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Mini-review

Targeting cancer stem cells by curcumin and clinical applications

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ABSTRACT

Curcumin is a well-known dietary polyphenol derived from the rhizomes of turmeric, an Indian spice. The anticancer effect of curcumin has been demonstrated in many cell and animal studies, and recent research has shown that curcumin can target cancer stem cells (CSCs). CSCs are proposed to be responsible for initiating and maintaining cancer, and contribute to recurrence and drug resistance. A number of studies have suggested that curcumin has the potential to target CSCs through regulation of CSC self-renewal pathways (Wnt/β-catenin, Notch, sonic hedgehog) and specific microRNAs involved in acquisition of epithelial–mesenchymal transition (EMT). The potential impact of curcumin, alone or in combination with other anticancer agents, on CSCs was evaluated as well. Furthermore, the safety and tolerability of curcumin have been well-established by numerous clinical studies. Importantly, the low bioavailability of curcumin has been dramatically improved through the use of structural analogues or special formulations. More clinical trials are underway to investigate the efficacy of this promising agent in cancer chemoprevention and therapy. In this article, we review the effects of curcumin on CSC self-renewal pathways and specific microRNAs, as well as its safety and efficacy in recent human studies. In conclusion, curcumin could be a very promising adjunct to traditional cancer treatments.

1. Introduction

Curcumin is a well-known dietary polyphenol derived from the rhizomes of turmeric (*Curcuma longa*), an Indian spice, which is usually used in preparation of mustard and curry [1,2]. Three curcuminoids, namely curcumin, demethoxycurcumin, and bisdemethoxycurcumin, are present in the natural extracts of *C. longa* with curcumin as the principal constituent (Fig. 1) [3]. This yellow color spice has been used for thousands of years as a traditional remedy. In Asian medicines, curcumin has been used for the treatment of acne, psoriasis, dermatitis, and diaper rash [4,5].

Curcumin is well known to possess anti-inflammatory, antioxidant, and antimicrobial activities [1,5,6], and has also been intensively studied as a cancer chemopreventive agent in a wide range of cancer models, including melanoma, head and neck, breast, colon, pancreatic, prostate, and ovarian cancers, over the past three decades [7–9]. A plethora of molecular targets and signaling pathways, such as NF-κB, Akt/mTOR, and HIF-1α [10–12], have been shown to be modulated by curcumin, resulting in inhibition of cancer cell proliferation, invasion, metastasis, angiogenesis, and induction of apoptosis [2,13–18].

It was believed by many researchers that majority of the cancer cells contribute substantially to tumor growth and maintenance and each subclone at different stages is considered to possess self-renewal capacity to different degrees [19,20]. However, recently a great deal of research has demonstrated the existence of cancer stem cells (CSCs) in a range of human cancer types [21–27]. In the CSC model, it is proposed that the initiation, maintenance, and growth of a tumor is driven by a minor population of cancer cells termed cancer stem cells (CSCs) [28,29]. These CSCs undergo continuous self-renewal and differentiate to heterogeneous cancer cells, yielding new tumors recapitulating the parental tumors, while the majority of cancer cells lack self-renewal capacity [28–30]. However, most currently available chemotherapeutic drugs and radiotherapy lack the ability to effectively kill CSCs [29,31–33], although they can shrink tumor volume [31]. As the result, tumor resistance and recurrence eventually occur [30,31]. Targeting of CSC population has thus emerged as a very promising concept and therapeutic option to eradicate tumors and prohibit resistance and recurrence [19,30,34].

2. Regulation of CSC self-renewal pathways by curcumin

Curcumin regulates many molecular targets involved in cancer development, as revealed by extensive cell and animal studies.

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During the past few years, a number of studies have suggested that curcumin may have the potential to target CSCs through direct or indirect influences on CSC self-renewal pathways (Table 1). Three major pathways have been identified to play pivotal roles in CSC self-renewal behavior, including Wnt/β-catenin, sonic hedgehog (SHH), and Notch. Understanding these pathways is essential for discovery and development of anticancer drugs targeting CSCs.

Wnt/β-catenin signaling is implicated in the CSC self-renewal of various cancers. In the absence of Wnt signaling, β-catenin is phosphorylated at Ser33/Ser37/Thr41 by GSK3β, followed by proteasome degradation [35]. Binding of Wnt proteins to Frizzled receptors triggers higher cellular level of β-catenin due to reduced degradation [36]. Once this essential mediator translocates into the nucleus, it cooperates with the transcription factors T cell factor/lymphoid enhancer factor (TCF/LEF), leading to activation of Wnt target genes, such as *c-Myc* and *cyclin D1*, which further promote self-renewal of CSCs [28,37,38].

Several studies have demonstrated that curcumin affects multiple components of Wnt/β-catenin signaling directly or indirectly in breast, gastric, colon, intestinal, osteosarcoma, and medulloblastoma cancer cells [1,39–43]. Curcumin was shown to reduce the levels of β-catenin and the activated (phosphorylated) form of Akt in medulloblastoma cells [42]. Furthermore, Jaiswal et al. suggested that curcumin induced caspase-3-mediated cleavage of β-catenin, leading to inactivation of Wnt/β-catenin signaling in HCT116 intestinal cancer cells [40]. The work of Park et al. further strengthened this point by demonstrating that curcumin decreased β-catenin/TCF transcription activity in all tested cancer cell lines, including gastric, colon, and intestinal cancer cells, which was associated with lower amounts of β-catenin and TCF-4 proteins in nucleus [1]. By utilizing a TCF-LEF Topflash reporter system in MCF7 cells, Kakarala et al. confirmed that the effect of curcumin on breast CSCs was mediated through its potent inhibitory effect on Wnt/β-catenin signaling [41]. Exposure to 10 μM curcumin for 12 h reduced GFP expression from 13% to 0.89% [41]. In addition, analysis of gene transcription profile revealed that the expression of Frizzled-1 (the receptor of Wnt proteins) was inhibited in curcumin-treated human head and neck squamous cell carcinoma cell line MDA-1986 [44]. Curcumin was also shown to be able to attenuate response of β-catenin to Wnt-3a in colon cancer cells through down-regulation of p300, a positive regulator of Wnt/β-catenin signaling [39].

Notch pathway is also believed to be dysregulated in CSCs [45]. Five Notch proteins have been identified as transmembrane receptors in a variety of CSCs [46]. Binding of ligands triggers serial cleavage events at the Notch proteins by a protease of the ADAM (a disintegrin and metalloprotease) family and γ-secretase [46]. Subsequently, the intracellular domain of Notch proteins is released and translocates into the nucleus, where it acts as a transcription co-activator of recombination signal sequence-binding protein Jκ (RBP-Jκ) to activate downstream target genes [47,48].

Wang and his colleagues demonstrated that curcumin down-regulated Notch-1 mRNA level in pancreatic cancer cells, indicating a transcriptional inactivation of Notch-1 by curcumin [49]. Curcumin-induced inactivation of nuclear factor-κB (NF-κB) DNA-binding activity might be mediated by Notch-1 signaling pathway [49]. A reduction in cell viability of curcumin-treated oral carcinoma CAL-27 cell line was associated with down-regulation of Notch-1 and NF-κB protein levels [50]. Furthermore, curcumin treatment resulted in suppressed Notch-1 activation through down-regulation of components of the γ-secretase complex proteins in esophageal cancer cells [51].

Another major pathway involved in CSC self-renewal is sonic hedgehog (SHH) signaling [52,53]. In the absence of SHH ligand, the transmembrane receptor Patched (Ptch) attaches to Smoothened (Smo), thereby blocking Smo function [28,53]. When secreted SHH ligand binds to Ptch, Smo is released and stabilized, initializing activation of transcription factors Gli that leads to expression of an array of stemness genes [28,53]. SHH pathway plays key roles in the maintenance of CSCs and the acquisition of epithelial-to-mesenchymal transition (EMT) [52–54].

Lim et al. performed microarray analysis and revealed a significant down-regulation of Gli1 expression after "nanocurcumin" (a polymeric nanoparticle formulation of curcumin) treatment in brain tumor cells, which was further supported by the results of quantitative real-time PCR [55]. Curcumin was reported to act similarly to the hedgehog antagonist cyclopamine, lowering Gli mRNA level as well as Gli reporter activity in prostate cancer cells [56]. The protein levels of SHH, Gli1, and Ptch1 all declined after curcumin treatment, triggering apoptosis of medulloblastoma cells [42].

Table 1
Effects of curcumin on self-renewal pathways of cancer stem cells and specific microRNAs involved in acquisition of epithelial–mesenchymal transition.

Type of cancer	Dose of curcumin	Effects on signaling pathway	References
Medulloblastoma	40 μM for 4–24 h	β-Catenin ↓, SHH ↓, Gli1 ↓, Ptch1 (receptor of SHH) ↓	[42]
Intestinal cancer	20 μM for 30 h;	Induces caspase-3-mediated cleavage of β-catenin;	[40]
	5–20 μM for 24 h	β-Catenin/TCF transcription activity ↓	[1]
Gastric cancer	5–20 μM for 24 h	β-Catenin/TCF transcription activity ↓	[1]
Colon cancer	5–20 μM for 24 h;	β-Catenin/TCF transcription activity ↓;	[1]
	20–40 μM for 15 h	Attenuates response of β-catenin to Wnt-3a through down-regulation of p300	[39]
Breast cancer	5–10 μM for 12 h	β-Catenin/TCF transcription activity ↓	[41]
Head and neck squamous cell carcinoma	50 μM for 8 h	Frizzled-1 (receptor of Wnt) ↓	[44]
Pancreatic cancer	5–15 μM for 72 h;	Notch-1 mRNA ↓;	[49]
	10 μM for 72 h;	miR-22 ↑, miR-199a ↓;	[73]
	1–4 μM for 72 h;	miR-200 ↑, miR-21 ↓;	[77]
	0.5 μM (CDF) for 72 h;	let-7a, b, c, d ↑, miR-26a ↑, miR-101 ↑, miR-146a ↑, miR-200b ↑, miR-200c ↑;	[80]
	4 μM (CDF) for 72 h	miR-21 ↓, miR-200b, c ↑	[81]
Oral carcinoma	2.5–7.5 μM for 72 h	Notch-1 ↓ (NF-κB ↓)	[50]
Esophageal cancer	30 μM for 24 h	Suppresses Notch-1 activation by down-regulation of γ-secretase complex components, miR-21 ↓, miR-34a ↓	[51]
Brain cancer	20 μM for 24 h	Gli ↓	[55]
Prostate cancer	10 μM for 24 h;	Gli mRNA ↓, Gli reporter activity ↓;	[56]
	0.5 μM (CDF) for 20 h	miR-21 ↓	[82]
Lung cancer	15 μM for 48 h	miR-186 ↓	[74,75]