Impact of curcumin on the regulation of microRNAs in colorectal cancer

Luis E. Simental-Mendía, Michele Caraglia, Muhammed Majeed & Amirhossein Sahebkar

To cite this article: Luis E. Simental-Mendía, Michele Caraglia, Muhammed Majeed & Amirhossein Sahebkar (2016): Impact of curcumin on the regulation of microRNAs in colorectal cancer, Expert Review of Gastroenterology & Hepatology, DOI: 10.1080/17474124.2017.1268528

To link to this article: http://dx.doi.org/10.1080/17474124.2017.1268528
Impact of curcumin on the regulation of microRNAs in colorectal cancer

Luis E. Simental-Mendía, Michele Caraglia, Muhammed Majeed and Amirhossein Sahebkar

Biomedical Research Unit, Mexican Social Security Institute, Durango, Mexico; Department of Biochemistry, Biophysics and General Pathology, Second University of Naples, Naples, Italy; Sabinsa Inc, Princeton, NJ, USA; Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran; Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

Article History
Received 13 October 2016; Accepted 1 December 2016

Keywords
Curcumin; colon cancer; micro-RNAs; signal transduction

1. Introduction
Colorectal cancer is the third leading cause of cancer-related death in both men and women [1], and approximately 1 million new cases and 500,000 deaths per year are reported in Western countries [2]. Moreover, the 5-year survival in patients with advanced stages of colon cancer is lower than 8% and its recurrence is about 50% even after tumor resection surgery and chemotherapy [2]. Hence, there is an important need for early diagnosis using molecular biomarkers, and novel treatments to help more effective chemotherapy for colorectal cancer management are warranted.

1.1. Role of microRNAs in cancer pathogenesis
MicroRNAs (miRNAs) are small RNA molecules generated post-transcriptionally that are linked to cancer pathogenesis in humans through regulating cell proliferation and apoptosis [3]. miRNAs are also involved in other regulatory processes such as cell differentiation [4] and development [5], and exhibit modulatory effects on the expression of both oncogenes and tumor-suppressor genes [6,7]. Therefore, miRNAs play an important role in oncogenesis and tumor progression and can serve as both potential tumor markers and therapeutic targets. While reduced expression of specific miRNAs, mainly miR-143, miR-145 and let-7 family, has been reported to be associated with tumorigenesis [8,9], reduced expression of some others such as miR-31, miR-96, miR-135b and miR-183 has been suggested to reflect suppression of colorectal tumor cells [10]. miR-21-5p, miR-29-3p and miR-148-3p have been the most studied miRNAs and can serve as prognostic biomarkers for colorectal cancer [11]; studies validating the usefulness of these miRNAs in clinical setting are scant.

2. Anti-cancer properties of curcumin
Curcumin is a dietary phytochemical obtained from the rhizomes of Curcuma longa L. commonly known as turmeric [12]. The safety and efficacy of curcumin for the treatment of human diseases have been confirmed in several randomized controlled trials [13–16,17,18]. Owing to its interaction with several biological targets involved in both inflammatory processes and different stages of tumor cell proliferation, this polyphenol exhibits many pleiotropic effects relevant to the treatment of human cancers [19]. Curcumin inhibits activation of the NF-κB pathway and expression of pro-inflammatory genes via suppression of inhibitory κB kinase phosphorylation [20]. This inhibition of NF-κB leads to the suppression of inflammatory response and tumorigenesis through down-regulation of cyclooxygenase-2, 5-lipoxygenase, and inducible nitric oxide synthase enzymes [20]. Curcumin exerts inhibitory effects on the initiation, proliferation, and progression stages of carcinogenesis. Recent evidence has suggested that curcumin could improve the efficacy of cancer chemotherapy by regulating Sonic Hedgehog, Notch-1, PI3K/Akt/mTOR, and Wnt/β-catenin signaling pathways, thereby impacting on the proliferation, differentiation, and survival of colorectal cancer stem cells (CSCs) [21].

3. Curcumin modulates mirnas in colorectal cancer
Hitherto, a number of studies have evaluated the impact of curcumin on miRNA regulation in colorectal cancer. In this context, a previous study reported that curcumin decreases miR-21 expression and induces down-regulation of the activator protein-1 resulting in the inhibition of cell proliferation, tumor growth, invasion, and metastasis [22]. In addition, curcumin was shown to induce the expression of programmed cell death protein-4 which is a post-transcriptional target of miR-21 and an important tumor-suppressor in colorectal cancer [22]. A novel curcumin analog with improved stability and bioavailability, difluorinated curcumin (CDF), has been shown to reduce miR-21 expression thus increasing miR-21 target protein, phosphatase, and tensin homolog (PTEN). This effect mediates the reduction of Akt activity and suppression of growth and metastasis of colon cancer cells [23]. It was also demonstrated that repression of miR-21 expression in HCT-116 and HT-29 colon cancer cells induces differentiation. CDF was significantly more active than conventional chemotherapy drugs (5-fluorouracil + oxaliplatin) in inducing cell growth inhibition in miR-21-depleted and differentiated colon cancer cells, and also potentiated the growth inhibitory effects of the chemotherapeutic combination [24].
of miR-34a, b, and c acts as tumor suppressor, hence its reduction in colonic mucosa leads to malignancy. Moreover, miR-34 family induces apoptosis in human cancer cells through targeting several anti-apoptotic members of the Bcl-2 family, and signal transduction factors including Akt and the ancestral receptor Notch-1 [24]. In this context, CDF was shown to restore the expression of miR-34a and miR-34c in an in vitro model of colon carcinoma, leading to the downregulation of their target gene Notch-1 [25]. This effect was likely due to the demethylation of miR-34a promoter induced by CDF. There is also evidence indicating that curcuminoids decrease the expression of miR-27a, miR-20a, and miR-17-5p, thereby up-regulating ZBTB10 and ZBTB4, down-regulating the specificity protein transcription factors (Sp1, Sp3, Sp4) and Sp-regulated genes, and inhibiting multidrug resistance protein 1 which collectively lead to growth suppression and apoptosis of colon cancer cells [26,27].

Curcumin has also been shown to down-regulate ZEB1, BMI1, EZH2, SUZ12, and Ring1b that are well-recognized markers of epithelial-mesenchymal transition (EMT), thereby inducing epithelial differentiation in chemo-resistant colorectal cancer cell lines [27]. Given that microRNAs exhibit a central role in the EMT, the effect of curcumin on the expression of miR-200b, miR-200c, miR-141, miR-429, miR-101, and miR-34a has been explored, and the results have revealed upregulation of these EMT-related miRNAs in 5-fluorouracil-resistant cell lines [27]. This suggests that the anti-tumor properties of curcumin in human colorectal cancer cells can be explained, at least in part, by the modulation of EMT-suppressive miRNAs.

4. Expert review

Altogether, regulation of miRNAs involved in the signaling pathways of tumorigenesis and metastasis appears as an important mechanism for the efficacy of curcumin in the chemoprevention and chemotherapy of colorectal cancer. However, although the promising therapeutic effect of curcumin through the modulation of EMT-suppressive microRNAs has been reported, additional experimental and clinical studies are worthwhile to validate the activities of curcumin on cancer-associated miRNAs. Application of anti-miRNA oligonucleotides in cellular and experimental models can also unveil the extent of anti-tumor effects conferred by curcumin through modulation of the above-mentioned miRNAs. A promising feature of the anti-tumor activity of curcumin is the suppressive effect of this phytochemical on colorectal CSCs.

Owing to their self-renewal capacity, CSCs are a major culprit for chemotherapy resistance as well as tumor recurrence and metastases. Curcumin and its analogues have been shown to suppress signaling pathways involved in the self-renewal capacity of CSCs (Hedgehog, Notch-1, PI3K/Akt/mTOR, and Wnt/β-catenin pathways). Mechanistic investigations could further clarify if the beneficial effects of curcumin against colorectal cancer are mediated by the alterations of the miRNAs controlling these signaling pathways. Finally, curcumin can reverse EMT – which is itself a key promoter of CSC formation and tumor invasion – and mitigate chemo-resistance via modulating the miRNA profile (mainly miR-200 family) in colorectal cancer. This latter effect may not only explain the therapeutic effects of curcumin in colorectal cancer, but also the value of combining curcumin with conventional chemotherapy regimens. We indeed believe that curcumin can represent the cross-road between ancient traditional medicine and modern molecular biology.

Funding

This paper was not funded.

Declaration of interest

M. Majied is the CEO of Sabinsa Corporation and Sami Labs Ltd. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

ORCID

Michele Caraglia http://orcid.org/0000-0003-2408-6091

References

25. Roy SLE, Majumdar AP, Sarkar FH. Expression of miR-34 is lost in colon cancer which can be re-expressed by a novel agent CDF. J Hematol Oncol. 2012;19(5):58.