HPV-p53-miR-34a axis in HPV-associated cancers

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Abstract: Human papillomaviruses (HPVs) are known to cause many cancers by altering multiple signalling pathways through their oncogene integration into host genome and expression. Studies have shown that many microRNAs (miRs) may function as oncogenes (called as oncomiRs) to promote an oncogenic effect. MiR-34a among the reported oncomiRs is a key player in the carcinogenesis caused by infection with HPVs. In this mini-review, we summarise the roles of miR-34a in HPV-caused cancers. MiR-34a is transcriptionally regulated by tumour suppressor p53. HPV oncogene E6 inhibits expression of p53 to decrease the levels of miR-34a, leading to the increased expression of multiple genes which are targeted by miR-34a. The upregulation of these genes increases cancer cell proliferation, survival and migration in HPV-associated cancers.

Keywords: E6 oncogene; proliferation; epithelial-mesenchymal transition (EMT); cyclin D1; Snail; Notch pathway

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Introduction

MicroRNAs (miRs) are non-coding regulatory RNAs that target mRNAs by binding to complementary regions of the 5' and 3' untranslated regions to regulate mRNA expression and degradation (1-3). In humans, several hundred genes have been identified to encode up to 1,000 miRs (4,5). These miRs regulate expressions and functions of approximately one third of human genes and play important roles in different cellular processes such as cell proliferation and apoptosis. MiRs may function as oncogenes (called as oncomiRs) that are associated with carcinogenesis, malignant transformation, and metastasis. While some oncomiRs are oncogenes, in that overexpression of these oncomiRs leads to cancerous growth, the other miRs are tumor suppressors in a normal cell. But, aberrant expression of the tumor suppressor miRs due to under-expressions of the corresponding genes also leads to cancerous growth, which is one of the multiple mechanisms of carcinogenesis (1-3,6).

It has been well known for a long time that infection with human papillomaviruses (HPVs) causes many cancers including cervical cancer, head and neck cancer, skin cancer and so on (7-11). HPV infections account for about 10-20% of total cancer incidence. It is also well known now that expression of high risk HPV oncogenes (*E6* and *E7*) can alter multiple intracellular signalling pathways (12-14). These signalling pathways play crucial roles in regulating cell proliferation and apoptosis through the altered gene expression and protein modification. Recently, the research advances in molecular pathology have demonstrated that many miRs are involved in HPV-induced carcinogenesis

and metastasis (15-18). Several independent studies have identified that as the most prevalent p53-induced miRNAs the members of the tumour suppressor miR-34 family are frequently altered in many human cancers. In this short review, thus, we focus on discussing the key roles of miR-34a, one of the miR-34, in HPV-induced cancers.

E6 oncogene/p53/miR-34a axis and HPV-induced carcinogenesis

Infection with HPVs causes human cancers via the oncogenic roles of expression of *E6* and *E7*. Expression of the two oncogenes either from genes-integrated host genomes or viral episomes activates different signalling pathways to promote cell proliferation and prevent cell apoptosis (9,12,19). p53 is a well-known tumour suppressor, whose biological effects are largely due to its cellular functions, which mediate cell growth arrest by regulating expression of different cell cycle genes through the cell cycle pathway (20,21) and induce cellular apoptosis by regulating gene expression such as *bcl-2* and *bax* through the mitochondrial apoptotic pathway (22). N-terminally truncated p53 family isoforms (ΔNp53, ΔNp63, and DNp73) play a critical role in carcinogenesis by counteracting cell cycle arrest and apoptosis (21). High-risk HPV E6 proteins bind to p53 to inhibit and degrade this tumour suppressor to abolish its cancer prevention effects. The abolished p53 cancer prevention effects include the decrease of cell apoptosis and accumulation of gene mutations and inappropriate response to DNA damage, which co-operate with other cellular changes, eventually leading to carcinogenesis (23-25). It is clear now that both benign and oncogenic HPV E6 proteins can bind to p53 by a region of C-terminal sequence (26,27). However, an N-terminal sequence is required for degradation; only oncogenic HPV's E6 proteins have such a conserved N-terminal sequence to degrade p53 (26,28,29), which is ubiquitin-mediated (30,31).

p53 binds and activates the promoter of the gene that encodes miR-34a to up-regulate expression of miR-34a (32-34). Processing of the primary transcript into mature miR-34a involves the excision of a 30 kb intron (34). Oncogenic HPV infection interrupts the expression of miR-34a through viral oncoprotein E6; E6 knockdown increases levels of both p53 and miR-34a (35). Thus, reduced miR-34a expression is associated with high-risk HPV infection in the p53-dependent pathway (36). Furthermore, significantly reduced expression of pri-miR-34a occurs not only in cervical cancer, but also in precancerous lesion even before morphologic change and cervical cancer-derived cell lines (35,36). The miR-34a levels detected were significantly lower in cervical intraepithelial neoplasia (CIN)2-3 than in CIN1 (37,38). Li *et al*. showed that miR-34a was reduced in both normal and damaged cervical tissues in HPV positive women (36). However, it has also been reported that miR-34a is increased in HPV-associated cancer (39,40). It has been reported that inactivation of miR-34a strongly attenuates p53-mediated apoptosis in cells exposed to genotoxic stress, whereas overexpression of miR-34a mildly increases apoptosis. Hence, miR-34a is a direct proapoptotic transcriptional target of p53 that can mediate some of p53's biological effects. Perturbation of miR-34a expression, as occurs in some human cancers, may thus contribute to tumorigenesis by attenuating p53-dependent apoptosis (34). The high-risk HPV E6-caused inhibition of miR-34a expression in the p53-dependent pathway is probably an early-onset event in the development of cervical cancer. Moreover, reduced miR-34a expression by HPV proteins appears to be correlated with promoting persistent infection and cervical cancer development (40) and invasive cervical cancer (41).

MiR-34a mediates HPV E6-caused cellular events

As a downstream molecule of p53, miR-34a also targets many other proteins to mediate their functions by decreasing cell proliferation, promoting apoptosis and preventing carcinogenesis (33,42,43). MiR-34a also causes cancer cell senescence (44). Therefore, miR-34a plays very important roles in carcinogenesis induced by HPV infections (*Figure 1*) (45-47).

Cell proliferation and viability

Cell proliferation is a major hallmark of cancer. HPV E6 protein can increase cell proliferation through multiple signalling pathways (48-51). Decreased miR-34a due to p53 inhibition is one of the mechanisms for increased cell proliferation of HPV-associated cancers. MiR-34a has been shown to regulate cyclin E2, cyclin D1, CDK4, CDK6, E2F1, E2F3, E2F5, survivin and Sirt1 to induce cell cycle arrest that ultimately inhibits cell proliferation (42-44,52). It has also been reported that miR-34a accumulates in G_0/G_1 phase cells (53) and inhibits the cell cycle and proliferation of lymphoma cells by repressing its target MAP2K1 (MEK1), which is a central component of MEK/ERK signaling (54). In addition, through regulating expression of E2F3 and survivin, miR-34a overexpression could inhibit HPV-positive cancer cell viability, whereas its down-regulation promoted

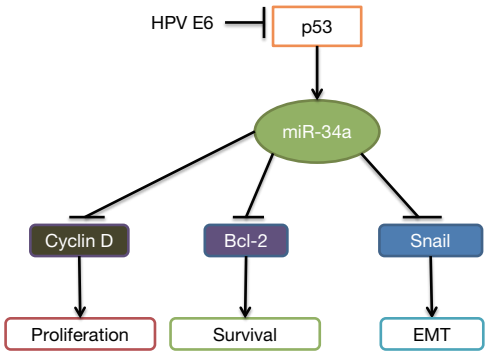

Figure 1 The role of miR-34a in HPV E6-mediated proliferation, survival and EMT. HPV E6 inhibits p53, leading to decreased miR-34a levels. Thus, the expression of its target genes is increased. Increased cyclin D expression causes increased cell proliferation, increased Bcl-2 expression results in increased cell survival and increased Sanail expression leads to increased EMT. HPV, human papillomavirus; EMT, epithelial-mesenchymal transition.

cell viability (55). Over-expression of miR-34a in HeLa cells and HPV negative colon cancer cell line HCT116 greatly decreased cell growth and caused moderate apoptosis (53).

Epithelial-mesenchymal transition (EMT)

EMT has been demonstrated to play a key role in HPV-associated head and neck cancer and other human cancers (56,57). Cancer cell EMT is critical for metastasis, which is regulated by transcriptional repressor Snail1. MiR-34a has been demonstrated to regulate Snail1 protein expression through binding to highly conserved 3' untranslated regions in *Snail1* mRNA (58). The loss of p53 function results in decreased miR-34a levels, leading to activated Snail1-dependent EMT in colon, breast, and lung carcinoma cells. Snail was shown the only mediator for p53-caused EMT. In addition, EMT is necessary step to cause spindle-shaped mesenchyme-like phenotype (59). In cultured epithelial cell line MDCK cells, expression of HPV E6 and E7 increased mesenchymal markers including slug, twist, ZEB1and ZEB2 (60). In the cells derived from head and neck patients, ZEBs are associated with HPV16. Mendelsohn *et al.* showed that increased Snail in head and neck cancer is a biomarker of poor prognosis indicated by poor differentiation, increased lymphovascular invasion and metastasis (57). However, increased Snail was not associated with HPV infection in this study (57). Further study is needed to clarify the pathway of HPV E6/p53/miR-34a/Snail/EMT.

MiR-34a and P18Ink4c

P18Ink4c is a member of INK4 family, which inhibits CDK4 and CDK6. It has been shown that p18Ink4c is up-regulated in cervical cancer (53). But increased p18Ink4c did not regulate cell cycle in cervical cancer. It may be caused by E7 protein on RB or miR-34a direct regulation of CDK6 (43). MiR-34a specifically targets p18Ink4c, a CDK4 and CDK6 inhibitor induced by E2F transactivation. HPV18(+) HeLa cells with ectopic miR-34a expression or by E6 siRNA knockdown-induced expression of endogenous miR-34a exhibited a substantial reduction of p18Ink4c in a dose-dependent manner. Suppression of endogenous miR-34a in cell lines with a miR-34a inhibitor also increased p18Ink4c (53). Therefore, p18Ink4c could be a biomarker of miR-34a.

MiR-34a-Notch pathway

Notch pathway plays a critical role in carcinogenesis and metastasis of many cancers (61,62). Activation of Notch pathway also increases drug resistance to anti-cancer agents (63). Decreased Notch 1 pathway mediated by miR-34a was demonstrated to reduce cancer invasion (64). Knockdown of miR-34a increased Notch1, Jagged 1 and Hes-1 expression. In Hela and JAR cells, transfection of pre-miR-34a reduced Notch expression by 24% and 31% respectively (64). The Notch downstream target gene *Hes-1* expression was also consistently reduced. Furthermore, a Notch ligand, Jagged1 that is highly expressed in colorectal cancer (CRC) has been shown to increase cancer development and metastasis (65). Knock down of Jagged1 using shRNA on CRC both *in vitro* and *in vivo* decreased colon cancer cell proliferation caused by reduced expression of cell cycle signalling molecules including Cyclin D1, Cyclin E and c-Myc. In a xenograft mouse model, inoculation of cells with knockdown of Jagged1 greatly decreased tumour growth compared with cells without knockdown (65). This was confirmed by markedly decreased cell proliferation markers (PCNA, Ki-67, and c-Myc). Knockdown of Jagged1 also decreased the migration ability of colon cancer cells (65).

MiR-34a/Bcl-2 and mitochondrial apoptotic pathway

Mitochondrial apoptotic pathway is a major pathway to cause cell apoptosis. The pathway is controlled by bcl-2 family (22,66,67). There are pro-apoptotic proteins and anti-apoptotic proteins. Bcl-2 is an anti-apoptotic protein

increased in many cancers (68-70). MiR-34a has been demonstrated to target *bcl-2* mRNA. Therefore, decreased levels of miR-34a in cancer can result in increased bcl-2 protein levels in several cancers (71-73). In cervical cancer, miR-34a has been shown to down-regulate bcl-2 protein expression (74). This indicates HPV-miR-34a-bcl-2 is also a mechanism for HPV-caused cancer.

Potential chemotherapeutic role of miR-34a

While several independent studies have shown that miR-34a is important in cancer prevention (45-47), other studies have suggested that miR-34a has greatly potential therapeutic role in cancer chemotherapy (75-78). Currently, chemotherapy is still a standard treatment regimen in cancer therapy. However, drug resistance is a major problem. It has been observed that miR-34a increases cancer cell sensitivity to chemotherapeutic agents (79). Therefore, miR-34a is of therapeutic importance. Decreased miR-34a was demonstrated to cause drug resistance to cisplatin in bladder cancer, to docetaxel in breast cancer and 5-FU in colon cancer (75-78).

Conclusions

MiR-34a is directly regulated by p53, which acting as a tumour suppressor is a down-streamer of the p53-network with key regulatory functions in cell proliferation, cellular apoptosis, G1-arrest, DNA repair and senescence. High-risk HPV E6 protein inhibits expression of miR-34a through the p53-pathway to increase virus-infected cell survival and enhance cancer cell proliferation and metastasis. Undoubtedly, miR-34a is a highly promising biomarker of HPV-associated cancers. Further study to characterize the expression of miR-34a in the various stages of the lesions caused by HPV infection may open a new avenue for the early diagnosis of HPV-associated cancers. Manipulation of miR-34a levels in HPV-associated cancers may have therapeutic significance.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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