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肿瘤转移相关microRNAs的研究进展

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摘要 转移是预测肿瘤患者预后的重要因素, 并且是肿瘤患者高死亡率的主要原因. 上皮间质转化在肿瘤转移及进展过程中发挥着重要作用. 最近的研究表明, microRNA(miRNA)在人类恶性肿瘤的发生和发展中起了重要作用. miRNA是长度约22个核苷酸的非编码小分子RNA, 其可通过与靶基因的3′UTR互补配对导致靶基因的翻译抑制和mRNA的降解. 许多研究表明, miRNA可通过EMT(epithelial-mesenchymal transition)相关和/或非EMT相关机制调控癌症转移的过程. 本综述着重阐述了miRNA在肿瘤中对EMT相关信号通路的调控作用.

关键词 微小RNA, 上皮间质转化, 上皮间质转化相关的转录因子, 癌症, 转移, 进展

肿瘤转移是原发性肿瘤细胞脱落, 从原发部位, 经淋巴道、血管或体腔等途径, 定植远端器官继续生长的过程[1]. 对于实体瘤来说, 远处转移是导致肿瘤患者死亡的主要原因[2]. 微环境中的肿瘤细胞传播并在次生环境中增殖, 经历的一系列过程称为转移级联事件[3]. 众所周知, 上皮间质转换(epithelial-mesenchymal transition, EMT)过程、金属蛋白酶(metalloproteinases, MMPs)、抗凋亡、血管生成/淋巴管生成是导致肿瘤转移和进展的主要原因. EMT过程中, 上皮细胞间的黏附结构、极性和细胞骨架都被改变, 从而使上皮细胞变形、迁移和运动能力增加, 提高了肿瘤细胞的迁移和侵袭能力, 使得肿瘤细胞更易于离开原发位置, 发生转移或者随血行、淋巴等途径转移到体内远处部位, 重新定位于新的组织或器官, 形成转移性肿瘤[4]. EMT过程被许多信号通路调控, 包括Wnt/β-catenin[5], 磷酸肌醇-3-激酶(phosphatidylinositol 3-kinase, PI3K)/蛋白激酶B(AKT)[6], Src信号通路[7]或转录因子像TWIST1(twist-related protein 1)[8], ZEB(zinc finger E-box binding homeobox)[9], Snail1[10]和Slug[11]. 此外, MMPs、凋亡、血管生成、淋巴管生成等非EMT相关机制也参与了肿瘤的转移.

microRNAs(miRNAs)是一类内源性的非编码小RNA, 长度约为22个核苷酸. miRNAs与靶基因的3′非翻译区域结合, 导致靶基因的翻译抑制或降解, 从而实现miRNAs在转录水平对基因表达的调控. 研究报道miRNA负性调控许多靶基因的表达, 在细胞生长、增殖、分化、凋亡等多种生物学过程中发挥重要作用[12]. 大量研究发现, miRNA通过多种信号

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通路参与肿瘤的EMT过程[4]进而影响肿瘤的发生和进展.

1 miRNAs对多种信号通路的调控

1.1 miRNA在Wnt/β-catenin信号通路中的作用(图1)

研究表明, Wnt/β-catenin信号通路在EMT发生、肿瘤转移和进展过程中发挥重要作用. 当Wnt配体与细胞表面受体卷曲蛋白(frizzled, FZD)和低密度脂蛋白受体(low density lipoprotein receptor, LDLR)结合形成复合物时, 经典的Wnt/β-catenin信号传导途径被激活. 随后, 胞质散乱蛋白(Dvl)磷酸化, 从而使β-catenin从"降解复合物"中分离, 最终抑制β-catenin泛素化. "降解复合物"是由轴蛋白(Axin)、结肠腺癌息肉蛋白(adenomatous polyposis coli, APC)和糖原合成激酶-3β(glycogen synthase kinase-3β, GSK3β)构成. 稳定的β-catenin在细胞质中聚集, 当β-catenin聚集达到一定量时, 可向细胞核内移位, 并与细胞核内的转录复合物(lymphoid enhancer-binding factor, LEF)/(transcription factors, TCF)结合, 该复合物作为转录激活因子可引起β-catenin下游靶基因的表达, 从而发挥调控作用. 当缺乏Wnt配体时, Axin结合的β-catenin快速被激活的CK1α和GSK3β磷酸化, 磷酸化后的β-catenin通过泛素化途径被蛋白酶体降解[13].

越来越多的证据表明, miRNAs与Wnt/β-catenin信号通路相互作用而调控肿瘤的进展[14]. Cai等人[15]报道, miR-374a抑制多个Wnt/β-catenin的负调控因子的表达包括WIF1(WNT inhibitory factor 1)和WNT5A(hWnt family member 5A)从而导致β-catenin磷酸化, 最终促进乳腺癌转移. Liu等人[16]报道miR-15b/16和miR-107下调Axin2表达, miR-29b, miR-101, miR-124和miR-129下调Gsk3β的表达, 从而减少胞质降解复合物的形成, 抑制胞质β-catenin降解. 据报道, miR-92b通过Nemo样激酶(Nemo-like kinase, NLK)调节Wnt/β-catenin信号转导途径来抑制胶质瘤侵袭, 其诱导TCF/LEF的磷酸化并进一步抑制β-catenin-TCF/LEF复合物介导的转录[17]. APC是细胞迁移的细胞骨架组织者, "降解复合体"成分之一, 可被miR-155和miR-27b负性调控. 因此, 较低水平的APC诱导β-catenin的核集聚, 从而在各种肿瘤中激活Wnt/β-catenin信号[18]. 类似地, 最近的研究表明miR-222过表达降低了DKK2蛋白水平, 导致Axin/APC/GSK3复合物的破坏, 从而减弱了DKK2对Wnt/β-catenin信号转导的抑制作用, 最终稳定了细胞质β-catenin的含量, 并促进了胶质瘤的发生[19]. 以上研究提供给我们一个重要思路: 针对调控Wnt/β-catenin关键分子的miRNAs进行筛选验证并构建miRNAs表达谱模型, 将可能抑制肿瘤EMT的发生或者逆转EMT, 从而阻断恶性肿瘤细胞的转移.

1.2 miRNA对PI3K/AKT信号通路的调控(图2)

PI3K/AKT信号通路在各种上皮癌中被激活. 编码

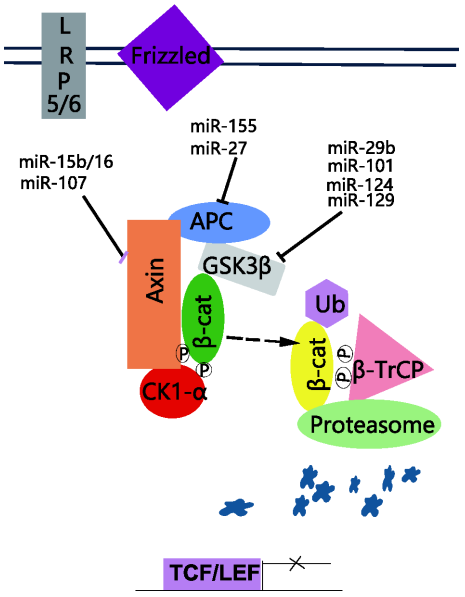

图 1 Wnt/β-连环蛋白信号通路的概述以及miRNAs对信号通路关键分子的调节(网络版彩图)

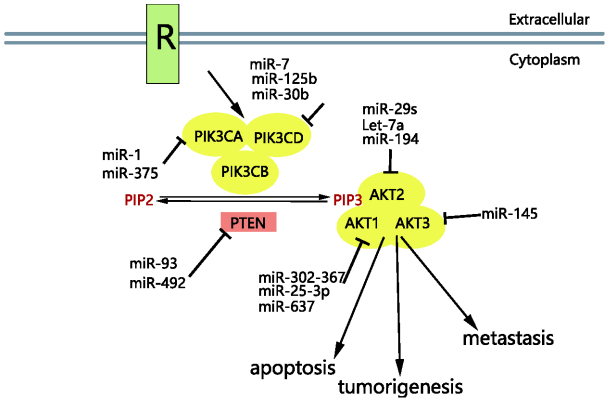

图 2 miRNA对PI3K/AKT信号通路的调控(网络版彩图)

脂质磷酸酶的磷酸酶-张力蛋白基因(phosphatase and tensin homolog, PTEN)主要是通过其脂质磷酸酶活性作用于PI3K的下游靶分子PIP3, 从而阻断PI3K/AKT信号通路来实现其抑癌作用. 磷酸化AKT(P-AKT)通过调控细胞的功能, 包括细胞增殖、凋亡、运动和转化, 在肿瘤发生和发展中起关键作用[20]. 研究表明, AKT通过3种途径参与肿瘤进展, 包括EMT过程、抗凋亡机制和血管生成[21].

研究发现, miRNAs在肿瘤转移及进展过程中参与PTEN/PI3K/AKT信号通路相关分子的调控. 例如, miR-93和miR-492在多种肿瘤中抑制PTEN表达从而激活PI3K/AKT途径最终促进肿瘤进展[22,23]. PIK3CA和PI3KCD是PI3K的两个催化亚基. PIK3CA在许多人类肿瘤中存在高频率的突变. PIK3CA内突变的位置意味着其能增强激酶活性并在人类肿瘤中增加其癌基因的作用. 有研究表明miRNA对PIK3CA的表达调控发挥着不可或缺的作用[24]. 例如, miR-1通过抑制PIK3CA的表达从而抑制非小细胞肺癌(non-small cell lung cancer, NSCLC)的进展[25]. Wang等人[26]报道, miR-375负性调控PIK3CA的表达, 并通过靶向PI3K/AKT信号通路抑制结直肠癌的进展. 类似地, 越来越多的研究表明miRNA在调控肿瘤中PIK3CD表达的作用. 研究表明miR-7可下调PIK3CD的表达, 从而抑制肿瘤生长和转移[27]. 此外, miR-125b[28]和miR-30b[29]也可直接下调PIK3CD的表达从而抑制多种肿瘤的进展.

近期的研究显示miRNA在调控AKT家族成员——AKT1中发挥作用. 例如, miR-637在神经胶质瘤组织中显著降低, 其可通过抑制AKT1的表达从而阻遏神经胶质瘤细胞的生长和侵袭[30]. 此外, miR-25-3P[31]和miR-302-367簇[32]可通过调控AKT1的表达, 进一步抑制肿瘤发生和转移. AKT2是肿瘤发生和进展过程的重要介导因子, 被认为是治疗恶性肿瘤的理想靶点. Zhang等人[33]报道, miR-29s可以靶向AKT2, 抑制其表达并抑制胃癌细胞的侵袭能力. 另外, AKT2表达也被miR-194[34]下调从而抑制肿瘤发生或转移. 而且, Let-7a通过靶向调控AKT2从而抑制甲状腺癌细胞的迁移、浸润和生长[35]. 类似地, miR-145[36]可负性调控AKT3表达进而抑制人类肿瘤的转移与进展. 另外, 本研究组[37]发现, miR-489在细胞水平和荷瘤裸鼠(*Xenografts*)体内均可以抑制癌细胞增殖、浸润和转移. miR-489具有直接抑制SPIN1表达的作用. 过表达miR-489可以通过抑制SPIN1介导的PI3K/AKT通路抑制乳腺癌转移. ERBB2过表达是导致乳腺癌浸润转移及预后差的主要因素之一, 我们发现miR-1268b通过靶向ERBB2负向调节PI3K/AKT通路, 进而诱导乳腺癌细胞凋亡, 抑制乳腺癌进展[38]. PI3K/AKT作为细胞内重要的信号通路之一, 与肿瘤的发生、发展关系密切. 因此, 调控PI3K/AKT信号通路的miRNAs有可能为肿瘤的治疗提供新策略.

1.3　miRNA在Src信号通路中的作用(图3)

Src原癌基因是一种多功能蛋白, 参与多种致癌过程的调控. Src在许多人类肿瘤中高表达, 包括乳腺癌、结直肠癌、前列腺癌、头颈癌和肺癌等[7], 通过促细胞增殖、侵袭和血管生成在肿瘤的发生和发展中发挥重要作用. Src通过调节多种信号通路参与肿瘤的发展和进展, 包括Ras/细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)通路和黏着斑激酶(focal adhesion kinase, FAK)通路. 研究报道, Src与E-钙黏蛋白或EMT相关, 从而增加肿瘤细胞的迁移和浸润[39].

大量报道证实miRNA在c-Src介导的肿瘤进展过程中发挥着重要作用. 例如, miR-1通过靶向调控Src从而抑制食管癌细胞的增殖[40]. miR-203负性调控Src表达并随后抑制了Src下游信号传导途径、如Src/Ras/ERK途径, 从而抑制肺癌细胞的增殖, 迁移并诱导细胞凋亡[41]. Src/Ras/ERK通路也可被miR-205调控, 最终抑制肾癌细胞迁移、侵袭和增殖[42]. 此外, 据报道miR-

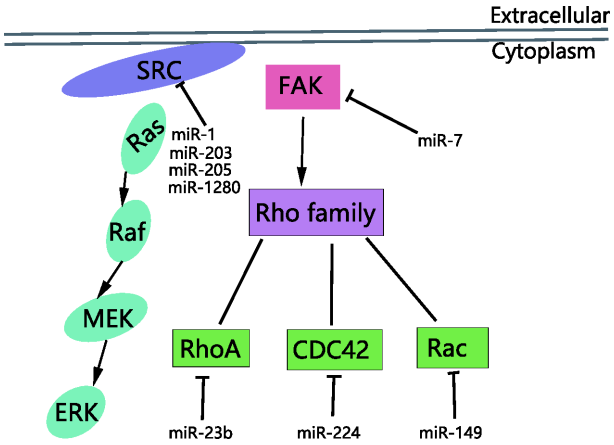

图 3　Src信号传导途径概述及miRNA对下游基因的调节(网络版彩图)

1280高表达导致Src下调, 从而抑制黑色素瘤细胞的增殖、浸润和细胞凋亡[43]. FAK在包括乳腺癌、结肠癌、神经母细胞瘤和甲状腺癌在内的几种侵袭性肿瘤组织中高表达, 是生长因子受体和整合素介导的信号关键调节因子[44]. 据报道, FAK可通过协调黏附结构(如肌动蛋白细胞骨架)的动态调节变化以及激活Rac, Rho和cdc42 GTP酶来控制细胞黏附、运动和侵袭. 这些黏附结构在调节细胞极性, 如细胞迁移过程中必须的板状伪足形成和高尔基重定向[45]中起着关键作用. MiR-7是FAK表达的直接调节因子, 可抑制宫颈癌[46]的侵袭和转移. 此外, FAK也是miR-548的直接靶基因[47]. 有趣地是, miR-151是染色体8q24.3上频繁扩增的miRNA, 通常与其宿主基因FAK一起表达. 然而, 它可以直接靶向HCC中特定的转移抑制因子RhoGDIA, 从而导致Rac1, Cdc42和Rho GTP酶的激活, 进而增加HCC细胞的运动和扩散[48]. 此外, 在乳腺癌中, miR-149低表达可诱导异常Rac激活从而促进了癌细胞的转移扩散[49]. Ke等人[50]报道, 在结直肠癌中miR-224通过下调cdc42表达从而抑制癌细胞的迁移. 同样地, miR-23b通过调节包括Rac, Rho和Cdc42在内的Rho家族成员来改善细胞间相互作用, 调节黏附连接并减少细胞运动和侵袭[51]. 虽然目前已有许多关于miRNAs调控Src信号通路的报道, 但这方面的研究还不够深入. 近年来研究发现miRNAs能够被化学小分子靶向. 利用小分子化合物靶向miRNAs将成为一种新型治疗肿瘤方法.

1.4 miRNAs对EMT相关转录因子的调控(图4)

E-钙黏蛋白是上皮细胞的主要黏附分子之一, 其低表达被认为是EMT发生的基本条件. E-钙黏蛋白介导的细胞黏附结构丧失被认为是肿瘤进展中的关键步骤. EMT相关转录因子包括Snail(Snail1/Snail2), basic helix-loop-helix (bHLH)(E47, E2-2和twist1/twist2)和ZEB(ZEB1/ZEB2), 可抑制E-钙黏蛋白的表达. E-钙黏蛋白可导致细胞间相互作用和基底细胞极性的丧失、迁移和侵袭能力的获得及波形蛋白、纤维蛋白和N-钙黏蛋白在内的间充质分子标记的表达增加[52].

越来越多的证据表明, miRNA可通过调控上皮-间质转化, 在肿瘤转移的发生中扮演着非常重要的角色. 包括miR-200a, miR-200b, miR-200c, miR-141或miR-429在内的miR-200家族和ZEB的关系已被广泛研究.

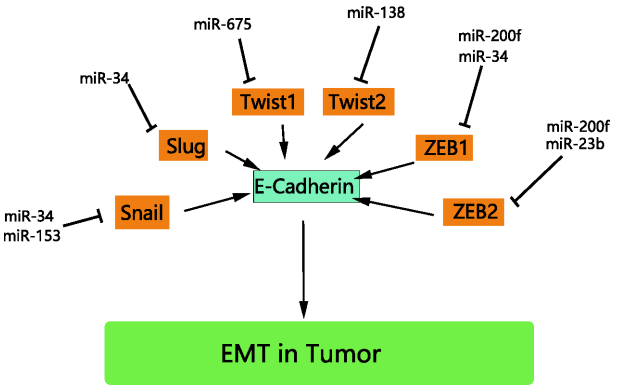

图 4 miRNA对EMT相关转录因子(EMT-TF)的调控(网络版彩图)

MiR-200家族直接靶向ZEB1和ZEB2进而增加E-钙黏蛋白表达, 最终抑制EMT过程和肿瘤进展; 另外, ZEB可负性调节miRNA-200家族转录. 这种相互作用构成miR-200家族与ZEB1/ZEB2之间的双重负反馈调节环[53]. 除了miR-200家族外, 其他miRNAs也参与调节ZEB1和ZEB2的表达, 从而抑制EMT和肿瘤转移. 例如, miR-23b[54]直接靶向ZEB2抑制多种肿瘤的侵袭和转移. 与miR-200家族/ZEB双重负反馈环相似. 最近几项研究表明Snail1建立了另外两个相互调节调控环, 分别是miR-34家族和miR-203. 这两个EMT核心网络可以作为恶性肿瘤分化、发展和进展过程中上皮细胞可塑性的分子马达[55]. 有趣的是, miR-34也可以下调ZEB1的表达. 相反, 转录因子ZEB1与miR-34家族和miR-200家族的启动子结合并因此抑制miR-34和miR-200的表达, 形成miR-34/Snail和miR-200/ZEB调控反馈环[56]. 此外, Snail1的表达水平也受miR-153[57]的调控. Slug(Snail2)由miR-34[58]等多个miRNA调控, 从而抑制EMT发生及人类肿瘤的侵袭和转移能力. Twist1 (Twist)和Twist2是两种基本的螺旋-环-螺旋转录因子, 通过直接抑制E-钙黏蛋白等上皮标志物的表达促进EMT过程及肿瘤的侵袭和转移能力[59]. 最近的几项研究表明, Twist1和Twist2可以被miRNA负调控. Long等人[60]发现miR-138在结直肠癌中的表达下降, 通过直接与Twist2结合导致癌细胞迁移和侵袭能力的显著抑制. 此外, miR-675[61]通过负性调控Twist1表达来抑制癌症转移. 我们研究发现, miR-145不仅通过下调胞质CTNND1表达, 而且通过下调N-cadherin诱导CTNND1和E-钙黏蛋白从细胞质转移至细胞膜[62]来抑制胃癌细

胞的侵袭; 另外还发现, miR-145通过抑制N-钙黏蛋白翻译, 进而间接下调其下游效应子MMP9, 从而抑制胃癌转移[63]. 所有这些研究表明miRNAs对EMT相关转录因子进行严格调控.

1.5　其他转移相关的miRNAs

除了调节与EMT相关的信号通路和转录因子的miRNA, miRNA还调节人类肿瘤中各种与转移相关的基因. 例如, 我们发现miR-100可被C/EBPα诱导, 并发挥抑癌基因的作用抑制ZBTB7A的表达, 从而抑制胃癌细胞的增殖和浸润[64]. 另外, miRNA-214的下调通过直接靶向CSF1来调节胃癌细胞的增殖、侵袭和迁移[65]. miR-27b, miR-101和miR-128通过下调胃癌中VEGF-C的表达来抑制血管生成和肿瘤进展[66].

2　总结

大量的数据证实, miRNAs与人类肿瘤的发生和进展密切相关. 近几年来, 肿瘤EMT是广大科研工作者探讨的重要议题之一, 参与EMT过程的信号通路更是吸引了不少科研工作者的关注. 各信号通路之间可形成复杂的信号网络共同调控肿瘤的转移. 目前研究证实, miRNA失调与肿瘤存在因果关系, miRNA可以作为肿瘤抑制剂或癌基因. miRNA模拟物和靶向miRNA的分子(anti miR)在临床应用发展中显示出极大的前景, 这将为肿瘤治疗提供新的途径.

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The roles of microRNAs related with progression and metastasis in human cancers

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Metastasis is an important factor in predicting the prognosis of the patients with cancers and contributes to high cancer-related mortality. It is well-known that the EMT processes are responsible for cancer progression and metastasis. Recent studies indicated that miRNAs played a functional role in the initiation and progression of human malignancies. MicroRNAs are small non-coding RNAs of about 22 nucleotides in length that can induce mRNA degradation or repress mRNA translation by binding to the 3′UTR of their target genes. Overwhelming reports indicated that miRNAs could regulate cancer invasion and metastasis via EMT-related and/or non-EMT-related mechanisms. In this review, we concentrate on the underlying mechanisms of miRNAs in regulating cancer progression and metastasis.

microRNA, EMT, EMT-TFs, cancer, metastasis, progression

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