Review Article

Development of Curcumin as an Epigenetic Agent

Siqing Fu, MD, PhD and Razelle Kurzrock, MD

The clinical benefits of curcumin as a single agent were demonstrated in patients with advanced pancreatic cancer in a phase 2 study despite pharmacokinetic analysis showing a much lower plasma concentration of curcumin in humans than in vitro. The diverse and broad biological activities of curcumin are mediated through direct interaction of curcumin with target proteins as well as epigenetic modulation of target genes, supported by evidence that curcumin modulates gene expression in a time- and concentration-dependent manner in human cancer cells. This review delineates the novel mechanisms of curcumin as an epigenetic agent through its interaction with histone deacetylases, histone acetyltransferases, DNA methyltransferase I, and microRNAs. Accumulating data support curcumin's functionality in modulating multiple biological processes at low concentrations through its activity as an epigenetic agent. The development of curcumin as an epigenetic agent warrants further preclinical and clinical studies to explore its diversity and efficacy in cancer treatment and in combination with other anticancer agents. ***Cancer* 2010;116:4670–6.** © *2010 American Cancer Society.*

KEYWORDS: curcumin, epigenetic, DNA methylation, histone acetyltransferase, histone deacetylase.

Curcumin as a single agent displayed clinical benefit in patients with advanced pancreatic cancer[1] despite pharmacokinetic analysis showing its much lower plasma concentration in humans than in vitro. A possible explanation for its activity in humans is that accumulation of curcumin and its metabolites in cells during daily exposure occurs because it is its highly hydrophobic nature.[2] Another explanation may be that curcumin exerts its biological activities through epigenetic modulation, which requires lower concentrations. This review summarizes the current data surrounding curcumin-mediated epigenetic modulation and its role in anticancer treatment.

Curcumin (diferuloylmethane), a yellow hued polyphenol, is an active component of the perennial herb *Curcuma longa*, commonly known as turmeric.[2] The major components in the curcuminoid complex are curcumin (approximately 80%), demethoxycurcumin (approximately 17%), and bisdemethoxycurcumin (approximately 3%).[3] Curcumin is minimally soluble in water but quite soluble in organic solvents. Its enolic and beta diketone forms are stable in acidic pH, but unstable in neutral and basic pH solutions, where they are degraded to ferulic acid and feruloylmethane. Curcumin is, however, more stable in 10% fetal calf serum and human blood, with <20% of curcumin decompensation in the first hour after administration.[4]

Curcumin has diverse molecular targets associated with numerous biochemical and molecular cascades with activity exerted via direct interaction with and/or epigenetic modulation of gene expression. To date, curcumin has been found to physically bind to as many as 33 different proteins, including thioredoxin reductase, COX2, protein kinase C, 5-lipoxygenase, and tubulin.[5] The various molecular targets modulated by curcumin include transcriptional factors, growth factors and their receptors, cytokines, enzymes, and genes regulating cell proliferation and apoptosis.

Cancer epigenetics is characterized by heritable patterns of specific DNA methylation and chromatin modification.[6] Epigenetic factors can also affect microRNA expression.[7] Neoplasia is characterized by distinct patterns of disrupted pathways involving genetic alterations and epigenetic changes mediated by DNA methyltransferases, methyl-CpG-binding domain proteins, histone acetyltransferase (HAT), histone deacetylase (HDAC), histone methyltransferases, and

Corresponding author: Siqing Fu, MD, PhD, Department of Investigational Cancer Therapeutics, Unit 0455, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030; Fax: (713) 745-3855; siqingfu@mdanderson.org

Department of Investigational Cancer Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

We thank Joann Aaron in the Department of Investigational Cancer Therapeutics at The University of Texas M. D. Anderson Cancer Center for editing the article.

DOI: 10.1002/cncr.25414, **Received:** January 12, 2010; **Revised:** March 26, 2010; **Accepted:** March 30, 2010, **Published online** July 1, 2010 in Wiley Online Library (wileyonlinelibrary.com)

histone demethylases, resulting in DNA global hypomethylation, and promoter-localized hypermethylation.[8] Here we delineate the factors responsible for curcumin's promise as an epigenetic agent for cancer therapy drug development.

Curcumin and Histone Deacetylases

At least 18 HDACs have been identified in humans, primarily occupying 4 classes based on homology with yeast deacetylases.[9] HDAC enzymes do not bind to DNA directly but rather interact with DNA through multiprotein complexes that include corepressors and coactivators.

Among 33 carboxylic acid derivatives, curcumin was the most effective HDAC inhibitor at 50 to 500 μM in HeLa nuclear extracts at an IC_{50} of 115 μM. Molecular docking studies performed for human HDAC8 showed that curcumin has a free binding energy (−8.55 ΔG kcal/mol) and inhibition constant (Ki = 539 nM) comparable to Trichostatin A and vorinostat (−8.59 and −7.65 ΔG kcal/mol, and Ki = 504 nM and 2.47 μM, respectively), and that it is more potent than valproic acid and sodium butyrate (−4.41 and −4.65 ΔG kcal/mol, and Ki = 564 and 365 μM, respectively). Analysis of curcumin's molecular docking in a complex with human HDAC8 revealed that the ligand adopted a stable binding conformation extended toward the entrance domain.[10]

One study showed that Raji cells, a cell line of Epstein-Barr virus-transformed lymphocytes with surface Fc receptors, treated with different concentrations of curcumin for 0, 24, 36, 48, 60, and 72 hours inhibited cell proliferation in a dose- and time-dependent manner with an IC_{50} of 36 hours at 24 μM.[11] Another study revealed that the expression of HDAC1, 3, and 8 was significantly higher in untreated Raji cells compared with curcumin-treated cells, leading to significantly greater levels of acetylated histone H4 in cells treated with 25 μM of curcumin for 24 hours. Western blots showed that HDAC1, 3, and 8 protein levels decreased in a dose-dependent manner with curcumin exposure,[12] but did not show whether curcumin could directly inhibit HDAC enzyme activity. Increased acetylated histone H4 was associated with decreased levels of HDAC1, 3, and 8 proteins. Another study found that curcumin at nanomolar concentrations restored corticosteroid function in monocytes exposed to oxidants by maintaining HDAC2 activity via preventing oxidant-induced degradation of HDAC2 through down-regulating gene expression associated with protein degradation.[13] Although controversy exists about the ability of curcumin to inhibit HDAC enzymes, it likely modulates HDAC activity through regulating gene expression. Further research is required to validate this hypothesis.

Curcumin and Histone Acetyltransferases

HATs including at least 25 members are organized into 4 families based on primary structure homology.[14] The disparate family of HATs, acetylates, histones, and nonhistone targets is involved in diverse processes such as transcription activation, gene silencing, DNA repair, and cell cycle progression.[15]

Recent enzymatic studies dealing with the p300 HAT domain support the existence of a Theorell-Chance catalytic mechanism combined with broad substrate specificity independent of a specific Asp/Glu general base mechanism. Despite evidence that p300 acts as a tumor suppressor, some studies showed that when p300 was down-regulated and inhibited, tumor regression resulted, along with activation of a senescence checkpoint, which is logical given the finding that p300/CBP is important for the G1/S cell cycle transition.[16] This suggests that the role of p300/CBP in cancer biology is versatile and context-dependent, supporting curcumin's role as a specific inhibitor of p300/CBP capable of inducing apoptosis in cancer cells without producing cytotoxic effects in healthy cells. Thus, p300/CBP HAT is an excellent target for novel cancer treatment drug development.[17]

Curcumin has been identified as a specific inhibitor of p300/CBP HAT activity in vitro and in vivo, but not of p300/CBP-associated factor, a HAT that associates with p300/CBP. Filter binding and gel HAT assays showed that acetylation of histones H3 and H4 by p300/CBP was strongly inhibited covalently by curcumin, with an IC_{50} of approximately 25 μM, whereas p300/CBP-associated factor HAT activity did not change even in the presence of 100 μM curcumin.[18] These findings demonstrate curcumin's high specificity for p300/CBP HAT activity, but not for other enzymes that have histone substrates. The binding site on p300/CBP was specific for curcumin, and binding led to a conformational change, resulting in a decrease in the binding efficiency of histones H3 and H4 and acetyl CoA.[19] These findings are significant in cancer because of the complex role of HATs in cancer, as is specifically explained later in this review.

Kinetic studies of enzymatic activity showed curcumin binding to p300, but not as an allosteric inhibitor with binding to active sites of histone or acetyl CoA.[18] In addition, curcumin was a potent and specific inhibitor

of p300/CBP HAT activity-dependent chromatin transcription. Curcumin induced cervical cancer cell apoptosis at concentrations of 50 to 100 μM associated with inhibiting acetylation of histones and p53 in vivo through specific inhibition of p300/CBP.[20] In brain glioma cell lines, curcumin induces histone hypoacetylation to activate poly adenosine diphosphate ribose polymerase- and caspase-3–mediated apoptosis.[21] In addition, inhibition of p300 mediated by curcumin decreases acetylation of RelA, which attenuates interaction with IκBα, leading to decreased IκBα-dependent nuclear export of the complex through a chromosomal region maintenance-1–dependent pathway.[22] Therefore, curcumin's ability to suppress p300/CBP HAT activity, may account, at least in part, for its potent nuclear factor kappa B (NF-κB) inhibitory activity.

Curcumin and DNA Hypomethylation

Molecular docking of the interaction between curcumin and DNA methyltransferase I suggested that curcumin covalently blocks the catalytic thiolate of C1226 of DNA methyltransferase I to exert its inhibitory effect.[23] Curcumin exists predominantly in solution as the enol form, which serves as a Michael acceptor to covalently block the catalytic thiol group in DNA methyltransferase I through the C3 keto-enol moiety of the curcumin compounds, demethoxycurcumin, and bisdemethoxycurcumin.

To validate the results of a DNA methyltransferase I homology modeling study, inhibition of the enzymatic activity of M.Sss1 (methyltransferase Sss1, an analog of DNA methyltransferase I) by curcumin was assessed in vitro. The methylation level of the double-strand oligonucleotide directly correlated with the enzymatic activity of M.Sss1 with exposure to various concentrations of curcuminoids from 1 nM to 100 μM. The apparent IC_{50} of curcumin with respect to M.Sss1 inhibition was identified as 30 nM.[23]

Genomic DNA was extracted from a leukemia cell line exposed to curcuminoids at concentrations of 0, 1, 3, and 30 μM for 72 hours. Analyses of global DNA methylation levels showed stability at 1 μM curcumin, but decreased by approximately 15% to 20% at 3 μM and 30 μM curcumin compared with untreated basal methylation levels, which was equivalent to decitabine-induced decreases in global DNA methylation levels.[23] These data show that curcumin is a potent DNA hypomethylating agent, which is consistent with its broad activity in inflammation, cancer, and many other diseases, while remaining relatively safe in normal healthy cells. Further exploration and validation of curcuminoids as DNA hypomethylating agents is warranted. Coincidentally, a phase 1 trial with curcumin administered several days before docetaxel in patients with metastatic breast cancer resulted in 5 partial remissions and stable diseases in 3 of 8 patients.[24] This unexpectedly high response rate might result from the clever sequential delivery of the 2 agents, which capitalized on and maximally used curcumin's epigenetic activity for cancer treatment.

Curcumin and Epigenetic Changes Impacting microRNAs

MicroRNAs are small, noncoding regulatory RNAs ranging in size from 17 to 25 nucleotides, which are matured by Dicer/Drosha (an RNase) from hairpin-structured precursors.[25] MicroRNAs post-transcriptionally repress gene expression by recognizing complementary target sites in the 3′-untranslated regions of target mRNAs. Currently, >500 microRNAs have been identified in humans.[26] Many microRNAs exhibit characteristic expression patterns.[27] Expression of a specific microRNA can be measured by Northern blot, RNase protection assay, primer extension assay, and global microRNA expression profiles.[28] MicroRNAs are aberrantly expressed in diverse cancers, differentially characteristic for specific cancer phenotypes, stages, and other clinical variables, and play important roles in cell cycling, programmed cell death, cell differentiation, tumor development, invasion, metastasis, and angiogenesis.[29]

Aberrant expression of microRNAs can arise through numerous mechanisms, including genomic abnormalities, transcriptional regulation, and processing of microRNAs.[7] Epigenetic factors also affect the expression of microRNAs.[25] In many cancers, hypermethylation of CpG islands in promoter regions and histone modifications result in heritable transcriptional silencing of tumor suppressor genes. Some microRNAs are up-regulated by hypomethylating agents[30] and/or inhibition of histone deacetylation.[31] In addition, microRNAs may counteract CpG methylation and the epigenome.[32] For example, miR-29 directly targets DNMT-3A and -3B. Consistent with this observation, ectopic expression of miR-29 resulted in a global reduction of DNA methylation, abrogating the expression of tumor suppressor genes previously silenced by promoter methylation in cancer cells.[33]

Interestingly, curcumin modulated microRNA expression in human pancreatic cells, up-regulating microRNA-22 and down-regulating microRNA-199a* through an unknown mechanism.[34] Combined with the

recent finding that curcumin is a DNA hypomethylating agent, epigenetic modulation of microRNA expression may be an important mechanism underlying curcumin's biological effects. Microarray analyses of microRNA expression in pancreatic cancer cells exposed to curcumin at concentrations of up to 10 μM for 72 hours revealed 11 microRNAs that were significantly up-regulated and 18 microRNAs that were significantly down-regulated. MicroRNA-22 demonstrated tumor suppressor activity through inhibition of at least 50 target genes, showing that a key effect of curcumin on cancer cells was mediated by epigenetic modulation of microRNAs, which, in turn, regulated many target genes involved in tumorigenesis, development, and metastasis. Modulating microRNA expression is yet another novel strategy that ultimately can be embraced as a potential therapy for the prevention and treatment of human cancer.[29]

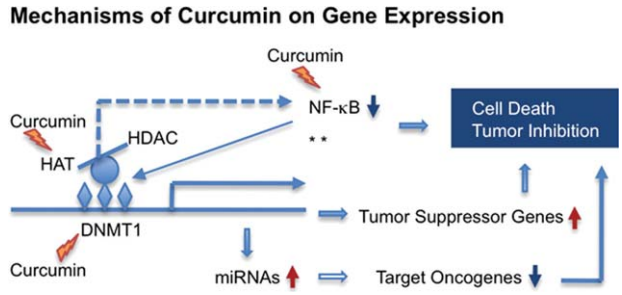

Figure 1. Schematic shows curcumin's roles in gene expression through direct interaction with transcriptional factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), epigenetic modulation via inhibiting DNA methyltransferase I (DNMT1), and histone acetyltransferase (HAT) and histone deacetylase (HDAC) complexes. Cancer cell death induced by curcumin is mediated by reactivating expression of tumor suppressor genes and/or inactivating expression of oncogenes via microRNA (miRNA) modulation.

Curcumin and Gene Expression

The diverse and broad biological activities of curcumin are mediated through direct interaction of curcumin with target proteins as well as epigenetic modulation of target genes, supported by evidence that curcumin modulates gene expression in a time- and concentration-dependent manner in human cancer cells.[35] Gene expression changes in human colon cancer cells in response to curcumin revealed early response genes, defined as differentially expressed genes after exposure to curcumin for 3 to 6 hours, involved in the cell cycle (p16INK4, BUB1B, STK6, STK12, PLK, Rb, p53, cyclin G1, and cyclin E1), signal transduction (STAT3, STAT5b, MAPK, AKT, VEGF, and FGFR1), DNA repair (hMLH1, MSH3, and ERCC2), gene transcription (HDAC1, ATF4, and EGF1), cell adhesion (annexin and integrins), and xenobiotic metabolism (GSTT2, GSTM4, and CYP1B1) while the cells accumulated in the G2/M phase with increased apoptosis. Expression of metallothionein genes changed in response to curcumin at 12 to 24 hours. Tubulin genes were down-regulated after 3 hours of exposure to curcumin at 25 μM, but up-regulated after 48 hours of exposure to curcumin at 100 μM.[36]

When RNA expression profiles were compared, diverse cell lines had variable responses to curcumin in a time- and concentration-manner, suggesting that clinical responses to curcumin differ because of substantial physiologic differences in cancer cells that contribute to diverse gene expression profiles.[37] In the LNCaP prostate cancer cell line, the number of genes regulated by curcumin with a >4-fold increase in expression were 8, 73, 181, 3, and 0 at 3, 6, 12, 24, and 48 hours, respectively. At 12 hours, curcumin up-regulated 181 genes and down-regulated 13 genes by >4-fold in the androgen-responsive LNCaP prostate cancer cell line, and 27 and 13 genes in the C4-2B androgen-refractory prostate cancer cell line, respectively.[37] Therefore, curcumin-induced gene expression was dependent on dose and cell context.

Treatment of cancer cells with curcumin results in a dose- and time-dependent inhibition of cell proliferation associated with time-, dose-, and cell context-dependent changes in gene expression. However, the precise mechanisms by which curcumin modulates gene expression have not been delineated. One theory is that curcumin modulates gene expression through direct interaction with diverse intracellular signal transduction pathways. Here we propose the hypothesis that curcumin produces an integrated modulation of signal transduction pathways and epigenetic modulation (Fig. 1). In addition to direct and indirect interactions with intracellular signal transduction pathways regulating gene expression, curcumin inhibits both DNA methyltransferase I and HATs to epigenetically modulate gene expression, as shown in Table 1.

Development of Curcumin as an Epigenetic Agent

Epidemiological evidence has shown that people who incorporate high doses of curcumin in their diets have a lower incidence of several common cancers such as breast, colorectal, and prostate cancer. Numerous preclinical reports demonstrated curcumin's anticancer activity

Table 1. Epigenetic Modulation by Curcumin

	Biological Activities of Curcumin
DNA methylation	1. Covalently blocks the catalytic thiolate of C1226 of DNA methyltransferase I[23]
	2. Inhibits methyltransferase M.SssI at an IC_{50} of 30 nM[23]
	3. Induces global genomic DNA hypomethylation[23]
Histone acetyltransferases	1. Directly inhibits p300[18-21,48-53]
	2. Down-regulates p300[11,54]
	3. Inhibits GCN5 associated with hypoacetylation of histone H3[55]
	4. Promotes p300 degradation[19]
HDACs	1. Acts as an HDAC2 activator[56]
	2. Increases HDAC2 protein expression[13]
	3. Acts as an HDAC8 inhibitor[10]
	4. Down-regulates HDAC1, 3, and 8[11,12,57]

HDAC indicates histone deacetylase.

through induction of apoptosis as well as sensitization of cancer cells to other anticancer agents. Phase 1 studies of curcumin as a single agent showed that it can be administered safely at oral doses of up to 8 g per day.[38,39] In a phase 2 study of curcumin in 21 evaluable advanced pancreatic cancer patients, single-agent curcumin achieved 1 partial response with a 73% tumor regression, and 1 patient had stable disease for approximately 2.5 years.[1] Although these data show curcumin's promise as a single agent for cancer control, its further development in combination with other anticancer agents is warranted. One strategy would be to target the NF-κB pathway for chemosensitization.[40] Another strategy would be to develop curcumin as a hypomethylating agent and HAT inhibitor.

DNA methylation plays an essential role in regulating normal biologic processes as well as carcinogenesis.[41] DNA methylation is a heritable, DNA methyltransferase-induced modification of DNA structure that does not alter the specific sequence of base pairs responsible for encoding the genome, but that can directly inhibit gene expression.[8] Two patterns of DNA methylation have been observed in cancer cells: global hypomethylation across the genome, and localized hypermethylation at specific CpG islands within the gene promoter regions of specific genes.[42] Decreased methylation because of global hypomethylation could facilitate the expression of previously quiescent proto-oncogenes and prometastatic genes and promote tumor progression. Alternatively, an aberrant increase in methylation patterns at previously unmethylated sites, such as the promoter regions of tumor suppressor genes, could result in transcriptional silencing and inability to control tumorigenesis.[42] Thus far, the US Food and Drug Administration has approved azacitidine and decitabine as hypomethylating agents for treating myelodysplastic syndrome. Preclinically and clinically, azacitidine and decitabine have demonstrated an ability to sensitize cancer cells to chemotherapeutic agents as well as biological targeted agents. Therefore, exploring curcumin as a hypomethylating agent to induce cancer cell chemosensitization is a particularly attractive anticancer strategy.

The reversible process of histone acetylation occurring at the ε-amino group of lysine residues in the N-terminal tails of core histones mediates conformational changes in nucleosomes, and is controlled by HATs and HDACs. The anticancer effects of HDAC inhibitors are well known and have been shown in clinical trials. In contrast, the chemotherapeutic potential of HATs has not yet been established. The role of HATs in cancer is complex. Because maintaining a specific histone acetylation process is crucial to various cell functions such as cell cycle progression, DNA repair, cell proliferation and differentiation, mutations and/or chromosomal translocations involving HAT genes result in development of malignancies. Loss of p300 heterozygosity and p300 mutations is associated with glioblastoma and colorectal cancer. CBP knockout mice had an increased incidence of cancers as well as defects in cell proliferation. Thus, p300/CBP appears to exert both tumor suppressor and tumor promoter properties, depending on the specific cellular context. Experiments with HAT inhibitors showed a clear correlation between the HAT-inhibitor potency of these compounds and their effects on cell proliferation, suggesting that HAT inhibitors have a potential role in cancer therapy.[43,44] In addition, coexposure of an HDAC inhibitor such as Trichostatin A improves the anticancer activity of low concentrations of curcumin in human leukemia cells,[45] providing evidence that inhibition of HDACs and HATs together may be a novel strategy for cancer treatment.

When HATs and HDACs are physically linked as a complex they interact with other regulators.[46] One might hypothesize that optimal therapeutic regimens can be developed by modulating histone acetylation along with other therapeutic approaches such as inhibition of DNA methylation, intracellular signal transduction pathways, and transcriptional factors, and induction of apoptotic pathways.[47] In addition to its direct interaction with intracellular signal transduction pathways, curcumin has enormous potential to be developed as an epigenetic agent. Specifically, its suppression of methylation and HATs warrants further exploration.

Although curcumin is able to directly interact with multiple intracellular signal transduction pathways and other target proteins, accumulating data support the concept that epigenetic modulation by curcumin might play a major role in cancer treatment. Thus, an understanding and application of the findings cited in this review will facilitate clinical development of curcumin in combination with other anticancer agents for cancer treatment.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Dhillon N, Aggarwal BB, Newman RA, et al. Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clin Cancer Res.* 2008;14:4491-4499.
2. Aggarwal BB, Sung B. Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. *Trends Pharmacol Sci.* 2009;30:85-94.
3. Lao CD, Ruffin MTt, Normolle D, et al. Dose escalation of a curcuminoid formulation. *BMC Complement Altern Med.* 2006;6:10.
4. Wang YJ, Pan MH, Cheng AL, et al. Stability of curcumin in buffer solutions and characterization of its degradation products. *J Pharm Biomed Anal.* 1997;15:1867-1876.
5. Anand P, Thomas SG, Kunnumakkara AB, et al. Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature. *Biochem Pharmacol.* 2008;76:1590-1611.
6. Yoo CB, Jones PA. Epigenetic therapy of cancer: past, present and future. *Nat Rev Drug Discov.* 2006;5:37-50.
7. Winter J, Jung S, Keller S, Gregory RI, Diederichs S. Many roads to maturity: microRNA biogenesis pathways and their regulation. *Nat Cell Biol.* 2009;11:228-234.
8. Das PM, Singal R. DNA methylation and cancer. *J Clin Oncol.* 2004;22:4632-4642.
9. Xu WS, Parmigiani RB, Marks PA. Histone deacetylase inhibitors: molecular mechanisms of action. *Oncogene.* 2007;26:5541-5552.
10. Bora-Tatar G, Dayangac-Erden D, Demir AS, Dalkara S, Yelekci K, Erdem-Yurter H. Molecular modifications on carboxylic acid derivatives as potent histone deacetylase inhibitors: activity and docking studies. *Bioorg Med Chem.* 2009;17:5219-5228.
11. Chen Y, Shu W, Chen W, Wu Q, Liu H, Cui G. Curcumin, both histone deacetylase and p300/CBP-specific inhibitor, represses the activity of nuclear factor kappa B and Notch 1 in Raji cells. *Basic Clin Pharmacol Toxicol.* 2007;101:427-433.
12. Liu HL, Chen Y, Cui GH, Zhou JF. Curcumin, a potent anti-tumor reagent, is a novel histone deacetylase inhibitor regulating B-NHL cell line Raji proliferation. *Acta Pharmacol Sin.* 2005;26:603-609.
13. Meja KK, Rajendrasozhan S, Adenuga D, et al. Curcumin restores corticosteroid function in monocytes exposed to oxidants by maintaining HDAC2. *Am J Respir Cell Mol Biol.* 2008;39:312-323.
14. Lee KK, Workman JL. Histone acetyltransferase complexes: 1 size doesn't fit all. *Nat Rev Mol Cell Biol.* 2007;8:284-295.
15. Carrozza MJ, Utley RT, Workman JL, Cote J. The diverse functions of histone acetyltransferase complexes. *Trends Genet.* 2003;19:321-329.
16. Wang L, Tang Y, Cole PA, Marmorstein R. Structure and chemistry of the p300/CBP and Rtt109 histone acetyltransferases: implications for histone acetyltransferase evolution and function. *Curr Opin Struct Biol.* 2008;18:741-747.
17. Dekker FJ, Haisma HJ. Histone acetyl transferases as emerging drug targets. *Drug Discov Today.* 2009;14:942-948.
18. Morimoto T, Sunagawa Y, Kawamura T, et al. The dietary compound curcumin inhibits p300 histone acetyltransferase activity and prevents heart failure in rats. *J Clin Invest.* 2008;118:868-878.
19. Marcu MG, Jung YJ, Lee S, et al. Curcumin is an inhibitor of p300 histone acetylatransferase. *Med Chem.* 2006;2:169-174.
20. Balasubramanyam K, Varier RA, Altaf M, et al. Curcumin, a novel p300/CREB-binding protein-specific inhibitor of acetyltransferase, represses the acetylation of histone/nonhistone proteins and histone acetyltransferase-dependent chromatin transcription. *J Biol Chem.* 2004;279:51163-51171.
21. Kang SK, Cha SH, Jeon HG. Curcumin-induced histone hypoacetylation enhances caspase-3-dependent glioma cell death and neurogenesis of neural progenitor cells. *Stem Cells Dev.* 2006;15:165-174.
22. Chen L, Fischle W, Verdin E, Greene WC. Duration of nuclear NF-kappaB action regulated by reversible acetylation. *Science.* 2001;293:1653-1657.
23. Liu Z, Xie Z, Jones W, et al. Curcumin is a potent DNA hypomethylation agent. *Bioorg Med Chem Lett.* 2009;19:706-709.
24. Bayet-Robert M, Kwiatkowski F, Leheurteur M, et al. Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer. *Cancer Biol Ther.* 2010;9:8-14.
25. Croce CM. Causes and consequences of microRNA dysregulation in cancer. *Nat Rev Genet.* 2009;10:704-714.
26. Bentwich I, Avniel A, Karov Y, et al. Identification of hundreds of conserved and nonconserved human microRNAs. *Nat Genet.* 2005;37:766-770.
27. Saito Y, Suzuki H, Hibi T. The role of microRNAs in gastrointestinal cancers. *J Gastroenterol.* 2009;44(suppl 19):18-22.
28. Mattie MD, Benz CC, Bowers J, et al. Optimized high-throughput microRNA expression profiling provides novel biomarker assessment of clinical prostate and breast cancer biopsies. *Mol Cancer.* 2006;5:24.
29. Negrini M, Ferracin M, Sabbioni S, Croce CM. MicroRNAs in human cancer: from research to therapy. *J Cell Sci.* 2007;120(pt 11):1833-1840.
30. Lujambio A, Ropero S, Ballestar E, et al. Genetic unmasking of an epigenetically silenced microRNA in human cancer cells. *Cancer Res.* 2007;67:1424-1429.
31. Scott GK, Mattie MD, Berger CE, Benz SC, Benz CC. Rapid alteration of microRNA levels by histone deacetylase inhibition. *Cancer Res.* 2006;66:1277-1281.
32. Friedman JM, Liang G, Liu CC, et al. The putative tumor suppressor microRNA-101 modulates the cancer epigenome by repressing the polycomb group protein EZH2. *Cancer Res.* 2009;69:2623-2629.
33. Fabbri M, Garzon R, Cimmino A, et al. MicroRNA-29 family reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B. *Proc Natl Acad Sci U S A.* 2007;104:15805-15810.

34. Sun M, Estrov Z, Ji Y, Coombes KR, Harris DH, Kurzrock R. Curcumin (diferuloylmethane) alters the expression profiles of microRNAs in human pancreatic cancer cells. *Mol Cancer Ther.* 2008;7:464-473.
35. Van Erk MJ, Teuling E, Staal YC, et al. Time- and dose-dependent effects of curcumin on gene expression in human colon cancer cells. *J Carcinog.* 2004;3:8.
36. Deeb D, Xu YX, Jiang H, et al. Curcumin (diferuloyl-methane) enhances tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis in LNCaP prostate cancer cells. *Mol Cancer Ther.* 2003;2:95-103.
37. Thangapazham RL, Shaheduzzaman S, Kim KH, et al. Androgen responsive and refractory prostate cancer cells exhibit distinct curcumin regulated transcriptome. *Cancer Biol Ther.* 2008;7:1427-1435.
38. Sharma RA, Euden SA, Platton SL, et al. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. *Clin Cancer Res.* 2004;10:6847-6854.
39. Cheng AL, Hsu CH, Lin JK, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res.* 2001;21:2895-2900.
40. Lin CL, Lin JK. Curcumin: a potential cancer chemopreventive agent through suppressing NF-kB signaling. *J Cancer Mol.* 2008;4:11-16.
41. Esteller M. Cancer epigenomics: DNA methylomes and histone-modification maps. *Nat Rev Genet.* 2007;8:286-298.
42. Ehrlich M. DNA hypomethylation in cancer cells. *Epigenomics.* 2009;1:239-259.
43. Eliseeva ED, Valkov V, Jung M, Jung MO. Characterization of novel inhibitors of histone acetyltransferases. *Mol Cancer Ther.* 2007;6:2391-2398.
44. Lee YH, Hong SW, Jun W, et al. Anti-histone acetyltransferase activity from allspice extracts inhibits androgen receptor-dependent prostate cancer cell growth. *Biosci Biotechnol Biochem.* 2007;71:2712-2719.
45. Chen J, Bai H, Wang C, Kang J. Trichostatin A improves the anticancer activity of low concentrations of curcumin in human leukemia cells. *Pharmazie.* 2006;61:710-716.
46. Hodawadekar SC, Marmorstein R. Chemistry of acetyl transfer by histone modifying enzymes: structure, mechanism and implications for effector design. *Oncogene.* 2007;26:5528-5540.
47. Sung B, Kunnumakkara AB, Sethi G, Anand P, Guha S, Aggarwal BB. Curcumin circumvents chemoresistance in vitro and potentiates the effect of thalidomide and bortezomib against human multiple myeloma in nude mice model. *Mol Cancer Ther.* 2009;8:959-970.
48. Chen S, Feng B, George B, Chakrabarti R, Chen M, Chakrabarti S. Transcriptional co-activator p300 regulates glucose induced gene expression in the endothelial cells. *Am J Physiol Endocrinol Metab.* 2010;298:E127-E137.
49. Chiu J, Khan ZA, Farhangkhoee H, Chakrabarti S. Curcumin prevents diabetes-associated abnormalities in the kidneys by inhibiting p300 and nuclear factor-kappaB. *Nutrition.* 2009;25:964-972.
50. Lee CW, Lin WN, Lin CC, et al. Transcriptional regulation of VCAM-1 expression by tumor necrosis factor-alpha in human tracheal smooth muscle cells: involvement of MAPKs, NF-kappaB, p300, and histone acetylation. *J Cell Physiol.* 2006;207:174-186.
51. Li HL, Liu C, de Couto G, et al. Curcumin prevents and reverses murine cardiac hypertrophy. *J Clin Invest.* 2008;118:879-893.
52. Singh N, Misra K. Computational screening of molecular targets in Plasmodium for novel non resistant anti-malarial drugs. *Bioinformation.* 2009;3:255-262.
53. Taniura H, Sng JC, Yoneda Y. Histone modifications in status epilepticus induced by kainate. *Histol Histopathol.* 2006;21:785-791.
54. Ryu H, Smith K, Camelo SI, et al. Sodium phenylbutyrate prolongs survival and regulates expression of anti-apoptotic genes in transgenic amyotrophic lateral sclerosis mice. *J Neurochem.* 2005;93:1087-1098.
55. Cui L, Miao J. Cytotoxic effect of curcumin on malaria parasite Plasmodium falciparum: inhibition of histone acetylation and generation of reactive oxygen species. *Antimicrob Agents Chemother.* 2007;51:488-494.
56. Barnes PJ. Role of HDAC2 in the pathophysiology of COPD. *Annu Rev Physiol.* 2009;71:451-464.
57. Hu J, Wang Y, Chen Y. Curcumin-induced histone acetylation in malignant hematologic cells. *J Huazhong Univ Sci Technolog Med Sci.* 2009;29:25-28.