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Commentary

Prostate cancer and curcumin

Add spice to your life

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Prostate cancer, the most prevalent malignancy in men in the United States and Western Europe, kills more men than any other cancer. The mean age of patients with prostate cancer is 72–74 years, and about 85% of the patients are diagnosed after the age of 65. The incidence varies as much as 90-fold between ethnic populations and countries. The lowest rates are usually in Asia (e.g., 7.9 per 100,000 in India), and the highest are in North America (e.g., 137 per 100,000 in African-American men in the USA; see Fig. 1). Why there is such a huge variation in prostate cancer incidence is not understood, but genetic susceptibility and environmental factors have been implicated.[1-3] That the risk of prostate cancer among Asians increases when they immigrate to North America further implicates environmental and lifestyle factors.[4]

It is possible that the factors that underlie the variations in incidence could be exploited to treat the tumor once it occurs. There are suggestions, for example, that dietary factors may affect the responsiveness of prostate tumors to androgen-ablative therapy. Although androgens are required for the normal growth and development of the prostate, they may also play a role in prostate carcinogenesis by acting either as initiators or promoters. Indeed, most patients respond initially to androgen-ablative therapies; the regression of the prostate tumors indicates that androgen functions as a survival factor. However, the disease generally recurs within 1 to 3 years of treatment, and the recurrent tumors no longer require androgen for growth or survival. Experimental evidence demonstrates a clonal outgrowth of androgen-independent prostate cancer cells from androgen-dependent tumors.[5] In addition, these tumors tend to be highly resistant to conventional cytotoxic agents such as cisplatin. Presently available treatments for advanced hormone-resistant prostate cancer are marginally effective, and so newer agents are needed to selectively kill the cancer cells.

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The prostate cancer resistance has been associated with the overexpression of Bcl-2, androgen receptor (AR) signaling, epidermal growth factor receptor, HER2, cyclin D1 and cyclooxygenase (COX-2), which are all linked with the activation of NFκB, a transcription factor.[5-10] Thus, an agent that can downmodulate these chemoresistant and cell survival mechanisms has the potential for both prevention and treatment of prostate cancer. Curcumin is one such agent that can modulate several of these pathways. Therefore, studies to demonstrate the potential of curcumin against prostate cancer are described.

What is Curcumin?

Curcumin (diferuloylmethane) is a component of turmeric (2–5%, w/w) a spice that gives the yellow color to curry powder. Traditionally, turmeric has been described in Ayurveda (the Science of long life) as a potent anti-inflammatory agent.[11] The suppression of cellular transformation, proliferation, invasion, angiogenesis and metastasis of tumors by curcumin has been reported.[11] Several phase I clinical trials carried out by our group and others show that doses as high as 12 g per day are well tolerated in humans.[12]

Why does Curcumin have Potential Against Prostate Cancer?

Curcumin has been shown by us and others to suppress the proliferation of both the androgen-dependent prostate cancer cell line, LNCaP, and the androgen-independent DU145 line.[13,14] Curcumin has also been shown to suppress the growth of heterotopically implanted LNCaP prostate cancer cells in nude mice.[15] It interferes with the activation of the osteoblastic and osteoclastic components of the advanced prostate cancer phenotype by interfering with growth factor receptor pathways and by inhibiting the NFκB activation process.[16] Recently, it was reported that administering curcumin prior to the implantation of PC-3 prostate xenografts inhibited their growth.[17] Curcumin has also been shown to sensitize prostate cancer cells in culture to gamma-irradiation.[18] How does curcumin mediate these effects? Several molecular targets of curcumin have been identified that are relevant to prostate cancer (Fig. 2).

Signaling Pathways Regulated by Curcumin

Curcumin targets proteins important in prostate cancer. Antiandrogens such as flutamide, have been approved for the treatment of prostate cancer but suffer from numerous side effects. Curcumin

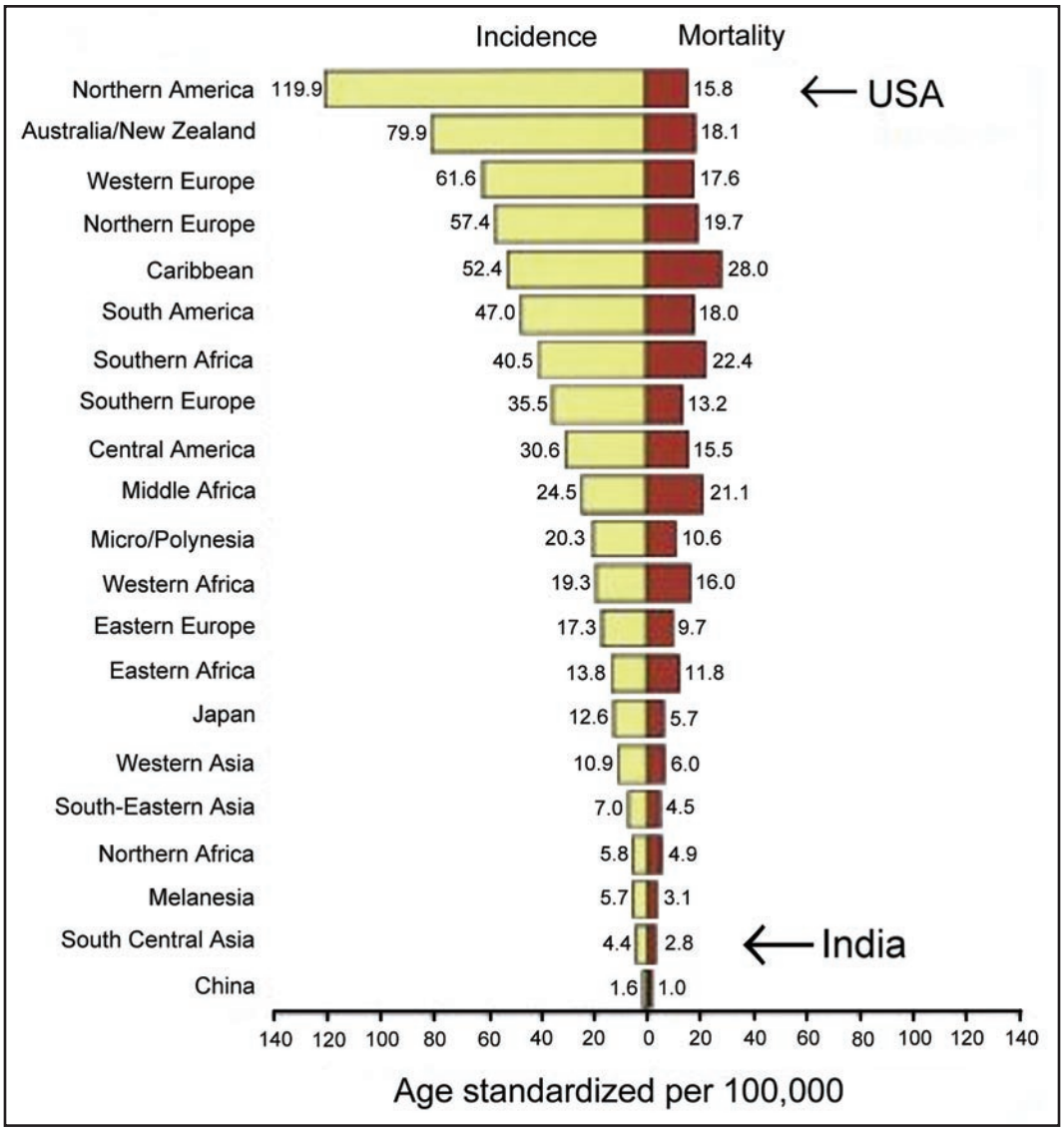

Figure 1. Age-standardized incidence and Mortality Rates for Prostate Cancer. Data shown per 100,000. Incidence and mortality due to prostate cancer around the World (Parkins DM, 2002).

has been shown to downregulate the transactivation and expression of AR and AR-related cofactors, leading to downregulation of the homeobox gene NKX3.1, a prostate-specific gene.[19,20] Additionally, curcumin has been shown to act as an androgen receptor antagonist.[21] Curcumin also inhibits prostate-specific antigen (PSA), a critical marker of prostate cancer progression upregulated in androgen-independent prostate cancer, through the activation of NFκB.[31,32]

Curcumin influences multiple growth factor signaling pathways. The EGF receptor is overexpressed in prostate cancer cells, and is needed for the proliferation of cells.[22] Curcumin has been shown to both downregulate the expression of EGFR and inhibit EGFR tyrosine kinase activity.[14,23] The HER2 receptor is also overexpressed in prostate cancer cells and mediates a critical role in their proliferation.[24,25] Curcumin has been shown to induce the proteolytic degradation of HER2 and inhibit its tyrosine kinase activity.[26,27] VEGF is a major mediator of angiogenesis, so inhibitors of VEGF, such as Avastin, are being explored as treatments for prostate cancer.[44] Curcumin is known to downregulate the expression of VEGF and angiogenesis in vivo.[45,46] Fibroblast growth factor 2 (FGF2) is a pleiotropic growth factor that has been implicated in prostate cancer formation and progression. Hatziapostolou found that exogenous FGF2 significantly increased LNCaP cell proliferation and migration.[33] Curcumin has been shown to inhibit the expression of the matrix metalloproteinase gelatinase B, which is stimulated by FGF-2, leading to suppression of angiogenic response.[34] Furthermore, curcumin has been shown to downregulate both the expression and action of IL-6, an autocrine growth factor for prostate cancer.[37-40]

Certain cancers have tendency to metastasize or "home" to bone. Hematopoietic cells also home to bone during embryonic development, where evidence points to the chemokine stromal cell-derived factor-1 (SDF-1 or CXCL12; expressed by osteoblasts and endothelial cells) and its receptor (CXCR4) as key elements in these processes. Evidence has shown that metastatic prostate carcinomas also use the SDF-1/CXCR4 pathway to localize to the bone, and CXCR4 expression has been reported for various human prostate cancer cell lines.[35] Recently, curcumin was found to downregulate

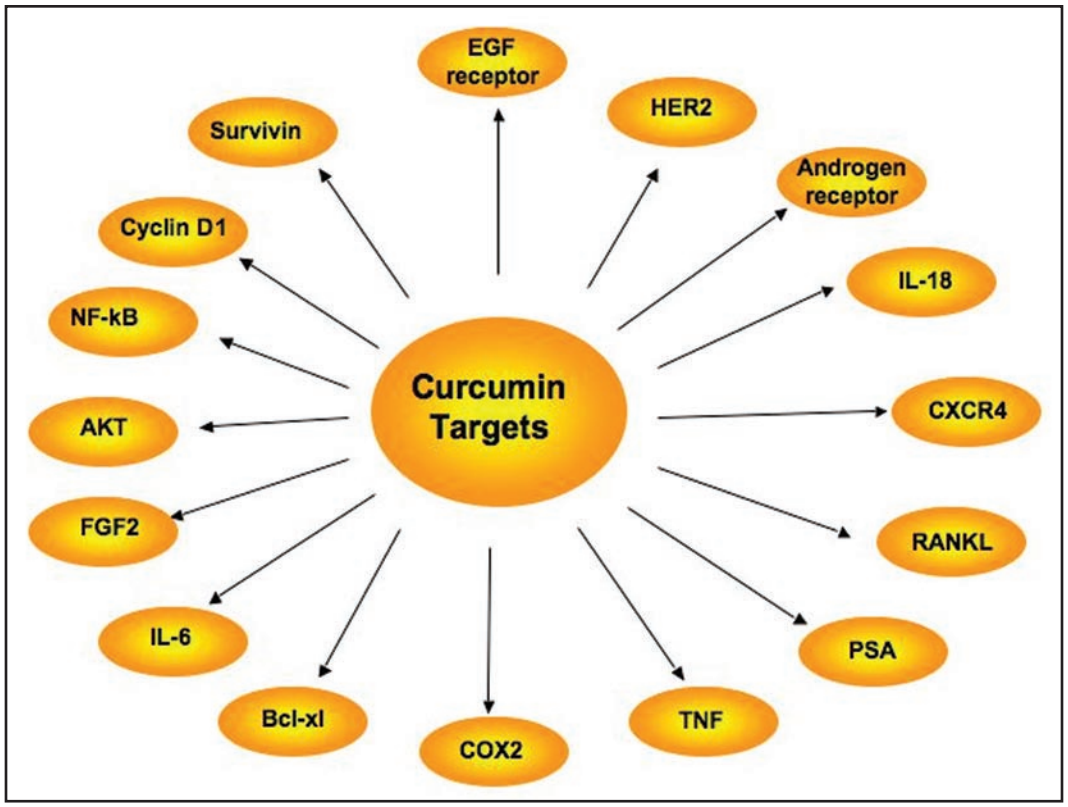

Figure 2. Modulation of multiple molecular targets by curcumin relevant to prostate cancer.

the expression of CXCR4.[36]

The PI-3K/AKT pathway plays a critical role in the proliferation of prostate cancer cells.[41,42] PTEN, the phosphatase that regulates this pathway, is mutated in prostate cancer, thus leading to constitutive activation of AKT. Therefore, inhibition of AKT has a potential for suppressing the proliferation of prostate cancer cells. Studies from our laboratory and others indicate that curcumin can inhibit the activation of AKT.[30]

Cyclin D1 is required for the progression of cells from the G_1 to the S phase of the cell cycle. Prostate cancer cells are known to overexpress cyclin D1. Our laboratory has shown that curcumin downregulates the expression of cyclin D1 in prostate cancer cells.[28]

Numerous anti-apoptotic proteins including bcl-2, bcl-X_L, XIAP, cFLIP and survivin, are expressed in prostate cancer cells and play an important role in the survival (i.e., resistance to treatment) of this cancer. Curcumin has been shown to downregulate the expression of all these proteins.[30,47,48]

Proteins that participate in the inflammatory response are also regulated by curcumin. COX2 is known to be upregulated in prostate inflammatory atrophy (PIA), a precursor of prostate intraepithelial neoplasia (PIN), and increased COX2 expression has been associated with high prostate tumor grade.[24,29] Studies from our laboratory and others indicate that curcumin can downregulate the expression of COX2.[30]

Constitutive activation of NFκB in prostate cancer cell lines and in patients with prostate cancer has been demonstrated.[28,49] Furthermore, inhibitors of NFκB have been shown to suppress angiogenesis, invasion and metastasis of prostate cancer.[50] Curcumin has been shown by us and others to be a potent inhibitor of NFκB activation.[51]

Evidence indicates that advanced prostate cancer that has metastasized to the bone induces osteoclastogenesis. RANKL, a member of the TNF superfamily, is a major mediator of osteoclastogenesis. Work from our laboratory has shown that curcumin can suppress RANKL-induced osteoclastogenesis.[43]

Together, all of these reports suggest that curcumin is a multitargeted agent that has potential both for prevention and therapy of prostate cancer. Work from our laboratory has shown that curcumin can suppress NFκB activation, STAT3 activation, COX-2 expression, AKT activation and cyclin D1 and TNF expression.[28,30,40,51-53]

The most frequently employed targets in cancer therapy today include EGFR, HER2, VEGF, the proteasome, COX2, and the microtubule assembly apparatus. Various studies suggest that agents that block only one of these pathways are minimally effective. Inhibition of multiple pathways is more likely to be successful. Much evidence suggests that this is also true for the treatment of prostate cancer. Furthermore, extensive review of the literature also suggests that the molecular targets employed for the prevention of cancer are equally relevant for the treatment of cancer.[54,55]

Because curcumin is effective in suppressing multiple pathways, it has a potential for both prevention and treatment of prostate cancer (see Fig. 2). This hypothesis is based on the following observations. First, curcumin has been traditionally described as an antioxidant and anti-inflammatory agent; and both antioxidants and NSAIDs have been linked to inhibition of prostate carcinogenesis. Second, curcumin has been shown to suppress both inducible and constitutive NFκB activation, inducible and constitutive STAT3 activation, AKT activation, COX-2 expression, EGFR expression and activity and inflammatory cytokine (e.g., TNF, IL-6, IL-8) expression in tumor

cells. Third, we have shown that curcumin prevents breast cancer metastasis to the lung in rodents. Fourth, in several studies, curcumin has been shown to suppress the survival mechanisms required for the proliferation of prostate cancer cells. Fifth, curcumin has been tested in patients and found to be pharmacologically safe even at 12 g/day. Sixth, curcumin is currently in clinical trials at our institute for the treatment of multiple myeloma and pancreatic cancers. Seventh, epidemiological evidence indicates that the incidence of prostate cancer in India, where curcumin is heavily consumed, is about 5% of the incidence in the United States.

New Developments

Although curcumin is known to act as an androgen receptor antagonist and is known to downregulate androgen receptor-mediated transactivation, which causes the downregulation of the homeobox gene NKX3.1, a prostate-specific gene; other AR-regulated downstream targets that are affected by curcumin are unknown.[19-21] In the current issue of Cancer Biology & Therapy, Thangapazham and colleagues used an unbiased approach to examine the differences between androgen-dependent and androgen-independent prostate cancer cells in global gene expression in response to curcumin treatment.[56] They employed the less-aggressive LNCaP as an androgen-dependent line and its subclone, C4-2B, as a more aggressive, androgen-independent cell line. The temporal expression profile was examined using a high-density, oligonulceotide Affymatrix human genome array; hierarchical clustering and functional classification. Using >four fold induction or <four fold repression over the controls as a cut off, they found 181 genes were upregulated at 12 h and 245 genes were downregulated at 24 h in LNCaP cells; whereas in C4-2B cells, 27 genes were upregulated at 12 h and 2 genes downregulated at 24 h. Among some of the genes upregulated were heme oxygenase-1 (by 25 fold), DNA-damage-inducible transcript-3, ATF3 and GADD45A. The curcumin-mediated upregulation of ATF3 is consistent with our report on squamous cell carcinoma.[57] As reported earlier, the expression of NKX3.1 and KLK3 (PSA) genes was found to be downregulated by curcumin.[20] The authors made two other major observations. First, curcumin downregulated the TMPSS2-ERG gene fusion, a common oncogenic alteration noted in 50–70% patients with prostate cancer. Second, the curry phytochemical also downregulated the expression of the EGFR and HER2 receptors in both prostate cancer cell lines. In general, the expression of protective genes in response to curcumin was more pronounced in the less-aggressive LNCaP than in C4-2B.

Conclusion

Thus the current report adds to those previously published in strongly suggesting that curcumin exhibits activity against prostate cancer. More animal studies and clinical trials testing curcumin against prostate cancer are needed to fully realize its potential. It is estimated that there are more than 2 million men alive with a diagnosis of prostate cancer at this time. Prostate cancer death is a systemic event. The mean age of prostate cancer diagnosis in men is 68 years old and the ability to tolerate the currently available toxic systemic therapy at this age is low. Because curcumin lacks toxicity in man and is highly affordable, it may provide a reasonable alternative for the prevention and even the treatment of prostate cancer. Thus "adding spice to your life" is highly recommended to all, especially those who are at high-risk for prostate cancer.

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