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.

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 
streptozotocin-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 
(CXCL8) cancer-promoting bio-activities. Hidaka
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epithelial cells (59) and reduced IL-8 levels in cultured 
monocytes previously treated with a high concentration 
(CXCL8). Curcumin caused a dose-dependent blockade 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-
flammatory effects against fibroblast-like synoviocytes, by 
blocking IL-1β and IL-6 (32). Curcumin has been shown to 
block NF-kB activation induced by this cytokine in bone

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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.

CXCRI and CXCR2

Cytokines of the CXC family bind to transmembrane (7-TM) proteins on the target cell, primarily CXCRI and CXCR2 (81-86). While CXCR2 binds multiple cytokines, including GROα (CXCL1) and GROβ (CXCL2), CXCRI only binds IL-8 and CXCL6 (87). CXCRI 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 CXCRI 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 CXCRI 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 hematopoietic 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 erythropoietin, 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 increased 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 capase 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 hepatoctyes 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 G2/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).

### 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>
<thead>
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<th>Cytokine</th>
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<tr>
<td>IL-6 (interferon-β2)</td>
<td>31-39, 59, 63</td>
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<tr>
<td>IL-8 (CXCL8)</td>
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<td>IL-1</td>
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<td>GROβ (CXCL2)</td>
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<td>SDF-1 (stromal cell-derived factor-1, CXCL12)</td>
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<td>IP-10 (CXCL10)</td>
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Table II. Curcumin: Major actions against molecular targets along key CSC pathways.

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<th>Effect on NSCs (Reference)</th>
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<td>▼ c-Myb (123, 124, 126, 223, 226, 227, 229, 268)</td>
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<td>▼ Wnt 3 (127)  ▼ Wnt 5 (127)</td>
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<td>▼ Matrix metalloproteinase-2 (150, 219)</td>
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<td>▼ Frizzled-1 (125, 229)</td>
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<td>▼ SLUG (SNAI2) (126, 230, 242*)</td>
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<td>▼ Adenomatous polyposis cell protein (229)</td>
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<td>ND – Serotonin receptor 1A RNA</td>
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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).

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