The critical roles of miR-21 in anti-cancer effects of curcumin

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Abstract: Curcumin is a well-known phytochemical that has various anti-cancer effects. Although it has been demonstrated that curcumin can inhibit multiple signalling pathways, the exact mechanisms for its demonstrated anti-cancer effects are not fully understood. Recent studies have revealed that curcumin may affect cancer initiation and progression through regulating microRNAs (miRs). In this review, we focus on the roles of microRNA-21 (miR-21) in the anti-cancer effects of curcumin and regulatory mechanisms for the effects of curcumin on miR-21. MiR-21 mediates various effects of curcumin on cancer cells including proliferation, apoptosis, metastasis and anti-cancer drug resistance. Several downstream pathways of miR-21 have been identified including phosphatase and tensin homolog (PTEN)/phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), programmed cell death protein 4 (PDCD4) and NF-κB pathways. Curcumin decreases miR-21 levels through both increasing miR-21 exosome exclusion from the cells and inhibiting the transcription of the *miR-21* gene in the cells by binding to its promoter.

Keywords: Curcumin; microRNA-21 (miR-21); phosphoinositide 3-kinase/protein kinase B (PI3K/Akt); programmed cell death protein 4 (PDCD4); Notch; NF-κB

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Introduction

Many risk factors have been shown to induce cancer including genetic defects, epigenetic alterations, diet, obesity and infection (1,2). These factors alter intracellular signalling pathways to promote cell proliferation and decrease apoptosis; thus increase cancer incidence (3). Activation of survival signalling pathways such as phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and mitogen activated protein kinase (MAPK), is also associated with the cancer cell resistance to anti-cancer therapeutic agents (4-8). Therefore, manipulation of signalling pathways has been targeted for cancer treatment. Indeed, many small molecule inhibitors of signalling molecules have been developed by various companies and tested extensively (9,10). Some of them have been used in multiple clinical trials. Interestingly some phytochmicals have been revealed to have property to inhibit multiple signalling pathways in cancer cells and thus are attractive candidates for cancer prevention and treatment (11). One among them is curcumin, which has been recently studied extensively (12-16).

Curcumin is extracted from a spice called turmeric, derived from a Zingiberaceae family plant *Curcuma longa L* (17). Indeed, turmeric has had medicinal applications in various diseases for thousands of years in Asian countries (17-20). Curcumin can decrease cell proliferation and increase apoptosis in many cancer cell lines *in vitro* including colon cancer, breast cancer, prostate, lung cancer, and so on (21-23). It has been demonstrated that curcumin is effective on many cancers caused by various risk factors such as obesity-associated cancers and HPV-caused

cancers. Obesity is known to increase cancer incidence and lead to vicious prognosis through activation of multiple signalling pathways (24-26). Curcumin is effective in the prevention and treatment of obesity-associated cancers in animal models (27). It has been shown to reduce colon poly formation in several animal models for obesity-associated colon cancer (28-30). Curcumin is also effective against HPV-caused cancers (31,32).

The mechanisms for the anti-cancer effects of curcumin have been suggested to be its inhibition of multiple signalling pathways and anti-oxidant property. Curcumin can inhibit several common cancer promoting pathways including MAPK, Akt, NF-κB and Cox-2 (33-35). Recent studies have shown that curcumin regulates many microRNAs (miRs) (36-38). In this review, we summarise the roles of miRNA-21 in the anti-cancer effects of curcumin and the associated mechanisms.

microRNA-21 (miR-21)

MiRs are endogenous RNAs which have 19-25 nucleotides (39-41). MiRs do not translate into proteins but can regulate gene expression. When miRs bind to complementary mRNAs, miRs can cause degradation of mRNAs or stop the translation of mRNAs and thus decrease target protein production. MiRs are involved in many physiological processes including cell proliferation, differentiation and survival (42,43). MiRs regulate about one third of gene expression in human body. It is thus not surprising that miRs play important roles in cancer development and progression. MiRs may target tumour suppressors to promote cancer formation (oncomirs) or target oncogenes to prevent cancer development (tumour suppressor miRs) (44).

MiR-21 is one of the most frequently up-regulated miRs in many cancers including breast, gastric, colon, lung, pancreatic and ovarian cancers (45,46). It can increase cell proliferation and decrease apoptosis and therefore increase cancer incidence (47). High level of miR-21 has been shown to be associated with poor prognosis in many cancer cases (48). MiR-21 stimulates multiple survival signalling pathways to mediate its roles in cancers. Therefore, targeting miR-21 has therapeutic implications.

The roles of miR-21 in various aspects of curcumin's anti-cancer effects

Curcumin has been found to decrease miR-21, which is a key mechanism for curcumin to have anti-cancer effects (49). MiR-21 mediates several important aspects of anti-cancer effects of curcumin including cell proliferation, metastasis, stemness and sensitivity to anti-cancer therapeutic agents.

Proliferation and apoptosis

Increased cell proliferation and decreased cell apoptosis are two major cellular characteristics of cancers (50,51). Inhibiting proliferation and inducing apoptosis are thus important approaches for the prevention and treatment of cancer. Cell proliferation is determined by cell cycle which includes four phases and is regulated by cell cyclins (3). Mudduluru *et al.* showed that curcumin reduced colon cancer cell cycles through down-regulation of miR-21 (49). Zhang *et al.* showed that curcumin decreased human non-small cell lung cancer A549 cell proliferation and increased apoptosis with decreased miR-21 (52). Over-expression of miR-21 in these cells decreased the effect of curcumin on A549 cells. Therefore, the level of miR-21 is critical for curcumin to inhibit cancer cell proliferation and induce cancer cell apoptosis

Metastasis

Metastasis is the major reason for cancer to cause deaths, which undergoes several stages including cell detachment, migration, attachment and growth (53,54). Curcumin has been revealed to reduce cancer cell migration via inhibiting miR-21 in various cancers including colon cancer (49). Bao *et al.* showed that curcumin analogue difluorinated-curcumin (CDF) reduced pancreatic cancer cell migration via decreasing miR-21 (55). Curcumin can also cause anoikis, which refers to cell death after detachment (56,57). Whether it is mediated by miR-21 is unknown.

Cancer stem cells (CSCs)

CSCs refer to those cells that can reproduce themselves and sustain cancer (58-60). They are responsible for drug resistance in cancer treatment. Therefore, it is critical to reduce stemness of cancer cells to increase treatment efficacy. Bao *et al.* showed that CDF reduced pancreatosphere formation via decreasing miR-21 (55). Hypoxia increased CSC biomarkers such as Nanog, Oct4 and EZH2 mRNA expression while CDF decreased the levels of these markers (55).

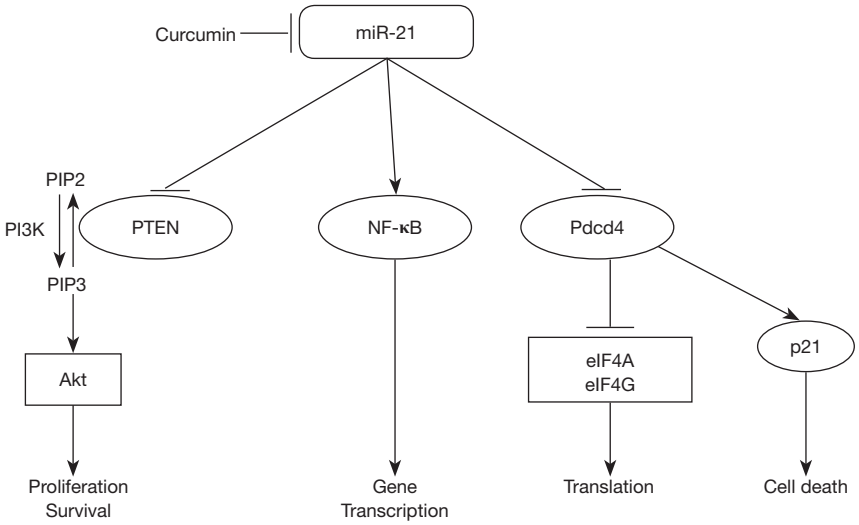

Figure 1 Curcumin blocks multiple cancer promoting pathways via miR-21. Curcumin decreases miR-21 and thus increases PTEN, leading to decreased PI3K/Akt pathway activity. is increased, leading to decreased eIF4A and eIF4G and thus decreased translation. PDCD4 can also increase cell death through p21. Blockage of miR-21 also results in decreased NF-κB activity and gene transcription. miR-21, microRNA-21; PTEN, phosphatase and tensin homolog; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B; PDCD4, programmed cell death protein 4.

Drug resistance

Drug resistance, either primary or acquired, is a major problem in the treatment of cancers (61-63). Application of curcumin has been shown to overcome drug resistance in several studies. It has been revealed that inhibition of miR-21 by curcumin could be an important mechanism. Inhibition of miR-21 by curcumin increased pancreatic cancer cell sensitivity to gemcitabine (64). Roy *et al.* showed that CDF decreased miR-21 in 5-FU and oxaliplatin resistant colon cancer cell lines through upregulation of phosphatase and tensin homolog (PTEN) and thus reduction of activity status of PI3K/Akt pathway (65). Activation of the PI3K/Akt pathway is well-known to cause drug resistance in colon cancer cells (5,6).

Multiple signalling pathways involved in miR-21 mediated curcumin's anti-cancer effect

Many studies have revealed that miR-21 mediates the anti-cancer effects of curcumin via multiple signalling pathways as described below. The common pathways affected include PTEN/PI3K/Akt, NF-κB and programmed cell death protein 4 (PDCD4) (*Figure 1*).

PTEN/PI3K/Akt pathway

PI3K/Akt is a common survival pathway. PI3K catalyses phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3), which recruits Akt and phosphoinositide dependent kinase (PDK) to allow PDK to phosphate and activate Akt (66,67). Activated Akt increases cell proliferation and decreases cell apoptosis via a broad range of downstream target proteins. PTEN is a negative regulate of PI3K/Akt pathway by turning PIP3 into PIP2. Curcumin restored PTEN expression via inhibiting miR-21 in colon cancer (68). Induction of miR-21 suppressed the anti-cancer of curcumin through decreasing PTEN (52). MiR-21 is known to cause drug resistance to cisplatin via decreasing PTEN (69). Studies also showed that miR-21 targeted PTEN by complementing its sequence (70,71).

Programmed cell death protein 4 (PDCD4)

PDCD4 is a tumour suppressor. MiR-21 was found to be inversely related with PDCD4 in both colon cancer cell lines and tissue samples from colon cancer patients (72-74). MiR-21 complements the 3-UTR of PDCD4 and thus inhibits the translation of PDCD4 (72). Mutation in the PDCD4 region that complementary with miR-21 abolished the regulation of

PDCD4 by miR-21. The PDCD4 regulated by miR-21 has been associated with cancer transformation and metastasis (72,75). MiR-21 mediated PDCD4 degradation has also been demonstrated in breast cancer (76), cervical cancer (77), Glioblastoma (78,79) and hepatocellular carcinoma (80). MiR-21 mediated PDCD4 degradation has been shown to be important in curcumin-reduced metastasis (49).

NF-κB

NF-κB is a transcriptional factor that can promote cancer development through upregulation of many oncogenes. Curcumin has been shown to decrease NF-κB via miR-21 (81). Curcumin is well known to cause decreased accumulation of NF-κB in the nuclei in many cancer cells. Yang *et al.* demonstrated that EF24, a curcumin analogue, caused apoptosis of prostate cancer and B16 murine melanoma cells through inhibition of NF-κB (81). The decreased miR-21 levels by EF24 may be important for NF-κB reduction. This is consistent to that miR-21 can increase NF-κB in other studies (82,83). However, it is not clear how miR-21 regulates NF-κB.

The mechanism for curcumin to decease miR-21

It has recently been found that curcumin decreases miR-21 by increasing its secretion carried in exosomes in chronic myelogenous leukemia (CML) cell lines K562 and LAMA84 (84). Exosomes are cell-derived nanosize vesicles that contain miRs and present in all biological fluids. In *in vivo* experiments, curcumin treatment of CML xenograft SCID mice has increased plasma exosomes containing miR-21 (84). This was accompanied by an increase in PTEN and a decrease in AKT phosphorylation in CML cells, indicating decreased miR-21 in the cells.

Curcumin has also been found to inhibit *miR-21* gene promoter activity directly. A motif in miR-21 to bind to activator protein 1 (AP-1) transcription factor has been identified (49). Curcumin can inhibit AP-1 binding and thus decrease the transcription of *miR-21* gene.

Conclusions

Curcumin has anti-cancer effects on many cancer cells. It can inhibit multiple signalling pathways, altering many cellular physiological processes. Recent findings showed that curcumin also affects many miRs, which are important regulators of oncogenes and tumour suppressors. Curcumin can decrease miR-21, a key oncomir, through increasing its exosome exclusion and inhibiting the transcription of *miR-21* gene. Inhibition of miR-21 mediates many aspects of anti-cancer effects of curcumin including cell proliferation, apoptosis, migration, stemness and drug resistance through PTEN/PI3K/Akt, PDCD4 and NF-κB.

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Footnote

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

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