DOI: 10.13376/j.cbls/2016058

文章编号：1004-0374(2016)04-0464-06

p53/miR-34a调控网络在肿瘤中的作用

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摘 要：MicroRNA 是重要的调控分子，长约 22 nt，属于非编码 RNA，对肿瘤的发生和发展起着重要的作用。miR-34a 是研究比较清楚的 microRNA，目前认为是重要的抑癌 microRNA。*p53* 是一个重要的抑癌基因。*p53* 与 miR-34a 形成的正反馈调控网络具有抑制肿瘤细胞生长、转移及抑制肿瘤干细胞的功能。现综述 *p53*/miR-34a 调控网络研究的最新进展，并探讨其在肿瘤诊断及治疗中的应用。

关键词：miR-34a；*p53*；信号通路；肿瘤

中图分类号：Q522；R730.2 **文献标志码**：A

p53/miR-34a signaling networks in tumor

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Abstract: MicroRNAs (miRNAs) are small noncoding RNAs with the length of ~22 nucleotides. They play important roles in tumorgenesis. miR-34a is considered to be a tumor suppressor. *p53* is a tumor suppressor. The positive feedback of *p53*/miR-34a could inhibit tumor cell growth and migration. This review will summarize the progress of *p53*/miR-34a network in tumor, and also discuss its application in diagnosis and treatment of cancer.

Key words: miR-34a; *p53*; signaling pathway; tumor

肿瘤是目前影响人类健康的主要疾病之一。肿瘤的发生涉及多条信号通路的异常。MicroRNA (miRNA) 参与了与肿瘤抑制及发生相关的通路调控。miRNA 是一类广泛存在于真核生物中，由 18~23 个核苷酸组成的保守、非编码单链 RNA。miRNA 已成为治疗癌症的新途径[1-4]。其中，miR-34a 是研究最多的 miRNA 之一。它是 miR-34 家族的成员，与另外两位成员不同，miR-34a 单独位于染色体 1p36，具有自身转录本。*p53* 基因是人类癌症中最容易发生突变的基因[5]，也是重要的抑癌基因。*p53* 对 DNA 损伤、细胞应激反应产生应答[6]。本文将综述 *p53* 所介导的 miR-34a 对肿瘤发生的影响。

1 *p53*与miR-34a

miR-34a 是最常见的受 P53 调控的 miRNA，*p53* 对肿瘤的抑制作用与 *p53* 介导的 miRNA 调控的靶基因有关 (图 1)。当细胞受到某些刺激，如 DNA 损伤、药物刺激等，会激活 *p53* 基因的表达以应对刺激。P53 使得 miR-34a 的 CpG 岛启动子区域去甲基化，激活 miR-34a 的表达，进而调控 miR-34a 的靶基因。Hermeking[7] 的研究表明，P53 蛋白对 miR-34a 的表达有直接靶向调节作用。此外，也有间接调控因子影响 p53 与 miR-34a 的表达，如沉默信息调节因子相关酶 1 (SIRT1)，它是一种 NAD^+ 依赖的去乙酰化酶。当它抑制 P53 蛋白的转录后去乙酰化时，P53 蛋白的活性就会下调。miR-34a 通过靶向抑制 *SIRT1* 的表达进而诱导 *p53* 的活性[8]。同时，miR-34a 是抑制肿瘤的重要分子，参与调控多种癌症的发生与发展过程，包括增殖、凋亡、迁移、侵袭、代谢、上皮间质转化 (epithelial-mesenchymal transition, EMT) 等，从而抑制肿瘤的生长和转移[9-11]。

收稿日期：2015-11-03；**修回日期**：2015-12-17

基金项目：国家自然科学基金项目(31170750)；重大横向项目(抗肺癌核酸药物的筛选)

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2　*p53*/miR-34a在肿瘤中的作用

2.1　对细胞周期的影响

对许多肿瘤的研究表明，miR-34a 异常表达时会抑制 *CDK4* 和 *CDK6* 的表达，从而促进细胞周期进程 [12-13]。2015 年，Kiyonari 等 [14] 研究表明，诱导 *p53* 表达积累促进 miR-34a 的表达，使得 E2F 转录因子 3 (E2F transcription factor 3, E2F3) 的表达受到了抑制，结果促进了细胞周期进程。另外，Ichimura 等 [15] 的研究也表明，miR-34a 能抑制 MEK/ERK 信号通路的重要成员 MAP2K1，从而达到抑制淋巴瘤细胞增殖的作用。不仅如此，miR-34a 还可以靶向作用于 NAD^+ 补救途径的关键限速酶烟酰胺磷酸核糖转移酶 (nicotinamide phosphoribosy-ltransferase, NAMPT)，从而调控 *SIRT1* 的活性 [16]。Liu 等 [17] 研究揭示，*SIRT1* 和 *c-MYC* 通过一个正反馈的环路相互调控 (图 2)。同时，miR-34a 也可以抑制 *c-MYC*/*SIRT1* 通路，从而激活 *p53*，进而上调 miR-34a 表达 [18-19]。

2.2　对细胞凋亡的影响

miR-34a 在许多癌症中都起到促凋亡的作用，抗凋亡基因 *c-Myc* 较早被证明是 miR-34a 的靶

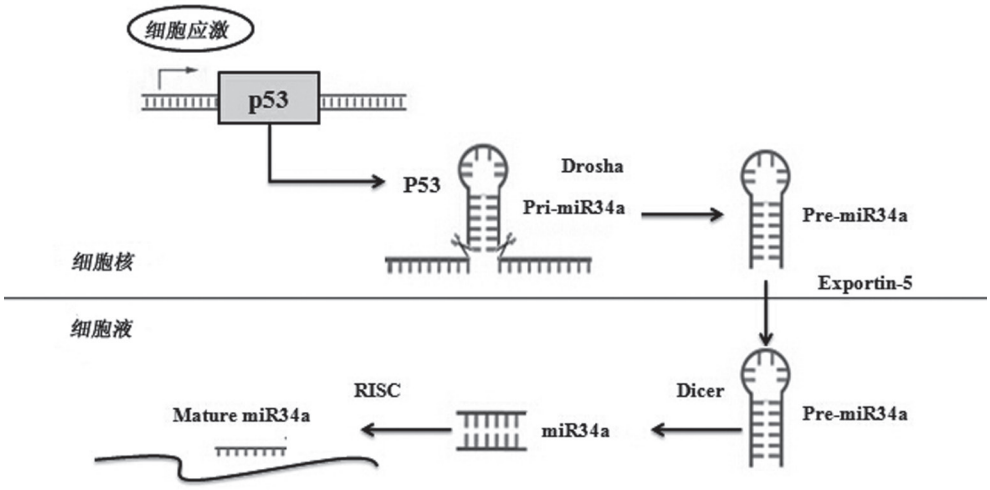

图1　P53调控miR-34a的表达

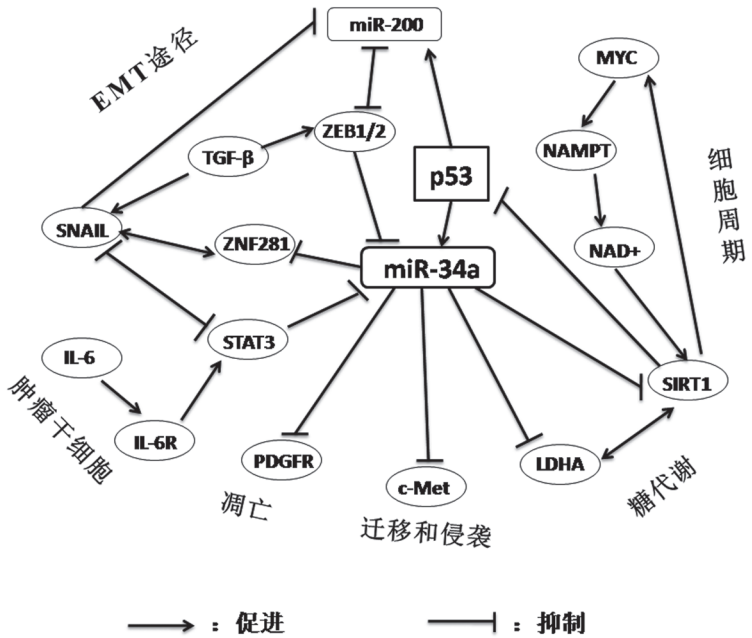

图2　*p53*/miR-34a调控网络

基因[19-20]。miR-34a 靶向调控 *Bcl-2*，诱导细胞凋亡[11]。在非小细胞肺癌 (non-small-cell lung carcinoma, NSCLC) 中，*PDGFR* 的表达量与 miR-34a 呈现负相关的关系。过表达 miR-34a 导致 *PDGFR* 的表达下调，进而促进癌细胞的凋亡[21]。死亡受体 CD95 (death receptor CD95, CD95) 有促进细胞凋亡的功能。同时，*CD95* 也是 *p53* 的靶基因之一。miR-34a 和 *CD95* 同时应答 *p53*，*CD95* 的表达能影响细胞激活 *p53*，以及 *p53* 调控 miR-34a 的能力[22]。miR-34a 与部分确证的靶基因的关系如表 1 所示。

2.3 对上皮间质转化(EMT)的影响

EMT 在肿瘤的发生过程中起到促进作用[36]。miR-34a 直接靶向抑制 EMT 诱导转录因子 SNAIL，进而抑制 EMT 过程[37-38]。P53 蛋白通过靶向作用 miR-34a 和 miR-200 家族来调控 EMT 途径和其相对的 MET 途径，从而在细胞的可塑性方面起到关键作用。p53、miR-34a 和 miR-200 家族与 SNAIL、锌指 E 盒结合同源框 1 (zinc finger E-box binding homeobox 1, ZEB1) 和锌指 E 盒结合同源框 2 (ZEB2) 组成了两条双负反馈回路 (图 2)[39-40]。ZEB1 和 SNAIL 与 miR-34a 启动子的 E-box 结合，起到了抑制 miR-34a 表达的作用，这也进一步增加了 miR-34a/*SNAIL* 和 miR-200/*ZEB* 两条回路的关联[37,41]。miR-34a 靶基因的产物锌指蛋白 281 (zinc finger protein 281, ZNF281)，受到 SNAIL 和 miR-34a 的共同调节。因此，*ZNF281* 的表达受到 miR-34a 和 *SNAIL* 相关回路的调控，一方面 miR-34a 能间接抑制其表达；另一方面 SNAIL 可以直接诱导 *ZNF281* 的表达[42]。

2.4 对迁移和侵袭途径的影响

miR-34a 的异常表达影响肿瘤恶化和迁移，miR-34a 低表达的原发性癌症患者体内肿瘤发生转移，这揭示出 miR-34a 在抑制肿瘤转移方面有着重要作用[43-45]。在小鼠实验中，过表达 miR-34a 能够抑制转移瘤形成。体内实验表明，miR-34a 稳定过表达可以明显降低乳腺癌、前列腺癌、肺癌、骨肉瘤细胞的转移[45-48]。许多研究表明，miR-34a 通过直接调控靶基因，如 *AXL*、*PDGFR-α/β* 和 *c-Met*，从而抑制癌细胞的迁移和侵袭。最近的一项研究表明，把直肠癌细胞培养在含有白细胞介素 -6 (interleukin-6, IL-6) 的培养基中，信号转导与转录激活因子 3 (signal transducer and activator of transcription 3, STAT3) 能直接抑制 miR-34a 的表达。*IL-6R/STAT3*/miR-34a 回路机制 (图 2)，即白细胞介素 -6 受体 (interleukin 6 receptor, *IL-6R*)、*STAT3* 和 miR-34a 存在一条正反馈调节的通路，这条通路的激活与初期直肠肿瘤和

表1 miR-34a与其靶基因的关系

microRNA	靶基因	癌症类型	信号通路	参考文献
miR-34a	*Bcl-2*	乳腺癌	PI3K-Akt	[23]
	CD24	乳腺癌		[24]
	LMTK3	乳腺癌		[25]
	SIRT1	结肠癌	AMPK	[26]
	MDM4	结肠癌	p53	[27]
	c-Kit	结肠癌		[28]
	E2F3	子宫颈癌		[29]
	AR	前列腺癌	PPAR	[30]
	*A*XL	实体肿瘤		[31]
	YY1	食管鳞状细胞癌		[32]
	PDGFR	肺癌	MAPK、Ras 、PI3K-Akt	[33]
	c-Myc	肝细胞性肝癌	MAPK、TGF-β	[34]
	*c-M*et	恶性间皮瘤	代谢通路	[35]

注：B细胞慢性淋巴细胞白血病/淋巴瘤2 (B-cell CLL/lymphoma 2, Bcl-2)；CD24分子(CD24 molecule, *CD24*)；狐猴酪氨酸激酶3 (lemur tyrosine kinase 3, LMTK3)；沉默信息调节因子2相关酶1 (sirtuin 1, *SIRT1*)；MDM4，p53调节基因(MDM4, p53 regulator, *MDM4*)；受体酪氨酸激酶(v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog, c-kit)；雄激素受体(androgen receptor, AR)；AXL受体酪氨酸激酶(AXL receptor tyrosine kinase, AXL)；YY1转录因子(YY1 transcription factor, YY1)；血小板衍生的生长因子受体(platelet-derived growth factor receptor, PDGFR)；v-myc禽骨髓细胞瘤病毒癌基因同源物(v-myc avian myelocytomatosis viral oncogene homolog, c-Myc)；上皮间质细胞转换因子(mesenchymal-epithelial transition factor gene, c-Met)。

直肠癌的侵袭和迁移有关。

2.5　对糖代谢调控的影响

miR-34a 介导抑制己糖激酶 1 (hexokinase 1, HK1)、己糖激酶 2 (HK2)、葡萄糖 -6- 磷酸异构酶 (glucose-6-phosphate isomerase, GPI) 和丙酮酸脱氢酶激酶 (pyruvate dehydrogenase kinase, isozyme 1, PDK1)，从而抑制糖酵解和增强线粒体呼吸 [42]。而 p53 则是通过 miR-34a 介导抑制这些酶，进而调控糖酵解和葡萄糖代谢。乳酸脱氢酶 A (lactate dehydrogenase A, LDHA) 催化丙酮酸转换为乳酸，在无氧酵解中有着关键作用。Kaller 等 [49] 证明了 *LDHA* 是 miR-34a 作用的靶位点。*SIRT1* 受到 LDHA 的调控。同时，*SIRT1* 的表达量受到抑制也会造成 LDHA 转录的下调 [50-51](图 2)。miR-34a 的靶基因 *SIRT1*，不仅在细胞周期中起到重要的调控作用，在 *p53*/miR-34a 介导的代谢调控中也起到了关键作用。

2.6　对肿瘤干细胞的影响

肿瘤干细胞 (cancer stem cells, CSCs) 具有干细胞的特性。Liu 等 [52] 研究表明，前列腺癌干细胞中 miR-34a 的表达量明显下调，上调 miR-34a 的表达则抑制 *CD44*$^{+}$组中肿瘤的再生和转移。miR-34a 在直肠癌干细胞中同样起到了重要作用 [53]，上调或者下调 miR-34a 的表达将影响到 miR-34a 靶基因 *Notch1* 介导的与 CSCs 有关的信号通路，从而改变了 CSCs 自我更新与分化之间的平衡 [54]。miR-34a 除了可以调控 Notch 信号通路外，还可以直接抑制 Notch 的配体 Dll1 (Delta-like ligand 1)[55]。通过这种机制，miR-34a 可以抑制绒癌细胞的增殖、迁移、侵袭以及异种移植肿瘤的生长 [56]。Siemens 等 [28] 在研究中发现，*c-kit* 不仅是 miR-34a 的靶基因，而且 *c-kit* 对 CSC 有负调控作用。在间皮瘤中，*p53*/miR-34 调控网络 (图 2) 与 CSC 的增殖密切相关，当下调 *p53* 或 miR-34a 时 *c-Met* 的表达量上调，从而促进了 CSC 的增殖。同时，其迁移和侵袭能力也有所增强 [35]。

3　展望

综上所述，在 miR-34a 参与调控的信号通路中，*p53*/miR-34a 调控网络对肿瘤发生与发展起着重要的调控作用。通过这条通路，miR-34a 可以直接或间接地调控不同基因，从而抑制肿瘤的发生或促进肿瘤细胞凋亡。所以，*p53*/miR-34a 调控网络与肿瘤的研究日趋深入。毫无疑问的是，进一步研究这两者之间的关系对于揭示肿瘤发生和发展的机制有着极其重要的意义。

从目前的研究结果来看，miR-34a 在癌症患者组织中是低表达的；同时，miR-34a 与肿瘤干细胞、肿瘤的恶性程度、肿瘤大小以及不良预后呈负相关。因此，检测 miR-34a 表达水平对于癌症患者的预后、诊断有着重要意义。在化疗耐药性方面，miR-34a 能够促进癌细胞对药物的敏感性，从而增强药物的疗效。例如，miR-34a 可以促进乳腺癌细胞对紫杉醇的敏感性 [57]。有关视网膜母瘤的研究中同样存在这种对药物的敏感性的作用机制 [58]。在美国，miR-34a 的类似物已经进入 I 期临床试验。miR-34a 及其调控网络的研究才仅仅是个开始，随着研究的深入，新药物靶点的开发和应用将为期不远，同时也是肿瘤精准医疗或个性化治疗的目标。

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