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Anticancer effect of curcumin on breast cancer and stem cells

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ABSTRACT

Numerous studies have shown that curcumin, a natural compound, exerts anticancer effects by inhibiting cancer cell proliferation and metastasis and by inducing cell cycle arrest and apoptosis. In particular, curcumin exhibits potent inhibitory effects on breast cancer, the most prevalent type of cancer among women worldwide. It has low maximal inhibitory concentration for breast cancer cell lines that express the hormone receptor ER and sensitizes cell lines to anticancer drugs. Moreover, it can induce apoptosis in cell lines independently of hormone receptor expression. In addition, curcumin inhibits the proliferation of breast cancer stem cells (BCSC), an important factor that influences cancer recurrence. The inhibition of BCSC proliferation suppresses metastasis and reattachment, ultimately limiting tumor formation. A xenograft study similarly showed that curcumin exerts tumor-suppression effects on cancer cells and cancer stem cells. Therefore, curcumin is a potential anticancer compound, and its concurrent application with other anticancer drugs appears promising.

1. General introduction to curcumin

Curcumin is a yellow pigment derived from turmeric. Over the past few years, numerous studies have demonstrated that curcumin exerts several anticancer effects in various types of cancers by suppressing cell proliferation and metastasis and inducing cell death. Curcumin also exhibits protective effects against cancer formation. Some targets related to the effects of curucmin are presented in Fig. 1.

The antiproliferative effect of curcumin could be attributed to its ability to regulate protein kinases, the cell cycle, and transcription factors, including NF-κB. In a melanoma cell line, curcumin exhibited a potent antiproliferation effect by inhibiting the binding activity of NF-KB [1]. Curcumin exerted similar effects on AP-1, EGR, and B-catenin [2–7].

Despite the many advances in cancer research over the past few years, the problem of cancer metastasis still requires further understanding. Curcumin modulates several signaling pathways through yet-unknown mechanisms to inhibit metastasis. The NF-κB signaling pathway is an important curcumin-regulated pathway [8–10].

The cell cycle is divided into four stages: G1, S, G2, and M. Many regulators are involved in the transition of one stage to the next [11]. Cyclin B1, a factor that participates in the cell cycle, is overexpressed in tumors. Cells require cyclin B1 to transition from the G2 phase to the M phase. The mRNA and protein levels of cyclin B1 decreased after 24 h of treatment with curcumin. A flow cytometry study showed that small-cell lung cancer (SCLC) cells were arrested by curcumin treatment [12]. Cyclin-dependent kinase2 (CDK2) is another regulator that is affected by curcumin. Curcumin inhibited CDK2 activity *in vitro* and decreased the proliferation rate of colon cancer cells in a dose-dependent manner. Higher percentages of sh-CDK2-transfected cells of the colon cancer cell line HCT116 were arrested in the G1 phase than control cells [13].

The extent of anticancer effects and apoptosis induction is a crucial research topic. Apoptosis occurs through intrinsic or mitochondrial pathways. Changes in membrane potential and protein release are important events in apoptosis irrespective of the pathway. Curcumin could activate apoptotic pathways by interacting with reactive oxygen species (ROS) [14,15]. For example, curcumin increased the ROS and superoxide radicals (SOR) levels of human lung adenocarcinoma epithelial cells. Curcumin could induce the

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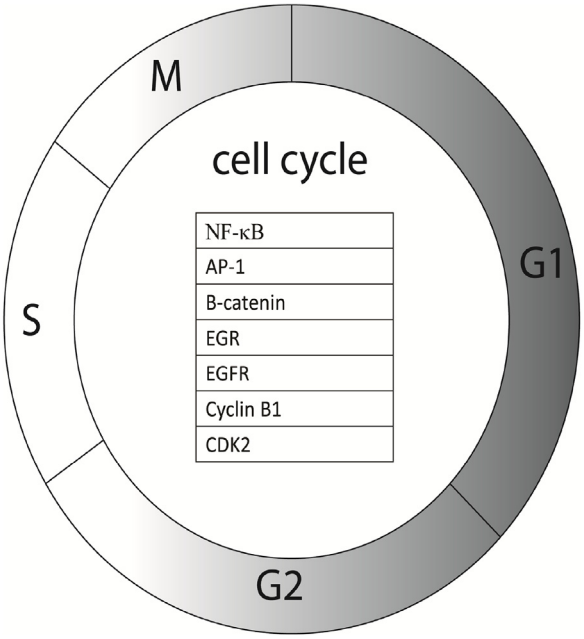

Fig. 1. Curcumin down regulate target in cellular proliferation.

formation of ROS, which activate apoptotic pathways in cancer cells [16]. Curcumin could also increase the intracellular levels of calcium, which participate in apoptosis induction by inducing changes in cell membrane poetical [17–19].

Curcumin also affects telomerase. Cancer cells can regain the ability to prolong their telomeres [20]. Curcumin inhibited telomerase activity in human leukemia cells [21,22] and brain tumor cells [23] in a dose-dependent and time-dependent manner.

However, the use of curcumin as an anticancer therapy remains limited given the poor water solubility and poor absorption of this compound. The most effective solvent for curcumin is DMSO, a cell-toxic solution. Several researchers have attempted to synthesize compounds that are similar to curcumin but with higher dissolution rates in water or other suitable solutions or to fabricate pills that prolong the retention of curcumin in the bioenvironment.

2. General information on breast cancer

Breast cancer is the second most prevalent cancer worldwide and causes high numbers of deaths among women every year [24]. Generally, breast cancer could be classified into several groups in accordance with biomarker expression. These markers include Her2, ER, and PR. Although patients may also be classified on the basis of tumor location and metastatic stage, patients are generally categorized on the basis of the expression levels of these three hormone receptors as Her2 positive, ER and PR strong positive (luminal A), ER and PR weak positive (luminal B), and triple negative [25].

Patients with luminal A breast cancer have high cure rates. This patient group accounts for more than 40% but less than half of breast cancer cases. Luminal A breast cancer responds poorly to chemotherapy but responds well to hormone therapy. Hormone therapy shows a powerful anticancer effect and drastically inhibits tumor growth upon initiation in this patient group. Patients with luminal A breast cancer have high 5-year survival rates.

Patients with luminal B breast cancer constitute the second-largest group of breast cancer patients and account for approximately 20% of breast cancer cases. Hormone therapy can still inhibit tumor growth in patients with Luminal B breast cancer. However, some subgroups of luminal B breast cancer may be more intractable than luminal A breast cancer. These subgroups are identified on the basis of the numbers and sites of gene mutations. Luminal B breast cancer has good therapeutic response to chemotherapy, which is provided as the conventional treatment for this subtype. The response of luminal B breast cancer to hormone therapy is similar to that of luminal A breast cancer. However, hormone therapy for the treatment of luminal B breast cancer requires additional control than that for the treatment of luminal A breast cancer given the higher variation in gene expression in the former cancer subtype. Luminal B cases also include Her2-positive cases. These cases were once considered as difficult-to-control subtypes but are now considered as the easiest to manage given the availability of two potent treatment approaches—hormone therapy and Her2 target therapy.

The Her2-positive subtype was once considered as the most intractable breast cancer subtype. It accounts for approximately 15% of all breast cancer cases. Her2-positive patients have strongly positive Her2 expression. Some of these patients may be classified as luminal A or B rather than Her2-positive. Her2 expression promotes cell growth, even in normal cells under normal conditions. Her2-positive cells overexpress Her2 and proliferate faster than Her2-negative cells. The Her2-positive group must have at least three positive responses in the IHC or FISH assay. Rapid proliferation increases the aggressiveness of tumor cells and promotes their metastasis to other organs. These effects, in turn, complicate cancer treatment and increase death rates. Fortunately, the anti-Her2 drug, (Transtuzumab) herceptin, has been developed. This drug inhibits the Her2 signaling pathway, which promotes tumor proliferation and growth, by directly working on Her2 receptor. Since the development of herceptin, the Her2-positive breast cancer subtype is not longer difficult to cure.

The triple-negative cancer subtype is unaffected by hormone therapy given its lack of hormone response. Thus, this cancer subtype could only be treated through chemotherapy. Triple-negative breast cancer, however, will develop chemoresistance after several rounds of treatment. This response hinders tumor control. Triple-negative breast cancer is the most intractable breast cancer type and is thus studied frequently. The above information are summarized in Table1.

Breast cancer is classified into five stages. The first stage is Stage 0. In this stage, the carcinoma remains in situ, and tumor cells remain only in breast tissue. Stage I is characterized by the presence of an infiltrating carcinoma, which has a size less of than 2 cm, and the absence of lymph invasion. Stage I progresses to Stage II if lymph invasion occurs and the tumor size ranges from 2 cm to 5 cm. Stage III is characterized by tumor sizes of more than 5 cm and lymph invasion. Stage IV is the most serious stage, wherein cancer cells have already migrated from the breast tissue into other organs, such as the bones, lungs, liver or even the brain. The overall survival rate decreases with stage: Stage I is associated with more than 95% survival rate, Stage III with approximately 70%, and Stage IV but with approximately 25%.

3. Effect of curcumin on breast cancer

Curcumin has anticancer effects. Her2-positive cell lines, such as SKBR3 and BT474, have a lower maximal inhibitory concentration (IC50) for curcumin than triple-negative cell lines. The decrease in IC50 may be related to the expression of ER rather than that of Her2. SKBR3 and MBA-MB-231, two ER-negative cell lines, have a lower IC50 for curcumin than BT474 and MCF7, which are both ER-positive cell lines [26,27]. Curcumin could induce apoptosis in most, but not all, breast cancer cell lines by inducing changes in cell membrane potential [28]. The mitochondrial-dependent apoptotic pathway induced by curcumin releases cytochrome C and upregulates caspase-9 and caspase-3 expression. Then, PARP causes DNA

Table 1
Perou 4 intrinsic subtype and their clinical therapy of breast cancer.

	Her2	PR	ER	percentage	Hormone therapy	Chemotherapy	Target therapy
Luminal A	–	Strong+	strong+	50–60%	Good response(major treatment)	Good response	Usually not use
Luminal B	±	Weak+	Weak+	20%	Good response(effect various)	Good response (effect various)	Usually not use
Her2 positive	+	–	–	15–20%	bad response	Good response	Good response(major treatment)
Triple negative	–	–	–	5%	No effect	Good response (easy resistance)	Usually not use

fragmentation and apoptosis. The upregulation of Bad and Bax expression or the downregulation of Bcl-2 and Bcl-XL expression may also participate in curcumin-induced apoptotic pathways in breast cancer cell lines [11]. The activation of these apoptosis pathways is independent of hormone receptor expression, and the response of triple-negative cell lines is not significantly different from that of cell lines that express ER, PR, or Her2 [29,30].

4. Effect of curcumin on breast cancer stem cells

Cancer stem cells are one of the major causes of cancer recurrence and treatment failure. Although most cancer cells are killed by anticancer therapies, the anticancer effect of these treatments will decrease or even disappear after several rounds. These results indicate that cancer stem cells confer drug resistance to cancer cells. Thus, the identification and development of approaches that can effectively kill all kinds of cancer cells, especially cancer stem cells, have become crucial research topics. Curcumin treatment decreases the IC50 of cancer therapy drugs and the number of stem cells simultaneously. Zhou et al. treated the breast cancer cell lines MBA-MB-231 and MCF-7 with paclitaxel, cisplatin, or doxorubicin alone or combined with curcumin or other natural compounds. Chemotherapy drugs decreased the survival rates and curcucmin decreased the IC50 of the experimental cell lines. The paclitaxel IC50 of MBA-MB-231cells cotreated with cucurmin decreased from 20 nmol/L to 10 nmol/L and that of MCF-7 decreased from 10 nmol/L to 7.5 nmol/L. The results for cisplatin and doxorubicin were similar to those for paclitaxel. The IC50 decreased by 50% under curcumin cotreatment relative to that under single drug treatment. The cisplatin IC50 of the MBA-MB-231 and MCF-7 cell lines decreased from 60 μmol/L to 40 μmol/L and from 40 μmol/L to 20 μmol/L, respectively. Similarly, the doxorubicin IC50 of the MBA-MB-231 and MCF-7 cell lines decreased from 15 μmol/L to 7.5 μmol/L and 5 μmol/L to 3 μmol/L, respectively. In addition, curcumin could enhance the efficacy of the chemotherapy drug Mitomycin C (MMC). The drug sensitivity of cancer stem cells harvested from MBA-MB-231 and MCF-7 cell lines increased by 15- and 5-fold, respectively, upon curcumin treatment [31]. Breast cancer stem cells (BCSCs) under the combined treatment of curcumin and MMC proliferate only until the fourth generation. A mammosphere formatting assay showed that treatment with MMC or curcumin alone rarely reduced the stem cell population. By contrast, the combined treatment of MMC and curcumin could decrease the population size of treated stem cells to less than 25% of the untreated population [32]. The potent effect of the combined treatment of curucmin and MMC has also been observed in MDA-MB-231 BCSC xenografts. A mouse model experiment showed that although curucmin or MMC treatment alone inhibited tumor growth, combined treatment with curcumin and MMC decreased tumor size more significantly than single treatments with curcumin or MMC. Moreover, curcumin may reverse the resistance of BCSCs to MMC. Thus, curucmin could improve the therapeutic effect of current breast cancer therapies by sensitizing breast cancer cells and may provide a novel approach for cancer therapy [31].

Zhou et al. confirmed that curcumin reduces chemoresistance while increasing the chemosensitivity of tumor cells. The regulation of Bcl-2-mediated apoptosis, which involves the PI3K and Wnt signaling pathways, may underlie these effects. The overexpression of Bcl-2 protein is an important factor for the development of chemoresistance. By interacting with other apoptosis-related proteins, Bcl-2 inhibits the tumor-suppressive effects of drugs and promotes drug resistance. Curcumin causes imbalances in the formation of the Bcl/Bax complex, thus increasing apoptosis rate by increasing the MMC sensitivity of tumor cells. MMC attenuates the renewal ability of BCSCs derived from the MCF-7 and MBA-MB-231 cell lines. This effect could be enhanced by curcumin, ultimately causing BCSCs to lose their proliferative ability by the fifth generation. The combined treatment of curcumin and MMC downregulates the expression of the antiapoptotic protein Bcl-2 while upregulating that of the proapoptotic proteins Bax, Bak, Bad, Bik, and Bim. The apoptosis signaling pathway is activated in BCSCs through the activation of caspase-3 and caspase-9 [32].

Curcumin inhibits the migratory ability of BSCS by amplifying the E-cadherin/β-catenin negative feedback loop. The nuclear translocation of β-catenin is related to the migration of cancer stem cells. The rates of E-cadferin/β-catenin complex formation and β-catenin membrane retention would decrease under high translocation rates. By contrast, the expression of target genes that promote epithelial–mesenchymal transition would be upregulated and ultimately cause the migration of BSCS. Curucmin could inhibit the nuclear translocation of β-catenin, as well as activate Slug and restore E-cadherin expression. These effects eventually increase the formation of E-cadherin/β-catenin complexes and the cytosolic retention of β-catenin cytosolic retention, thus ultimately inhibiting the migration of BCSCs [33].

Curcumin inhibits the reattachment of BCSCs. Microtentacles (McTNs), which are protrusions that comprise plasma membrane tubulin, are necessary for reattachment. High levels of McTN expression reflect the increased efficiency of detached or suspended cells to attach to distant tissues and thus indicate that metastatic efficiency is promoted. Curcumin could rapidly extinguish McTN in BCSCs, hindering the reattachment of suspended BCSCs to the target surface [34]. Finally, curcumin could inhibit tumor formation by BCSCs that have successfully migrated from breast tissues and that have reattached to other organs, such as the bones, lungs, or liver. Chen et al. encapsulated curcumin in phosphorylated calixarene POCA4C6, which could carry and release drugs in accordance with the change in environmental pH. POCA4C6-encapsulated curcumin inhibited the proliferation, invasion, migration, and tumor formation of the breast cancer cell line BT-549. Curcumin efficiently inhibited the proliferation of tumor xenografts without any obvious toxicity. Moreover, curcumin decreased the CD44+/CD133+ level of breast cancer stem cells. This effect indicated that curcumin could inhibit the expression of BSCS markers in vivo [35]. The results of these experiments indicate that curcumin could inhibit breast cancer cells and BCSCs. Moreover, curcumin could exert its anticancer effect alone or in combination with other cancer drugs and is thus a potential novel therapy for breast cancer.

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