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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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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).

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References

1 Gangemi R, Paleari L, Orengo AM, Cesario A, Chessa L, Ferrini S and Russo P: Cancer stem cells: A new paradigm for understanding tumor growth and progression and drug resistance. Curr Med Chem *16*: 1688-1703, 2009.

2 Boman BM and Huang E: Human colon cancer stem cells: A new paradigm in gastrointestinal oncology. J Clin Oncol *26*: 2826-2838, 2008.

3 Singh AK, Arya RK, Maheshwari S, Singh A, Meena S, Pandey P, Dormand O and Datta D: Tumor heterogeneity and cancer stem cell paradigm: Updates in concept, controversies and clinical relevance. Int J Cancer doi: 10.1002/ijc.28804, 2014.

4 Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, Henkleman RM, Cusimano MD and Dirks PB: Identification of human brain tumor initiating cells. Nature *432*: 396-401, 2004.

5 Rao G, Liu H, Li B, Hao J, Yang Y, Wang M, Wang X, Wang J, Jin H, Du L and Chen Q: Establishment of a human colorectal cancer cell line P6C with stem cell properties and resistance to chemotherapeutic drugs. Acta Pharmacologica Sinica *34*: 793-804, 2013.

6 Galli R, Binda E, Orfanelli U, Cipelletti B, Gritti A, De Vitis S, Fiocco R, Foroni C, Dimeco F and Vescovi A: Isolation and characterization of tumorigenic, stem-like neural precursors from human glioblastoma. Cancer Res *64*: 7011-7021, 2004.

7 Ebben JD, Treisman DM, Zorniak M, Kutty RG, Clark PA and Kuo JS: The cancer stem cell paradigm: A new understanding of tumor development and treatment. Expert Opin Ther Targets *14*: 621-632, 2010.

8 Fan X, Khaki L, Zhu T, Soules M, Talsma C, Gul N, Koh C, Zhang J, Li Y, Maciaczyk J, Nikkhah G, DiMeco F, Piccirillo S, Vescovi A and Eberhart C: Notch pathway blockade depletes CD133-positive glioblastoma cells and inhibits growth of tumor neurospheres and xenografts. Stem Cells *28*: 5-16, 2010.

9 Li X, Lewis MT, Huang J, Gutierrez C, Osborne CK, Wu MF, Hilsenbeck SG, Pavlick A, Zhang X, Chamness GC, Wong H, Rosen J and Chang JC: Intrinsic resistance of tumorigenic breast cancer cells to chemotherapy. J Natl Cancer Inst *100*: 672-679, 2008.

10 Diehn M, Cho RW, Lobo NA, Kalisky T, Dorie MJ, Kulp AN, Qian D, Lam JS, Ailles LE, Wong M, Joshua B, Kaplan MJ, Wapnir I, Dirbas FM, Somlo G, Garberoglio C, Paz B, Shen J, Lau SK, Quake SR, Brown JM, Weissman IL and Clarke MF: Association of reactive oxygen species levels and radioresistance in cancer stem cells. Nature *458*: 780-783, 2009.

11 Kabos P, Haughian JM, Wang X, Dye WW, Finlayson C, Elias A, Horwitz KB and Sartorius CA: Cytokeratin 5 positive cells represent a steroid receptor negative and therapy resistant subpopulation in luminal breast cancers. Breast Cancer Res Treat *128*: 45-55, 2010.

12 Iliopoulos D, Hirsch HA, Wang G and Struhl K: Inducible formation of breast cancer stem cells and their dynamic equilibrium with non-stem cancer cells *via* IL-6 secretion. Proc Natl Acad Sci USA *108*: 1397-1402, 2011.

13 Singh J, Simoes B, Howell S, Farnie G and Clarke R: Recent advances reveal IL-8 signaling as a potential key to targeting breast cancer stem cells. Breast Cancer Res *15*: 210-218, 2013.

14 Korkaya H, Liu S and Wicha MS: Regulation of cancer stem cells by cytokine networks: Attacking cancer's inflammatory roots. Clin Cancer Res *17*: 6125-6129, 2011.

15 Tanei T, Morimoto K, Shimazu K, Kim SJ, Tanji Y, Taguchi T, Tamaki Y and Noguchi S: Association of breast cancer stem cells identified by aldehyde dehydrogenase 1 expression with resistance to sequential paclitaxel and epirubicin-based chemotherapy for breast cancers. Clin Cancer Res *15*: 4234-4241, 2009.

16 Creighton CJ, Li X, Landis M, Dixon JM, Neumeister VM, Sjolund A, Rimm DL, Wong H, Rodriguez A, Herschkowitz JI, Fan C, Zhang X, He X, Pavlick A, Gutierrez MC, Renshaw L, Larionov AA, Faratian D, Hilsenbeck SG, Perou CM, Lewis MT, Rosen JM and Chang JC: Residual breast cancers after conventional therapy display mesenchymal as well as tumor-initiating features. Proc Natl Acad Sci USA *106*: 13820-13825, 2009.

17 Wang Y, Li LZ, Ye L, Niu XL, Liu X, Zhu YQ, Sun WJ and Liang YJ: Chemotherapy resistance induced by interlukin-6 in ovarian cancer cells and its signal transduction pathways. Zhonghua Fu Chan Ke Za Zhi *45*: 691-698, 2010.

18 Waugh DJJ and Wilson C: The interleukin-8 pathway in cancer. Clin Cancer Res 14: 6735-6741, 2008.

19 Waldner MJ, Foersch S and Neurath MF: Interleukin-6 - A key regulator of colorectal cancer development. Int J Biol Sci *8*: 1248-1253, 2012.

20 Goswami B, Mittal P and Gupta N: Correlation of levels of IL-6 with tumor burden and receptor status in patients of locally advanced carcinoma breast. Indian J Clin Biochem *28*: 90-94, 2013.

21 Gado K, Domjan G, Hegyesi H and Falus A: Role of interleukin-6 in the pathogenesis of multiple myeloma. Cell Biol Int *24*: 195-209, 2000.

22 Smith PC, Hobisch A, Lin DL, Culig Z and Keller ET: Interleukin-6 and prostate cancer progression. Cytokine Growth Factor Rev *12*: 33-40, 2001.

23 Leonard M, Ryan MP, Watson AJ, Schramek H and Healy E: Role of MAP kinase pathways in mediating IL-6 production in human primary mesangial and proximal tubular cells. Kidney Internat *56*: 1366-1377, 1999.

24 Scheller J, Chalaris A, Schmidt-Arras D and Rose-John S: The pro- and anti-inflammatory properties of the cytokine interleukin-6. BBA- Mol Cell Res *1813*: 878-888, 2011.

25 Hodge DR, Hurt EM and Farrar WL: The role of IL-6 and STAT3 in inflammation and cancer. Eur. J. Cancer *41*: 2502-2512, 2005.

26 Rattigan Y, Hsu J-M, Mishra PJ, Glod J and Banerjee D: Interleukin 6 mediated recruitment of mesenchymal stem cells to the hypoxic tumor milieu. Exp Cell Res *316*: 3417-3424, 2010.

27 Ancrile B, Lim KH and Counter CM: Oncogenic Ras-induced secretion of IL6 is required for tumorigenesis. Genes Dev *21*: 1714-1719, 2007.

28 Guthrie GJK, Roxburgh CSD, Richards CH, Horgan PG and McMillan DC: Circulating IL-6 concentrations link tumour necrosis and systemic and local inflammatory responses in patients undergoing resection for colorectal cancer. Brit J Cancer *109*: 131-137, 2013.

29 Wang Y, Li L, Guo X, Jin X, Sun W, Zhang X and Xu RC: Interleukin-6 signaling regulates anchorage-independent growth, proliferation, adhesion and invasion in human ovarian cancer cells. Cytokine 59: 228-236, 2012.

30 Shi Z, Yang WM, Chen LP, Yang DH, Zhou Q, Zhu J, Chen JJ, Huang RC, Chen ZS and Huang RP: Enhanced chemo-sensitization in multidrug-resistant human breast cancer cells by inhibition of IL-6 and IL-8 production. Breast Cancer Res Treat *135*: 737-747, 2012.

31 Jain SK, Rains J, Croad J, Larson B and Jones K: Curcumin supplementation lowers TNF-α, IL-6, IL-8, and MCP-1 secretion in high glucose-treated cultured monocytes and blood levels of TNF-α, IL-6, MCP-1, glucose, and glycosylated hemoglobin in diabetic rats. Antioxid Redox Signal *11*: 241–249, 2009.

32 Kloesch B, Becker T, Dietersdorfer E, Kiener H and Steiner G: Anti-inflammatory and apoptotic effects of the polyphenol curcumin on human fibroblast-like synoviocytes. Int Immunopharmacol *15*: 400-405, 2013.

33 Moriasi CM, Trevino C, Subramaniam D, Ramalingam S, Awasthi V, Shanjana A and Anant S: Curcumin regulates Interleukin-6 expression in colon cancer cells Cancer Res *71*: 4606-4606, 2011.

34 Cohen AN, Veena MS, Srivatsan ES and Wang MB: Suppression of interleukin 6 and 8 production in head and neck cancer cells with curcumin *via* inhibition of Iκβ kinase. Arch Otolaryngol Head Neck Surg *135*: 190-197, 2009.

35 Bisht S, Feldmann G, Soni S, Ravi R, Karikar C, Maitra A and Maitra A: Polymeric nanoparticle-encapsulated curcumin ("nanocurcumin"): A novel strategy for human cancer therapy. J Nanobiotechnol *5*: 3, 2007.

36 Gulcubuk A, Altunatmaz K, Sonmez K, Haktanir-Yatkin D, Uzun H, Gurel A and Aydin S: Effects of curcumin on tumour necrosis factor-alpha and interleukin-6 in the late phase of experimental acute pancreatitis. J Vet Med A Physiol Pathol Clin Med *53*: 49-54, 2006.

37 Bharti AC, Donato N and Aggarwal BB: Curcumin (diferuloylmethane) inhibits constitutive and IL-6- inducible STAT3 phosphorylation in human multiple myeloma cells. J Immunol *171*: 3863-3871, 2003.

38 Liu Y, Fuchs J, Li C and Lin J: IL-6, a risk factor for hepatocellular carcinoma : FLLL32 inhibits IL-6 induced STAT3 phosphorylation in human hepatocellular cancer cells. Cell Cycle *9*: 3423-3427, 2010.

39 Park J, Ayyappan V, Bae EK, Lee C, Kim BS, Kim BK, Lee YY, Ahn KS and Yoon SS: Curcumin in combination with bortezomib synergistically induced apoptosis in human multiple myeloma U266 cells. Mol Oncol *2*: 317-326, 2008.

40 Wang Y, Qu Y, Niu XL, Sun WJ, Zhang XL and Li LZ: Autocrine production of interleukin-8 confers cisplatin and paclitaxel resistance in ovarian cancer cells. Cytokine *56*: 365-375, 2011.

41 Takahashi M, Ishiko T, Kamohara H, Hidaka H,Ogawa M and Baba H: Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione) blocks the chemotaxis of neutrophils by inhibiting signal transduction through IL-8 receptors. Mediators Inflamm *2007*: 10767, 2007.

42 Koch AE, Polverini PJ, Kunkel SL, Harlow LA, DiPietro LA, Elner VM, Elner SG and Strieter RM: Interleukin-8 as a macrophage-derived mediatior of angiogenesis. Science *258*: 1798-1801, 1992.

43 Holmes WE, Lee J, Kuang WJ, Rice GC and Wood WI: Structure and functional expression of a human interleukin-8 receptor. Science *253*: 1278-1280, 1991.

44 Abraham RT: Chemokine to the rescue: Interleukin-8 mediates resistance to PI3K-pathway-targeted therapy in breast cancer. Cancer Cell *22*: 703-705, 2012.

45 Chuntharapai A and Kim KJ: Regulation of the expression of IL-8 receptor A/B by IL-8: Possible functions of each receptor. J Immunol *155*: 2587-2594, 1995.

46 Brat DJ, Bellail AC and Van Meir EG: The role of interleukin-8 and its receptors in gliomagenesis and tumoral angiogenesis. Neuro Oncol *7*: 122-133, 2005.

47 Vlahopoulos S, Boldogh I, Casola A and Brasier AR : Nuclear factor-κβ-dependent induction of interleukin-8 gene expression by tumor necrosis factor α: Evidence for an antioxidant sensitive activating pathway distinct from nuclear translocation. Blood *94*: 1878-1889, 1999.

48 Ginestier C, Liu S and Wicha MS: CXCR1 blockade selectively targets human breast cancer stem cells *in vitro* and in xenografts. J Clin Invest *120*: 485-487, 2010.

49 Yao C, Lin Y, Chua MS, Ye CS, Bi J, Li W, Zhu YF and Wang SM: Interleukin-8 modulates growth and invasiveness of estrogen receptor- negative breast cancer cells. Int J Cancer *121*: 1949-1957, 2007.

50 Benoy IH, Salgado R, Van Dam P, Geboers K, Van Marck E, Scharpe S, Vermeulin PB and Dirix LY: Increased serum interleukin-8 in patients with early and metastatic breast cancer correlates with early dissemination and survival . Clin Cancer Res *10*: 7157-7162, 2004.

51 Shi Q, Abbruzzese JL, Huang S, Fidler IJ, Xiong Q and Xie K: Constitutive and inducible interleukin-8 expression by hypoxia and acidosis renders human pancreatic cancer cells more tumorigenic and metastatic. Clin Cancer Res *5*: 3711-3721, 1999.

52 Freund A, Chauveau C, Brouillet JP, Lucas A, Lacroix M, Licznar A, Vignon F and Lazennec G: IL-8 expression and its possible relationship with estrogen-receptor-negative status of breast cancer cells. Oncogene *22*: 256-265, 2003.

53 Inoue K, Slaton JW, Kim SJ, Perrotte P, Eve BY, Bar-Eli M, Radinsky R and Dinney CP: Interleukin 8 expression regulates tumorigenicity and metastasis in human bladder cancer. Cancer Res *60*: 2290-2299, 2000.

54 Seaton A, Scullin P, Maxwell PJ, Wilson C, Pettigrew J, Gallagher R, O'Sullivan JM, Johnston PG and Waugh DJ: Interleukin-8 signaling promotes androgen independent proliferation of prostate cancer cells *via* induction of androgen receptor expression and activation. Carcinogenesis *29*: 1148-1156, 2008.

55 Zhu YM, Webster SJ, Flower D and Woll PJ: Interleukin-8/CXCL8 is a growth factor for human lung cancer cells. Br J Cancer *91*: 1970-1976, 2004.

56 Kitadai Y, Takahashi Y, Haruma K, Naka K, Sumii K, Yokozaki H, Yasui W, Mukaida N, Ohmoto Y, Kajiyama G, Fidler IJ and Tahara E: Transfection of interleukin-8 increases angiogenesis and tumorigenesis of human gastric carcinoma cells in nude mice. Br J Cancer *81*: 647-653, 1999.

57 Singh S, Sadanandam A, Nannuru KC, Varney ML, Mayer-Ezell R, Bond R and Singh RK: Small-molecule antagonists for CXCR2 and CXCR1 inhibit human melanoma growth by decreasing tumor cell proliferation, survival and angiogenesis. Clin Cancer Res *15*: 2380-2386, 2009.

58 Hidaka H, Ishiko T, Furuhashi T, Kamohara H, Suzuki S, Miyazaki M, Ikeda O, Mita S, Setoguchi T and Ogawa M: Curcumin inhibits interleukin 8 production and enhances interleukin 8 receptor expression on the cell surface: Impact on human pancreatic carcinoma cell growth by autocrine regulation. Cancer *95*: 1206-1214, 2002.

59 Raflee P, Nelson VM, Manley S, Wellner M, Floer M, Binion DG and Shaker R: Effect of curcumin on acidic pH-induced expression of IL-6 and IL-8 in human esophageal epithelial cells (HET-1A): Role of PKC, MAPKs, and NF-κB. Am J Physiol Gastrointest Liver Physiol *296*: G388-G398, 2009.

60 Wang X, Wang Q, Ives KL and Evers BM: Curcumin inhibits neurotensin-mediated interleukin-8 production and migration of HCT116 human colon cancer cells. Clin Cancer Res *12*: 5346-5355, 2006.

61 Biswas SK, McClure D, Jimenez LA, Megson IL and Rahman I: Curcumin induces glutathione biosynthesis and inhibits NF-κB activation and interleukin-8 release in alveolar epithelial cells : Mechanism of free radical scavenging activity. Antioxid Redox Signal *7*: 32-41, 2005.

62 Abe Y, Hashimoto S and Horie T: Curcumin inhibition of inflammatory cytokine production by human peripheral blood monocytes and alveolar macrophages. Pharmacol Res *39*: 41-47, 1999.

63 Zhang QY, Mo ZN and Liu XD: Reducing effect of curcumin on expressions of TNF-alpha, IL-6 and IL-8 in rats with chronic nonbacterial prostatitis. Nat J Andrology *16*: 84-88, 2010.

64 Weber A, Wasiliew P and Kracht M: Interleukin-1 (IL-1) pathway. Sci Signal 3:cm1.doi:10.1126/scisiggnal.3105cm1, 2010.

65 Dinarello CA: Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood *117*: 3720-3732, 2011.

66 Contassot, E, Beer HD and French LE: Interleukin-1, inflammasomes, autoinflammation and the skin. Swiss Med Wkly 142: w13590.doi:10.4414/smw.2012.13590, 2012.

67 McKenzie RC, Oran A, Dinarello CA and Sauder DN: Interleukin-1 receptor antagonist inhibits subcutaneous B16 melanoma growth in vivo. Anticancer Res *16*: 437-441, 1996.

68 Chirivi RG, Garofalo A, Padura IM, Mantovani A and Giavazzi R: Interleukin-1 receptor antagonist inhibits the augmentation of metastasis induced by interleukin-1 or lipopolysaccharide in a human melanoma/nude mouse system. Cancer Res *53*: 5051-5054, 1993.

69 Anasagasti MJ, Alvarez A, Martin JJ, Mendoza L and Vidal-Vanaclocha F: Sinusoidal endothelium release of hydrogen peroxide enhances very late antigen-4 mediated melanoma cell adherence and tumor cytotoxicity during interleukin-1 promotion of hepatic melanoma metastasis in mice. Hepatology *25*: 840-846, 1997.

70 Vidal-Vanaclocha F., Amezaga C, Asumendi A, Kaplanski G and Dinarello CA: Interleukin-1 receptor blockade reduces the number and size of murine B16 melanoma hepatic metastases. Cancer Res *54*: 2667-2672, 1994.

71 Voronov E, Shouval DS, Krelin Y, Cagnano E, Benharroch D, Iwakura Y, Dinarello CA and Apte RN: IL-1 is required for tumor invasiveness and angiogenesis. Proc Natl Acad Sci USA *100*: 2645-2650, 2003.

72 Colasante A, Mascetra N, Brunetti M, Lattanzio G, Diodoro M, Caltagirone S, Musiani P and Aiello FB : Transforming growth factor beta 1, interleukin-8 and interleukin-1, in non-small cell lung tumors. Am J Respir Crit Care Med *156*: 968-973, 1997.

73 Jedinak A, Dudhgaonkar S and Silva D: Activated macrophages induce metastatic behavior of colon cancer cells. Immunobiology *215*: 242-249, 2010.

74 Li Y, Wang L, Pappan L, Galliher-Beckley A and Shi J: IL-1β promotes stemness and invasiveness of colon cancer cells through Zeb1 activation. Molecular Cancer *11*: 87-94, 2012.

75 Kaler P, Augenlicht L and Klampfer L: Macrophage-derived IL-1beta stimulates Wnt signaling and growth of colon cancer cells: A crosstalk interrupted by vitamin D3. Oncogene *28*: 3892-3902, 2009.

76 Xu YX, Pindolia KR, Janakiraman N, Chapman RA and Gautam SC: Curcumin inhibits IL-1α and TNF-α induction of AP-1 and NF-κB DNA-binding activity in bone marrow stromal cells. Hematopathol Mol Hematol *11*: 49-62, 1997-1998.

77 Henrotin Y, Clutterbuck AL, Allaway D, Lodwig EM, Harris P, Mathy-Hartert M, Shakbaei M and Mobasheri A: Biological actions of curcumin on articular chondrocytes. Osteoarthritis Cartilage *18*: 141-149, 2010.

78 Shakibaei M, John T, Schulze-Tanzil G, Lehmann I and Mobasheri A: Suppression of NF-κβ activation by curcumin leads to inhibition of expression of cyclo-oxygenase-2 and matrix metalloprotreinase-9 in human articular chondrocytes. Biochem Pharmacol *73*: 1434-1445, 2007.

79 Jobin C, Bradham CA, Russo MP, Juma B, Narula AS, Brenner DA and Sartor RB: Curcumin blocks cytokine-mediated NF-κβ activation and proinflammatory gene expression by inhibiting inhibitory factor I-κβ kinase activity. J Immunol *163*: 3474-3483, 1999.

80 Kalinski T, Sel S, Hutten H, Ropke M, Roessner A and Nass N: Curcumin blocks interleukin-1 signaling in chondrosarcoma cells. PloS ONE *9*: e99296, 2014.

81 Rossi D and Zlotnik A: The biology of chemokines and their receptors. Annu Rev Immunol *18*: 217-242, 2000.

82 Lee J, Horuk R, Rice GC, Bennett GL, Camarato T and Wood WI: Characterization of two high affinity human interleukin-8 receptors. J Biol Chem *160*: 16283-16287, 1992.

83 Holmes WF, Lee J, Kuang WI, Rice GC and Wood WI: Structure and functional expression of a human interleukin-8 receptor. Science *253*: 1278-1280, 1991.

84 Murphy PM and Tiffany HL: Cloning of complementary DNA encoding a functional human interleukin-8 receptor. Science *253*: 1280-1283, 1991.

85 Hammond MEW, Lapointe GR, Feucht PH, Hilt S, Gallegos CA, Gordon LA, Gieden MA, Mullenbach G and Tekamp-Olson P: IL-8 induces neutrophil chemotaxis predominantly *via* type I IL-8 receptor. J Immunol *155*: 1428-1433, 1995.

86 Rose JJ, Foley JF, Murphy PM and Venkatesan S: On the mechanism and significance of light-induced internalization of human neutrophil chemokine receptors CXCR1 and CXCR2. J Biol Chem *279*: 24372-24386, 2004.

87 Ahuja SK and Murphy PM: The CXC chemokines growth-regulated oncogene (GRO) alpha, GRObeta, GROgamma, neutrophil-activating peptide-2, and epithelial cell-derived neutrophil-activating peptide-78 are potent agonists for the type B, but not the type A, human interleukin-8 receptor. J Biol Chem *271*: 20545-20550, 1996.

88 Murdoch C, Monk PN and Finn A: CXC chemokine receptor expression on human endothelial cells. Cytokine *11*: 704-712, 1999.

89 Flynn G, Maru S, Loughlin J, Romero IA and Male D: Regulation of chemokine receptor expression in human microglia and astrocytes. J Neuroimmunol *136*: 84-93, 2003.

90 Charafe-Jauffret E, Ginestier C, Iovino F, Wicinski J, Cervera N, Finetti P, Hur MH, Diebel ME, Monville F, Dutcher J, Brown M, Viens P, Xerri L, Bertucci F, Stassi G, Dontu G, Birnbaum D and Wicha MS: Breast cancer cell lines contain functional cancer stem cells with metastatic capacity and a distinct molecular structure. Cancer Res *69*: 1302-1313, 2009.

91 Brew R, Erikson JS, West DC, Kinsella AR, Slavin J and Christmas SE: Interleukin-8 as an autocrine growth factor for human colon carcinoma cells *in vitro*. Cytokine *12*: 78-85, 2000.

92 Lang K, Niggeman B, Zanker KS and Entschladen F: Signal processing in migrating T24 human bladder carcinoma cells:

Role of the autocrine interleukin-8 loop. Int J Cancer *99*: 673-680, 2002.

93 De Larco JE, Wuertz BRK, Rosner KA, Erickson SA, Gamache DE, Manivel JC and Furcht LT: A potential role for interlaukin-8 in the metastatic phenotype of breast carcinoma cells. Am J Pathol *158*: 639-646, 2001.

94 Kamohara H, Takahashi M, Ishko T, Ogawa M and Raha H: Induction of interleukin-8 (CXCL-8) by tumor necrosis factor-α and leukemia inhibitory factor in pancreatic carcinoma cells: Impact of CXCL-8 as an autocrine growth factor. Int J Oncol *31*: 627-632, 2007.

95 Takamori H, Oades ZG, Hoch OC, Burner M and Schraufstatter IU: Autocrine growth effect of IL-8 and GROα on a human pancreatic cancer cell line, Capan-1. Pancreas *21*: 52-56, 2000.

96 Wu D, LaRosa GJ and Simon MI : G protein-coupled signal transduction pathways for interleukin-8. Science *261*: 101-103, 1993.

97 Wang S, Wu Y, Hou Y, Guan X, Castelvetere MP, Oblak JJ, Banerjee S, Filtz TM, Sharkar F., Chen X, Jena B and Li C: CXCR2 macromolecular complex in pancreatic cancer: A potential therapeutic target in tumor growth. Transl Oncol *6*: 216-225, 2013.

98 Campbell LM, Maxwell PJ and Waugh DJJ: Rational and means to target pro-inflammatory interleukin-8 (CXCL8) signaling in cancer. Pharmaceuticals *6*: 929-959, 2013.

99 Tazzyman S, Barry ST, Ashton S, Wood P, Blakey D, Lewis CE and Murdoch C: Inhibition of neutrophil infiltration into A549 lung tumors *in vitro* and *in vivo* using a CXCR2-specific antagonist is associated with reduced tumor growth. Int J Cancer *129*: 847-858, 2011.

100 Shishodia S, Chaturvedi MM and Aggarwal BB: Role of curcumin in cancer therapy. Curr Probl Cancer 31:243-305, 2007.

101 Fan G, Lapierre LA, Goldenring JR, Sai J and Richmond A: Rab11 family interacting protein 2 and myosin Vb are required for CXCR2 recycling and receptor mediated chemotaxis. Mol Biol Cell *15*: 2456-2469, 2004.

102 Stenmark H and Olkkonen VM: The Rab GTPase family. Genome Biol *2*: Reviews 3007- Reviews 3007.7, 2001.

103 Nusse R: Wnt signaling and stem cell control. Cell Research *18*: 523-527, 2008.

104 Komiya Y and Habas R: Wnt signal transduction pathways. Organogenesis *4*: 68-75, 2008.

105 Klaus A and Birchmeier W: Wnt signaling and its impact on development and cancer. Nature Reviews Cancer *8*: 387-398, 2008.

106 Logan CY and Nusse R: The Wnt signaling pathway in development and disease. Annu Rev Cell Dev Biol *20*: 781-810, 2004.

107 Rao T and Kuhl M: An updated overview on Wnt signaling pathways: A prelude for more. Circulation Research *106*: 1798-1806, 2010.

108 Welters HJ and Kulkarni RN: Wnt signaling: Relevance to beta-cell biology and diabetes. Trends Endocrinol Metab *19*: 349-355, 2008.

109 Zhai L, Ballinger SW and Messina JL: Role of reactive oxygen species in injury-induced insulin resistance. Mol Endocrinol *25*: 492-502, 2011.

110 Yoon JC, Ng A, Kim BH, Bianco A, Xavier RJ and Elledge SJ: Wnt signaling regulates mitochondrial physiology and insulin sensitivity. Genes Dev *24*: 1507-1518, 2010.

111 Wan W, Xia S, Kalionis B, Liu L and Li Y: The role of Wnt signaling in the development of Alzheimer's disease: A potential therapeutic target? BioMed Res Int *2014*: 301575, 2014.

112 MacDonald BT, Tamai K and He X: Wnt/beta-catenin signaling: Components, mechanisms, and diseases. Developmental Cell *17*: 9-26, 2009.

113 Inestrosa NC, Montecinos-Oliva C and Fuenzalida M: Wnt signaling: Role in Alzheimer's disease and schizophrenia. J Neuroimmune Pharmacol *7*: 788-807, 2012.

114 Howe L and Brown A: Wnt signaling and breast cancer. Cancer Biol Ther *3*: 36-41, 2004.

115 Sundhram V, Chauhan SC, Ebeling M and Jaggi M: Curcumin attenuates β-catenin signaling in prostate cancer cells through activation of protein kinase D1. PLoS ONE 7 e35368, 2012.

116 Giles RH, Van Es JH and Clevers H: Caught up in a Wnt storm :Wnt signaling in cancer. Biochim Biophys Acta *1653*: 1-24, 2003.

117 Gamallo C, Palacios J, Moreno G, Calvo de Mora J, Suarez A and Armas A: Beta-catenin expression in pattern in stage I and II ovarian carcinomas: Relationphip with beta-catenin gene mutations, clinicopathological feature, and clinical outcome. Am J Pathol *155*: 527-536, 1999.

118 Garcia-Rostan G, Tallini G, Herrero A, D'Aquila TG, Carcangiu ML and Rimm DL : Frequent mutation and nuclear localization of beta-catenin in anaplastic thyroid carcinoma. Cancer Res *59*: 1811-1815, 1999.

119 Kanwar SS, Yu Y, Nautiyal J, Patel BB and Majumdar APN: The Wnt/β-catenin pathway regulates growth and maintenance of colonospheres. Mol Cancer *9*: 212-224, 2010.

120 Korkaya H, Paulson A, Charafe-Jauffret E, Ginestier C, Brown M, Dutcher J and Clouthier SG: Regulation of mammary stem/progenitor cells by PTEN/Akt/beta-catenin signaling. PLoS Biol *7*: e1000121, 2009.

121 Zhao C, Blum J, Chen A, Kwon HY, Jung SH, Cook JM, Lagoo A and Reya T: Loss of β-catenin impairs the renewal of normal and CML stem cells *in vivo*. Cancer Cell *12*: 528-541, 2007.

122 Kakarala M, Brenner DE, Khorkaya H, Cheng C, Tazi K, Ginestier C, Liu S, Dontu G and Wicha MS : Targeting breast stem cells with the cancer preventive compounds curcumin and piperine. Breast Cancer Res Treat *122*: 777-785, 2010.

123 Leow PC, Tian Q, Ong ZY, Yang Z and Ee PL: Antitumor activity of natural compounds, curcumin and PKF118-310, as Wnt/β-catenin antagonists against human osteosarcoma cells. Invest New Drugs *28*: 766-782, 2010.

124 Xu MX, Zhao L, Deng C, Yang L, Wang Y, Guo T, Li L, Lin J and Zhang L: Curcumin suppresses proliferation and induces apoptosis of human hepatocellular carcinoma cells *via* the Wnt signaling pathway. Int J Oncol *43*: 1951-1959, 2013.

125 Yan C, Jamaluddin MS, Aggarwal B, Myers J and Boyd DD: Gene expression profiling identifies activating transcription factor 3 as a novel contributor to the proapoptotic effect of curcumin. Mol Cancer Ther *4*: 233-241, 2005.

126 Prasad CP, Rath G, Mathur S, Bhatnagar D and Ralhan R: Potent growth suppressive activity of curcumin in human breast cancer cells: Modulation of Wnt/beta-catenin signaling. Chem Biol Interact *181*: 263-271, 2009.

127 Ryu MJ, Cho M, Song JY, Yun YS, Choi IW, Kim DE, Park BS and Oh S: Natural derivatives of curcumin attenuate the Wnt/β-catenin pathway through down-regulation of the transcriptional coactivator p300. Biochem Biophys Res Commun *377*: 1304-1308, 2008.

128 Miele L: Notch signaling. Clin Cancer Res *12*: 1074-1079, 2006.
129 Nickoloff BJ, Qin JZ, Chaturvedi V, Denning MF, Bonish B and Miele L: Jagged-1 mediated activation of Notch signaling induces complete maturation of human keratinocytes through NF-κB and PPARγ. Cell Death Differ *9*: 842-855, 2002.
130 Wilson A and Radtke F: Multiple functions of Notch signaling in self-renewing organs and cancer. FEBS Letts *580*: 2860-2868, 2006.
131 Dievart A, Beaulieu N and Jolicoeur P: Involvement of Notch1 in the development of mouse mammary tumors. Oncogene *18*: 5973-5981, 1999.
132 Artavanis-Tsakonas S, Rand MD and Lake RJ: Notch signaling: Cell fate control and signal integration in development. Science *284*: 770-776, 1999.
133 Mumm JS and Kopan R: Notch signaling: From the outside in. Develop Biol *228*: 151-165, 2000.
134 Ohlstein B, Kai T, Decotto E and Spradling A: The stem cell niche: Theme and variations. Curr Opin Cell Biol *16*: 693-699, 2004.
135 Ohlstein B and Spradling A: Multipotent drosophilia intestinal stem cells specify daughter cell fates by differential Notch signaling. Science *315*: 988-992, 2007.
136 Joseph NM and Morrison SJ: Toward an understanding of the physiological function on mammalian stem cells. Dev Cell *9*: 173-183, 2005.
137 Ohlstein B and Spradling A: The adult Drosophilia posterior midgut is maintained by pluripotent stem cells. Nature *439*: 470-474, 2006.
138 Androutsellis-Theotokis A, Leker RR, Soldner F, Hoeppner DJ, Ravin R, Poser SW, Rueger MA, Bae SK, Kittappa R and McKay RDG: Notch signaling regulates stem cell numbers *in vitro* and *in vivo*. Nature *442*: 823-826, 2006.
139 Dontu G, Jackson KW, McNicholas E, Kawamura MJ, Abdallah WM and Wicha MS: Role of Notch signaling in cell-fate determination of human mammary stem/progenitor cells. Breast Cancer Res *6*: R605-R615, 2004.
140 Masuda S: Dysfunctional transforming growth factor-beta signaling with constitutively active Notch signaling in Barrett's esophageal adenocarcinoma. Cancer *118*: 1956-1957, 2012.
141 Peters JH and Avisar N: The molecular pathogenesis of Barrett's esophagus: Common signaling pathways in embryogenesis metaplasia and neoplasia. J Gastrointest Surg *14(Suppl 1)*: S81-S87, 2010.
142 Subramaniam D, Ponnurangam S, Ramamoorthy P, Standling D, Battafarano RJ, Anant S and Sharma P: Curcumin induces cell death in esophageal cancer cells through modulating notch signaling. PloS One *7*: e30590, 2012.
143 Collins BJ, Kleeberger W and Ball DW: Notch in lung development and lung cancer. Semin Cancer Biol *14*: 357-364, 2004.
144 Wang Z, Li Y, Banerjee S and Sarkar FH: Emerging role of Notch in stem cells and cancer. Cancer Lett *279*: 8-12, 2009.
145 Allenspach EJ, Maillard I, Aster JC and Pear WS: Notch signaling in cancer. Cancer Biol Ther *1*: 466-476, 2002.
146 Houde C, Li Y, Song L, Barton K, Zhang Q, Godwin J, Nand S, Toor A, Aikan S, Smadia NV, Avet-Loiseau H, Lima CS, Miele L and Coignet LJ: Overexpression of the Notch ligand JAG2 in malignant plasma cells from multiple myeloma patients and cell lines. Blood *104*: 3697-3704, 2004.
147 Wang Z, Ahmad A, Li Y, Azmi A, Miele L and Sarkar FH: Targeting Notch to eradicate pancreatic cancer stem cells for cancer therapy. Anticancer Res *31*: 1105-1113, 2011.
148 Phillips TM, Kim K, Vlashi E, McBride WH and Pajonk F: Effects of recombinant erythropoietin on breast cancer-initiating cells. Neoplasia *9*: 1122-1129, 2007.
149 Liu ZC, Yang ZX, ZhouJS, Zhang HT, Huang QK, Dang LL, Liu GX and Tao KS: Curcumin regulates hepatoma cell proliferation and apoptosis through the Notch signaling pathway. Int J Clin Exp Med *7*: 714-718, 2014.
150 Kong T, Wang Y, Xiao L and Liao L: Curcumin inhibits cell survival and migration by suppression of Notch-1 activity in prostate cancer cells. Int J Urol Nephrol *1*: 35-39, 2013.
151 Aziz MTA, Khaled HM, Hindawi AE, Roshdy NK, Rashed LA, Sabry D, Hassouna AA, Taha F and Ali WI: Effect of mesenchymal stem cells and a novel curcumin derivative on Notch-1 signaling in hepatoma cell line. BioMed Res Int *2013*: e129629, 2013.
152 Ingham PW and McMahon AP: Hedgehog signaling in animal development: Paradigms and principles. Genes Dev *15*: 3059-3087, 2001.
153 Hooper JE and Scott MP: Communicating with Hedgehogs. Nat Rev Mol Cell Biol *6*: 306-317, 2005.
154 McMahon AP, Ingham PW and Tabin CJ: Developmental roles and clinical significance of Hedgehog signaling. Curr Top Dev Biol *53*: 1-114, 2003.
155 Bhardwaj G, Murdoch B, Wu D, Baker DP, Williams KP, Chadwick K, Ling LE, Karanu FN and Bhatia M: Sonic hedgehog induces the proliferation of primitive human hematopietic cells *via* BMP regulation. Nature Immunol *2*: 172-180, 2001.
156 Ahn S and Joyner AL: *In vivo* analysis of quiescent adult neural stem cells responding to Sonic hedgehog. Nature *437*: 894-897, 2005.
157 Liu S, Dontu G, Mantle ID, Patel S, Ahn NS, Jackson KW, Suri P and Wicha MS: Hedgehog signaling and Bmi-1 regulate self-renewal of normal and malignant human mammary stem cells. Cancer Res *66*: 6063-6071, 2006.
158 Izrailit J and Reedijk M: Developmental pathways in breast cancer and breast tumor-initiating cells: Therapeutic inplications. Cancer Letters *317*: 115-126, 2012.
159 Zhao C, Chen A, Jamieson CH, Fereshteh M, Abrahamsson A, Blum J, Kwon HY, Kim J, Chute JP, Rizzieri D, Munchhof M, Van Arsdale T, Beachy PA and Reya T: Hedgehog signaling is essential for maintenance of cancer stem cells in myeloid leukemia. Nature *458*: 776-779, 2009.
160 Karamboulas C and Ailles L: Developmental signaling pathways in cancer stem cells of solid tumors. Biochim Biophys Acta *1830*: 2481-2495, 2013.
161 Takezaki T, Hide T, Takanaga H, Nakamura H, Kuratsu J and Kondo T: Essential role of the Hedgehog signaling pathway in human glioma-intiating cells. Cancer Sci *102*: 1306-1312, 2011.
162 Li SH, Fu J, Watkins DN, Srivastava RK and Shankar S: Sulforaphane regulates self-renewal of pancreatic cancer stem cells through the modulation of Sonic hedgehog-GLI pathway. Mol Cell Biochem *373*: 217-227, 2013.
163 Huang FT, Zhuan-Sun YX, Zhuang YY, Wei SL, Tang J, Chen WB and Zhang SN: Inhibition of hedgehog signaling depresses self-renewal of pancreatic cancer stem cells and reverses chemoresistance. Int J Oncol *41*: 1707-1714, 2012.

164 Tang SN, Fu J, Nall D, Rodova M, Shankar S and Srivastava RK: Inhibition of sonic hedgehog pathway and pluripotency maintaining factors regulate human pancreatic cancer stem cell characteristics. Int J Cancer *131*: 30-40, 2012.
165 Riobo NA, Saucy B, DiLizio C and Manning DR: Activation of heterotrimeric G proteins by Smoothened. PNAS *103*: 12607-12612, 2006.
166 Shen F, Cheng L, Douglas AE, Riobo NA and Mannig DR: Smoothened is a fully competent activator of the heterotrimeric G protein Gi. Mol Pharmacol *83*: 691-697, 2013.
167 Varjosalo M and Taipale J: Hedgehog: Functions and mechanisms. Genes Dev *22*: 2454-2472, 2008.
168 Sun XD and Liu XE: Curcumin induces apoptosis of pancreatic cancer cells by inhibiting Ras-ERK and Shh-Gli1 signal pathways. Chin J Pathophysiol *28*: 996-1000, 2012.
169 Sun XD, Liu XE and Huang DS: Curcumin reverses the epithelial-mesenchymal transition of pancreatic cancer cells by inhibiting the Hedgehog signaling pathway. Oncol Rep *29*: 2401-2407, 2013.
170 Elamin MH, Shinwari Z, Hendrayani SF, Al-Hindi H, Al-Shail E, Khafaga Y, Al-Kofide A and Aboussekhra A: Curcumin inhibits the Sonic Hedgehog signaling pathway and triggers apoptosis in medulloblastoma cells. Mol Carcinog *49*: 302-314, 2010.
171 Lim KJ, Bisht S, Bar EE, Maitra A and Eberhart CG: A polymeric nanoparticle formulation of curcumin inhibits growth, clonogenicity and stem-like fraction in malignant brain tumors. Cancer Biol Ther *11*: 464-473, 2011.
172 Slusarz A, Shenouda NS, Sakla MS, Drenkhahn SK, Narula AS, MacDonald RS, Besch-Williford CL and Lubahn DB: Common botanical compounds inhibit the Hedgehog signaling pathway in prostate cancer. Cancer Res *70*: 3382-3390, 2010.
173 Song G, Ouyang G and Bao S: The activation of Akt/PKB signaling pathway and cell survival. J Cell Mol Med *9*: 59-71, 2005.
174 Brunet A, Bonni A, Zigmond MJ, Lin MZ, Juo P, Hu LS, Anderson MJ, ArdenKC, Blenis J and Greenberg ME: Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor. Cell *96*: 857-868, 1999.
175 Berns K, Horlings HM, Hennessy BT, Madiredjo M, Hijmans EM, Beelen K, Linn SC, Gonzalez-Angulo AM, Stemke-Hale K, Hauptmann M, Beijersbergen RL, Mills GB, van de Vijver MJ and Bernards R: A functional genetic approach identifies the PI3K pathway as a major determinat of trastuzumab resistance in breast cancer. Cancer Cell *12*: 395-402, 2007.
176 Han Z, Hong L, Han Y, Wu K, Han S, Shen H, Li C, Yao L, Qiao T and Fan D: Phospho Akt mediates multidrug resistance resistance of gastric cancer cells through regulation of P-gp, Bcl-2 and Bax. J Exp Clin Cancer Res *26*: 261-268, 2007.
177 Shafee N, Smith CR, Wei S, Kim Y, Mills GB, Hortobagyi GN, Stanbridge EJ and Lee EY: Cancer stem cells contribute to cisplatin resistance in BRAC1/p53-mediated mouse mammary tumors. Cancer Res *68*: 3243-3250, 2008.
178 Frattini M, Saletti P, Romagnani E, Martin V, Molinari F, Ghisletta M, Camponovo A, Etienne LL, Cavalli F and Mazzucchelli L: PTEN loss of expression predicts cetuximab efficacy in metastatic colorectal cancer patients. Br J Cancer *97*: 1139-1145, 2007.
179 Chu EC and Tarnawski AS: PTEN regulatory functions in tumor suppression and cell biology. Med Sci Monit *10*: RA235-RA241, 2004.
180 Di Cristofano A, Pesce B, Cordon-Cardo C and Pandolfi PP: PTEN is essential for embryonic development and tumour suppression. Nat Genet *19*: 348-355, 1998.
181 Lee JO, Yang H, Georgescu MM, Di Cristofano A, Maehama T, Shi Y, Dixon JE, Pandolfi P and Pavletich NP: Crystal structure of the PTEN tumor suppressor: Implications for its phosphoinositide phosphatase activity and membrane association. Cell *99*: 323-334, 1999.
182 Napoli E, Ross-Inta C, Wong S, Hung C, Fujisawa Y, Sakaguchi D, Angelastro J, Omanska-Klusek A, Schoenfeld R and Giulivi C: Mitochondrial dysfunction in Pten haplo-insufficient mice with social deficits and repetitive behavior: Interplay between Pten and p53. PLoS ONE *7*: e42504, 2012.
183 Zhang J, Grindley JC, Yin T, Jayasinghe S, He XC, Ross JT, Haug JS, Rupp D, Porter-Westpfahl KS, Wiedemann LM, Wu H and Li L: PTEN maintains haematopoietic stem cells and acts in lineage choice and leukemia prevention. Nature *441*: 518-522, 2006.
184 Yilmaz OH, Valdez R, Theisen BK, Guo W, Ferguson DO, Wu H and Morrison SJ: PTEN dependence distinguishes haemotopoietic stem cells from leukemia-initiating cells. Nature *441*: 475-482, 2006.
185 Wang S, Garcia AJ, Wu M, Lawson DA, Witte ON and Wu H: PTEN deletion leads to the expression of a prostatic stem/progenitor cell subpopulation and tumor initiation. Proc Natl Acad Sci USA *103*: 1480-1485, 2006.
186 Chen Z, Trotman LC, Shaffer D, Lin HK, Dotan ZA, Niki M, Koutcher JA, Scher HI, Ludwig T, Gerald W, Cordon-Cardo C and Pandolfi PP: Crucial role of p53-dependent cellular senescence in suppression of Pten-deficient tumorigenesis. Nature *436*: 725-730, 2005.
187 Shu M, Misi H, Guiyan L, Xiong Z, Yu L and Li T: Curcumin suppresses proliferation and induces apoptosis in human medulloblastoma cell *via* P13K/AKT signaling pathway. J Third Mil Med Univ *35*: 518-522, 2013.
188 Chen CC, Sureshbabul M, Chen HW, Lin YS, Lee JY, Hong QS, Yang YC and Yu SL: Curcumin suppresses metastasis *via* Sp-1, FAK inhibition, and E-Cadherin upregulation in colorectal cancer. Evid Based Complement Alternat Med *2013*: 541695, 2013.
189 Yu S, Shen G, Khor TO, Kim JH and Kong AN: Curcumin inhibits Akt/mTOR signaling through protein phosphatase-dependent mechanism. Mol Cancer Ther *7*: 2609-2620, 2008.
190 Wang J, Wang Z, Wang H, Zhao J and Zhang Z: Curcumin induces apoptosis in EJ bladder cancer cells *via* modulating C-Myc and P13K/Akt signaling pathway. World J Oncol *2*: 113-122, 2011.
191 Hussain AR, Al-Rasheed M, Manogaran PS, Al-Hussain KA, Platanias LC, Al Kuraya K and Uddin S: Curcumin induces apoptosis *via* inhibition of P13-kinase/AKT pathway in acute T-cell leukemias. Apoptosis *11*: 245-254, 2006.
192 Wu J, Tang Q, Zhao S, Zheng F, Wu Y, Tang G and Hahn SS: Extracellular signal-related kinase signaling-mediated induction and interaction of FOXO3a and p53 contribute to the inhibition of nasopharyngeal carcinoma cell growth by curcumin. Int J Oncol *45*: 95-103, 2014.
193 Kunwar A, Bank A, Mishra B, Rathinasamy K, Pandey R and Priyadarsini KI: Qunatative cellular uptake, localization and cytoxicity of curcumin in normal and tumor cells. Biophysica Acta *1780*: 673-679, 2008.

194 Li L and Neaves WB: Normal stem cells and cancer cells: The niche matters. Cancer Res *66*: 4553-4557, 2006.

195 Fahey AJ, Robins RA and Constantinescu CS: Curcumin modulation of IFN-β and IL-12 signaling and cytokine induction in human T cells. J Cell Mol Med *11*: 1129-1137, 2007.

196 Gao X, Kuo J, Jiang H, Deeb D, Liu Y, Divine G, Chapman RA, Dulchavsky SA and Gautam SC: Immunomodulatory activity of curcumin: Suppression of lymphocyte proliferation, development of cell-mediated cytotoxity, and cytokine production *in vitro*. Biochem Pharmacol *68*: 51-61, 2004.

197 Bachmeier BE, Mohrenz IV, Mirisola V, Schleicher E, Romeo F, Hohneke C, Jochum M, Nerlich AG and Pfeffer U: Curcumin downregulates the inflammatory cytokines CXCL1 and -2 in breast cancer cells *via* NFkappaB. Carcinogenesis *29*: 779-789, 2008.

198 Xiaoling MU, Jing Z, Fang X and Liangdan T: Curcumin inhibits invasion and metastasis in the human ovarian cancer cells SKOV3 by CXCL12-CXCR4 axis. African J Biotechnol *9*: 8230-8234, 2010.

199 Shekhani MT, Jayanthy AS, Maddodi N and Setaluri V: Cancer stem cells and tumor transdifferentiation: Implications for novel therapeutic strategies. Am J Stem Cell *2*: 52-61, 2013.

200 Pham PV, Phan NLC, Nguyen NT, Truong NH, Duong TT, Le DV, Truong KD and Phan NK: Differentiation of breast cancer stem cells by knockdown of CD44: Promising differentiation therapy. J Transl Med doi.10.1186/1479-5876-9-269 2011.

201 Almanaa TN, Geusz ME and Jamasbi RJ: Effects of curcumin on stem-like cells in human esophageal squamous carcinoma cell lines. BMC Complementary and Alternative Medicine *12*: 195, 2012.

202 Gu Q, Cai Y, Huang C, Shi Q and Yang H: Curcumin increases rat mesenchymal stem cell osteoblast differentiation but inhibits adipocyte differentiation. Pharmacogn Mag *8*: 202-208, 2012.

203 Mujoo K, Nikonoff LE, Sharin VG, Bryan NS, Kots AY and Murad F: Curcumin induces differentiation of embryonic stem cells through possible modulation of nitric oxide-cyclic GMP pathway. Protein Cell *3*: 535-544, 2012.

204 Chen F, Wang X, Xiang X, Yuan J, Chu W, Xue X, Zhu H, Ge H, Zou M, Feng H and Lin J: Curcumin increased the differentiation rate of neurons in neural stem cells *via* Wnt singnaling *in vitro* study. J Surg Res doi:10.1016/j.jss.2014.06.026, 2014.

205 Buhrmann C, Mobasheri A, Matis U and Shakibaei M: Curcumin mediated suppression of nuclear factor-κB promotes chondrogenic differentiation of mesenchymal stem cells in a high-density co-culture microenvironment. Arthritis Res Ther *12*: R127, 2010.

206 Zhuang W, Long L, Zheng B, Ji W, Yang N, Zhang Q and Liang Z: Curcumin promotes differentiation of glioma-initiating cells by inducing autophagy. Cancer Science *103*: 684-690, 2012.

207 Roy S, Yu Y, Padhye SB, Sarkar FH and Majumdar APN: Difluorinated-curcumin (CDF) restores PTEN expression down-regulating miR-21. PLoS ONE 8:e68543, 2013.

208 Batth BK, Tripathi R and Srinivas UK: Curcumin-induced differentiation of mouse embryonal carcinoma PCC4 cells. Differentiation *68*: 133-140, 2001.

209 Watson JL, Greenshields A, Hill R, Hilchie A, Lee PW, Giacomantonio CA and Hoskin DW: Curcumin-induced apoptosis in ovarian carcinoma cells is p53-independent and involves p38 mitogen-activated protein kinase activation and downregulation of Bcl-2 and survivin expression and Akt signaling. Mol Carcinog *49*: 13-24, 2010.

210 Hua WF, Fu YS, Liao YJ, Xia WJ, Chen YC, Zeng YX, Kung HF and Xie D: Curcumin induces down-regulation of EZH2 expression through the MAPK pathway in MDA-MB-435 human breast cancer cells. Eur J Pharmacol *637*: 16-21, 2010.

211 Collett GP and Campbell FC: Curcumin induces c-jun N-terminal kinase-dependent apoptosis in HCT116 human colon cancer cells. Carcinogenesis *25*: 2183-2189, 2004.

212 Han X, Xu B, Beevers CS, Odaka Y, Chen L, Liu L, Luo Y, Zhou H, Chen W, Shen T and Huang S: Curcumin inhibits protein phosphatase 2A and 5, leading to activation of mitogen-activated protein kinases and death in tumor cells. Carcinogenesis *33*: 868-875,2012.

213 Yang CW, Chang CL, Lee HC, Chi CW, Pan JP and Yang WC: Curcumin induces the apoptosis of human monocytic leukemia THP-1 cells *via* the activation of JNK/ERK pathways. BMC Complementary and Alternative Medicine *12*: 22, 2012.

214 Zhang H, Yu T, Wen L, Wang H, Fei D and Jin C: Curcumin enhances the effectiveness of cisplatin by suppressing CD133+ cancer stem cells in laryngeal carcinoma treatment. Exp Ther Med *6*: 1317-1321, 2013.

215 Rao J, Xu DR, Zheng FM, Long ZJ, Huang SS, Wu X, Zhou WH, Huang RW and Liu Q: Curcumin reduces expression of Bcl-2, leading to apotosis in daunorubicin-insensitive CD34+ acute myeloid leukemia cell lines and primary sorted CD34+ acute myeloid leukemia cells. J Transl Med *9*: 71, 2011.

216 Liu TY, Tan ZJ, Jiang L, Gu JF, Wu XS, Cao Y, Li ML, Wu KJ and Liu YB: Curcumin induces apoptosis in gallbladder carcinoma cell line GBC-SD cells. Cancer Cell International *13*: 64, 2013.

217 Yallapu MM, Maher DM, Sundram V, Bell MC, Jaggi M and Chauhan SC: Curcumin induces chemo/radio-sensitization in ovarian cancer cells and curcumin nanoparticles inhibit ovarian cancer cell growth. J Ovarian Res *3*: 11, 2010.

218 Alexandrow MG, Song LJ, Altiok S, Gray J, Haura EB and Kumar NB: Curcumin: A novel Stat3 pathway inhibitor for chemoprevention of lung cancer. Eur J Cancer Prev *21*: 407-412, 2012.

219 Yang CL, Liu YY, Ma YG, Xue YX, Liu DG, Ren Y, Liu XB, Li Y and Li Z: Curcumin blocks small cell lung cancer cells migration, invasion, angiogenesis, cell cycle and neoplasia through janus kinase-STAT3 signaling pathway. PLoS ONE *7*: e37960, 2012.

220 Glienke W, Maute L, Milz E, Bauer N and Bergmann L: Curcumin inhibits constitutive STAT3 phosphorylation in human pancreatic cancer cell lines and down-regulates survivin/BIRC5 gene expression. J Clin Oncol *25*: 15030, 2007.

221 Mackenzie GG, Queisser N, Wolfson ML, Fraga CG, Adamo AM and Oteiza PI: Curcumin induces cell-arrest and apoptosis in association with the inhibition of constitutively active NF-κB and STAT3 pathways in Hodgkin's lymphoma cells. Int J Cancer *123*: 56-65, 2008.

222 Tiwari SK, Agarwal S, Seth B, Yadav A, Nair S, Bhatnagar P, Karmakar M, Kumari M, Chauhan LK, Patel DK, Srivastava V, Singh D, Gupta SK, Tripathi A, Chaturvedi RK and Gupta KC: Curcumin-loaded manoparticles potently induce adult neurogenesis and reverse cognitive deficits in Alzheimer's disease model *via* canonical Wnt/β-catenin pathway. ACS Nano *8*: 76-103, 2014.

223 Jaiswal AS, Marlow BP, Gupta N and Narayan S: β-catenin-mediated transactivation and cell-cell adhesion pathways are

important in curcumin (diferuylmethane)-induced growth arrest and apoptosis in colon cancer cells. Oncogene *21*: 8414-8427, 2002.

224 He M, Li Y, Zhang L, Li L, Shen Y, Lin L, Zheng W, Chen L, Bian X, Ng HK and Tang L: Curcumin suppresses cell proliferation through inhibition of the Wnt/β-catenin signaling pathway in medulloblastoma. Oncol Rep *32*: 173-180, 2014.

225 Gupta KK, Bharne SS, Rathinasamy K, Naik NR and Panda D: Dietary antioxidant curcumin inhibits microtubule assembly through tubulin binding. FEBS Journal *273*: 5320-5332, 2006.

226 Qi LL, Wang JB, Wang HZ, Luo YT and Wu TX: Curcumin induces cleavage of β-catenin by activation of caspases and downregulates the β-catenin/Tcf signaling pathway in HT-29 cells. African J Biotechnol *8*: 5527-5533, 2009.

227 Park CH, Hahm ER, Park S, Kim HK and Yang CH: The inhibitory mechanism of curcumin and its derivative against β-catenin/Tcf signaling. FEBS Letters *579*: 2965-2971, 2005.

228 Liu YL, Yang HP, Gong L, Tang CL and Wang HJ: Hypomethylation effects of curcumin, demethoxycurcumin and bisdemethoxycurcumin on WIF-1 promoter in non-small cell lung cancer cell lines. Mol Med Rep *4*: 675-679, 2011.

229 Mimeault M and Batra SK: Potential applications of curcumin and its novel synthetic analogs and nanotechnology-based formulations in cancer prevention and therapy. Chinese Med *6*: 31, 2011.

230 Liu D and Chen Z: The effect of curcumin on breast cancer cells. J Breast Cancer *16*: 133-137, 2013.

231 Kim SJ, Son TG, Park HR, Park M, Kim MS, Kim HS, Chung HY, Mattson MP and Lee J: Curcumin stimulates proliferation of embryonic neural progenitor cells and neurogenesis in the adult hippocampus. J Biol Chem *283*: 14497-14505, 2008.

232 Hsuuw YD, Chang CK, Chan WH and Yu JS: Curcumin prevents methylglyoxal-induced oxidative stress and apoptosis in mouse embryonic stem cells and blastocysts. J Cell Physiol *205*: 379-386, 2005.

233 Mujoo K, Nikonoff LE, Sharin VG, Bryan NS, Kots AY and Murad F: Curcumin induces differentiation of embryonic stem cells through possible modulation of nitric oxide-cyclic GMP pathway. Protein Cell *3*: 535-544, 2012.

234 Goel A, Boland CR and Chauhan DP: Specific inhibition of cyclooxygenase-2 (COX-2) expression by dietary curcumin in HT-29 human colon cancer cells. Cancer Lett *172*: 111-118, 2001.

235 Khan MA, Gahlot S and Majumdar S: Oxidative stress induced by curcumin promotes the death of cutaneous T-cell lymphoma (HuT-78) by disrupting the function of several molecular targets. Mol Cancer Ther *11*: 1873, 2012.

236 Anto RJ, Mukhopadhyay A, Denning K and Aggarwal BB: Curcumin (diferuloylmethane) induces apoptosis through activation of caspase-8, BID cleavage and cytochrome c release: Its suppression by ectopic expression of Bcl-2 and Bcl-xl. Carcinogenesis *23*: 143-150, 2002.

237 Kim HI, Huang H, Cheepala S, Huang S and Chung J: Curcumin inhibition of integrin (alpha6beta4)-dependent breast cancer cell motility and invasion. Cancer Prev Res (Phila) *1*: 385-391, 2008.

238 Chen A and Xu J: Activation of PPAR{gamma} by curcumin inhibits Moser cell growth and mediates suppression of gene expression of cyclin D1 and EGFR. Am J Physiol Gastrointest Liver Physiol *288*: G447-G456, 2005.

239 Bharti AC, Donato N, Singh S and Aggarwal BB: Curcumin (diferuloylmethane) down-regulates the constitutive activation of nuclear factor-kappa B and IkappaBalpha kinase in human multiple myeloma cells, leading to suppression of proliferation and induction of apoptosis. Blood *101*: 1053-1062, 2003.

240 Wu SY, Lee YR, Huang CC, Li YZ, Chang YS, Yang CY, Wu JD and Liu YW: Curcumin-induced heme oxygenase-1 expression plays a negative role for its anti-cancer effect in bladder cancers. Food Chem Toxicol *50*: 3530-3536, 2012.

241 Saini S, Arora S, Majid S, Shahryari V, Chen Y, Deng G, Yamamura S, Ueno K and Dahiya R: Curcumin modulates micrRNA-203 mediated regulation of the Src-Akt axis in bladder cancer. Cancer Prev Res (Phila) *4*: 1698-1709, 2011.

242 Yu CC, Tsai LL, Wang ML, Yu CH, Lo WL, Chang YC, Chiou GY, Chou MY and Chiou SH: miR145 targets the SOX9/ADAM17 axis to inhibit tumor-initiating cells and IL-6-mediated paracrine effects in head and neck cancer. Cancer Res *73*: 3425-3440, 2013.

243 Lin L, Liu Y, Li H, Fuchs J, Shibata H, Iwabuchi Y and Lin J: Targeting colon cancer stem cells using a new curcumin analogue, GO-YO30. Br J Cancer *105*: 212-220, 2011.

244 Yu Y, Kanwar SS, Patel BB, Nautiyal J, Sarkar FH and Majumdar AP: Elimination of colon cancer stem-like cells by the combination of curcumin and FOLFOX. Transl Oncol *4*: 32-328, 2009.

245 Charpentier MS, Whipple RA, Vitolo MI, Boggs AE, Slovic J, Thompson KN, Bhandary L and Martin SS: Curcumin targets breast cancer stem-like cells with microtentacles that persist in mammospheres and promote reattachment. Cancer Res *74*: 1250, 2013.

246 Bao B, Ali S, Kong D, Sarkar SH, Wang Z, Banerjee S, Aboukameel A, Padhye S, Philip PA and Sarkar FH: Anti-tumor activity of a novel compound-CDF is mediated by regulating miR-21, miR-200, and PTEN in pancreatic cancer. PLoS ONE *6*: e17850, 2011.

247 Chen CQ, Yu K, Yan QX, Xing CY, Chen Y, Yan Z, Shi YF, Zhao KW and Gao SM: Pure curcumin increases the expression of SOCS1 and SOCS3 in myeloproliferative neoplasms through suppressing class I histone deacetylases. Carcinogenesis *34*: 1442-1449, 2013.

248 Kang SK, Cha SH and Jeon HG: Curcumin-induced histone hypoacetylation enhances caspase-3-dependent glioma cell death and neurogenesis of neural progenitor cells. Stem Cells Dev *15*: 165-174, 2006.

249 Gao Z, Ure K, Ding P, Nashaat M, Yuan L, Ma J, Hammer RE and Hsieh J: The master negative regulator REST/NRSF controls adult neurogenesis by restraing the neurogenic program in quiescent stem cells. J Neurosci *31*: 9772-9786, 2011.

250 Chang KW, Hung PS, Lin IY, Hou CP, Chen LK, Tsai YM and Lin SC: Curcumin up-regulates insulin-like growth factor binding protein-5 (IGFBP-5) and C/EBPα during oral cancer suppression. Int J Cancer *127*: 9-20, 2010.

251 Bae YH, Ryu JH, Park HJ, Kim KR, Wee HJ, Lee OH, Jang HO, Bae MK, Kim KW and Bae SK: Mutant p53-Notch signaling axis in involved in curcumin-induced apoptosis of breast cancer cells. Korean J Physiol Pharmacol *17*: 291-297, 2013.

252 Song MY, Yim JY, Yim JM, Kang IJ, Rho HW, Kim HS, Yhim HY, Lee NR, Song EK, Kwak JY, Sohn MH and Yim CY: Use of curcumin to decrease nitric oxide production during the induction of antitumor responses by IL-2. J Immunother *34*: 149-164, 2011.

253 Chearwae W, Shukla S, Limtrakul P and Ambudkar SV: Modulation of the function of the multidrug resistance-linked ATP-binding cassette transporter ABCG2 by the cancer chemopreventive agent curcumin. Mol Cancer Ther *5*: 1995-2006, 2006.

254 Chearwae W, Wu CP, Chu HY, Lee TR, Ambudkar SV and Limtrakul P: Curcuminoids purified from turmeric powder modulate the function of human multidrug resistance protein 1 (ABCC1). Cancer Chemother Pharmacol *57*: 376-388, 2006.

255 Yanes O, Clark J, Wong DM, Patti GJ, Sanchez-Ruiz A, Benton HP, Trauger SA, Desponts C, Ding S and Siuzdak G: Metabolic oxidation regulates embryonic stem cell differentiation. Nature Chem Biol *6*: 411, 2010.

256 Das L and Vineyak M: Curcumin attenuates carcinogenesis by down regulating proinflammatory cytokine interleukin-1 (IL-1αand IL-1β) *via* modulation of AP-1 and NF-IL6 in lymphoma bearing mice. Int Immunopharmacol *20*: 141-147, 2014.

257 Herman JG, Stadelman HL and Roselli CE: Curcumin blocks CCL2-induced adhesion, motility and invasion, in part, through down-regulation of CCL2 expression and proteolytic activity. Int J Oncol *34*: 1319-1327, 2009.

258 Xu YX, Pindolia KR, Janakiraman N, Noth CJ, Chapman RA and Gautam SC: Curcumin, a compound with anti-inflammatory and anti-oxidant properties, down regulates chemokine expression in bone marrow stromal cells. Exp Hematol *25*: 413-422, 1997.

259 Ahmed MM, Khan A and Rainsford KD: Synthesis of thiophene and NO-curcuminoids for anti-inflammatory and anti-cancer activities. Molecules *18*: 1483-1501, 2013.

260 Tahmasebi Mirgani M, Isacchi B, Sadeghizadeh M, Marra F, Bilia AR, Mowla SJ, Najafi F and Babaei E: Dendrosomal curcumin nanoformulation downregulates pluripotency genes *via* miR-145 activation in U87MG glioblastoma cells. Int J Nanomedicine *9*: 403-417, 2014.

261 Chang YC, Chang WC, Hung KH, Yang DM, Cheng YH, Liao YW, Woung LC, Tsai CY, Hsu CC, Lin TC, Liu JH, Chiou SH, Peng CH and Chen SH: The generation of induced pluripotent stem cells for macular degeneration as a drug screening platform: Identification of curcumin as a protective agent for retinal pigment epithelial cells against oxidative stress. Front Aging Neurosci doi:10.3389/fnagi.2014.00191, 2014.

262 Utpadel D, Goldbrunner R, Lange M, Shan B, Schaaf C, Curic S, Onofri C, Stalla GK and Renner U: Studies on the role of platelet-derived growth factor (PDGF) in human meningiomas. Exp Clin Endocrinol Diabetes *116*: N22, 2008.

263 Aravindan S, Natarajan M, Herman TS, Awasthi V and Aravindan N: Molecular basis of 'hypoxic' breast cancer cell radio-sensitization: Phytochemicals converge on radiation induced Rel signaling. Rad Oncol *8*: 46, 2013.

264 Aziza SAH, Abdel-Aal SA and Mady HA: Chemopreventive effect of curcumin on oxidative stress, antioxidant status, DNA fragmentation and caspase-9 gene expression in 1,2-dimethylhydrazine-induced colon cancer in rats. American J Biochem Mol Biol *4*: 22-34, 2014.

265 Gu QL, Cai Y, Huang C and Yang HL: Effect of curcumin on osteogenic differentiation of rat bone marrow mesenchymal stem cells. Chinese J Tissue Eng Res *16*: 5057-5061, 2012.

266 Wang Z, Zhang Y, Banerjee S, Li Y and Sarkar FH: Notch-1 down-regulation by curcumin is associated with the inhibition of cell growth and the induction of apoptosis in pancreatic cancer cells. Cancer *106*: 2503-2513, 2006.

267 Moos PJ, Edes K, Mullaly JE and Fitzpatrick FA: Curcumin impairs tumor suppressor p53 function in colon cancer cells. Carcinogenesis *25*: 1611-1617, 2004.

268 Han SS, Chung ST, Robertson DA, Ranjan D and Bondada S: Curcumin causes the growth arrest and apoptosis of B cell lymphoma by downregulation of egr-1, c-myc, bcl-XL, NF-kappa B, and p53. Clin Immunol *93*: 152-161, 1999.

269 Fan S, Xu Y, Li X, Tie L, Pan Y and Li X: Opposite angiogenic outcome of curcumin against ischemia and Lewis lung cancer models : in silico, *in vitro* and *in vivo* studies. Biochimica *et Biophysica Acta 1842*: 1742-1754, 2014.

270 Hua WM, Liang ZQ, Fang Y, Gu ZL and Guo CY: Mechanisms of curcumin protecting endothelial cells against ischemia and reperfusion injury. Chinese Pharmacol Bull *8*: 13,2009.

271 Han J, Pan XY, Xu Y, Xiao Y, An Y, Tie L, Pan Y and Li XJ: Curcumin induces autophagy to protect vascular endothelial cell survival from oxidative stress damage. Autophagy *8*: 812-825, 2012.

272 Xu Y, Ku B, Cui L, Li X, Barish PA, Foster TC and Ogle WO: Curcumin reverses impaired hippocampal neurogenesis and increases seratonin receptor 1A mRNA and brain-derived neurotrophic factor expression in chronically stressed rats. Brain Res *1162*: 9-18, 2007.

273 Wang YD, Hu Y and Sun CY: Inhibitory effect of curcumin on angiogenesis induced by brain derived neurotrophic factor from multiple myeloma cells. Zhongguo Shi Yan Xue Ye Xue Za Zhi *14*: 70-74, 2006.

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