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文献综述 REVIEW

MicroRNAs与p53基因在肿瘤中相互关系的研究进展

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■背景资料
miRNAs是近年来生命科学领域的一个研究热点, 这类非编码小分子RNA, 参与调控发育、分化、细胞增殖和凋亡等重要的生理病理过程. miRNAs在翻译水平上特异性抑制靶基因表达, 在肿瘤的发生发展过程中被认为是一组新的致癌基因或抑癌基因, 其具体作用机制还不明了. 抑癌基因p53的突变是人类肿瘤中最常见的基因异常现象, 人类大部分的肿瘤与之相关. 最新研究表明miRNAs与抑癌基因p53在肿瘤中有一定的相关性.

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Research progress of the relationship between microRNAs and p53 gene in oncogenesis

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Abstract
The initiation and development of oncogenesis are a multi-step and complicated process, in which activation of oncogenes and inactivation of tumor suppressor genes are involved. MicroRNAs (miRNAs) are a new class of endogenous, non-coding small RNA molecules. It has been demonstrated that their expression levels are closely associated with human pathogenesis of cancers. They may participate in regulating the abnormal expression of oncogenes and tumor suppressor genes. Mutation in tumor suppressor gene p53 is the most frequent phenomenon in human cancer, and up to now, almost 50% human cancers are demonstrated associated with p53 mutation. Recent studies showed that miRNAs might play a role in regulating the tumor-suppressor activity of p53 gene. In this review, the research progress in this field is discussed.

Key Words: MicroRNAs; Tumor suppressor gene p53; Oncogenesis; Progress

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摘要
肿瘤的发生、发展是多基因共同参与的多步骤的复杂过程, 包括癌基因的异常激活和抑癌基因的失活. MicroRNAs(miRNAs)是一组真核细胞内源性产生的单链小RNA分子, 研究发现miRNAs的表达水平与人类肿瘤发生有着密切的关系, 可能参与调控癌基因和抑癌基因的异常表达. 抑癌基因p53的突变是人类肿瘤中最常见的基因异常现象, 目前已证实人类大约有50%的肿瘤与之相关. 近来发现miRNAs的表达水平与p53的抑癌活性相关, 本文就这一研究进展作一综述.

关键词: miRNAs; p53抑癌基因; 肿瘤生成; 进展

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0 引言
miRNAs是近年来生命科学领域的一个研究热点, 他广泛存在于真核生物中, 是一类保守、短序列、非编码的单链小分子RNA, 通过与其靶mRNA分子的3'端非编码区(3'-UTR)互补结合, 在翻译水平上特异性抑制基因表达, 从而参与调控生物的生长和发育等许多复杂生命过程[1-3]. 最初人们在线虫中发现lin-4和let-7这两种miRNAs具有调控基因表达的功能[4-5]. 目前发现并证实的人类miRNAs已达到470多种, 他们与肿瘤、心脏疾病以及艾滋病等多种疾病密切相关, 尤其在肿瘤的发生发展过程中, 扮演着重要的角色[6-11]. 抑癌基因p53的突变是人类肿瘤中最常见的基因异常现象, 人类大部分的肿瘤与之相关[11-19]. 本

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文就miRNAs与抑癌基因p53在肿瘤中相互关系的最新研究进展作一综述.

■研发前沿
miRNAs与抑癌基因p53在肿瘤中相关性报道并不多, 揭示miRNAs和p53基因在肿瘤形成过程中的相互调控机制, 是研究miRNA功能的重点.

1 miRNAs与肿瘤

miRNAs是一类长度为22-24 nt的非编码小分子RNA, 其5'端有一个磷酸基团, 3'端为羟基, 他具有保守性、基因簇集现象和特异性表达和不具有蛋白质编码基因和开放阅读框架等特点. 成熟miRNAs由长约80 nt含有茎环结构的小片段RNA-miRNA前体(pre-miRNA)经Dicer酶加工而成. miRNAs参与调控生物体的发育、神经分化、细胞增殖、凋亡和脂肪代谢等, 是细胞增殖分化和生物体发育过程中重要的调控因子[20]. 生物信息学分析表明, miRNAs调控着人类大约三分之一的基因. 其机制是在翻译水平上, 通过与靶mRNA分子的3'端非翻译区(untranslated region, UTR)不完全配对结合, 影响靶mRNA的成熟、转运及稳定性或直接调控翻译过程, 从而起到调节蛋白质表达水平的功能[21].

miRNAs与肿瘤的发生发展密切相关, 被认为是一组新的致癌基因或抑癌基因[22-27]. miRNAs既可作为抑癌基因, 下调原癌基因的活性; 也可作为癌基因, 下调抑癌基因的活性. 在肺癌的研究中发现, let-7在肺癌中呈明显低表达[28], 并且证实let-7是通过抑制RAS基因的表达而在肺癌发生中发挥功能的[29]. 多顺反子miR-17-92簇被发现在肺癌和淋巴瘤中呈高表达[30-31]. O'Donnell *et al*[32]指出*c-Myc*基因可同时激活E2F1和miR-17-92的转录, 调节他们的表达, 从而影响通过ARE-p53通路介导的细胞调亡. *c-Myc*是一个最具代表性的致癌基因, 他的异常表达常常导致人类恶性疾病的发生[33-36]. Meng *et al*[37-38]检测正常肝细胞和肝癌细胞中的197种miRNAs分子的浓度, 发现高浓度的miR-21会抑制PTEN基因活性, 而PTEN基因与肿瘤生长、转移和侵袭等紧密相关, 从而证明了miRNAs能下调抑癌基因的活性, 促进肝癌细胞的生长和扩散.

大量的研究资料表明, 肿瘤的miRNAs表达谱具有其组织特异性, 即在肿瘤组织或细胞中有着与正常组织细胞显著差异的miRNAs表达谱, 不同类型的肿瘤组织有着不同组合的miRNAs异常表达谱. Iorio *et al*[39]发现在乳腺癌组织中, miR-125b, miR-145, miR-21和miR-155等表达量显著减少, miRANs的表达水平与乳腺癌的病理类型、分期等都密切相关. 同样, 他们发现在卵巢癌中的miRNA表达又不同, 其中miR-200a, miR-141, miR-200c和miR-200b明显高表达, 而miR-199a, miR-140, miR-145和miR-125b1表达降低[40]. Murakami *et al*[41]发现在肝癌组织中, miR-18a和miR-224呈明显高表达, 而miR-195、miR-199a、miR-200a和miR-125a等呈现低表达. Volinia *et al*[42]发现了在大部分实体肿瘤中miR-20a、miR-21、miR-92、miR-106a和miR-155等呈过量表达.

2 p53基因与肿瘤

从1979年第一次发现p53基因以来, 成千上万的文献对这个基因的重要性进行了报道. p53基因定位于染色体17p13.1, 由20 kb的11个外显子构成, 他有野生型和突变型两种构型. 野生型p53基因为正常的p53基因, 编码的蛋白质称为p53蛋白, 是由393个氨基酸组成的与细胞分裂周期相关的核磷酸蛋白质. 作为肿瘤抑制基因的核转录因子, p53基因以“基因卫士”的关键角色, 依靠对其下游因子的激活或抑制来调节细胞的生长与凋亡[43-44]. 正常的p53蛋白在DNA损伤或缺氧时以序列专一的方式与DNA结合后起转录因子的作用, 使依赖p53的CDK抑制物p21WAF1/CIP1活化, 抑制CDK活性, 阻滞细胞在G_1/G_0期, 抑制细胞的增生. 同时, 野生型p53基因还可和某些与细胞增殖相关基因的TATA结合蛋白(TBP)结合, 使TBP不能与启动子TATA盒结合而抑制转录起始, 从而起着抑制肿瘤发生的作用[45]. 现已证明, 野生型p53基因通过调控p21、GADD45、CD95/Fas和PUMA等[46-48]下游基因来抑制细胞的生长和诱导细胞凋亡. 最近, 对野生型p53基因诱导细胞凋亡的研究又有新突破. Chipuk *et al*[49]首次发现p53基因不仅在细胞核同时也能在细胞质中发挥抑制肿瘤的功能, 是通过一种促进细胞死亡的Bcl-2同类蛋白-Bax的激活来诱导细胞凋亡. Sykes *et al*[50]发现, hMOF和TIP60两种酶在细胞DNA受损后, 通过改变结合位点赖氨酸120, 影响p53蛋白与DNA结合的能力, 从而影响p53蛋白判断靶标基因的能力, 诱导受损细胞凋亡. 而突变型p53基因则失去对细胞生长的抑制作用, 促进细胞转化和过度增殖, 导致肿瘤的发生.

3 miRNAs与p53

miRNAs在翻译水平上调节基因的表达, 是RNA干扰通路中的一个重要调节分子[51-55]. 有趣的是, p53抑癌基因也是在翻译水平上被调控[56-58]. 作为转录因子的p53可以直接调控多种基因mRNA

■相关报道
最新文献证明miR-372和miR-373通过抑制p53途径促进人类生殖细胞癌生成.

的转录表达, 也可以通过调节miRNAs的表达水平, 间接影响下游靶基因mRNA的转录[59-63]. Xi *et al*[64]发现, 结肠癌表达的326个miRNAs中46%有p53基因的结合位点, 通过下调p53基因活性, 削弱p53基因在细胞中对miRNAs的调节, 表明p53基因和miRNAs在基因表达水平上相互影响. 而在结肠癌的研究中, Slaby *et al*[65]发现miR-21和miR-31表达明显上调, 而miR-143和miR-145则表达下调. 锌指蛋白Wig-1已被发现在p53基因的调控途径中有着重要的功能[66]. Méndez Vidal *et al*[67]证实由p53基因诱导产生的锌指蛋白Wig-1能结合带有miRNAs结构特征的dsRNA, 表明Wig-1在由miRNAs介导的基因调控中扮演着重要的角色, 间接提示了miRNAs与p53基因的联系. 现已证实在肿瘤中与p53基因密切相关的有两大miRNAs家族:

3.1 miR-372和miR-373 最近, Voorhoeve *et al*[68]筛选了大量与细胞致癌基因相关miRNAs, 发现两个miRNAs: miR-372和miR-373是定位于致癌基因RAS和野生型p53初始细胞癌变和肿瘤化的关键因子, 在生殖细胞瘤(testicular germ cell tumors, TGCTs)中起着促进细胞的生长和肿瘤形成的作用. 研究人员同时还发现, miR-372和miR-373抑制了p53介导的CDK抑制因子的作用, 这种作用可能是通过直接抑制肿瘤抑制因子LATS2的表达来实现的, 这是继miR-17-92簇后发现的又一组潜在的新致癌基因, 其机制可能是通过沉默p53途径来参与人生殖细胞瘤的形成.

3.2 miR-34家族 p53基因抑癌网络是通过对包括细胞DNA损伤, 应激或不恰当的有丝分裂刺激等的反应而激发的, 通过抑制细胞生长或凋亡来抑制不合适的细胞增殖, 从而抑制肿瘤形成[69]. 最近, He *et al*[70-71]在比较野生型和缺陷型p53细胞的miRNAs表达谱后, 发现了一组参予p53肿瘤抑制网络的重要miRNAs家族miR-34(包括miR-34a, miR-34b和miR-34c), 他们具有调节细胞增殖和调亡的功能, 是p53基因的直接转录靶标之一. 在体内体外实验证明, miR-34可以依赖于p53的肿瘤胁迫(oncogenic stress)和DNA的损伤诱导产生. Chang *et al*[72]还发现miR-34a被p53基因调控影响其表达可促进细胞凋亡. 而Tazawa *et al*[73]发现具有抑癌活性的miR-34a在结肠癌中能通过E2F诱导细胞老化. Corney *et al* [74]同样也证实了miR-34b和miR-34c是p53基因的直接转录靶标之一, 参与调控着细胞的增殖和黏附能力. miR-34家族在人类多种肿瘤细胞中缺失, 是促使p53基因抑制肿瘤形成的关键. 目前, 仅在哺乳动物身上发现了多个p53基因的靶标, 而miR-34不同于其他靶标, 他同时还存在于果蝇和线虫中, 说明miR-34与p53基因间的联系在p53基因抑癌网络演化的早期就出现了.

4 结论

大量的研究证明miRNAs这类小分子在细胞内直接或间接地影响基因的表达调控, 尤其在肿瘤的发生发展过程中, 通过不同的途径来调节细胞增殖、分化和凋亡等. p53作为一个重要的抑癌基因,在肿瘤发生、发展及预后中具有举足轻重的地位. 最新的研究提出了miRNAs可通过p53基因抑制肿瘤细胞生长, 促进细胞凋亡的新观点, 同时又证明了miRNAs是一种可以通过抑制p53途径促进人类生殖细胞瘤生成的新致癌基因, 这些都为研究miRNAs和p53基因在肿瘤形成过程中的调控机制提供了新的证据. 随着各项生物学技术的发展, 相信会有更多的研究证实miRNAs与p53基因的紧密关系, 这将有利于我们进一步认识肿瘤的发生机制, 为肿瘤的诊断、治疗提供新的视野.

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■应用要点
揭示miRNAs和p53基因在肿瘤形成过程中的相互调控机制, 有利于进一步认识肿瘤的发生机制, 为肿瘤的诊断、治疗提供新的视野.

■同行评价
本文内容新颖、前沿, 具有一定的学术价值.

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