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REVIEW

Chemopreventive potential of curcumin in prostate cancer

Marie-Hélène Teiten · François Gaascht · Serge Eifes · Mario Dicato · Marc Diederich

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Abstract The long latency and high incidence of prostate carcinogenesis provides the opportunity to intervene with chemoprevention in order to prevent or eradicate prostate malignancies. We present here an overview of the chemopreventive potential of curcumin (diferuloylmethane), a well-known natural compound that exhibits therapeutic promise for prostate cancer. In fact, it interferes with prostate cancer proliferation and metastasis development through the down-regulation of androgen receptor and epidermal growth factor receptor, but also through the induction of cell cycle arrest. It regulates the inflammatory response through the inhibition of pro-inflammatory mediators and the NF-κB signaling pathway. These results are consistent with this compound's ability to up-induce pro-apoptotic proteins and to down-regulate the anti-apoptotic counterparts. Alone or in combination with TRAIL-mediated immunotherapy or radiotherapy, curcumin is also reported to be a good inducer of prostate cancer cell death by apoptosis. Curcumin appears thus as a non-toxic alternative for prostate cancer prevention, treatment or co-treatment.

Keywords Curcumin · Prostate cancer · Androgen receptor · Inflammation · Apoptosis

Introduction

Prostate diseases are among the most common malignancies in men in the Western world and prostate cancer is the third cause of death from cancer in men. There is a huge difference in the rate of incidence of prostate cancer between Western (120 per 100,000 in Northern America) and East Asian countries (less than 10 per 100,000 in Asia) [82]. Moreover, when Asian people migrate to Western countries, their rate of prostate cancer incidence increases. This supports the idea that lifestyle, aspects of the diet and environmental factors as well as genetic factors promote prostate cancer development [49, 84, 116]. Current therapies (radical prostatectomy, chemotherapy, local radiotherapy, or hormonotherapy), although successful to treat localized, androgen-dependent, prostate cancer are of limited efficacy against androgen-independent, metastatic disease [42]. Novel treatment modalities are therefore needed to treat hormone-resistant tumors and to prevent progression of hormone-sensitive prostate cancer to the hormone-refractory stage. Primary prevention appears as an attractive strategy to eradicate prostate cancer if one considers the high prevalence of prostate cancer and the slow progressive development of healthy prostatic epithelium to dysplasia, prostatic intraepithelial neoplasia (PIN), locally invasive adenocarcinoma and finally, metastatic disease [16, 68].

Chemoprevention with dietary phytochemicals

Chemoprevention is a prophylactic method using non-toxic natural or synthetic compounds that reverse, inhibit, or prevent the development of cancer by inhibiting specific molecular steps in the carcinogenic pathway. The goal of chemoprevention consists in the decrease of cancer incidence, by reducing simultaneously both treatment-related side effects and mortality. Most of these natural substances are present in food, notably in fruits and vegetables. These

M.-H. Teiten · F. Gaascht · S. Eifes · M. Dicato · M. Diederich (✉)
Laboratoire de Biologie Moléculaire et Cellulaire du Cancer, Hôpital Kirchberg, 9 rue Edward Steichen, 2540 Luxembourg, Luxembourg
e-mail: marc.diederich@lbmcc.lu

chemopreventive agents regulate cell proliferation, cell survival or cell death as well as angiogenesis, and development of metastasis [33, 99, 107].

Curcumin

Curcumin or diferuloylmethane, a polyphenolic molecule extracted from the rhizome of the plant *Curcuma longa*, is a promising chemopreventive compound. This natural compound is a yellow spice used as curry ingredient and is used since centuries in Ayurvedic, Chinese, and Hindu medicine systems as a potent anti-inflammatory agent. It is under investigation since several years for its major mechanisms of action and functions [3, 48, 51]. The reported studies revealed that curcumin possesses anti-oxidant [11, 56, 86], anti-inflammatory [71, 109], anti-proliferative [40, 85], and anti-angiogenic [13, 117] properties against several cancer cell types [3, 62] and also demonstrates anti-microbial activities [24, 26]. Nowadays, curcumin is under clinical trials mainly for cancer and related diseases (Tables 1, 2) [34, 59]. Interestingly, phase I clinical trials already demonstrated the safety of curcumin even at high doses (12 g/day); the clinical advancement of this promising natural compound is hampered by its poor water solubility and short biological half-life, resulting in low bioavailability in both plasma and tissues [5]. In fact, after oral administration of free curcumin (up to 12 g/day), only nanomolar concentrations of curcumin or corresponding metabolites were found in patient serum [23, 45]. A more recent phase II clinical study has pointed out that these low concentrations of curcumin were able to reach a similar biological impact on NF-κB, COX-2 and phosphoSTAT-3 in peripheral blood mononuclear cells derived from treated patients than the ones observed in vitro with 5–50 μM of curcumin [34, 65]. The poor bioavailability of curcumin as well as its high hydrophobicity should be overcome for future clinical applications and i.v. administration of curcumin.

Curcumin safety and bioavailability

The potential safety of curcumin was initially demonstrated in animal models [93] and was confirmed by pharmacokinetic studies carried out in healthy human volunteers [63]. These studies revealed a high tolerance to curcumin (0.5–12 g) administrated orally with only few side effects (nausea, diarrhea). No free curcumin was found in the plasma of patients but glucuronide and sulfate conjugates could be detected [115]. Phase I clinical trials conducted in high-risk patients with pre-malignant or malignant lesions also presented curcumin as a safe and well-tolerated molecule even at high doses during several months [21, 23, 94, 95].

Albeit its high safety, the clinical advancement of curcumin has been hindered by its low solubility and its low bioavailability after oral administration (only 51.2 ng/ml in human serum after 12 g administrated orally) [5]. The low solubility (11 ng/ml in aqueous buffer pH 5.0) [113] is responsible for the poor absorption of curcumin by the human digestive tract. The low bioavailability of curcumin seems to be linked to its poor absorption, rapid metabolism, and rapid systemic elimination from the organism. In fact, the intestinal tractus is equipped with specific enzymes (UDP-glucuronosyltransferase, sulfotransferase, alcohol deshydrogenase, and p450) able to convert curcumin in relative inactive substances [57]. In order to overcome these limitations, several approaches have been tested. They include the combination of curcumin with adjuvants (e.g. piperine), and the development of delivery vehicles consisting of liposomes, nanoparticles, and phospholipid formulations of curcumin.

Curcumin analogs and structure-related activity

The comparison of curcumin with its naturally occurring analogs, corresponding to its demethoxy derivatives (demethoxycurcumin, bisdemethoxycurcumin) and to its active hydrogenated metabolites (tetrahydrocurcumin,

Table 1 Completed clinical trials with curcumin in patients affected by cancer

Subjects	Cancer type	Dose	References
10 volunteers	Healthy	500 mg/day for 1 week	Soni and Kuttan [103]
25 patients	Pre-malignant lesions	500–12,000 mg/day for 3 months	Cheng et al. [23]
15 patients	Advanced colorectal cancer	18 mg	Plummer et al. [83]
15 patients	Colorectal cancer	36–180 mg	Sharma et al. [95]
15 patients	Advanced colorectal cancer	450–3,600 mg/day for 4 months	Sharma et al. [94]
12 patients	Hepatic metastases from colorectal cancer	450–3,600 mg/day for 1 week	Garcea et al. [45]
12 patients	Colorectal cancer	450–3,600 mg/day for 1 week	Garcea et al. [46]
24 volunteers	Healthy	500–12,000 mg/day	Lao et al. [63]
17 patients	Advanced pancreatic cancer	8,000 mg/day for 2 months	Dhillon et al. [34]

Table 2 Ongoing clinical trials involving curcumin in patients affected by cancer

Status	Trial name	Disease	Treatment applied	Clinical phase study
Active, not recruiting	Curcumin (diferuloylmethane derivative) with or without bioperine in patients with multiple myeloma	Multiple myeloma	Curcumin; bioperine	nd
Recruiting	Curcumin with pre-operative capecitabine and radiation therapy followed by surgery for rectal cancer	Rectal cancer	Radiation: radiotherapy; capecitabine; curcumin; placebo	Phase II
Recruiting	Curcumin for prevention of oral mucositis in children chemotherapy	Chemotherapy induced mucositis	Curcumin liquid extract	Phase III
Completed	Pharmacokinetics of curcumin in healthy volunteers	Healthy	Curcumin	nd
Active, not recruiting	Trial of curcumin in advanced pancreatic cancer	Adenocarcinoma; pancreatic neoplasms	Curcumin	Phase II
Active, not recruiting	Curcumin in preventing colon cancer in smokers with aberrant crypt foci	Colorectal cancer; precancerous/ nonmalignant condition	Dietary supplement: curcumin	Phase II
Not yet recruiting	Bio-availability of a new liquid tumeric extract	Healthy	Liquid tumeric/curcumin extract	Phase I
Recruiting	Pilot study of curcumin formulation and Ashwagandha extract in advanced osteosarcoma	Osteosarcoma	Dietary supplement: curcumin powder, Ashwagandha extract	Phase I and II
Recruiting	Gemcitabine with curcumin for pancreatic cancer	Pancreatic cancer	Curcumin (+gemcitabine)	Phase II
Not yet recruiting	Phase III trial of gemcitabine, curcumin and celebrex in patients with metastatic colon cancer	Colon Neoplasm	Celecoxib; curcumin	Phase III
Suspended	Curcumin for treatment of intestinal adenomas in familial adenomatous polyposis (FAP)	Familial adenomatous polyposis	Dietary supplement: curcumin; dietary supplement: placebo	Phase II
Recruiting	Curcumin for treatment of intestinal adenomas in familial adenomatous polyposis (FAP)	Familial adenomatous polyposis	Curcumin	nd
Terminated	Use of curcumin in the lower gastrointestinal tract in familial adenomatous polyposis patients	Familial adenomatous polyposis	Curcumin	Phase II
Recruiting	Phase III Trial of Gemcitabine, Curcumin and Celebrex in patients with advance or inoperable pancreatic cancer	Pancreatic cancer	Gemcitabine; Curcumin; Celebrex	Phase III
Completed	Curcumin for the prevention of colon cancer	Colorectal cancer	Dietary supplement: curcumin	Phase I
Completed	The effects of curcuminoids on aberrant crypt foci in the human colon	Aberrant crypt foci	Sulindac; curcumin	nd
Not yet recruiting	A nutritional supplement capsule containing curcumin, green tea extract, polygonum cuspidatum extract, and soybean extract in healthy participants	Healthy, no evidence of disease	Dietary supplement: curcumin/green tea extract/Polygonum cuspidatum extract/ soybean extract capsule	nd
Suspended	Sulindac and plant compounds in preventing colon cancer	Colorectal cancer	Dietary supplement: curcumin, rutin Drug: quercetin, sulindac	nd
Recruiting	Curcumin for the chemoprevention of colorectal cancer	Adenomatous polyps	Curcuminoids	Phase II
Recruiting	Effect of oral curcumin on Heme-1 (HO-1) in healthy male subjects	Healthy	Dietary supplement: curcumin	Phase I

The table was generated by using the registry of federally and privately supported clinical trials conducted in the United States and around the world (http://clinicaltrials.gov)

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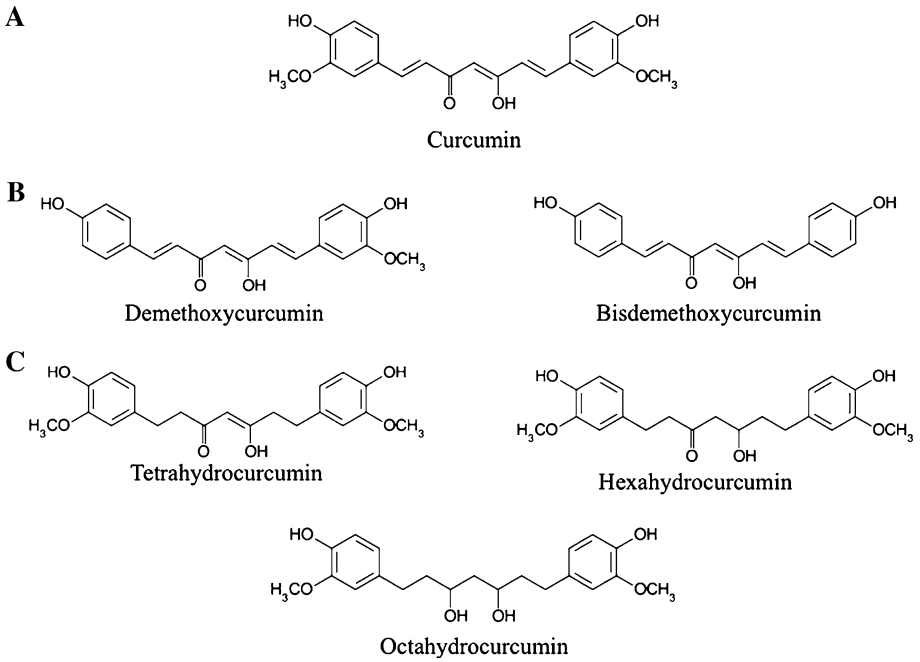

Fig. 1 Chemical structure of curcuminoids. Curcumin (**a**), Curcumin demethoxy derivatives (Demethoxy-curcumin and Bisde-methoxycurcumin) (**b**) and Curcumin hydrogenates metabolites (Tetrahydrocurcumin, Hexahydrocurcumin and Octahydrocurcumin) (**c**)

hexahydrocurcumin and octahydrocurcumin) (Fig. 1) pointed out structure–activity correlations. In fact, these studies revealed that the high number of *ortho*-methoxy substitutions and the high level of hydrogenation of the heptadiene moiety of curcumin are responsible for the high radical scavenging potential of the curcuminoids [86, 101]. In contrast, the highest anti-inflammatory and anti-tumoral potential of curcuminoids are related to the lowest hydrogenation, to the highest level of unsaturation of the diketone moiety, and to the highest methoxylation status of the molecules [106].

Structure–activity relationships were taken into account in order to design synthetic analogs with enhanced bioactivities [6]. The modification of the basic structure of curcumin can be achieved by acetylation, alkylation, and glycosylation of the phenolic hydroxyl group as well as by alterations of the number of carbons in the middle linker chain. Glycosylation of the curcumin aromatic ring provides a more water-soluble compound with a greater kinetic stability and a good therapeutic index [43].

Several curcumin analogs have also been designed and evaluated as potential androgen receptor antagonists to be used against androgen-dependent and -independent prostate cancer cells. These experiments revealed that the co-planarity of the β-diketone moiety and the presence of strong hydrogen bond donor group were crucial for the anti-androgenic activity of these curcumin analogs. By this way, these curcumin analogs seem to be good candidates to control androgen–receptor mediated prostate cancer growth as they may function as 17α-substituted dihydrotestosterone [81]. Following studies established an advanced structure–activity relationship for the design of new curcumin analogs to be used as potential anti-prostate cancer agents. First, the aromatic rings are required for the cytotoxic and anti-androgenic activities. The C-2′ positions of the phenyl rings should be unsubstituted. The C-3′ and C-4′ positions should be substituted with 3′ and 4′-dimethoxy and 3′-methoxy-4′-hydroxy substituents on the phenyl ring. Elongation of the linkers results in the loss of cytotoxicity and anti-androgenic activity. Finally, an unsaturated and conjugated linker is required for the cytotoxic and anti-androgenic activities [69]. Recent synthesis led to the design of a highly specific analog, containing a pentadienone moiety. It was reported to be 50 times more potent than curcumin to inhibit the growth of androgen-dependent and -independent prostate cancer cells with IC50 values in sub-micromolar range [44].

Curcumin formulations

To enhance the bioavailability of curcumin and to bring this natural compound to the forefront of therapeutic agents, numerous other approaches have been investigated [6].

The use of adjuvant like piperine (that inhibits UGTs and p450s), quercetin (that inhibits sulfotransferases) and genistein (that inhibits alcohol dehydrogenase) are mainly used to counteract the enzymes implicated in curcumin metabolism. Piperine from black pepper increases the bioavailability of curcumin by 154% in rats and by 2000% in humans without adverse effects [97].

On the other hand, nanoparticles, liposomes [77], micelles [64], and phospholipid complexes appear also as promising novel formulations as they provide longer circulation, lower hydrophobicity, better permeability of

membrane barriers, and resistance to metabolic stress [5]. Curcumin encapsulated in polymeric nanoparticles demonstrates in vitro therapeutic efficacy and mechanisms of action (induction of apoptosis, inactivation of NF-κB…) comparable to free curcumin, but with a higher solubility in aqueous media [15]. Moreover, the bioavailability of encapsulated curcumin appears to be ninefold increased when compared to curcumin administered with piperine as absorption enhancer [89]. Evaluation of liposomal curcumin pointed out that this nanotechnology increases the antiproliferative properties of curcumin in prostate cancer cells with tenfold lower dose compared to free curcumin [110].

Curcumin: a chemopreventive agent for prostate cancer

Curcumin is a highly pleïotropic molecule that modulates numerous cell signaling pathways implicated in the growth and survival of several cancer cell types, including prostate cancer [1]. In the following we report the state-of-the-art concerning the chemopreventive potential of curcumin on the different stages of prostate cancer and the signaling pathways implicated (Figs. 2, 3). Curcumin was effectively shown to have a positive impact against non-cancerous chronic bacterial prostatitis [18], androgen sensitive LNCaP and 22rv1, but also against androgen-independent DU145, and bone metastatic LNCaP-derivative C4-2B prostate cancer cells.

Down-regulation of the androgen receptors and co-factors

Androgens, including testosterone and their corresponding androgen receptors (AR), are essential for the morphogenesis and development of the prostate but are also involved into the malignant transformation of this gland [87]. Hormonotherapy by androgen depletion was thus considered as a potential treatment to eradicate prostate cancer. Unfortunately, these therapies are often ineffective as prostate cancer cells become progressively androgen-independent and lead to metastasis [42]. Uncontrolled AR gene amplification, AR mutations, and increase of AR expression appear to be a selective driving force for the progression of prostate cancer to the hormone refractory state. Curcumin was shown to have an influence on the expression level of typical prostate marker proteins. In fact, in response to curcumin treatment, the AR expression was strikingly down-regulated as well as the AR binding activity to the androgen response element of the prostate-specific antigen protein (PSA) gene, and the PSA expression in LNCaP cells [38, 76, 114]. This phenomenon is expected to deprive these cells of a critical growth advantage and classifies thus this phytochemical as a

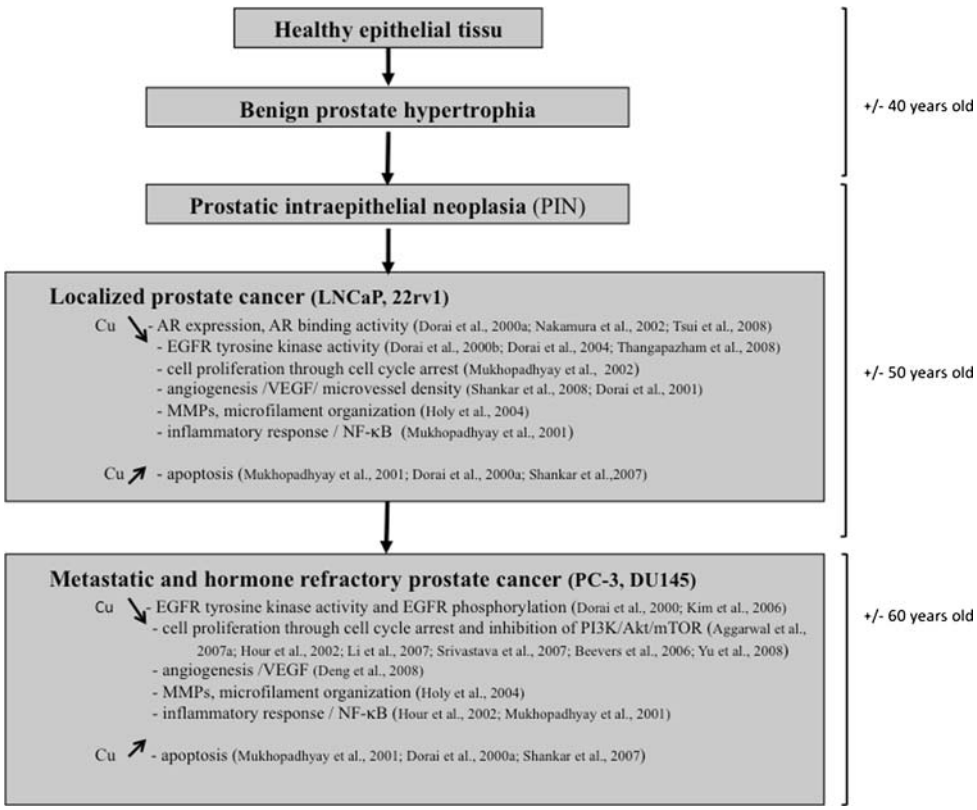

Fig. 2 Molecular events targeted by curcumin at different stages of prostate cancer development

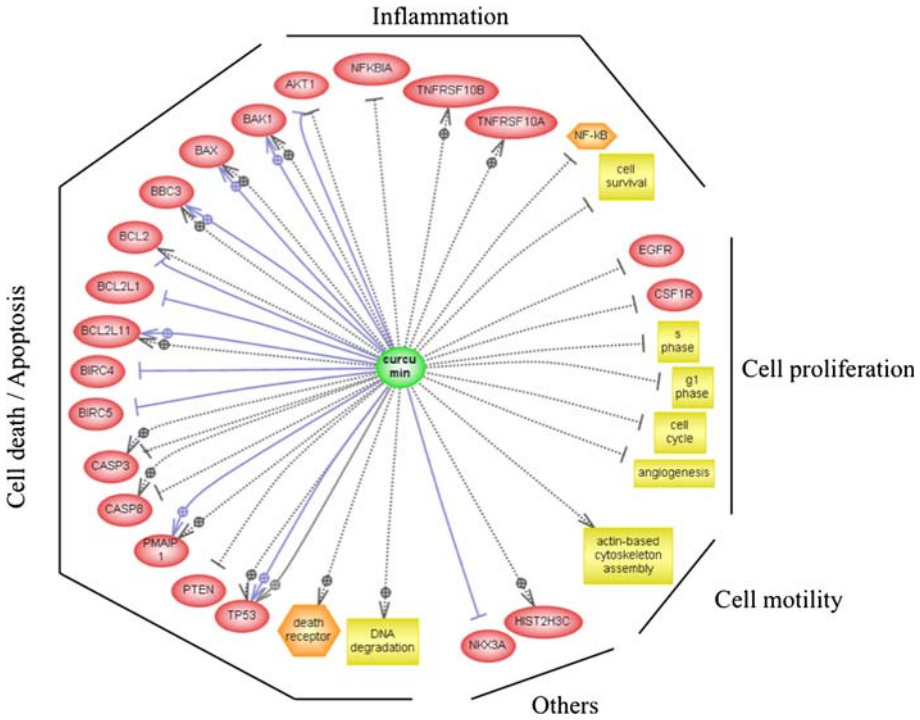

Fig. 3 Network of proteins, functional classes and cell processes modulated in prostate cancer cells after curcumin treatment. All of these data were extracted from PubMed abstracts using the MedScan Reader software (version 1.1) [25, 80] and then imported to the Pathway Studio software tool (Version 5.0) [78] for visualization. Nodes correspond to proteins (in *red*), functional classes (in *orange*). *Lines* represented the different types of interactions and relationships between the corresponding nodes and curcumin: expression (in *black*), regulation (in *blue*). *Arrow line* represented induction/activation, *blunt-ended line* represented repression/inactivation

non-toxic approach to the management of AR-dependent prostate cancer [38]. Several analogs of curcumin were also shown to act as androgen receptor antagonists [81]. Such a downregulation of AR expression and the blockage of its DNA binding activity by curcumin lead also to the inhibition of the homeobox gene NKX3.1 [119], an androgen-regulated NK-class homeobox gene thought to play an important role in normal prostate organogenesis and carcinogenesis [14].

Impact on prostate cancer cell proliferation

The inappropriate and accelerated proliferation of cancer cells is linked not only to the over-expression of epidermal growth factor receptor (EGFR), to modifications of the balance between the cell cycle checkpoint and the different cyclins, but also to the deregulation of specific signaling pathways (Fig. 4).

The EGFR family, including HER2, is an important mediator of cell proliferation and is highly expressed in prostate cancer cells in which it is associated with poor prognosis [41]. Experiments performed on LNCaP and PC-3 cells revealed that curcumin is a potent inhibitor of EGFR signaling as it down-regulates the EGFR expression, inhibits the EGFR tyrosine kinase activity and the ligand-induced activation of the EGFR [39]. This polyphenolic compound was also shown to suppress the EGFR phosphorylation (Y845 and Y1068) in PC-3 cells [61]. Such results were confirmed by clustering methods and functional classification of the curcumin–gene expression profile that revealed that curcumin is able to down-regulate EGFR in LNCaP cells [111], and in cells derived from LNCaP with high metastatic potential in which it also inhibits the EGFR tyrosine kinase activity [37].

Curcumin was also shown to have an impact on cyclins implicated in the cell cycle. Cyclin D1, for instance, is a proto-oncogene that plays an important role in cell proliferation through the activation of cyclin-dependant kinases and is required for the progression of cells from the G1 to the S phase. Curcumin was shown to down-regulate cyclin D1 expression through activation of both transcriptional and post-transcriptional mechanisms in LNCaP prostate cancer cells [74]. Such a cell cycle arrest in G1/S phase was also observed in DU145 and PC-3 cells not only through the up-regulation of the expression of cyclin-dependent kinase (CDK) inhibitors p16, p21, and p27 and the inhibition of the expression of cyclin E, cyclin D1, but also through the hyperphosphorylation of retinoblastoma (Rb) protein [104]. The down-regulation of cyclin E was shown to be mediated by the proteasome [2]. These effects lead to cell proliferation arrest and disruption of cell cycle control resulting in cell death by apoptosis. Others studies showed that curcumin induces an arrest in G2/M phase in PC-3 and LNCaP cells [96].

The anti-proliferative property of curcumin was confirmed in vivo by the observation of the growth of LNCaP cells tumors heterotypically implanted in nude mice. BrDU incorporation assays revealed that curcumin causes a marked decrease in the extent of prostate cell proliferation in mice [36], which is consistent with the observed induction of p21 and p27 and the inhibition of cyclin D1 [91].

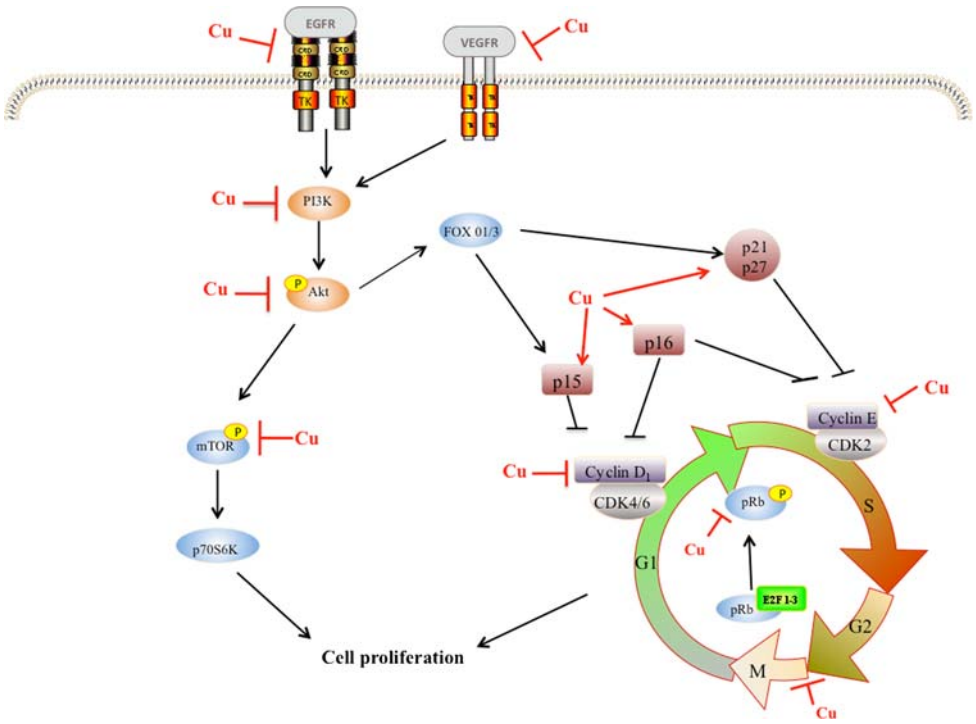

Fig. 4 Curcumin's targets intracellular components implicated in cell proliferation signaling pathway in prostate cancer cells. Curcumin highly repressed the EGFR and VEGFR signaling pathways as well as cyclins implicated in cell cycle regulation in prostate cancer cells. *Arrow line* represented induction/activation and *blunt-ended line* represented repression/inactivation. This figure was generated by using ScienceSlides software with modifications

The phosphatidylinositol 3-kinase (PI3 K)/Akt (protein kinase B)/mammalian target of rapamycin (mTOR) signaling plays a central role in tumorigenesis and is often deregulated in metastatic prostate cancers through the mutation of the phosphatase and tensin homolog (PTEN) leading to the constitutive activation of Akt [20, 105]. Curcumin was shown to inhibit the phosphorylation of mTOR in DU145 [12] and PC-3 [66]. Other studies explored the molecular mechanisms implicated and revealed that curcumin activates the PP2A serine/threonine protein phosphatase and subsequently inhibits the phosphorylation of Akt/PKB, mTOR, and their downstream substrates in a concentration- and time-dependent manner in PC-3 cells leading thus to the inhibition of cell proliferation [118]. Curcumin was shown to inhibit the expression of phosphatidyl-inositol-3 kinase (PI3K) p110 and p85 subunits, and phosphorylation of Ser 473 AKT/PKB [92].

In order to stop the growth of solid tumors, it is important to block angiogenesis and its major mediator, vascular endothelial growth factor (VEGF), highly associated with metastasis development [67]. In fact, VEGF facilitates the entry of tumor cells into the blood stream and the development of distant metastasis by enhancing the hyper-permeability of vessels, the endothelial cell proliferation, and migration. VEGF is known to be highly involved in prostate cancer development [31]. Curcumin was shown to inhibit angiogenesis in vitro and in vivo [10] by suppressing the proliferation of human endothelial cells [98] and by abrogating the fibroblast growth factor-2-induced angiogenic response in vivo [73]. The effect of curcumin on the regulation of angiogenesis revealed that this natural compound down-regulates the expression of pro-angiogenic genes (*angiopoietin 1, angiopoietin 2, VEGF* and *Kinase Domain Region* (*KDR*)) in HUVECs and EAT cells [50]. Due to the presence of NF-κB binding sites on the promoter of *KDR* gene [55], the downregulation of *KDR* gene expression could be explained by the inhibitory activity of curcumin on NF-κB signaling.

Deng et al. [32] have reported that curcumin reduces the expression of VEGF mRNA and proteins in PC-3 cells. Similar results were obtained with LNCaP xenografts growing in nude mice in which curcumin decreased the number of VEGF receptor-2 positive endothelial cells and VEGF protein expression [91] and also the microvessel density [36].

Prevention of prostate cancer cell motility and metastasis

Highly proliferative prostate cancer cells also acquire the ability to invade surrounding tissues. Curcumin was shown to induce a marked reduction of matrix metalloproteinases (MMPs) MMP-2 and MMP-9 activity leading to a reduction of metastatic nodules in tumor-bearing mice as MMPs are known to be important prerequisite for tumor invasion and metastasis [53].

Moreover, the propensity of prostate cancer cells to establish osseous metastasis is wide as these cells are able to acquire "bone-like" properties that are facilitated by several surrounding factors. Curcumin is also able to

counteract this potential as it was shown to inhibit the ligand-stimulated autophosphorylation of EGF-R and CSF1-R (colony stimulating factor 1 receptor) that were crucially involved in the development of osteomimetic properties of prostate cancer C4-2B cells. This natural compound is also able to inhibit the expression of the core-binding factor a-1 that is responsible for the expression of several bone-specific proteins. By this way, curcumin could inhibit the growth factor collaboration between the prostate cancer cells and the osteoblast/stromal cells in order to prevent the establishment of bone metastasis [37].

Using time-lapse video and immunofluorescence, curcumin was shown to significantly alter microfilament organization and cell motility in PC-3 and LNCaP human prostate cancer cells in vitro [52]. Curcumin increases stress fibers and the overall quantity of f-actin and also appears to be a potential inhibitor of angiogenesis and metastasis in prostate cancer.

The regulation of metastasis by curcumin was confirmed in vivo as the treatment of xenograft nude mice with curcumin results in the inhibition of MMPs and urokinase-type Plasminogen Activator (uPA) expression normally associated with the metastatic potential of prostatic cells [91].

Regulation of the inflammatory response

Inflammation emerges as a major risk factor for the development of prostate cancer and is associated with poor prognosis of treatment. In parallel, modulation of cellular signaling involved in inflammatory response (TNFα/NF-κB) seems to be an important strategy for chemoprevention. The anti-inflammatory potential of curcumin was first described by Aggarwal and coworkers. They pointed out that curcumin inhibits the nuclear transcription factor-κB (NF-κB) activation through the inhibition of IκBα proteasomal degradation and thereby the nuclear translocation of p65 subunit [100]. Further investigations of curcumin mechanism of action revealed that the inhibition of p65 nuclear translocation was due to the sequential suppression of IκBα kinase activity, IκBα phosphorylation, IκBα degradation, p65 phosphorylation, p65 nuclear translocation, and p65 acetylation. Curcumin was also reported to inhibit the subsequent NF-κB-regulated gene expression through the inhibition of IKK and Akt activation [4]. Such an inhibitory effect of curcumin on NF-κB activation was reported to be linked to the impairment of the proteasome function by curcumin [35, 72].

In prostate cancer cell lines and in patients affected by prostate cancer, curcumin was shown to be a promising regulator of many proteins implicated in the regulation of the inflammatory response, especially as a potent inhibitor of the constitutively activated or TNFα-induced NF-κB [54, 75]. Mechanistic studies revealed that curcumin inhibits the expression of NF-κB expression by blocking the phosphorylation of IκBα and its degradation by the proteasome [28], but also by suppressing the phosphorylated Akt kinase in prostate cancer cell lines [27].

Curcumin also up-regulates the mitogen-activated protein kinase phosphatase-5 (MKP5) [79]. This protein selectively dephosphorylates the jun N-terminal kinase (JNK) and stress-activated protein kinase p38, that is a mediator of cellular pro-inflammatory responses, known to contribute to prostate cancer development. Downstream anti-inflammatory effects of p38 inhibition can include decreased activation of NF-κB, reduced COX-2 expression and decreased the production of pro-inflammatory cytokines such as IL-6, an autocrine growth factor for prostate cancer [47]. The subsequent decrease of COX-2 is highly relevant for prostate cancer eradication as high constitutive levels of COX-2 expression are considered as survival factors for prostate cancer [70]. So, this up-regulation of MPK5 may thus subsequently decrease pro-inflammatory signaling in both normal prostatic epithelial cells and prostate cancer cells (Fig. 5).

Induction of prostate cancer cell death by apoptosis

Prostate cancer cells express several anti-apoptotic proteins that play an important role in cell survival and resistance to conventional treatment. Using curcumin seems really interesting as this natural compound was shown to induce apoptosis in both androgen-dependent and androgen-independent prostate cancer cells (Fig. 6).

In several cancers, curcumin was shown to induce apoptosis not only through intrinsic (mitochondrial) and extrinsic (receptor-mediated) pathways but also through increased stress of the endoplasmic reticulum [60, 85]. The intrinsic induction of apoptosis by curcumin is activated in response to cellular signals including stress or DNA damage. It implicates the up-regulation of pro-apoptotic proteins from the Bcl-2 family (Bim, Bax, Bak, Puma and Noxa) and the down-regulation of anti-apoptotic proteins (XIAP, Bcl-2, Bcl-xL). This leads to the opening of permeability transition pore, the release of cytochrome c, the activation of the apoptosome (caspase-9/apaf-1/cytochrome c) and the subsequent cleavage of caspase-3, -6 and -7, Poly (ADP-ribose) polymerase (PARP), and finally the death of cells [19, 102, 112]. After curcumin treatment, the extrinsic pathway is initiated by the activation of receptors (Fas, TRAIL) at the cell surface [9, 17]. This leads to the assembly of the DISC (death-inducing signaling complex) containing Fas, FAD, and caspase-8 and -10. These activated caspases converged then to the intrinsic pathway by the induction of Bid cleavage and the subsequent release of cytochrome c, and the activation of the cascade of caspases.

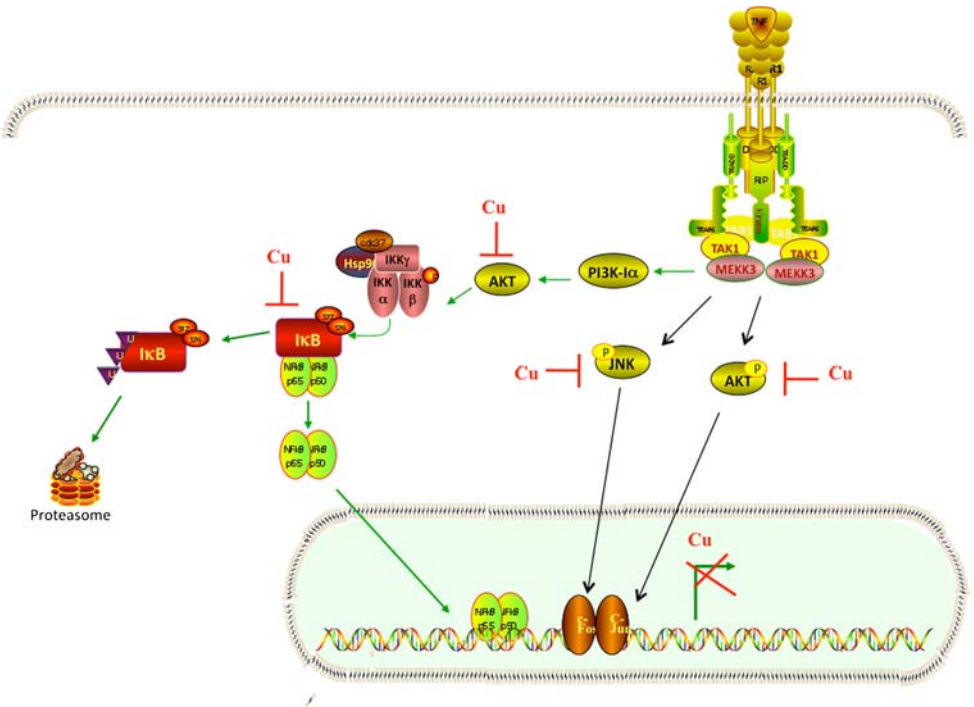

Fig. 5 Effect of curcumin on intracellular network implicated in inflammation signaling in prostate cancer cells. Curcumin regulates mainly proteins implicated in NF-κB and AP-1 signaling. *Arrow line* represented induction/activation and *blunt-ended line* represented repression/inactivation. This figure was generated by using ScienceSlides software with modifications

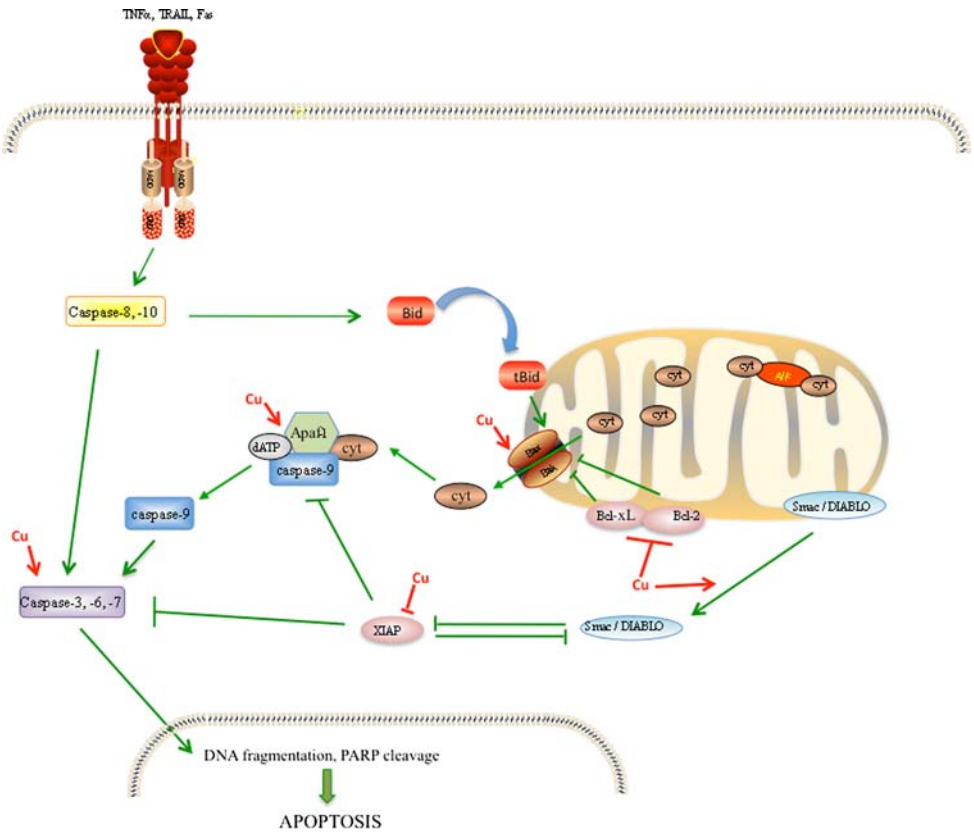

Fig. 6 Impact of curcumin on molecules implicated in signaling pathways leading to prostate cancer cell death by apoptosis. Curcumin appears as a good inhibitor of anti-apoptotic proteins (Bcl-2, Bcl-xL, XIAP) and as a good inducer of pro-apoptotic proteins (Bax, Bak), of the release of cytochrome c, and of the cascade of caspases. *Arrow line* represented induction/activation and *blunt-ended line* represented repression/inactivation. This figure was generated by using ScienceSlides software with modifications

In the case of prostate cancer, several studies revealed that this natural compound is able to down-regulate apoptosis suppressor protein such as Bcl-2 and Bcl-xL and to induce the cleavage of PARP and the appearance of apoptotic figures [38, 75]. Other experiments were performed to analyze the cascade of events leading to apoptosis after curcumin treatment of prostate cancer cells. They pointed out that curcumin treatment results in the

translocation of Bax and p53 to mitochondria, the production of reactive oxygen species, a decrease of mitochondrial membrane potential, the release of cytochrome c, Smac/DIABLO, and the activation of caspase-3. They concluded that Akt plays an important role in modulating the direct action of p53 on the caspase-dependent mitochondrial death pathway and they suggested that these important biological molecules interact at the level of the mitochondria to influence curcumin sensitivity [92]. Curcumin also down-regulates murine double minute 2 (MDM2) protein and mRNA, an important negative regulator of the p53 tumor suppressor allowing thus prostate cancer cells to undergo apoptosis [66]. The pro-apoptotic potential of curcumin was confirmed in vivo in nude mice implanted heterotypically with LNCaP cells [36].

Experiments performed on cervical cancer HeLa and neuroblastoma Neuro2a cells reported that the induction of apoptosis by curcumin, through mitochondrial pathway involving caspase-9 activation, could also be mediated through the impairment of the ubiquitin–proteasome system [58].

Curcumin also appeared to be a good candidate to sensitize prostate cancer cells for TRAIL-mediated immunotherapy. TNFα related apoptosis-inducing ligand (TRAIL) is an inducer of apoptosis in many cancer cells and is an attractive cytokine for the treatment of advanced cancers including prostate cancer. Although prostate cancer cells (DU145, PC-3 and LNCaP) are mostly resistant to TRAIL, they can be sensitized with curcumin to TRAIL-induced apoptosis [28, 29, 90]. In fact, the combined curcumin and TRAIL treatment induced DNA fragmentation, the cleavage of pro-caspase-3, pro-caspase-8 and pro-caspase-9, as well as the truncation of Bid and cytochrome c release [29, 30, 90]. This chemosensitization to TRAIL involved the inhibition of constitutively active NF-κB through the suppression of IκBα phosphorylation [28]. It was also related to the down-regulation of p-Akt, which leads to the inhibition of Akt-regulated NF-κB-dependent antiapoptotic Bcl-2, Bcl-xL and XIAP [27]. These results were confirmed by pre-clinical studies performed in PC-3 xenografts [8] and in TRAIL-resistant LNCaP xenografts [91].

Moreover, curcumin used in combination with radiation enhanced significantly the radiation-induced clonogenic inhibition and induced apoptosis. The combination of treatment alters the Bax/Bcl2 ratio but activates cytochrome c, caspase-9 and caspase-3. This means that curcumin exhibits also a potent radiosensitizing effect in prostate cancer [22].

Conclusion

The initiation of prostate cancer from non-malignant prostate is a relative lengthy process that takes several years and is often related to fatty diet, inflammation, and oxidative stress [88]. The blockade of prostate carcinogenesis at really early stage by the use of chemopreventive molecules found mainly in our diet (fruits, vegetables, spices, seeds) appears then promising. In fact, as we reported here, curcumin is able to prevent prostate cancer initiation or progression as it inhibits inflammation signaling pathway highly implicated in prostate cancer progression through the regulation of NF-κB and cofactors. However, despite the fact that curcumin is well described in several cancer types for its anti-oxidant potential through the induction of phase II enzymes (glutathione *S*-transferase, heme oxygenase), especially by the regulation of the transcription factor Nrf2 (nuclear factor-erythroid 2-related factor 2 erythroid) [7, 11, 108], nothing was published until today concerning prostate cancer.

Several data pointed out that curcumin is able to suppress the proliferation of both androgen-dependent and androgen-independent prostate cancer cell line but also of LNCaP xenografts by interfering with growth factor receptors, cell cycle, angiogenesis, and metastasis potential of prostate cancer cells. This natural compound also promotes the induction of prostate cancer cell death by apoptosis through a well-described cascade of events and could be useful in combination with conventional treatment such as immunotherapy and radiotherapy.

With this in mind, the use of curcumin in diet or as a treatment appears as an alternative, non toxic modality for prostate cancer prevention, treatment or co-treatment with conventional therapy by which the clinician may prevent the progression of prostate cancer to its hormone refractory state or to treat advanced prostate cancer. This also gives a rationale for the prospective of curcumin in translational studies in prostate cancer cells.

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