-Mediated Autophagy. *Orthopaedic Surgery*, **11**, 285-293. https://doi.org/10.1111/os.12442

[62] 王存硕, 王帅, 薛海滨, 罗小波. 骨肉瘤治疗研究进展[J]. 标记免疫分析与临床, 2022, 29(10): 1789-1793. https://doi.org/10.11748/bjmy.issn.1006-1703.2022.10.031

[63] Wan, J.L., Wang, B., Wu, M.L., Li, J., Gong, R.M., Song, L.N., Zhang, H.S., Zhu, G.Q., Chen, S.P., Cai, J.L., Xing, X.X., Wang, Y.D., Yang, Y., Cai, C.Z., Huang, R., Liu, H. and Dai, Z. (2022) MTDH Antisense Oligonucleotides Reshape the Immunosuppressive Tumor Microenvironment to Sensitize Hepatocellular Carcinoma to Immune Checkpoint Blockade Therapy. *Cancer Letters*, **541**, Article ID: 215750. https://doi.org/10.1016/j.canlet.2022.215750

[64] Shen, M., Xie, S., Rowicki, M., Michel, S., Wei, Y., Hang, X., Wan, L., Lu, X., Yuan, M., Jin, J.F., Jaschinski, F.,

Zhou, T., Klar, R. and Kang, Y. (2021) Therapeutic Targeting of Metadherin Suppresses Colorectal and Lung Cancer Progression and Metastasis. *Cancer Research*, **81**, 1014-1025. https://doi.org/10.1158/0008-5472.CAN-20-1876

[65] Shen, M., Smith, H.A., Wei, Y., Jiang, Y.Z., Zhao, S., Wang, N., Rowicki, M., Tang, Y., Hang, X., Wu, S., Wan, L., Shao, Z.M. and Kang, Y. (2022) Pharmacological Disruption of the MTDH-SND1 Complex Enhances Tumor Antigen Presentation and Synergizes with Anti-PD-1 Therapy in Metastatic Breast Cancer. *Nature Cancer*, **3**, 60-74. https://doi.org/10.1038/s43018-021-00280-y