REVIEW ARTICLE

Curcumin and Lung Cancer: the Role of microRNAs

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Abstract: *Background:* Lung cancer is one of the most common types of cancer worldwide and is characterized by a poor prognosis, related to both late diagnosis and lack of effective treatments. In the last years, microRNAs (miRNAs) have been demonstrated to have an important role in tumor microenvironment and immune regulation. These RNAs can be categorized into tumor-suppressor genes, such as let-7 family and miR-34, and oncogenes such as miR-221 and miR-222. Curcumin is a bioactive polyphenol that is documented to have promising anti-cancer activity, and to be well tolerated in humans.

Methods: The present review aims to gather available evidence on the involvement of mRNAs in the therapeutic effects of curcumin against lung cancer.

Results: The anti-cancer properties of curcumin against lung cancer have been shown in both cellular and experimental models and are mediated by modulation of several molecular targets that regulate the expression of transcription factors, inflammatory cytokines, enzymes, growth factors, receptors, adhesion molecules, antiapoptotic proteins, and cell cycle proteins, leading to cell apoptosis, inhibition of cell proliferation and migration, and also chemo- and radio-sensitization of lung cancer cells. Recent studies have documented that pharmacological effects of curcumin in lung cancer are also mediated by modulation of several miRNAs, such as downregulation of oncogenic miR-21 and upregulation of oncosuppressive miR-192-5p and miR-215.

Conclusion: Further studies are necessary to explore this very promising field and the link between regulation of oncogenic and tumor-suppressive miRNAs and putative anti-cancer properties of curcumin.

Keywords: Curcumin, epigenetic, lung cancer, MicroRNA, RNA interference, tumor.

INTRODUCTION

Lung cancer is one of the most common types of cancer worldwide; it is classically differentiated in non-small cell lung cancer (NSCLC), that represents about 80% of all lung cancers, and small cell lung cancer (SCLC), that represents the remaining 20% [1]. This disease represents the first cause of death from cancer, accounting for more than 1,4 million deaths each year [2]. Despite improvements in diagnostic and therapeutic strategies, the overall 5-year survival from lung cancer remains only 10-20% [1]. Poor prognosis is generally related to late diagnosis and lack of effective treatments [3].

Micro-RNAs (MiRNAs) are small single-strand non-coding RNAs, with a size range of 19-25 nucleotides that are implicated in post-transcriptional regulation of gene expression. MiRNAs are loaded into the RNA-induced silencing complex (RISC) that recognizes the complementary sequence of target mRNAs and induces their degradation or translational repression. MiRNAs can silence multiple genes owing to their partial base complementarity with corresponding mRNAs [4,5]. Therefore, miRNAs can regulate multiple genes and have an important role in cell differentiation, proliferation, growth, mobility, and apoptosis. MiRNAs can be categorized into oncogenes and tumor-suppressor genes [6], and are implicated in tumor microenvironment regulation such as stimulation of angiogenesis, matrix degradation [7], and activation of cancer-associated fibroblasts that generate an environment promoting tumor growth and invasiveness [8]. MiRNAs can also regulate

immune response through multiple mechanisms such as downregulation of MHC I [9], ICAM-1 [10], regulatory T lymphocytes (Tregs), CXCL12, and TGF-β production [11].

Curcumin is a component of turmeric, derived from Curcuma longa, and characterized by many biological and pharmacological effects, that are mediated by modulation of several molecular targets and signalling pathways. Therefore, curcumin regulates the expression of several transcription factors, inflammatory cytokines, enzymes, growth factors, receptors, adhesion molecules, antiapoptotic proteins, and cell cycle proteins, with associated anti-inflammatory, antioxidant, and anticancer activity [12]. Furthermore, curcumin is well tolerated in humans [13]. Anti-cancer activity of curcumin has been demonstrated in different types of cancer, such as melanoma [14], colon [15], pancreatic [16], and lung [17] cancer. These effects are, at least in part, mediated by modulation of miRNAs. For example, in human colon cancer cell lines, curcumin down-regulates in a dose-dependent manner miR-21, an oncogenic miRNA, and induces the expression of the tumour suppressor Programmed Cell Death Protein 4 (PDCD4), which is a target of miR-21. These data are also confirmed in *in vivo* chicken-embryo-metastasis assay, where it is demonstrated to inhibit cancer cell metastasis [18]. MiRNA-21 is also implicated in pancreatic cancer, and it is a target of difluorinated curcumin (CDF), a curcumin analogue characterized by greater bioavailability [19]. In fact, in human pancreatic cell lines, CDF inhibits miR-21 and consequently induces tumor-suppressor phosphatase and tensin (PTEN), a target of miR21 [20]. Curcumin modulation of miRNAs is documented also in melanoma: Dahmke *et al.* described that dietary intake of curcumin modulates the expression of 147 miRNAs in an engrafting mouse melanoma model, the most up-regulated of which was mmu-miR-205-5p, with consequent down-regulation of Bcl-2 and

proliferating cell nuclear antigen (PCNA), that are involved in cancer-related pathways, including apoptosis and proliferation [21].

In this review, we briefly describe the action of curcumin in regulating the miRNA involved in lung cancer

microRNAs AND LUNG CANCER

In the last years, microRNAs (miRNAs) have been demonstrated to have an important role in the pathogenesis of lung cancer and development of drug-resistance. Recent studies have reported an aberrant expression of miRNAs in lung tumor tissues compared with the corresponding normal lung tissues, suggesting the involvement of miRNAs in lung cancer pathogenesis [22].

In NSCLC, many miRNAs described to have a tumor-suppressor activity are down-regulated, while those inducing proliferation are up-regulated. The let-7 family of miRNA inhibits the expression of oncogenes (e.g. Ras, Myc and cyclin D) that are implicated in cell-cycle regulation and proliferation and thus inhibit tumor growth both *in vitro* and *in vivo* [23,24]. Another miRNA with tumor-suppressor activity is miR-34 that is transcriptionally activated by p53 in response to DNA damage. This miRNA regulates cell cycle, apoptosis and senescence by targeting *Bcl-2*, *Myc*, *MET* and *PDGFR* genes [25]. Both let-7 and miR-34 are down-regulated in NSCLC cell lines [26]. MiR-29 family members may target DNA methyltransferases (DNMT3A and DNMT3B) and restore patterns of DNA methylation and expression of silenced tumor-suppressor genes in lung cancer, thus inhibiting tumorigenicity both *in vitro* and *in vivo* [27].

On the other hand, many miRNAs are described to have an oncogenic function in NSCLC by targeting tumor-suppressor genes. For example, the miR-17-92 cluster targets PTEN which participates in the cell-survival signaling pathway [27]. It also targets the hypoxia-inducible factor 1 α (HIF-1α) which transactivates the genes involved in multiple biological processes such as angiogenesis, apoptosis, extracellular metabolism, cell proliferation, invasion and metastasis [28]. MiR-221 and miR-222 target PTEN and tissue inhibitor of metalloprotease-3 (TIMP-3), thereby enhancing survival and migration of NSCLC cells [29].

Overall, miRNAs have been suggested as key regulators of biological processes involved in lung cancer and could thus serve as potential therapeutic targets in this type of cancer [22].

CURCUMIN AND LUNG CANCER

Conventional therapies for lung cancer are poorly effective and burdened with serious adverse effects [30]. The anti-cancer properties of curcumin are mediated by modulation of several molecular targets that regulate the expression of transcription factors, inflammatory cytokines, enzymes, growth factors, receptors, adhesion molecules, antiapoptotic proteins, and cell cycle proteins, leading to cell apoptosis, inhibition of cell proliferation and migration, and also chemo- and radio-sensitization of lung cancer cells [31,32]. For example, this compound has been shown to increase ROS levels [33,34] and, in a dose-dependent manner, reduce the expression of DNA repair proteins and enhance p53 levels [35], which jointly result in the induction of apoptosis.

The most important pathway by which curcumin inhibits lung cancer cell proliferation is the JAK2/STAT3 pathway. This pathway also suppresses migration, invasion and angiogenesis [36,37]. JAK2/STAT3 is inhibited by curcumin also in cancer stem cells [38], which are implicated in tumor recurrence and in drug resistance; this activity leads to the inhibition of tumor growth *in vivo* [39]. Another mechanism by which curcumin inhibits the proliferation of lung cancer cells is induction of forkhead box protein O1 (FOXO1), a transcription factor that regulates cell proliferation, differentiation, and DNA damage repair [40,41]. Inhibition of cell proliferation by curcumin also results from epigenetic effects such as reactivation of silenced tumor-suppressor genes like RARβ that

is induced by curcumin, leading to the inhibition of tumor growth [42].

The antineoplastic action of curcumin is also mediated by the inhibition of cancer cell migration. Curcumin down-regulates early growth response protein 1 (EGR-1) via enhancement of cell-cell adhesion [43]. Moreover, this compound inhibits the production and activity of matrix metalloproteinases (MMPs) through several mechanisms such as down-regulation of phosphokinase A, with consequent inhibition of MMP-9 production through NADPH oxidase-2 pathway [44], or the inhibition of the Rac1/PAK1 pathway, leading to the down-regulation of MMP-2 and MMP-9 [45].

Finally, curcumin has chemosensitizing properties documented for many chemotherapeutic agents. Cisplatin, the most common chemotherapeutic agent used in NSCLC, has a biological cellular resistance that is generally associated with cellular DNA repair mechanisms [46], and this resistance has been shown to be reversed by curcumin. Furthermore, curcumin enhances the cisplatin-mediated inhibition of proliferation and induction of apoptosis by inhibition of the Fanconi anemia/BRCA pathway [47] and HIF-1α [48].

CURCUMIN AND microRNAs IN LUNG CANCER

Several lines of recent evidence have shown that the pharmacological effects of curcumin in lung cancer are also mediated by modulation of several miRNAs (Table **1** and Fig. **1**). Zhang *et al.*, through qRT-PCR analysis, documented that curcumin down regulates the expression of miR-21 in a dose-dependent manner in lung cell line A549, with a reduction in miR-21 expression of about 60% in cells exposed to 40 μM of curcumin. In these experimental model, flow cytometric analysis showed that curcumin at 20-40 μM increased the portion of apoptotic annexin V-positive cells by approximately 2-5-fold, and inhibited cell proliferation and induced apoptosis. PTEN, the putative target of miR-21, was significantly elevated in curcumin-treated A549 cells, as determined by Western blot analysis [49].

Ye *et al*. documented through miR microarray that 15 μM of curcumin up-regulate the tumour suppressive miR-192-5p and miR-215 in A549 cells (p53 wild type), but not in H1299 cells (p53 null). Curcumin up-regulates and activates p53 in the p53 wild type H460, A427, and A549 NSCLC cells; the lack of p53 in H1299 cells impaired curcumin-mediated up-regulation of miR-192-5p/215. As documented by a dual luciferase activity assay, X-linked inhibitor of apoptosis (XIAP) is a target of miR-192-5p/215. Therefore, curcumin induced apoptosis through activation of the p53-miR-192-5p/215-XIAP pathway in NSCLC cells [50]. Moreover, induction of miR-192-5p by curcumin inhibits cell proliferation and induces apoptosis through inhibition of the Pi3K/Akt pathway, a pathway implicated in growth factor-mediated cell survival [42].

Another miRNA that is modulated by curcumin is miR-186* which is an oncogenic molecule implicated in the down-regulation of proapoptotic genes in lung cancer. Tang *et al.* [51] and Zhang *et al.* [52,53] studied the effect of curcumin on the expression of miR-186* in A549/DDP human lung cancer cells. Microarray analysis and qRT- PCR showed that curcumin may induce apoptosis by down-regulating miR-186* expression in these cells. The target of miR-186*, predicted using the Miranda database and confirmed by using dual luciferase reporter assays and Western blot analysis, was caspase-10, an initiator caspase in death receptor signaling, crucial for apoptotic signaling. This caspase was significantly increased in curcumin-treated lung cancer cells. Therefore, curcumin induces A549 cell apoptosis through the miR-186* pathway in a dose- and time-dependent manner, by increasing caspase-10 [51-53].

Another miRNA modulated by curcumin is miR-874, a tumor suppressive miRNA, which has been shown to target matrix metalloprotease-2 (MMP-2) in NSCLC cell lines. In fact, Ahmad *et al*

Table 1.   Modulation of miRNA expression by curcumin.

miRNA	Modulation	Cell line	Reference
miR-21	-	A549	Zhang *et al.* d
miR-192-5p	+	p53 wild-type H460, A427, A549	Ye *et al.*
miR-215	+	p53 wild-type H460, A427, A549	Ye *et al.*
miR-186*	-	A549	Zhang *et al.* and Tang *et al.* (Tang *et al.*, 2010a; Zhang *et al.*, 2010b; Zhang *et al.*, 2010d)
miR-874	+	A549, H1299	Ahmad *et al.*
let-7c	+	A549	Wu *et al.*
miR-101	+	A549	Wu *et al.*
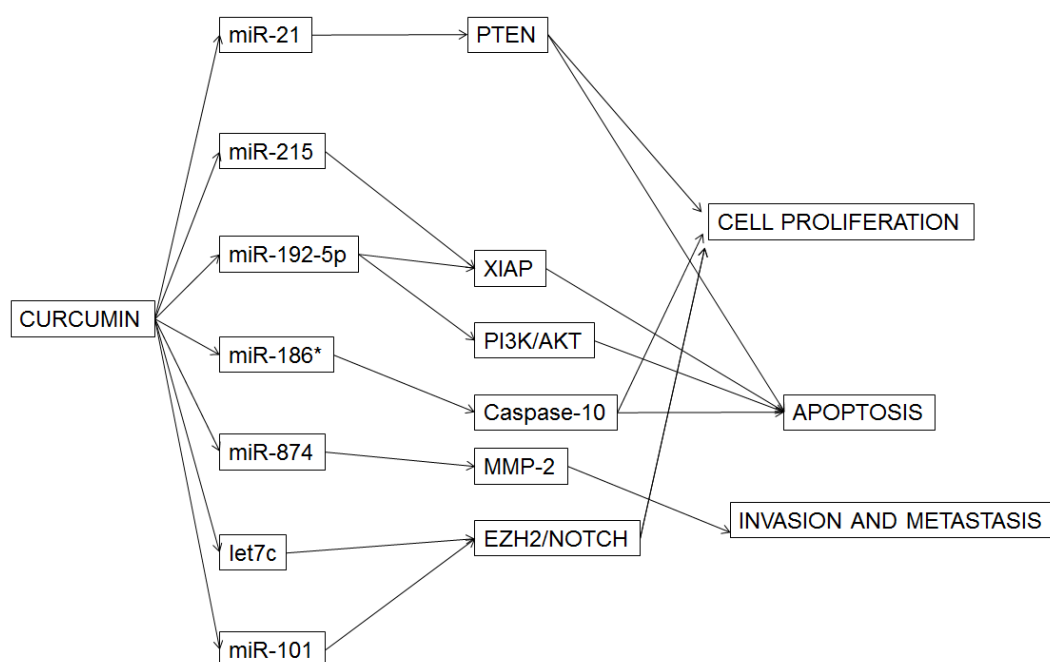
Fig. (1). MiRNA-mediated mechanisms of action of curcumin in lung cancer. PTEN: tumor-suppressor phosphatase and tensin; XIAP: X-linked inhibitor of apoptosis; PI3K/AKT: Phosphatidylinositol-4,5-bisphosphate 3-kinase/AKT; EZH2/NOTCH: enhancer of zeste homolog 2.

documented that curcumin inhibits MMP-2 expression and activity through up-regulation of miR-874 in A549 e H1299 cell lines [54].

Finally, Wu *et al.* documented with miRNA microarray analysis and qPCR that curcumin up-regulates miRNA-let7c and miR-101 in A549 cells. Enhancer of zeste homolog 2 (EZH2), an oncogene that regulates cell cycle progression through activation of NOTCH signaling pathway was significantly down-regulated in A549 cells with overexpression of miRNA-let7c and miR-101. Therefore, the effect of curcumin on this miRNA may lead to the inhibition of lung cancer cell growth [55].

CONCLUSION

In the last years miRNAs have been demonstrated to play a primary role in the pathogenesis of lung cancer and emerged as candidate therapeutic targets. Recent studies have documented that curcumin's anti-cancer activity is also mediated by modulation of miRNAs [56]. Further studies are necessary to explore this very promising field and the potential of curcumin to regulate oncogenic and tumor-suppressive miRNAs in the clinical setting as well in other pathological states due to imbalance in miRNA homeostasis.

CONFLICT OF INTERESTS

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