ANTICANCER RESEARCH *35*: 599-614 (2015)

Review

Curcumin and Cancer Stem Cells: Curcumin Has Asymmetrical Effects on Cancer and Normal Stem Cells

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Abstract. *Curcumin has been shown to have numerous cytotoxic effects on cancer stem cells (CSCs). This is due to its suppression of the release of cytokines, particularly interleukin (IL)-6, IL-8 and IL-1, which stimulate CSCs, and also to its effects at multiple sites along CSC pathways, such as Wnt, Notch, Hedgehog and FAK. In spite of its multiple actions targeting CSCs, curcumin has little toxicity against normal stem cells (NSCs). This may be due to curcumin's different effects on CSCs and NSCs.*

The use of cytotoxic therapies remains the standard treatment for patients with metastatic cancer. The efficacy of these treatments is limited, with recurrence common. According to the cancer stem cell paradigm, cancers contain distinct subpopulations of cancer stem/progenitor cells (CSCs) characterized by self-renewal mechanisms and resistance to conventional treatments (1-3). When CSCs are transferred to an immune-deficient mouse, these cells can reconstitute the original cancer in the animal (4-6). Even a small number of stem cells (as few as 100) can be effective in bringing about the transplantation (7). However, tumors depleted of stem cells do not grow as xenografts (8).

These CSCs have been shown to be resistant to chemotherapy (9), radiation (10) and hormone therapy (11). For this reason, metastases from solid tumors, in particular, will re-appear even after initially successful treatments and prolonged periods of complete remission. Further, an unintended consequence of induced cancer cell death is the release of inflammatory cytokines, which can stimulate replication of CSCs (12-14). The percentage of CSCs in the cancer has been shown to increase in patients receiving neoadjuvant chemotherapy (9, 15, 16). Thus, an "equilibrium" may be formed where chemotherapy-induced tumor cell death results in increased stimulation of tumor growth (12). In addition, the cytokines secreted during induced cancer cell death can result in resistance to cytotoxic agents, so that metastases, when they occur, may be refractory to therapy (14, 17, 18). This suggests, for therapy to be effective on a consistent basis, it must eliminate both CSCs and non-stem cell cancer cells.

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Key Words: Curcumin, cancer stem cells, interleukin-6, interleukin-8, interleukin-1, CXCR1, CXCR2, Wnt pathway, Notch pathway, Hedgehog pathway, FAK pathway, review.

Curcumin and Interleukin-6 (IL-6)

IL-6 (also known as interferon (IFN)-β2) is a multi-functional cytokine involved in the immune and inflammatory response and progression from inflammation to cancer. Increased IL-6 activity has been found in multiple cancers, including multiple myeloma, as well as breast, colon and prostate carcinoma, and IL-6 has been associated with decreased survival and more aggressive disease in these patients (19-22). IL-6 signals through a heterodimeric receptor complex that contains the ligand binding IL-6α chain (CD126) and the common cytokine receptor signal-transducing subunit glycoprotein-130 (gp130, CD130) (19, 23). This leads to activation of the JAK family of tyrosine kinases (Janus kinases), which stimulate multiple pathways, including MAPK, STAT-3 and AKT (19, 23-25). IL-6 promotes chemoresistance, angiogenesis and invasion (12, 17, 26-29). Furthermore, IL-6 has been shown to convert regular cancer cells to CSCs in established breast and prostate cancer cell lines (12). When investigators in this latter study added an anti-IL-6 antibody to the culture medium, this did not occur, demonstrating the crucial role of IL-6 in non-stem cell cancer cell to CSC conversion (12). Shi *et al.* used multiple chemotherapy agents, including 5-fluorouracil, paclitaxel and doxorubicin, standard drugs for the

treatment of breast cancer, to induce formation of the multi-drug-resistant tumor breast cancer cell line MCF-7/R (30). IL-6 levels were markedly increased in the line previously treated with chemotherapy compared to the untreated line. Suppression of IL-6 and companion cytokine IL-8 in this study was shown to reverse the multi-drug resistance in the treated cell line, while increased expression of IL-6 or IL-8 increased the resistance of the cells to treatment.

One mechanism by which curcumin targets CSCs is inhibition of IL-6 release from cells, thus preventing CSC stimulation. Curcumin has been shown to decrease IL-6 levels or inhibit IL-6 function in multiple experimental systems. Jain *et al*. studied the effects of curcumin on the human pro-monocytic cell line U937, which had been maintained with a high concentration of glucose. A marked inhibition of IL-6 secretion from the monocytes was noted (31). This effect was dose-dependent. The investigators also studied rats with streptozoticin-induced hyperglycemia. The diabetic animals demonstrated high IL-6 levels compared to controls. Curcumin significantly reduced the previously elevated IL-6 levels (31). In another study, curcumin was found to prevent IL-6 expression in human rheumatoid synovial fibroblasts (32). Moriasi *et al*. found that IL-6 expression could be suppressed in a colon cancer cell line treated with curcumin (33). Cohen *et al*. reported that curcumin inhibited IL-6 production in four head and neck squamous cell carcinoma cell lines (34). Of note was the fact that this effect was also dose-dependent, with the more aggressive head and neck carcinoma cell lines demonstrating higher levels of IL-6 before treatment and requiring higher concentrations of curcumin to inhibit IL-6 compared to the less aggressive cell lines. Similarly, a dose-dependent decrease in IL-6 levels was found in human pancreatic cell lines after treatment with a nanoparticle-encapsulated formulation of curcumin (35). Curcumin was shown to block production of IL-6 in an experimental acute pancreatitis rat model (36). Bharti *et al*. reported that curcumin was able to block IL-6-induced STAT-3 phosphorylation in a multiple myeloma cell line (37). The curcumin analog FLLL3 was also shown to reduce IL-6-induced STAT-3 phosphorylation (38). Park *et al*. showed that curcumin increased the activity of bortezomib against human multiple myeloma U266 cells by decreasing IL-6 production and blocking STAT-3 phosphorylation (39).

Curcumin and Interleukin-8 (IL-8)

IL-8 (CXCL8) is an important cytokine, which increases after tumor cell death, stimulates CSCs and results in tumor re-growth and resistance to chemotherapy (18, 40). IL-8 is a 72-amino-acid protein belonging to the CXC cytokine family. This cytokine has numerous functions including the induction of neutrophil chemotaxis, neutrophil activation, regulation of cell adhesion, promotion of angiogenesis, histamine release and regulation of receptor protein signaling pathways (13, 41-45). Release of IL-8 can be caused by many stimuli, including infection, trauma, hypoxia, acidosis, corticosteroids, androgens or chemotherapy (18, 46-47). Docetaxel, a commonly-used chemotherapeutic agent for the treatment of prostate, breast, lung and ovarian cancers, has been shown to markedly increase IL-8 levels (48). As with IL-6, elevated levels of IL-8 have been detected in human cancers and have been associated with a poor prognosis (13, 49-52). IL-8 has been found to increase tumor growth in cancer cell lines and in xenografts (53-57).

Curcumin is a potent inhibitor of IL-8 production, as well as of numerous IL-8 cancer-promoting bio-activities. Hidaka *et al*. measured IL-8 levels in the human pancreatic carcinoma cell line SUIT-2 after incubation with 10-100 μM concentration of curcumin. The magnitude of the decrease in IL-8 production was dose-dependent. The investigators also reported that curcumin markedly reduced IL-8 receptor internalization. These changes were accompanied by marked suppression of tumor cell growth (58). Curcumin prevented the acid-induced production of IL-8 in human esophageal epithelial cells (59) and reduced IL-8 levels in cultured monocytes previously treated with a high concentration glucose (31). Curcumin caused a dose-dependent blockage of IL-8 production in human head and neck carcinoma cell lines (34). Wang *et al*. reported that curcumin suppressed neurotensin-mediated IL-8 production in the human colon cancer line HCT166, thus blocking colon cancer cell migration (60). It has been reported that curcumin blocked IL-8 release in alveolar epithelial cells (61) and in human peripheral blood monocytes and alveolar macrophages (62). Curcumin was found to reduce chronic non-bacterial prostatitis in rats by blocking IL-8 release (63).

Curcumin and Interleukin-1 (IL-1)

The interleukin-1 family is a group of proteins intimately involved in the body's response to injury or infection (64-66) but which also play a key role in the development and spread of tumors (67-70). Voronou *et al*. have shown that one of these cytokines, IL-1β, is required for tumor angiogenesis (71). Elevated levels of IL-1β have been found in patients with cancer (72), while increased cancer cell growth after IL-1β stimulation has been found in multiple experimental systems (73-75). Li *et al*. found that this cytokine was effective in stimulating the growth of a subpopulation of cancer cells with characteristics of CSCs (74).

As with IL-8, curcumin inhibits the production of IL-1β and other cytokines by monocytes and macrophages (62). Kloesch *et al*. found that curcumin caused significant anti-inflammatory effects against fibroblast-like synoviocytes, by blocking IL-1β and IL-6 (32). Curcumin has been shown to block NF-κB activation induced by this cytokine in bone

marrow stromal cells (76), human articular chondrocytes (77-78) and colonic epithelial cells (79). Kalinski *et al*. have shown that IL-1β-induced NF-κB gene expression could be blocked by curcumin in two human chondrosarcoma cell lines (80). They also showed that curcumin blocked recruitment of the receptor-associated kinase (IRAK) to the IL-1 receptor, thus preventing signaling. Inhibition of IRAK likely occurs because of curcumin's blockage of IRAK thiols.

CXCR1 and CXCR2

Cytokines of the CXC family bind to transmembrane (7-TM) proteins on the target cell, primarily CXCR1 and CXCR2 (81-86). While CXCR2 binds multiple cytokines, including GROα (CXCL1) and GROβ (CXCL2), CXCR1 only binds IL-8 and CXCL6 (87). CXCR1 appears to be the most important mediator of IL-8-stimulated chemotaxis (85). These receptors occur not only on leukocytes but also on tumor cells, as well as on most normal cells (46, 88-89). Increased production of inflammatory cytokines can, thus, result in increased stimulation of CXCR1 and CXCR2 on tumor cells, particularly on CSCs (51, 53, 90). Studies on human cancer cells lines have confirmed that malignant cells respond to the effects of autocrine/paracrine IL-8 signaling, resulting in cell proliferation and metastases (91-95). Therefore, it has been suggested that these receptors may be primary targets for prevention of tumor growth and recurrence (58, 90, 96-98). Ginestier *et al*. has reported that in both human breast cancer cell lines and human breast cancer cells heterotransplanted into nude mice, the use of an anti-CXCR1 antibody, or of repertaxin, a CXCR1 inhibitor, not only caused a reduction in the number of bulk tumor cells but a major reduction in CSCs as well (48). Likewise, the CXCR2 antagonist A210397767 has been shown to inhibit leukocyte-infiltration into cancerous tissue, thus retarding tumor growth (99).

In addition to blocking cytokine release, curcumin inhibits cytokine bioactivities by its actions against CXCR1 and CXCR2 (58, 100). For example, Hidaka *et al*. have reported that curcumin has major effects on cytokine function by both a reduction of IL-8 production and an effect on CXCR1 and CXCR2. Curcumin was found to regulate the "recycling" of CXCR1 and CXCR2 from the cytoplasm to the cell surface, thus preventing cytokine-induced receptor internalization (58). In another study, by the same investigators, Takahashi *et al*. reported that curcumin's prevention of IL-8-induced neutrophil chemotaxis appears to occur because of the regulation by curcumin of the Rab11 trafficking molecule, a low-molecular weight G protein (101, 102), which in malignant cells associates more with CXCR1 and CXCR2. The anti-CSC effect induced by curcumin is caused by the stacking of the Rab 11 vesicle complex with CXCR1 and CXCR2 in the endocytic pathway (41).

The Wnt Pathways

The Wnt signaling pathways regulate multiple processes during embryonic development, as well as gene transcription, cell migration, cell proliferation and tissue homeostasis in the adult organism (103-107). These pathways occur in multiple species, including drosophila, where much of the original work was done, as well as mice and humans (103). Mutations involving the Wnt pathways have been shown to lead to the development of multiple diseases including type 2 diabetes, Alzheimer's, autism, osteoporosis and schizophrenia (106, 108-113), as well as to multiple types of cancer (103, 105, 114-118). Wnt signaling regulates levels of the protein β-catenin. Wnt signaling is associated with a decrease in β-catenin phosphorylation, so β-catenin accumulates and, in turn, stimulates the genes for VEGF, cyclin D1 and c-Myc. Aberrant Wnt signaling and excessive levels of β-catenin can result in carcinogenesis and uncontrolled cell proliferation. Kanwar *et al*. studied colon carcinoma cells that had been made resistant to FOLFOX chemotherapy and were enriched with CSCs (119). These cells can be made to grow in spheroid colonies called colonospheres. Decreased levels of phosphorylated β-catenin, a marker of β-catenin degradation, and increasing levels of β-catenin were associated with an increased number of cells in the colonosphere that were positive for $CD44^+$. Decreased levels of β-catenin were correlated with a decreased number of CSCs and decreased colonosphere formation. Similar results were found with mammospheres by Korkaya *et al*. (120). Zhao *et al*. developed a strain of β-catenin deficient mice and reported that the absence of β-catenin resulted in the impairment of self-renewal of both normal hematopoetic stem cells and chronic myelogenous leukemia stem cells (121).

Curcumin modulates Wnt signaling. Karkarala *et al*. have shown that curcumin can inhibit Wnt signaling and the formation of mammospheres in breast cancer cell lines, as well as in normal breast cell lines (122). Likewise, curcumin has been shown to cause a marked decrease in cell migration and invasion in a human osteosarcoma cell line (123). This effect was dose-dependent. In this study, no change in the cytosolic β-catenin was seen but there was a marked decrease in nuclear β-catenin with curcumin. Evidence indicates that curcumin can act at multiple points along the Wnt pathway. Xu *et al*. reported that curcumin induced apoptosis in a human hepatocellular carcinoma cell line by decreasing β-catenin activity, thus reducing stimulation of the β-catenin target genes (124). They suggested this was an effect of the maintenance of the β-catenin destruction complex by curcumin, which prevented axin recruitment to the cell membrane (124). In a human head and neck carcinoma cell line, MDA-1986, curcumin reduced cell growth by increasing activating factor 3, thus causing the inhibition of the receptor Frizzled-1 (125). Prasad studied the effects of curcumin on the human breast

cancer cell lines MCF-7 and MDA-MB-231 and found that curcumin blocked malignant cell growth at multiple sites along this pathway, causing suppression of β-catenin, cyclin-D1, slug and dishevelled and also altering the levels of E-cadherin and GSK3β (126). Derivatives of curcumin have been shown to inhibit colon cancer cells by decreasing the amount of the transcriptional coactivator p300 (127).

The Notch Pathway

Like the Wnt pathways, the Notch pathway has been conserved among species through evolution. The Notch signaling pathway plays a critical role in regulating cell differentiation, cell proliferation and apoptosis (128-133). Notch signaling is known to regulate the functioning of normal stem cells (134-139). Aberrant Notch signaling has been implicated in the progression from Barrett's esophagus to esophageal carcinoma (140-141), as well as in the development of carcinomas of the breast, lung and pancreas, of multiple myeloma and of other cancers (142-146). The role of the Notch pathway in the preservation of CSCs has been emphasized (8, 147). A ten-fold increase in mammosphere formation was seen after addition of a Notch activating peptide to a breast cancer cell line (139). Phillips showed that the number of breast cancer stem cells could be increased by the use of recombinant human erythropoetin, which stimulated the Notch pathway by induction of Jagged-1 (148).

Curcumin acts to suppress tumor cells at multiple sites along the Notch pathway. Liu *et al*. showed that increasing doses of curcumin caused increasing inhibition of SMMC-7721 hepatoma cells in culture and these changes paralleled decreases in *NOTCH-1* mRNA and protein expression (149). Subramanian *et al*. showed that curcumin inhibited the formation of esophagospheres through its actions on the Notch pathway causing capsase 3 activation and reducing Notch-1 activation through reduction of γ-secretase complex proteins (142). Kong showed that curcumin inhibited Notch-1 activity in two prostate cancer cell lines by down-regulating the genes *MT1-MMP* and its target molecule MMP2 (150). Aziz *et al*. showed curcumin caused destruction of hepatoma cells through down-regulation of Notch-1 and its target genes *HES1* and CyclinD1 (*CCND1*) (151).

The Hedgehog Pathways

Like the Wnt and Notch pathways, the Hedgehog pathways have a key role in embryonic development (152-154), as well as the regulation of normal stem cell activity (155-157). Three, closely related, pathways are known but the Sonic Hedgehog pathway (Shh) is the most investigated. Abnormal functioning of the Hedgehog pathways has been implicated in the development of many types of cancer and has been associated with stimulation of CSCs, thus, with an increased risk of tumor recurrence after therapy (158-161). It has also been shown that blockage of the Hedgehog pathway can suppress CSCs and reverse chemoresistance (162-164). Tumorigenesis occurs in these pathways because of the 7-transmembrane protein Smoothened. Smoothened is normally suppressed by the 12-transmembrane proteins Patched-1 and Patched-2. During aberrant Hedgehog signaling, one of the Hh proteins is released and binds to Patched, freeing Smoothened and leading to the activation of the transcription factors Gli2 and Gli3, which cause transcription of the target genes, such as *GLI1*, cyclinD (*CCND1*), cyclinE (*CCNE*), Patched 1 (*PTCH1*), *c-MYC* and *n-MYC* (165-167).

Curcumin can inhibit these pathways by multiple mechanisms. Sun *et al*. studied the effects of curcumin on the pancreatic carcinoma cell line PANC-1 and found a marked inhibition of cell proliferation (168-169). Significant decreases in Shh and Gli1 expression were noted, suggesting one of curcumin's many effects is through suppression of the Hedgehog pathway. Elamin *et al*. studied curcumin's effect on medulloblastoma cells and found cell-cycle arrest at the G_2/M phase. Down-regulation of Shh, Gli1 and Patched-1 was seen, as well as of effectors cyclinD1, c-Myc and n-Myc (170). Lim *et al*. utilized a unique polymeric nanoparticle formulation of curcumin against medulloblastoma and glioblastoma cell lines and found inhibition of the expression of Gli1 and Patched-1, as well as marked reduction in the number of CSCs expressing the stem cell marker CD133 (171). Slusarz reported that curcumin caused major reductions in *GLI1* mRNA concentrations in transgenic prostate carcinoma (TRAMP) mice and in prostate carcinoma cell lines (172).

The FAK/AKT/FOXO3A Pathway

The FAK/AKT/FOXO3A pathway plays an important role in the regulation of normal stem cells (173-174). Aberrant signaling through the pathway can stimulate the formation of CSCs, resulting in tumor recurrence and the conferring of resistance to chemotherapy (175-178). Under normal conditions, activity of this pathway is suppressed by the phosphatase and tensin homolog (PTEN), which acts as a tumor suppressor gene (179-181). Inhibition of PTEN allows for uncontrolled pathway signaling, blocking apoptosis of CSCs. Loss or a deficiency of PTEN has been linked with many diseases, including autism (182). PTEN deficiency has been associated with myeloproliferative disorders and pre-leukemia (183-184). Loss of PTEN results in increases in CSCs in prostate cell lines (185), while epidemiological studies show that up to 70% of prostate cancer patients have lost a *PTEN* gene (186).

Multiple investigators have shown that curcumin is effective in destroying CSCs by inhibition of this pathway. Shu *et al*. have shown that addition of curcumin to a human

medulloblastoma cell line resulted in marked decreases in phosphorylated Akt and phosphoinositide 3-kinase (PI3K), markers of FAK/AKT/FOXO3A pathway activity (187). Likewise, Chen *et al*. have shown that curcumin inhibited focal adhesion kinase (FAK, PTK2) phosphorylation at multiple sites (TYR397, 407, 576, 577, 861 and 925) in HCT-116 colon carcinoma cells, causing pathway suppression and allowing apoptosis (188). Yu *et al*. reported similar results (189). Wang *et al*. showed that curcumin could inhibit this pathway in human bladder carcinoma cells by increasing the activity of PTEN (190). Hussain *et al*. showed that addition of curcumin to T-cell acute lymphoblastic leukemia caused the de-phosphorylation of Akt and of FOXO transcription factor, thus inhibiting the FAK/AKT/FOXO3A pathway and allowing apoptosis of cancer cells to proceed (191). Wu reported that curcumin caused apoptosis in a nasopharyngeal carcinoma cell line by inducing p53 and FOXO3A, a downstream effector of PTEN (192).

Table I. *Curcumin: Suppression of key inflammatory cytokines*.

Cytokine	Reference
IL-6 (interferon-β2)	31-39, 59, 63
IL-8 (CXCL8)	31, 34, 35, 58-63, 79, 259
IL-1	32, 33, 62, 76-80, 259
TNF-α	31, 35, 36, 62, 63, 76, 78, 196, 259
MCP-1 (monocyte chemotactic protein-1) (CCL2)	31, 62, 257, 258
MIP-1α (macrophage inflammatory protein-α)	62
Interferon-γ	195, 196
IL-12	195, 196
IL-2	196
GROα (CXCL1)	197
GROβ (CXCL2)	197
SDF-1 (stromal cell-derived factor-1, CXCL12)	198
IP-10 (CXCL-10)	258

Curcumin and Normal Stem Cells

The safety of curcumin has been long established, as it has been used for centuries as a dietary spice. The question arises as to why curcumin does not seem to have the same deleterious effects on normal stem cells (NSCs) as it does on CSCs. There are several possible reasons that curcumin has toxic effects on CSCs, while sparing NSCs. Curcumin has been shown to have a much greater uptake by malignant cells compared to normal cells. Kunwar *et al*. studied the differential uptake of curcumin and the fluorescence spectra of curcumin-loaded cells in two normal cell lines (NIH373 mouse fibroblast cells and a mouse spleen lymphocyte line) and in two malignant cell lines (MCF human breast carcinoma and EL4 murine T-cell lymphoma) (193). Much higher uptake was measured in the malignant lines. In addition, fluorescence intensity was at least 3-8 times greater in the two malignant cell lines. Since curcumin has been shown to accumulate more in cancer cells than in bulk tumor cells, it might be expected as well that it would accumulate more in CSCs compared to NSCs.

Another explanation is that curcumin not only directly affects cells but their microenvironment as well. Under normal conditions, there is a delicate balance between proliferation-promoting and proliferation-inhibiting signals from the environment (194). Curcumin appears to shift the microenvironment around these cells to one that is adverse to proliferation of CSCs, but conducive to NSCs. As noted, curcumin has been shown to suppress the release of pro-inflammatory cytokines (Table I).

A third explanation is that curcumin's direct actions against CSCs may not be solely through its toxic effects. It has been suggested that it is possible to target CSCs not by causing cell death but by inducing these stem cells to differentiate. Many authors have suggested this as a strategy for depleting the CSC population and, thus, preventing recurrence (199-200). Almanaa *et al*. have suggested that induction of CSC differentiation may be one of the ways curcumin depletes CSCs. They tested cell lines that contained a large number (up to 40.4%) of ALDH1A1-stained cells with curcumin. After treatment, the cells with this stem cell marker were either markedly diminished or gone, suggesting either the destruction of the CSC population or their differentiation into less malignant cells (201). Studies have shown that curcumin indeed causes differentiation of both CSCs and NSCs. Gu *et al*. showed that curcumin can stimulate rat mesenchymal stem cell differentiation into osteoblasts (202). Likewise, Mujoo *et al*. showed curcumin could induce the differentiation of human embryonal stem cells (203). In another study, curcumin increased the differentiation rate of neural stem cells in rats (204). Curcumin was also shown to increase differentiation of mesenchymal stem cells in culture by suppression of NF-κB, one of the mechanisms by which curcumin attacks CSCs (205). Zhuang *et al*. showed that curcumin could cause the differentiation of glioblastoma–initiating cells in immunocompromised mice (206). Roy *et al*. have shown that difluorinated-curcumin could stimulate differentiation of colonic stem cells causing restoration of PTEN (207). Likewise, Batth *et al*. reported that curcumin could induce differentiation in a murine embryonal carcinoma cell line (208).

These factors may help explain why curcumin has a less toxic effect against NSCs than on CSCs. Still, in view of curcumin's activities at numerous sites along multiple cancer pathways, curcumin's lack of substantial toxicity to

Table II. *Curcumin: Major actions against molecular targets along key CSC pathways*.

	Effect on Pathway	Effect on NSCs (Reference)
Wnt	↓ Nuclear β-catenin (122*, 123, 124, 126, 127, 170*, 217, 224, 226, 227)	↑ (204, 222)
	↓ c-Myc (123, 124, 170*, 223, 226, 227, 229, 268)	
	↓ Wnt 3 (127)	↑ (204, 222)
	↓ Matrix metalloprotenase-2 (150, 219)	
	↓ Matrix metalloprotenase-9 (123, 229)	
	↑ Axin (124)	↓ (222)
	↓ Frizzled-1 (125, 229)	↑ (222)
	↓ SLUG (SNAI2) (126, 230, 242*)	
	↓ Dishevelled (126)	↑ (222)
	↓ Transcriptional coactivator p300 (127)	
	↓ TcF/LeF (223, 226, 227, 229)	↑ (222)
	↑ Adenomatous polyposis cell protein (229)	↓ (222)
	↓ Nestin (206*)	↑ (222)
	↑ β-tubulin (206*); ↓ (225)	↑ (222); ↓ (255)
	↑ Wnt inhibitory factor-1 (WIF-1) (228)	↓ (222)
	↓ BDNF (273)	↑ (272)
	↓ EGFR (HER1) (244*)	
	↑ Dnmt 1 (DNA methyltransferase) (244*)	
	ND – Neuro D1	↑ (222)
	ND – DCX (Doublecortin)	↑ (222)
	ND – Neurogenin	↑ (222)
	ND – Neureglin	↑ (222)
	ND – Neuroligin	↑ (222)
	ND – Reelin	↑ (222)
	ND – Serotonin receptor 1A RNA	↑ (272)
	ND – Pax 6 (Aniridia type II protein)	↑ (222)
	ND – LRP5/6	↑ (222)
	ND – DKK1 (Dickkorf-related protein 1)	↓ (220)
	ND – Wnt 1	↔ (222)
	ND – Wnt 5	↔ (222)
Notch	↓ Notch-1 (142*, 149, 151, 243*, 266*)	
	↓ Notch-3 (243*)	
	↓ Jagged-1 (142*)	
	↑ Caspase 3 (142*, 190, 191, 215, 235, 236, 243*)	↓ (205, 232, 271+)
	↑ Caspase 7 (239, 246*)	
	↑ Caspase 8 (235, 236)	
	↑ Caspase 9 (235, 239)	↓ (271+)
	↑ PARP cleavage (215*, 235, 236, 239, 243*, 245*)	↓ (232)
	↓ miR-21 (142*, 207*, 246*)	
	↓ miR-34a (142*)	
	↑ let 7a (142*)	
	↓ HES 1 (142*, 150, 151, 226*); ↔ (171*)	
	↔ HES 5 (171*)	
	↔ HEY 2 (171*)	
	↑ BAX (142*, 216)	↓ (270+)
	↓ Presenilin 1 (142*)	
	↓ Presenilin 2 (142*)	
	↓ Nicastrin (142*)	
	↓ APH 1 (142*)	
	↓ PEN 2 (142*)	
	↑ p53 (192, 251); ↓ (267, 268)	↑ (233)
	↑ p21/WAF1 (142*)	↑ (233)
Hedgehog	↓ Shh (168, 169, 170*)	
	↓ Gli-1(168, 169, 170*, 171*, 172)	↑ (222)
	↓ Cyclin D1 (39, 123, 126, 142*, 151, 170*, 221, 224, 226, 229, 230, 239, 243*)	
	↓ Vimentin (169, 242*)	
	↓ Patched-1 (170*, 171*)	
	↑ Olig 2 (206*)	
	↑ E-cadherin (161, 188, 242*)	
	↑ GSK3β (126, 189, 191, 224, 234)	↓ (222)
FAK	↓ Phosphorylation of Akt (170*, 171*, 187, 188, 189, 191, 207*)	↑ (269+)
	↓ PI3K (187)	
	↓ VEGF (31, 219, 229, 230, 246*, 269)	↑ (269+); ↓(261**)
	↓ VEGFR (269)	↑ (269+)
	↓ Phosphorylated m-Tor/m-Tor (189, 269)	↑ (269+, 271+)
	↓ HIF1α (hypoxia-inducible factor 1α) (269)	↑ (269+)
	↓ Signal tranducer CD24 (188)	
	↑ Acetylation histone H1 (247*)	
	↔ Acetylation histone H2 (247*)	
	↑ Acetylation histone H3 (247*)	↓ (248)
	↑ Acetylation histone H4 (247*)	↓ (248, 249)
	↑ Acetylation histone H8 (247*)	
	↓ Bcl-2 (B-cell lymphoma 2) (142*, 170*, 171*, 190, 209, 215*, 216, 230, 239, 243*)	↑ (270+)
	↓ Bcl- xL (142*, 170*, 217, 221, 235, 239, 243*, 266*, 268)	
	↓ SRC (241)	↑ (205)
	↓ IGF-1 (insulin-like growth factor 1) (171*)	
	↓ IGF-2 (171*)	
	↓ IGF-1R (171*)	
	↓ P-IGF1Rβ (171*)	
	↑ IGFBP (250)	↓ (261**)
	↑ Heme oxigenase-1 (214)	↑ (202, 261**)
	↓ β-integrin (237)	↑ (205)
	↓ Fibronectin (242*)	
	↑ PTEN (190, 207*, 246*)	
	↓ Conversion of LC3-1 (microtubule-associated protein-1 light chain 3) to LC3-11 (235)	↑ (271+)
	↑ FOXO3a (192)	
	ND – mlc 2 (myosin light chain 2)	↑ (233)
	ND – Homebox protein Nkx-2.5	↑ (233)
MAPK	↑ p38 MAPK (189, 209, 210, 211)	↑ (231)
	↓ Survivin (BIRC5) (123, 209, 219, 220, 229, 241, 243*, 263)	
	↑ ERK (210, 212, 213) ;	↑ (205, 231);
	↔(171*, 211)	↓ (233)
	↑ JNK (210, 211, 212, 213, 233)	↓ (232, 261**)
	↑ ATF 3 (Activating transcription factor 3) (125)	
	↓ ABCG2 (214*, 253*)	
	↓ ABCC1 (254*)	
	↓ Oct-4 (260)	↑ (255)
	↓ GPX (glutamate peroxidase) (264)	↑ (261**)
	↓ Cyclin B1 (219)	

Table II. *continued*

Table II. *continued*

	Effect on Pathway	Effect on NSCs (Reference)
	↑ PKD1 (protein kinase D1) (115)	
	↓ Nanog (260)	↑(255)
	↓ SOX-2 (SRY-box2) (260)	
	↑ miR-145 (260)	
	↓ EZH2 (Zesle homolog 2) (210, 230)	
	↓ beclin-1 (235)	↑ (271+)
	↑ c-jun (211, 213, 241)	
	↓ AP-1 (activator protein-1) (256)	↓ (76)
	↓CCL2 (MCP-1) (257)	↓ (76)
	↓ pp2A (protein phosphatase 2A) (212)	
	↓ pp5 (protein phosphatase 5) (212)	
	↑ jun-B (213)	
	↑ ROS (reactive oxygen species) (235)	↓ (232, 261**)
	↑ PPAR γ (peroxisome proliferator-activated receptor γ) (238)	↓ (202)
	↓ Transcription factor sp-1 (188)	
	↓ Calmodulin (188)	
	↓ EphB2 (Ephrin type-B receptor 2) (188)	
	↓ AIP-1/Alix protein (230)	
	↓ PCNA (proliferating cell nuclear antigen) (230)	
	↓ Ki67 (230)	
	↑ GFAP (glial fibrillary acidic protein) (206*)	
	↑ C/EBPα (Ccaat-enhancer binding protein α) (250)	↓ (202)
	ND – RUNX 2 (Runt-related transcription factor 2)	↑(202, 265)
	ND – CSPG (chondroitin sulfate proteoglycan)	↑ (205)
JAK/ STAT3	↓ DNA replication licensing factor MCM2 (218, 219)	
	↓ STAT3-p (39, 171*, 218, 219, 221, 243*)	
	↓PDGFB (platelet-derived growth factor B) (262)	↓ (261**)
	↓ SOD-2 (superoxide dismutase 2, mitochodrial) (263)	↑ (261**)
	↓ RB phosphorylation (243*)	
	↓ ICAM-1 (intercellular adhesion molecule; CD54) (219)	
	↓ CKD4 protein (39)	
	↔ STAT 1 (243*)	
	↔ STAT 6 (243*)	
	↓ Nitric oxide synthase (252)	↑ (233)
	↑ SOCS 1 protein (247*)	
	↑ SOCS 3 protein (247*)	
	ND – CXCL10 (IP-10)	↓ (258)
NF-κB	↓ NF-κB (170*, 201*, 239, 246*, 268)	↓ (76, 205)
	↓ Iκ-Bα (239)	↓ (205)
	↓ TNFα (35, 196, 263)	↓ (76)
	↓ IL-1α (256)	↓ (76)
	↓IL-1β (80)	↓ (205)
	↓ IL-6 (239, 242*)	
	↓ s IL-6R (242*)	
	↓ SOX-9 (242*)	
	↓ ADAM 17 (ADAM metallopeptidase domain 17; TNF-α converting enzyme) (242*)	
	↓ Hsp90 (heat shock protein 90)	
	↓ COX2 (234, 236, 246*)	↑ (205)
	↑ Cytochrome-C release (235, 236)	
	↓ c-FLIP (CFLAR) (235)	
	↓ X-linked IAP (BIRC4) (235), ↔ (215*)	↓ (205)
	↓ cIAP-2 (BIRC3) (235)	

*Study done on lines with high proportion of CSCs. **Study done on induced pluripotent stem cell line. +Study done on human umbilical vein endothelial cells, not progenitor cells. ND- No data on curcumin's effect on cancer cell lines.

normal tissues is significant. Table II lists important targets of curcumin along key CSC pathways. The assignment of these targets is somewhat arbitrary as many of these biomolecules are situated along the intersection of multiple pathways. It is clear, however, that curcumin often has different effects on CSCs and NSCs in these crucial pathways. For example, studies on CSCs have demonstrated that part of curcumin's toxicity to CSCs involves suppression of molecular abnormalities in the Wnt pathway, such as its inhibition of β-catenin (122, 125-126). Curcumin has opposite effects on neural stem cells as it stimulates neurogenesis. Curcumin increases β-catenin, cyclin D1, dishevelled and frizzled but reduces expression of the components of the β-catenin destruction complex, including the tumor suppressors GSK-3β, APC (adenomatous polyposis cell protein) and axin. Curcumin has contrary, but doubly-beneficial, actions like inhibiting CSCs, while at the same time stimulating normal NSC function (204, 222).

Acknowledgements

The Authors wish to thank Diana C. Sordillo, M.S. for her review of the manuscript and her helpful suggestions.

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Received September 14, 2014
Revised October 19, 2014
Accepted October 24, 2014