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The regulation of the p53/MDM2 feedback loop by microRNAs

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Abstract

Tumor suppressor p53 and its signaling pathway play a central role in tumor prevention. The E3 ubiquitin ligase MDM2, which is a direct p53 transcriptional target and also the most critical negative regulator of p53, forms an autoregulatory negative feedback loop with p53 in the cell to tightly regulate the levels and activity of p53. MicroRNAs (miRNAs) are endogenously expressed small non-coding RNAs that play a critical role in the post-translational regulation of gene expression. Recent studies have revealed that miRNAs directly regulate the levels of p53 or MDM2 to modulate the p53 function in tumor suppression. Recently, we identified miR-339-5p as a new miRNA that directly represses MDM2 to activate p53 and enhance p53 function in tumor suppression. Thus, miRNAs have become a new but important component of the p53 signaling pathway through regulating the p53/MDM2 feedback loop.

Keywords

p53; MDM2; microRNA; tumor

Tumor suppressor p53 and its signaling pathway play a central role in tumor prevention [1-3]. p53 is a transcription factor, and exerts its tumor suppressive function mainly through regulation of the expression of many downstream target genes. In response to stress signals, p53 selectively regulates its target genes to initiate a wide variety of cellular responses, including cell cycle arrest, senescence, DNA repair, and apoptosis, depending on the type of cells, the type and degree of stress signals, and environmental contexts as well [1-3]. Through these cellular responses, p53 prevents the propagation of damaged and mutant cells that could potentially give rise to tumors. The p53 gene is mutated in almost every type of cancer and over half of all cancers, which makes p53 the most frequently-mutated gene in human cancer. In addition to DNA mutations, p53 is frequently inactivated by different mechanisms in cancer. For instance, p53 is frequently inactivated by the DNA amplification and/or overexpression of its negative regulator MDM2 in many types of tumors, such as sarcoma, breast cancer and colorectal cancer [4, 5]. MDM2 is a direct transcriptional target of p53. p53 binds to the p53 consensus DNA binding sequences in the promoter region of MDM2, and transcriptionally induces MDM2 expression under both non-stressed and stressed conditions. In turn, as an E3 ubiquitin ligase, MDM2 is the most critical negative regulator

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of p53. MDM2 binds to p53 and ubiquitinates p53 to promote its degradation [6, 7]. Thus, p53 and MDM2 form an autoregulatory negative feedback loop in the cell to maintain the balance between p53 and MDM2, which is critical for the p53 function in tumor suppression [6, 7]. The disruption of the balance between p53 and MDM2 by the MDM2 amplification and/or overexpression in cancer impairs the function of p53 in tumor suppression, which constitutes an important mechanism for p53 inactivation in cancer to promote tumorigenesis [3, 6].

MicroRNAs (miRNAs) are endogenously expressed small non-coding RNAs which play a critical role in the regulation of gene expression in the cell [8, 9]. miRNAs bind to the partially complementary sites in the 3′-UTRs of specific mRNAs to inhibit the translation and/or induce the degradation of these mRNAs, and thereby regulate the expression of genes at the post-transcriptional level. miRNAs are involved in the regulation of a wide variety of critical biological processes, such as development and differentiation, cell growth and proliferation, cell death and survival, metabolism, etc [8, 9]. These biological processes are often perturbed in cancer, which contributes to tumorigenesis. It has been well-documented that the expression patterns of many miRNAs are often altered in various types of cancer, which leads to the perturbation of above-mentioned biological processes and there by contributes to tumorigenesis [10, 11]. Through the negative regulation of the expression of many different oncogenes and tumor suppressor genes, miRNAs have been demonstrated to function as either tumor suppressors or oncomiRs in cancer [10, 11].

Recent studies have demonstrated that miRNAs play an important role in regulating the p53 function in tumor suppression through regulating the balance between p53 and MDM2. So far, over 20 miRNAs have been identified as the direct negative regulators of p53 through binding to 3′-UTR of the p53 mRNA, including miR-125b, miR-504, miR-380-5p, miR-1285, miR-92, miR-141, miR-25, miR-33, miR-98, miR-453, miR-15a, miR-16, etc [12-15]. Among them, miR-125b and miR-504 were the first group of miRNAs that were identified to directly target p53 [16, 17]. The miR-125b was first reported to reduce p53 protein levels and impair p53-induced apoptosis in human cells and the brain of zebrafish [16]. Our previous study reported that miR-504 directly reduces the p53 protein levels and therefore negatively regulates p53-mediated apoptosis and cell cycle arrest in cancer cells. Furthermore, overexpression of miR-504 promotes the tumorigenicity of colorectal cancer cells in xenograft tumor models *in vivo* in a largely p53-dependent manner [17]. In addition to miR-125b and miR-504, many other miRNAs that directly target p53 were reported to promote cancer cell proliferation through repressing the p53 mediated-apoptosis, cell cycle arrest and/or senescence [12, 18-20]. Many of these miRNAs have been reported to be overexpressed in different types of cancer, which can directly repress the p53 protein levels to impair the tumor suppressive function of p53 [12, 18, 19].

In addition to the above-mentioned miRNAs that directly repress p53, a group of miRNAs has been identified to activate p53 by directly repressing MDM2, such as miR-192, miR-194, miR-215, miR-605, miR-25, miR-32, miR-17-3p, miR-143, miR-145, miR-661, miR-660, etc [12, 18, 21]. Almost all of these miRNAs have been demonstrated to be able to inhibit cancer cell proliferation through promoting the p53-mediated apoptosis, cell cycle arrest and/or senescence [12, 18, 21]. Some of them were also reported to repress the migration

and invasion of cancer cells and reverse epithelial-mesenchymal-transition (EMT) to inhibit cancer metastasis [22, 23]. Interestingly, some of these miRNAs, such as miR192, miR-194, miR-215, miR-605, miR-143 and miR-145, were also identified to be the transcriptional targets of p53. These miRNAs form positive feedback loops with p53 and help to activate p53 especially under the condition of stress [12, 18, 21].

Recently, we identified miR-339-5p as an additional miRNA that activates p53 through directly binding to the 3′-UTR of MDM2 mRNA [24]. We found that miR-339-5p reduces the MDM2 protein levels to increase p53 protein levels, leading to the enhanced p53 functions in inducing apoptosis and senescence and inhibiting cell migration and invasion as well. MiR-339-5p also represses the growth of colorectal xenograft tumors in mice through p53 activation [24]. MiR-339-5p has been reported to be frequently down-regulated in different types of cancers, such as colorectal, breast and lung cancers [25-27]. Furthermore, the down-regulation of miR-339-5p was reported to be associated with cancer metastasis and poor prognosis in cancer patients [25-27]. Consistent with our findings, a recent study from another group also reported that MDM2 is a direct target for miR-339-5p [28]. Furthermore, they found a negative correlation between miR-339-5p and MDM2 expression in both human colorectal cancer and renal clear-cell carcinoma [28]. These studies together indicate an important role of miR-339-5p in tumor suppression through its regulation of the p53/MDM2 negative feedback loop.

In addition to the regulation of p53 or MDM2 by miRNAs, recent studies have also demonstrated that p53 can either induce or repress the expression of many different miRNAs, which in turn function as mediators for p53 in tumor suppression [12, 18-20]. Thus, through regulating the p53 levels or mediating the p53 function in tumor suppression, miRNAs have become a new but important component of the p53 signaling pathway.

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