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Lycopene Effects Contributing to Prostate Health

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Epidemiological evidence links lycopene consumption with decreased prostate cancer risk. Several signaling pathways have been identified as players in prostate cancer development. Chronic prostatitis, for example, due to infections, is a suggested risk factor for prostate cancer. Endogenous production of reactive oxygen species during inflammation may lead to oxidative DNA damage, which can be mutagenic, if unrepaired. Androgen signaling, cytokine (IL-6, IL-4) and growth factor signaling (e.g., IGF, Wnt/β-catenin) cross-talk via PI3K/Akt, MAPK, and Jak/STAT pathways have been identified as major controllers of prostate growth. During disease progression, and after androgen ablation therapy, the remaining operational pathways are upregulated to compensate for the lost growth signal, finally resulting in androgen-independent prostate cancer. Lycopene modulates several of the aforementioned pathways, providing a promising rationale for prostate cancer risk reduction by lycopene: In many experimental setups, lycopene reduced inflammatory signals, prevented oxidative DNA damage, modulated the expression or activity of IGF axis members, of Wnt/β-catenin and androgen signalling, and enhanced gap junctional communication. Lycopene's influence on these pathways likely contributes to the observed cell growth inhibition and apoptosis induction by lycopene. A substantial part of the lycopene effects can be explained by its antioxidant action, but other mechanisms might also be involved.

INTRODUCTION

Prostate cancer is the leading cause of cancer death in men in Western countries, with estimated 186,320 new cases for 2008 in the US (1). American men have a lifetime risk of about 18% for prostate cancer diagnosis (2). Large international variations in prostate cancer risk and increased risk for migrants from low- to high-risk countries suggest a considerable influence of environmental factors (3,4). Low-frequency genes linked to familial prostate cancer (5,6) explain only $\approx$ 9% of all cases. Hereditary factors are more relevant for prostate cancer in younger men and contribute here as much as 43% to the overall prostate cancer risk (5). Regarding the lifetime risk for prostate cancer, the impact of the identified genetic factors is, however, less pronounced compared to the influence of lifestyle habits, including nutrition.

Lycopene is a nonprovitamin A carotenoid, which is mainly consumed via tomato-based food. Watermelon, pink grapefruit, and guava are also sources of dietary lycopene. Lycopene is the strongest antioxidant carotenoid (7) with respect to singlet oxygen quenching (8) and lipid peroxyl radical scavenging (9,10). This suggests antioxidant protection of biomolecules (lipids, proteins, and DNA) by lycopene also in the in vivo situation. Lycopene was shown to influence important biological processes, which determine cell fates, for example, cell cycle progression, cell communication, cell adhesion, and inflammatory, hormonal, and growth factor signaling pathways (11). It is as yet unknown whether all these effects can be explained by the antioxidant action of lycopene or whether additional mechanisms are involved.

Epidemiological evidence links tomato consumption (12–14), lycopene intake (15), or lycopene plasma levels (16) with a reduced prostate cancer risk. Further studies have found that high lycopene plasma levels are connected to a lower risk of sporadic prostate cancers in older men (17) and with more advanced disease (18).

Several preliminary clinical trials have supported a lycopene effect on prostate health. Lycopene (8 mg/day for 1 yr, tomato oleoresin) reduced serum levels of prostate specific antigen (PSA) by 42% in high-grade PIN patients. During the study period, the serum PSA levels increased in controls by 23% (19). In patients with localized prostate cancer, lycopene (30 mg for 3 wk) from pasta sauce (20) or from tomato oleoresin (21) decreased PSA levels by 17–18%. In another study, lycopene (10 mg/day for 1 yr) from tomato oleoresin reduced PSA velocity in prostate cancer patients (22). First evidence also suggests a benefit of lycopene in BPH patients. Tomato paste intervention (50 g for 10 wk) decreased serum PSA levels by 10.8% in BPH patients (23). Also, pure lycopene (15 mg/day for 6 mo) decreased serum PSA levels by 11.3%, improved International Prostate Symptom Score, and tended to prevent prostate enlargement in BPH patients (24).

LYCOPENE EFFECTS CONTRIBUTING TO PREVENTION OF PROSTATE CANCER INITIATION

Prostate cancer initiation is thought to be caused by accumulation of mutations in critical control genes for growth and

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differentiation [e.g., (25)]. Such mutations can be the consequence of oxidative DNA damage, for instance, occurring due to the reactive oxygen species (ROS) released by macrophages to fight bacterial prostatitis. DNA damaged by oxidative insults contains oxidized bases, for example, 8-oxo-desoxy-guanosine (80 HdG), which are repaired by the base excision machinery. Furthermore, single strand breaks or double strand breaks can be found, as detectable by the Comet assay. Alternatively, exposure to exogenous carcinogens can cause DNA damage. Once the cellular genome surveillance systems detect DNA damage, cell cycle arrest is induced until DNA integrity has been restored. In case the DNA damage is too profound, the affected cells will undergo apoptosis. Failure to recognize and/or repair damaged DNA results in mutations and possibly cancer initiation. Thus, prevention of DNA damage is relevant for primary cancer prevention.

Prevention of Oxidative DNA Damage

Lockett et al. (26) indeed found that a high susceptibility of lymphocytes to H_2O_2-induced DNA damage is associated with a 1.6-fold increased risk for incident prostate cancer. Lycopene reduced oxidative DNA damage in cell culture and in rat prostate tissue (27,28) in an iron-induced oxidative stress model. In clinical trials, lycopene provided as tomato purree (29,30), pasta sauce (31), tomato oleoresin (32), or as pure lycopene (33) reduced oxidative DNA damage in lymphocytes [reviewed in (34,35)]. First evidence that lycopene also reduces oxidative DNA damage in human prostate tissue came from Chen et al. (31). Polymorphisms of XRCC1, a gene involved in DNA repair, influence the effect of lycopene and other antioxidants on prostate cancer risk reduction. In men with an Arg/Arg genotype at codon 889, lycopene was linked to a reduced prostate cancer risk but not in men with an Arg/Gln or Gln/Gln genotype (36).

Induction of Phase II Enzymes

Upregulation of Phase II enzymes is crucially involved in detoxifying and eliminating toxic low molecular agents including exogenous carcinogens (37). Silencing of the Phase II enzyme glutathione-S-transferase Π1 (GSTP1) by promoter methylation is found frequently in prostate cancer (38). GSTP1 silencing has also been detected in proliferative inflammatory atrophy (PIA) lesions (see below) (39).

Lycopene increased the activity of the Phase II enzymes quinone reductase (QR), glutathione peroxidase (GP), glutathione-S-transferase (GST), and glutathione reductase (GR) as well as GSH levels in several animal models [healthy rats (40,41); rat model for gastric carcinogenesis (42), DMBA-induced hamster buccal pouch carcinogenesis model (43,44); T2-toxin-treated chicken (45)]. Induction of Phase II enzymes was linked to suppressed DMBA-induced oral carcinogenesis in hamsters (43). Also, enzymes of oxidative defense were induced (40), and lipid peroxidation was reduced (42–44). Genes encoding Phase II enzymes and the oxidative defense system are coregulated by the Nrf2/Keap1 system via the antioxidant response element (ARE) in the promoter of these genes (46). Ben-Dor et al. (47) showed that lycopene, and possibly also polar lycopene metabolites, indeed are capable of activating the ARE in an Nrf2-dependent manner. Tomato intervention in humans for 60 days significantly increased the serum levels of the Phase II enzymes SOD, GPx, GR, and reduced GSH (48).

Upregulation of Phase II enzymes indicates that lycopene improves the protection against exogenous toxins including carcinogens.

Together with lycopene's ability to reduce oxidative damage of DNA, the induction of Phase II enzymes by lycopene should contribute to improved DNA integrity and thus reduced prostate cancer initiation (Fig. 1).

LYCOPENE EFFECTS CONTRIBUTING TO PROSTATE CANCER PROGRESSION

Prostate cancer progression involves the cross-talk of several signaling pathways, which synergistically promote growth and inhibit apoptosis (Fig. 2A). Crucial pathways implicated in prostate cancer development include steroid hormone signaling, inflammatory signaling, and growth factor signaling [for review, see (49–54)]. Inflammatory signaling activates NFκB, for example, via TLR4 in case of a bacterial prostatitis, leading to the induction of inflammatory mediators, including IL-6. IL-6, in turn, actiates the Jak/STAT pathway and further stimulates inflammation but also growth and survival. Growth factor signaling, for example, IGF-I signaling, act via the MAPK pathway to promote cell proliferation, and via the PI3K/AKT pathway to inhibit apoptosis. AKT links PI3K signaling to Wnt/β-catenin signaling by phosphoinhibition of GSK3β, resulting in more β-catenin available for gene regulation. Activation of Wnt/β-catenin signaling promotes growth by induction of target genes, such as c-myc, cyclin D1, uPA, CD44, FGF2, MMP4, and others, by complexes of TCF/Lef-1 type transcription factors and β-catenin (53).

Androgens, especially dihydrotestosterone (DHT), represent the most important mitogen in prostate tissue. DHT is activated from testosterone (T) by 5α-reductases. The androgen receptor (AR) induces androgen target genes (e.g., PSA) as a homodimer in a ligand dependent manner (genomic pathway). In addition, the AR also signals growth promotion and apoptosis inhibition via PI3K and MAPK [nongenomic pathway; (55)].

The aforementioned pathways cross-talk in prostate cancer development, since STAT3 (upon IL-6 signalling) and β-catenin (after Wnt pathway activation) can bind and activate the AR in the absence of androgens, thus contributing to the progression to androgen-independent prostate tumor growth (51,53).

Inflammation

Chronic prostatitis and PIA lesions have been recognized as risk factors for development of prostate cancer and BPH (56,57). The prevalence of chronic prostatitis is high already in approximately 20-yr-old men. Depending on the threshold

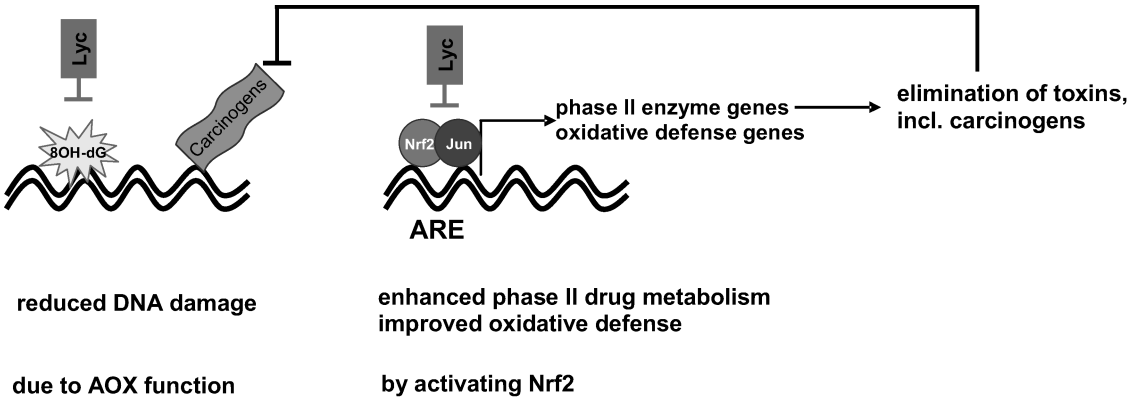

FIG. 1. Modes of action of lycopene to contribute to reduced prostate cancer initiation. Lyc reduces oxidative DNA damage and induces Phase II drug metabolizing enzymes as well as genes involved in oxidative defense. Phase II enzymes are involved in the detoxification of toxins, including carcinogens. 8OH-dg, 8-hydroxy-2-deoxy-guanosine; ARE, antioxidant response element; AOX, antioxidant.

criteria applied, the prevalence of asymptomatic prostatitis was determined as 6 or 19% in addition to a prevalence of 10 to 14% for symptomatic prostatitis (58). The etiology of prostatitis is not entirely clear, but bacterial (and viral) infections are involved.

Molecular mechanisms, which could contribute to an elevated risk for prostate cancer and/or BPH in chronicly inflamed tissue, are, for example, oxidative DNA damage due to ROS generation by macrophages. In addition, IL-6, COX2, and LOXs are induced by activation of TLR4 and the NFκB pathway (59) by bacterial LPS. IL-6 is an important mitogen in normal and androgen-independent prostate cells. IL-6 can also activate the androgen receptor, and contributes to androgen-independence of prostate tumors (51). COX and LOX activities generate 4HNE (4-hydroxynonenal) and MDA (malondialdehyde) as byproducts (60), which further stimulate the inflammatory response. Last but not least, NFκB activation can counterbalance apoptosis induction.

Lycopene downregulated inflammatory regulators, among these cytokines, enzymes, and transcription factors, in cell culture systems. COX-2, iNOS, IRF-1, and STAT-1a expression was decreased in mouse macrophages (61). Lycopene also downregulated MMP-9 in human liver cancer cells, implying reduced tissue destruction during chronic inflammation, as well as a lower risk for metastasis (62). Lycopene also decreased expression of IL-1β, MIP-2, LIX, markers for immune cell infiltration in healthy rat prostate tissue (63). Interestingly, lycopene (9 mg/kg BW for 2 wk) synergized with the antibiotic ciprofloxacin to ameliorate inflammation in a rat model for bacterial prostatitis (64). In rat prostate tumors (Dunning MatLyLu), lycopene decreased IL-6 expression (65). Furthermore, TNFα serum level was reduced in humans by 34% after supplementation with 5.7 mg/day lycopene for 26 days from tomato oleoresin (66).

Inhibition of NFκB activation explains at least part of the anti-inflammatory effect of lycopene (67). Anti-inflammation reduces the likelihood for progression to androgen-independent growth.

Inhibition of Androgen Activation and Signaling

Androgens represent the major mitogens for prostate cells. Studies of prostate biology suggest that 5-α-dihydrotestosterone is the principal androgen responsible for both normal and hyperplastic growth of the prostate gland. 5-α-dihydrotestosterone is produced from testosterone by steroid 5-α-reductase. Lycopene reduced androgen signalling in reactive prostate stroma cells (68). Reactive stroma is stroma located adjacent to tumorous prostate epithelium, which is hence exposed to the altered signals emanating from the diseased epithelial cells. Upon DHT treatment, reactive, but not normal, stroma secretes IGF-I. At the same time, DHT increases nuclear localization of AR and β-catenin, arguing that AR/Wnt/β-catenine signaling cross-talk is involved in DHT-induced IGF-I secretion.

Lycopene (Fig. 2b), in dietary concentrations, decreased DHT-induced IGF-I production by reactive stromal cells and reduced DHT-induced nuclear localization of AR by 60% and of β-catenin by 50% in reactive stromal cells (68). Lycopene reduced androgen signalling, including expression of AR target genes, also in healthy rat prostate tissue, where 5α-reductase 2 (to 66% DL/81% LL), and androgen target genes (prostatic steroid binding protein C1 and C3; cystatin related protein 2, and seminal vesicle secretion protein IV) were downregulated (63). Similarly, in rat prostate tumors (65), lycopene reduced expression of 5-α-reductase I (to 36%) and androgen target genes (up to 50-fold; cystatin related protein 1 and 2, prostatic spermine-binding protein, prostatic steroid-bg protein C1, C2, and C3 chain, probasin).

In several preliminary clinical intervention trials, lycopene reduced serum levels of PSA (20–22,69) in prostate cancer and BPH patients (23,24). The gene encoding PSA is one of the well known androgen target genes (70). Decrease of serum PSA levels is therefore in line with an antiandrogen effect of lycopene also in the human prostate. Lycopene (at 1.5 μM) reduced PSA secretion by LNCaP cells by 55%. The mode of action of interfering with expression of androgen target genes is not clear. Lycopene is not a ligand for the androgen receptor (71).

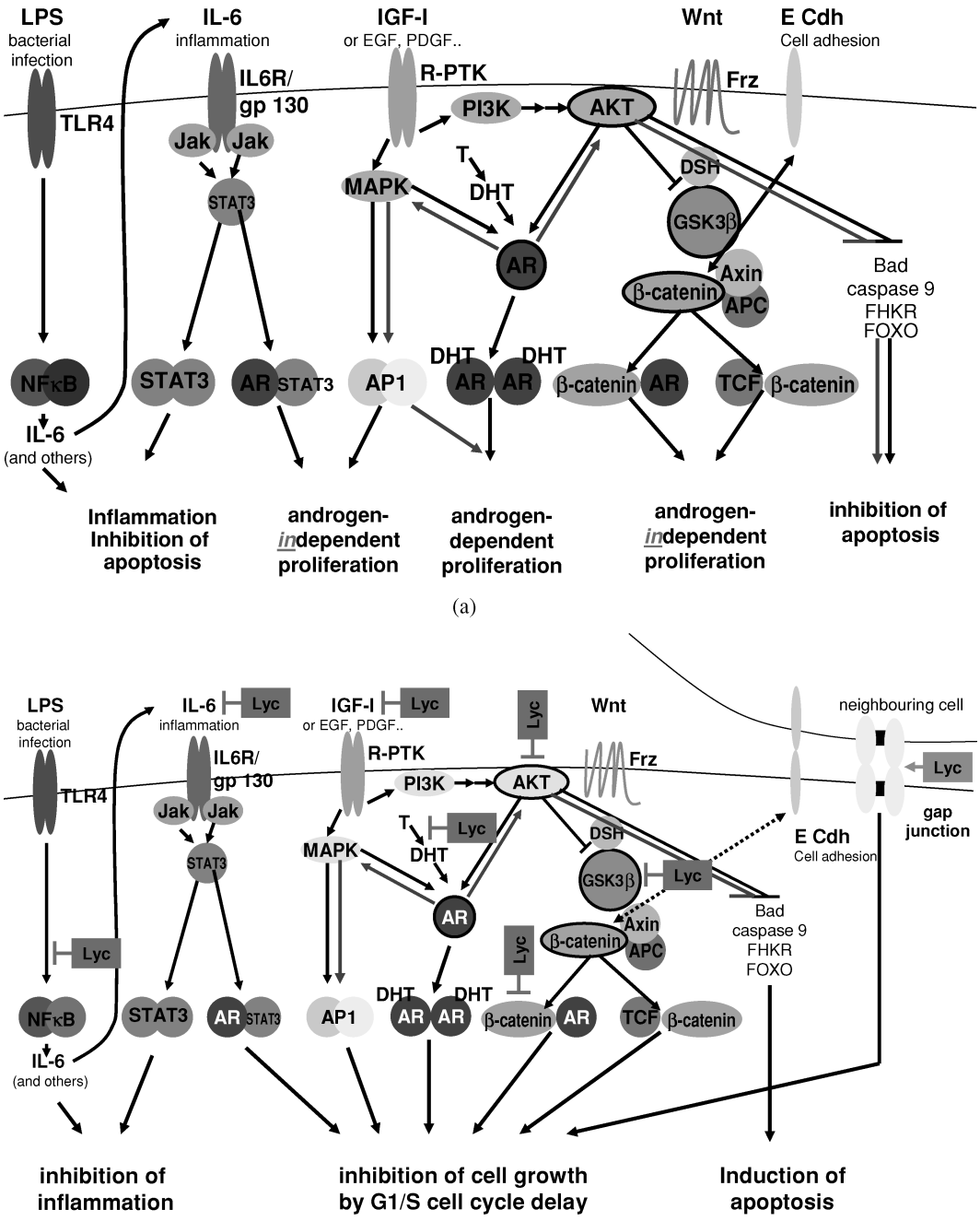

FIG. 2. A: Molecular pathways crucially involved in prostate cancer development and progression: Inflammatory signaling activates NFκB, for example via TLR4 in case of a bacterial prostatitis, leading to the induction of inflammatory mediators including IL-6. IL-6 then actiates the Jak/STAT pathway and further stimulates inflammation but also growth and survival. Growth factor signaling, for example, IGF-I signaling, promote cell proliferation via the MAPK pathway, and inhibit apoptosis via the PI3K/AKT pathway. AKT links PI3K signaling to Wnt/β-catenin signaling by phosphorylation of GSK3β, resulting in more βcatenin available for gene regulation. Activation of Wnt/β-catenin signaling promotes growth by induction of target genes. The androgen DHT is activated from T by 5α-reductases. The androgen receptor (AR) induces androgen target genes (e.g., PSA) as a homodimer in a ligand-dependent manner (genomic pathway). In addition, the AR also signals growth promotion and apoptosis inhibition via PI3K and MAPK (nongenomic pathway). STAT3 (on IL-6 signaling) and β-catenin (on Wnt pathway activation) can bind and activate the AR in the absence of androgens, thus contributing to the progression to androgen-independent prostate tumor growth. B: Lycopene inhibits multiple pathways, which are linked in cross-talk in prostate cancer development, resulting in anti-inflammation, growth reduction, and apoptosis induction. LPS, lipopolysaccharide.

In conclusion, downregulation of androgen signalling by lycopene should contribute to a decreased androgen-dependent prostate growth. Androgen deprivation is the therapy of choice against prostate cancer.

Inhibition of IGF-I Signal Transduction

The IGF-I axis is regarded as a major pathway in prostate cancer development [reviewed in (72)]. IGF-I and IGF-II signal [reviewed in (73)] via the IGF1R, and can promote cell survival and cell proliferation via IRS-1 and the PI3K/Akt and MAPK pathways. IGF also induces cell differentiation (mediated by Shc). Furthermore, IGF is involved in the control of cell motility via IRS-2. There are 6 IGF-binding proteins, which control the availability of circulating IGF. High IGF-I serum levels are linked to an elevated risk for prostate cancer (74,75). Moreover, IGF-I expression is upregulated during tumor progression in the TRAMP mouse prostate cancer model (76). Overexpression of IGF-I in prostate epithelium leads to epithelial hyperplasia (77) and prostatic intraepithelial neoplasia (78). The IGF1R is required for prostate cell sensitivity to oncogenic transformation by SV40 large T, EGFR, PDGFR, or activated Ras. Also, IGF1R is frequently overexpressed in prostate cancer, in part due to inactivation of p53, BRCA1, or VHL. The IGF pathway interacts with other pathways relevant in prostate cancer development, such as androgen signaling or Wnt/β-catenin signaling (79). Activation of Akt, the key kinase mediating IGF-I signals, is probably important for the progression of prostate cancer to an androgen-independent state. Poorly differentiated tumors exhibit increased expression of a phosphorylated (activated) form of AKT compared to normal tissue, PIN, or well-differentiated prostate cancer (80,81). The IGF pathway was identified as one of three gene networks upregulated in prostate cancer in comparison with BPH (82).

Lycopene (Fig. 2b) inhibits IGF-I signalling at different levels of the signaling pathway (Fig. 2B). In LNCaP prostate tumor cells, lycopene decreased IGF1R expression and activation, increased IGFBP 2 expression, and decreased AKT activation (83). In healthy rat prostate tissue (63) and in rat prostate tumors (65), lycopene decreased the local expression of IGF-I mRNA. In humans, the highest lycopene plasma response after tomato drink consumption was connected to 5.7% lowering of IGF-I plasma level in healthy probands (84). Tomato oleoresin supplementation (21) did not alter IGF-I levels in prostate cancer patients. However, since the bulk of IGF-I in the circulation is secreted from the liver, a downregulation of IGF-I in the prostate by lycopene is not necessarily reflected in the serum IGF-I concentration and suggests that the lycopene effect on IGF signals calls for analysis in prostate tissue in addition to serum.

In conclusion, inhibition of IGF signalling by lycopene helps to reduce the likelihood for progression to androgen-independent growth of prostate cancer.

Inhibition of Wnt/β-Catenin Signaling

Wnt/β-catenin is one of the most important pathways involved in tumor growth in general. Wnt ligands bind to Frizzled to activate Disheveled and to phospoinhibit GSK3β. GSK3β, if active, phosphorylates β-catenin and targets it for ubiquitination and proteasomal degradation. Inhibition of GSK3β leaves more β-catenin available to relocate to the nucleus where it induces expression of genes involved in cell proliferation and survival together with Lef-1/TCF-type transcription factors. Wnt/β-catenin signaling cross-talks with androgen signaling, since β-catenin also binds and activates the AR. In addition, Wnt/β-catenin signaling is linked with PI3K/AKT signaling because AKT also activates Wnt/β-catenin signaling by phosphoinhibiting GSK3β. Together, Wnt/β-catenin signaling is involved in progression to androgen-independent disease via cross-talk with androgen and PI3K/AKT signaling (53,85). Lycopene (Fig. 2b) reduced Wnt/β-catenin signaling in reactive (but not normal) prostate stroma cells (68) by decreasing DHT-induced nuclear localization of AR and β-catenin. As a result, lycopene reduced DHT-induced IGF-I excretion by reactive stroma cells. In normal prostate epithelial cells (68) treated with IGF-I, lycopene reduced AKT activation and subsequently GSK3β phosphoinhibition.

Increase of Gap Junctional Communication

Gap junctions, connexons, are formed by assembly of transmembrane connexin proteins and have various functions including intercellular communication. Accumulating evidence suggest that gap junctional communication is also important for controlling cell proliferation and tissue maintenance in epithelial tissues. Of all the known connexins, Cx43 and Cx32 are expressed in exocrine and endocrine glands. In healthy prostate tissue, Cx43 protein is present in basal epithelial cells and Cx32 in luminal epithelial cells. In prostate cancer tissue, Cx43 and Cx32 expression is decreased compared to healthy prostate tissue (86). Forced Cx43 expression induces growth arrest in androgen-responsive but not in androgen-independent prostate cancer cells due to impaired connexin trafficking to the cell surface (87,88).

Lycopene (Fig. 2b) inhibited carcinogen-induced neoplastic transformation in cell culture. This activity involved upregulation of Cx43 expression and improved gap junctional communication (89,90). Lycopene upregulation of Cx43 mRNA is independent of de novo protein synthesis, and involves a Sp1/Sp3 GC-box within -158 bp and $+209$ bp of the Cx 43 transcription start site (91). First data in humans indicate that lycopene may indeed increase Cx43 expression in the prostate (21). In conclusion, improved gap junctional communication by lycopene contributes to reduced cell proliferation and transformation. This mechanism may be more important during the androgen-dependent stages of the disease.

Lycopene Interference With Growth Factor Signaling Pathways Leads to Cell Cycle Arrest and Apoptosis Induction

The lycopene effects described above (Fig. 2B) all point toward an inhibition of cell proliferation and a reduction in cell survival signals. Accordingly, lycopene has been shown to reduce cell proliferation in prostate cancer cells (83,92–95). Lycopene at 1 μM reduced cell proliferation by 40% after 24 h and by 70% after 48 h (96). In normal prostate epithelial cells, lycopene at 1 μM inhibited DNA synthesis by 48.9% (22). Lycopene at concentrations of 2 μM and higher inhibited cell growth by 80% (97). Growth inhibition was associated with a delayed G1-S cell cycle progression and involved downregulation of cyclin D1 and E, cyclin-dependent kinase 4, and suppressed Rb phosphorylation. Hwang and Bowen (96) found in LNCaP that lycopene may also inhibit G2/M phase transition.

Moreover, lycopene induced apoptosis in prostate cancer cells [LNCaP (83,96)]. A clinical study with tomato-based lycopene intervention (30 mg for 3 wk) indeed found an increased apoptotic index in hyperplastic and neoplastic cells in human prostate tissue–both in benign hyperplastic and in cancerous tissue (20,98).

MECHANISTIC INTEGRATION OF LYCOPENE EFFECTS AND OUTLOOK

The various molecular lycopene effects reported result in increased antioxidant protection and oxidative defense, anti-inflammation, reduced cell proliferation, and induction of apoptosis. The cascade of molecular events, however, has so far not been elucidated. Lycopene, due to its lipophilic character, is expected to reside in cellular membranes. The majority of lycopene is located in the nuclear membrane and in the nuclear matrix [in LNCaP cells (71)]. The remainder of lycopene was detected in the microsomal fraction, including the cellular membrane. It is conceivable that lycopene in the nucleus helps to prevent DNA oxidation, as well as lipid oxidation. Lipids in the nuclear matrix have been implicated in chromatin modification (99) and therefore gene regulation. Moreover, lycopene may contribute to protection of membrane lipids from oxidation. Cholesterol oxidation in the nuclear membrane was shown to inhibit NTPase activity. NTPase is involved in generating the energy required for protein transport to and mRNA transport from the nucleus to the cytoplasm (100). This implies that oxidation of nuclear membrane cholesterol has an effect on overall gene expression due to its interference with NTPase activity.

Lipid oxidation not only changes the function and structure of lipids but also gives rise to intermediate lipid peroxides (LOOH), as well as to end products of lipid peroxidation such as 4HNE, 4-hydroxy-2-hexenal, and MDA, which have effects on their own. Lipid peroxidation end products form protein adducts and cross-links, causing impaired protein and hence cell dysfunction, inflammation, cell proliferation, later growth arrest, and finally apoptosis or necrosis (101). These effects of lipid peroxidation end products are conveyed by JNK/SAPK signaling, inhibition of proteasome-mediated protein degradation, and initial activation and later inhibition of growth factor receptors (PDGFR, EGFR, IGF-1R). Moreover, 4-HNE also forms DNA adducts and thus is mutagenic. In prostate cancer patients, MDA plasma levels are elevated (102–107). Tam et al. (108) showed in the TRAMP mouse prostate cancer model that prostatic premalignant lesions contain 4-HNE-protein-adducts, which where not present in prostates of nontransgenic littermates. Lycopene reduced lipid peroxidation in prostate cancer cells [LNCaP; (109)] and in rat prostate tissue [Fe-induced oxidative stress; (28)]. Lycopene and MDA plasma levels were inversely correlated in prostate cancer patients (105). Furthermore, tomato intervention lowered the lipid peroxidation rate [in hypertensive probands (48). Regarding the prevention of protein oxidation, several important signaling molecules have been identified as targets for oxidation, for example, MAPK pathway members, NFκB, and STAT3 (110). Redox balance of these proteins is crucial for maintaining a physiological equilibrium of signals for cell proliferation, differentiation, inflammation, and apoptosis.

In summary, lipid and protein oxidation activates many of the pathways that are inhibited by lycopene. Even if the proof for the cascade of molecular events has not been established, it is plausible to assume that reduction of lipid and/or protein oxidation may be the initial event for many gene regulations by lycopene.

Lycopene could also act by mechanisms independent of its antioxidant function. Possible modes of action include changes in membrane fluidity, for example, in lipid rafts. The cell membrane contains lipid rafts of highly organized domains rich in cholesterol and sphingolipids. Lipid rafts have a crucial role in cell signaling, since receptors and other proteins required for signal transduction are recruited into lipid rafts. Also nongenomic androgen receptor signaling depends on lipid rafts (55). In membrane models, lycopene incorporation into cholesterol-containing model membranes led to membrane disorganization (111). Thus, lycopene could inhibit signaling pathways also by interfering with lipid raft-associated signaling processes.

CONCLUSION

Prostate cancer is the leading cause of cancer death in men in Western countries. Epidemiological evidence links lycopene/tomato intake to reduced prostate cancer risk. Several preliminary clinical intervention studies have further supported the epidemiological evidence. Prostate cancer development and progression involves several molecular pathways, which are connected in cross-talk, and which can compensate for each other to promote prostate (tumor) growth, if one pathway is inhibited selectively. Interestingly, lycopene is able to modulate several of the aforementioned pathways, providing a promising rationale for the prostate cancer risk reduction by lycopene: In many different experimental setups, lycopene reduced inflammatory signals; modulated the expression or activity of members

of the IGF axis, the Wnt/β-catenin pathway, and of androgen signaling; and also enhanced gap junctional communication. It is likely that lycopene's influence on these pathways contributes to decreased cell proliferation and apoptosis induction observed on lycopene supplementation. In addition, lycopene reduces DNA damage and improves carcinogen detoxification, thus reducing the risk for cancer initiation. Initial data suggest also a benefit of lycopene for BPH patients. The health benefits of lycopene have been predominantly linked to its antioxidant function. It is indeed conceivable that a substantial part of the lycopene effects on diverse biological pathways are mediated by its antioxidant action, but also other mechanisms might be involved.

REFERENCES

1. American Cancer Society: *Cancer Facts and Figures*. 2008. Available at http://seer.cancer.gov/csr
2. Wigle DT, Turner MC, Gomes J, and Parent ME: Role of hormonal and other factors in human prostate cancer. *J Toxicol Environ Health B Crit Rev* **11,** 242–259, 2008.
3. Matos EL, et al.: Cancer in migrants to Argentina. *Int J Cancer* **49,** 805–811, 1991.
4. Shimizu H, et al.: Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. *Br J Cancer* **63,** 963–966, 1991.
5. Giovannucci E: How is individual risk for prostate cancer assessed? *Hematol Oncol Clin North Am* **10,** 537–548, 1996.
6. Brothman AR: Cytogenetics and molecular genetics of cancer of the prostate. *Am J Med Genet* **115,** 150–156, 2002.
7. Edge R, et al.: Relative one-electron reduction potentials of carotenoid radical cations and the interactions of carotenoids with the vitamin E radical cation. *J Am Chem Soc* **120,** 4087–4090, 1998.
8. Di Mascio P, Kaiser S, and Sies H: Lycopene as the most efficient biological carotenoid singlet oxygen quencher. *Arch Biochem Biophys* **274,** 532–538, 1989.
9. Woodall AA, Britton G, and Jackson MJ: Carotenoids and protection of phospholipids in solution or in liposomes against oxidation by peroxyl radicals: relationship between carotenoid structure and protective ability. *Biochim Biophys Acta* **1336,** 575–586, 1997.
10. Woodall AA, et al.: Oxidation of carotenoids by free radicals: relationship between structure and reactivity. *Biochim Biophys Acta* **1336,** 33–42, 1997.
11. Wertz K, Siler U, and Goralczyk R: Lycopene: modes of action to promote prostate health. *Arch Biochem Biophys* **430,** 127–134, 2004.
12. Mills PK, Beeson WL, Phillips RL, and Fraser GE: Dietary habits and breast cancer incidence among Seventh-Day Adventists. *Cancer* **64,** 582–590, 1989.
13. Giovannucci E, et al.: Intake of carotenoids and retinol in relation to risk of prostate cancer. *J Natl Cancer Inst* **87,** 1767–1776, 1995.
14. Etminan M, Takkouche B, and Caamano-Isorna F: The role of tomato products and lycopene in the prevention of prostate cancer: a meta-analysis of observational studies. *Cancer Epidemiol Biomarkers Prev* **13,** 340–345, 2004.
15. Giovannucci E, et al.: A prospective study of tomato products, lycopene, and prostate cancer risk. *J Natl Cancer Inst* **94,** 391–398, 2002.
16. Gann PH, et al.: Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. *Cancer Res* **59,** 1225–1230, 1999.
17. Wu K, et al.: Plasma and dietary carotenoids, and the risk of prostate cancer: a nested case-control study. *Cancer Epidemiol Biomarkers Prev* **13,** 260–269, 2004.
18. Key TJ, et al.: Plasma carotenoids, retinol, and tocopherols and the risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition study. *Am J Clin Nutr* **86,** 672–681, 2007.
19. Mohanty NK, et al.: Lycopene as a chemopreventive agent in the treatment of high-grade prostate intraepithelial neoplasia. *Urol Oncol* **23,** 383–385, 2005.
20. Bowen P, et al.: Tomato sauce supplementation and prostate cancer: lycopene accumulation and modulation of biomarkers of carcinogenesis. *Exp Biol Med (Maywood)* **227,** 886–893, 2002.
21. Kucuk O, et al.: Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. *Cancer Epidemiol Biomarkers Prev* **10,** 861–868, 2001.
22. Barber NJ, et al.: Lycopene inhibits DNA synthesis in primary prostate epithelial cells in vitro and its administration is associated with a reduced prostate-specific antigen velocity in a phase II clinical study. *Prostate Cancer Prostatic Dis* **9,** 407–413, 2006.
23. Edinger MS and Koff WJ: Effect of the consumption of tomato paste on plasma prostate-specific antigen levels in patients with benign prostate hyperplasia. *Braz J Med Biol Res* **39,** 1115–1119, 2006.
24. Schwarz S, et al.: Lycopene inhibits disease progression in patients with benign prostate hyperplasia. *J Nutr* **138,** 49–53, 2008.
25. Girinsky T, et al.: Attenuated response of p53 and p21 in primary cultures of human prostatic epithelial cells exposed to DNA-damaging agents. *Cancer Res* **55,** 3726–3731, 1995.
26. Lockett KL, et al.: DNA damage levels in prostate cancer cases and controls. *Carcinogenesis* **27,** 1187–1193, 2006.
27. Matos HR, Di Mascio P, and Medeiros MH: Protective effect of lycopene on lipid peroxidation and oxidative DNA damage in cell culture. *Arch Biochem Biophys* **383,** 56–59, 2000.
28. Matos HR, et al.: Lycopene and beta-carotene protect in vivo iron-induced oxidative stress damage in rat prostate. *Braz J Med Biol Res* **39,** 203–210, 2006.
29. Riso P, Pinder A, Santangelo A, and Porrini M: Does tomato consumption effectively increase the resistance of lymphocyte DNA to oxidative damage? *Am J Clin Nutr* **69,** 712–718, 1999.
30. Porrini M and Riso P: Lymphocyte lycopene concentration and DNA protection from oxidative damage is increased in women after a short period of tomato consumption. *J Nutr* **130,** 189–192, 2000.
31. Chen L, et al.: Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention. *J Natl Cancer Inst* **93,** 1872–1879, 2001.
32. Porrini M, et al.: Daily intake of a formulated tomato drink affects carotenoid plasma and lymphocyte concentrations and improves cellular antioxidant protection. *Br J Nutr* **93,** 93–99, 2005.
33. Zhao X, et al.: Modification of lymphocyte DNA damage by carotenoid supplementation in postmenopausal women. *Am J Clin Nutr* **83,** 163–169, 2006.
34. Ellinger S, Ellinger J, and Stehle P: Tomatoes, tomato products and lycopene in the prevention and treatment of prostate cancer: do we have the evidence from intervention studies? *Curr Opin Clin Nutr Metab Care* **9,** 722–727, 2006.
35. Basu A and Imrhan V: Tomatoes versus lycopene in oxidative stress and carcinogenesis: conclusions from clinical trials. *Eur J Clin Nutr* **61,** 295–303, 2007.
36. Goodman M, et al.: Lycopene intake and prostate cancer risk: effect modification by plasma antioxidants and the XRCC1 genotype. *Nutr Cancer* **55,** 13–20, 2006.
37. Kwak MK, et al.: Role of phase 2 enzyme induction in chemoprotection by dithiolethiones. *Mutat Res* **480–481,** 305–315, 2001.
38. Lee WH, Isaacs WB, Bova GS, and Nelson WG: CG island methylation changes near the GSTP1 gene in prostatic carcinoma cells detected using the polymerase chain reaction: a new prostate cancer biomarker. *Cancer Epidemiol Biomarkers Prev* **6,** 443–450, 1997.

39. Nakayama M, et al.: Hypermethylation of the human glutathione S-transferase-pi gene (GSTP1) CpG island is present in a subset of proliferative inflammatory atrophy lesions but not in normal or hyperplastic epithelium of the prostate: a detailed study using laser-capture microdissection. *Am J Pathol* **163,** 923–933, 2003.
40. Breinholt V, Lauridsen ST, Daneshvar B, and Jakobsen J: Dose-response effects of lycopene on selected drug-metabolizing and antioxidant enzymes in the rat. *Cancer Lett* **154,** 201–210, 2000.
41. Zackheim HS: Re: Tomatoes, tomato-based products, lycopene, and prostate cancer: review of the epidemiologic literature. *J Natl Cancer Inst* **91,** 1331, 1999.
42. Velmurugan B, Bhuvaneswari V, Burra UK, and Nagini S: Prevention of N-methyl-N'-nitro-N-nitrosoguanidine and saturated sodium chloride-induced gastric carcinogenesis in Wistar rats by lycopene. *Eur J Cancer Prev* **11,** 19–26, 2002.
43. Bhuvaneswari V, et al.: Chemopreventive efficacy of lycopene on 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. *Fitoterapia* **72,** 865–874, 2001.
44. Bhuvaneswari V, Velmurugan B, and Nagini S: Induction of glutathione-dependent hepatic biotransformation enzymes by lycopene in the hamster cheek pouch carcinogenesis model. *J Biochem Mol Biol Biophys* **6,** 257–260, 2002.
45. Leal M, Shimada A, Ruiz F, and E Gonzalez de Mejia: Effect of lycopene on lipid peroxidation and glutathione-dependent enzymes induced by T-2 toxin in vivo. *Toxicol Lett* **109,** 1–10, 1999.
46. Dhakshinamoorthy S, Long II DJ, and Jaiswal AK: Antioxidant regulation of genes encoding enzymes that detoxify xenobiotics and carcinogens. *Curr Top Cell Regul* **36,** 201–216, 2000.
47. Ben-Dor A, et al.: Carotenoids activate the antioxidant response element transcription system. *Mol Cancer Ther* **4,** 177–186, 2005.
48. Bose KS and Agrawal BK: Effect of lycopene from tomatoes (cooked) on plasma antioxidant enzymes, lipid peroxidation rate and lipid profile in grade-I hypertension. *Ann Nutr Metab* **51,** 477–481, 2007.
49. Edwards J and Bartlett JM: The androgen receptor and signal-transduction pathways in hormone-refractory prostate cancer. Part 2: androgen-receptor cofactors and bypass pathways. *BJU Int* **95,** 1327–1335, 2005.
50. Canene-Adams K, et al.: Combinations of tomato and broccoli enhance antitumor activity in dunning r3327-h prostate adenocarcinomas. *Cancer Res* **67,** 836–843, 2007.
51. Corcoran NM and Costello AJ: Interleukin-6: minor player or starring role in the development of hormone-refractory prostate cancer? *BJU Int* **91,** 545–553, 2003.
52. Joshua AM, et al.: Prostatic preneoplasia and beyond. *Biochim Biophys Acta* **1785,** 156–181, 2008.
53. Mulholland DJ, Dedhar S, Coetzee GA, and Nelson CC: Interaction of nuclear receptors with the Wnt/beta-catenin/Tcf signaling axis: Wnt you like to know? *Endocr Rev* **26,** 898–915, 2005.
54. El Sheikh SS, et al.: Androgen-independent prostate cancer: potential role of androgen and ErbB receptor signal transduction crosstalk. *Neoplasia* **5,** 99–109, 2003.
55. Freeman MR, Cinar B, and Lu ML: Membrane rafts as potential sites of nongenomic hormonal signaling in prostate cancer. *Trends Endocrinol Metab* **16,** 273–279, 2005.
56. De Marzo AM, Marchi VL, Epstein JI, and Nelson WG: Proliferative inflammatory atrophy of the prostate: implications for prostatic carcinogenesis. *Am J Pathol* **155,** 1985–1992, 1999.
57. Krieger JN, et al.: Epidemiology of prostatitis. *Int J Antimicrob Agents* **31**(**1** Suppl), S85–S90, 2008.
58. Korrovits P, Ausmees K, Mandar R, and Punab M: Prevalence of asymptomatic inflammatory (National Institutes of Health Category IV) prostatitis in young men according to semen analysis. *Urology* **71,** 1010–1015, 2008.
59. Kundu SD, et al.: The toll-like receptor pathway: a novel mechanism of infection-induced carcinogenesis of prostate epithelial cells. *Prostate* **68,** 223–229, 2008.
60. Furstenberger G, Krieg P, Muller-Decker K, and Habenicht AJ: What are cyclooxygenases and lipoxygenases doing in the driver's seat of carcinogenesis? *Int J Cancer* **119,** 2247–2254, 2006.
61. De Stefano D, et al.: Lycopene, quercetin and tyrosol prevent macrophage activation induced by gliadin and IFN-gamma. *Eur J Pharmacol* **566,** 192–199, 2007.
62. Huang CS, Fan YE, Lin CY, and Hu ML: Lycopene inhibits matrix metalloproteinase-9 expression and down-regulates the binding activity of nuclear factor-kappa B and stimulatory protein-1. *J Nutr Biochem* **18,** 449–456, 2007.
63. Herzog A, et al.: Lycopene reduced gene expression of steroid targets and inflammatory markers in normal rat prostate. *Faseb J* **19,** 272–274, 2005.
64. Han CH, et al.: Synergistic effect between lycopene and ciprofloxacin on a chronic bacterial prostatitis rat model. *Int J Antimicrob Agents* **31**(**1** Suppl), S102–S107, 2008.
65. Siler U, et al.: Lycopene and vitamin E interfere with autocrine/paracrine loops in the Dunning prostate cancer model. *Faseb J* **18,** 1019–1021, 2004.
66. Riso P, et al.: Effect of a tomato-based drink on markers of inflammation, immunomodulation, and oxidative stress. *J Agric Food Chem* **54,** 2563–2566, 2006.
67. Kim GY, et al.: Lycopene suppresses the lipopolysaccharide-induced phenotypic and functional maturation of murine dendritic cells through inhibition of mitogen-activated protein kinases and nuclear factor-kappaB. *Immunology* **113,** 203–211, 2004.
68. Liu X, Allen JD, Arnold JT, and Blackman MR: Lycopene inhibits IGF-I signal transduction and growth in normal prostate epithelial cells by decreasing DHT-modulated IGF-I production in co-cultured reactive stromal cells. *Carcinogenesis* **29,** 816–823, 2008.
69. Ansari MS and Gupta NP: A comparison of lycopene and orchidectomy vs orchidectomy alone in the management of advanced prostate cancer. *BJU Int* **92,** 375–378, 2003.
70. Denmeade SR, et al.: Dissociation between androgen responsiveness for malignant growth vs. expression of prostate specific differentiation markers PSA, hK2, and PSMA in human prostate cancer models. *Prostate* **54,** 249–257, 2003.
71. Liu A, et al.: Absorption and subcellular localization of lycopene in human prostate cancer cells. *Mol Cancer Ther* **5,** 2879–2885, 2006.
72. Papatsoris AG, Karamouzis MV, and Papavassiliou AG: Novel insights into the implication of the IGF-1 network in prostate cancer. *Trends Mol Med* **11,** 52–55, 2005.
73. Hartog H, Wesseling J, Boezen HM, and van der Graaf WT: The insulin-like growth factor 1 receptor in cancer: old focus, new future. *Eur J Cancer* **43,** 1895–1904, 2007.
74. Furstenberger G and Senn HJ: Insulin-like growth factors and cancer. *Lancet Oncol* **3,** 298–302, 2002.
75. Pollak M: Insulin-like growth factors and prostate cancer. *Epidemiol Rev* **23,** 59–66, 2001.
76. Kaplan PJ, et al.: The insulin-like growth factor axis and prostate cancer: lessons from the transgenic adenocarcinoma of mouse prostate (TRAMP) model. *Cancer Res* **59,** 2203–2209, 1999.
77. Kaplan-Lefko PJ, et al.: Enforced epithelial expression of IGF-1 causes hyperplastic prostate growth while negative selection is requisite for spontaneous metastogenesis. *Oncogene* **27,** 2868–2876, 2008.
78. DiGiovanni J, et al.: Deregulated expression of insulin-like growth factor 1 in prostate epithelium leads to neoplasia in transgenic mice. *Proc Natl Acad Sci USA* **97,** 3455–3460, 2000.
79. Playford MP, Bicknell D, Bodmer WF, and Macaulay VM: Insulin-like growth factor 1 regulates the location, stability, and transcriptional activity of beta-catenin. *Proc Natl Acad Sci USA* **97,** 12103–12108, 2000.
80. Ghosh PM, Malik S, Bedolla R, and Kreisberg JI: Akt in prostate cancer: possible role in androgen-independence. *Curr Drug Metab* **4,** 487–496, 2003.

81. Shen MM and C Abate-Shen: Pten inactivation and the emergence of androgen-independent prostate cancer. *Cancer Res* **67,** 6535–6538, 2007.
82. Savli H, Szendr A, Romics I, and Nagy B: Gene network and canonical pathway analysis in prostate cancer: a microarray study. *Exp Mol Med* **40,** 176–185, 2008.
83. Ivanov NI et al.: Lycopene differentially induces quiescence and apoptosis in androgen-responsive and -independent prostate cancer cell lines. *Clin Nutr* **26,** 252–263, 2007.
84. Riso P, Brusamolino A, Martinetti A, and Porrini M: Effect of a tomato drink intervention on insulin-like growth factor (IGF)-1 serum levels in healthy subjects. *Nutr Cancer* **55,** 157–162, 2006.
85. Mulholland DJ, Dedhar S, Wu H, and Nelson CC: PTEN and GSK3beta: key regulators of progression to androgen-independent prostate cancer. *Oncogene* **25,** 329–337, 2006.
86. Neveu M and Bertram JS: Gap junctions and neoplasia. In: *Gap Junctions* Hertzberg EL and Bittar EE (eds.). Greenwich, CT: JAI Press, 2000, pp. 221–262.
87. Govindarajan R et al.: Impaired trafficking of connexins in androgen-independent human prostate cancer cell lines and its mitigation by alpha-catenin. *J Biol Chem* **277,** 50087–50097, 2002.
88. Mehta PP et al.: Suppression of human prostate cancer cell growth by forced expression of connexin genes. *Dev Genet* **24,** 91–110, 1999.
89. Bertram JS et al.: Diverse carotenoids protect against chemically induced neoplastic transformation. *Carcinogenesis* **12,** 671–678, 1991.
90. Zhang LX, Cooney RV, and Bertram JS: Carotenoids enhance gap junctional communication and inhibit lipid peroxidation in C3H/10T1/2 cells: relationship to their cancer chemopreventive action. *Carcinogenesis* **12,** 2109–2114, 1991.
91. Vine AL, Leung YM, and Bertram JS: Transcriptional regulation of connexin 43 expression by retinoids and carotenoids: similarities and differences. *Mol Carcinog* **43,** 75–85, 2005.
92. Kotake-Nara E et al.: Carotenoids affect proliferation of human prostate cancer cells. *J Nutr* **131,** 3303–3306, 2001.
93. Hall AK: Liarozole amplifies retinoid-induced apoptosis in human prostate cancer cells. *Anticancer Drugs* **7,** 312–320, 1996.
94. Tang L, Jin T, Zeng X, and Wang JS: Lycopene inhibits the growth of human androgen-independent prostate cancer cells in vitro and in BALB/c nude mice. *J Nutr* **135,** 287–290, 2005.
95. Kim L, Rao AV, and Rao LG: Effect of lycopene on prostate LNCaP cancer cells in culture. *J Med Food* **5,** 181–187, 2002.
96. Hwang ES and Bowen PE: Cell cycle arrest and induction of apoptosis by lycopene in LNCaP human prostate cancer cells. *J Med Food* **7,** 284–289, 2004.
97. Obermuller-Jevic UC et al.: Lycopene inhibits the growth of normal human prostate epithelial cells in vitro. *J Nutr* **133,** 3356–3360, 2003.
98. Kim HS et al.: Effects of tomato sauce consumption on apoptotic cell death in prostate benign hyperplasia and carcinoma. *Nutr Cancer* **47,** 40–47, 2003.
99. Zaina S, Dossing KB, Lindholm MW, and Lund G: Chromatin modification by lipids and lipoprotein components: an initiating event in atherogenesis? *Curr Opin Lipidol* **16,** 549–553, 2005.
100. Ramjiawan B et al.: Oxidation of nuclear membrane cholesterol inhibits nucleoside triphosphatase activity. *Free Radic Biol Med* **23,** 556–562, 1997.
101. Negre-Salvayre A, Coatrieux C, Ingueneau C, and Salvayre R: Advanced lipid peroxidation end products in oxidative damage to proteins. Potential role in diseases and therapeutic prospects for the inhibitors. *Br J Pharmacol* **153,** 6–20, 2008.
102. Aryal M et al.: Oxidative stress in patients with benign prostate hyperplasia. *JNMA J Nepal Med Assoc* **46,** 103–106, 2007.
103. Surapaneni KM and Venkata GR: Lipid peroxidation and antioxidant status in patients with carcinoma of prostate. *Indian J Physiol Pharmacol* **50,** 350–354, 2006.
104. Ozmen H et al.: Comparison of the concentration of trace metals (Ni, Zn, Co, Cu, and Se), Fe, vitamins A, C, and E, and lipid peroxidation in patients with prostate cancer. *Clin Chem Lab Med* **44,** 175–179, 2006.
105. Almushatat AS et al.: Vitamin antioxidants, lipid peroxidation, and the systemic inflammatory response in patients with prostate cancer. *Int J Cancer* **118,** 1051–1503, 2006.
106. Aydin A et al.: Oxidative stress and antioxidant status in non-metastatic prostate cancer and benign prostatic hyperplasia. *Clin Biochem* **39,** 176–179, 2006.
107. Yossepowitch O et al.: Advanced but not localized prostate cancer is associated with increased oxidative stress. *J Urol* **178,** 1238–1243, 1243–1244, 2007.
108. Tam NN et al.: Differential attenuation of oxidative/nitrosative injuries in early prostatic neoplastic lesions in TRAMP mice by dietary antioxidants. *Prostate* **66,** 57–69, 2006.
109. Hwang ES and Bowen PE: Effects of lycopene and tomato paste extracts on DNA and lipid oxidation in LNCaP human prostate cancer cells. *Biofactors* **23,** 97–105, 2005.
110. Sen CK and Packer L: Antioxidant and redox regulation of gene transcription. *Faseb J* **10,** 709–720, 1996.
111. McNulty HP et al.: Differential effects of carotenoids on lipid peroxidation due to membrane interactions: X-ray diffraction analysis. *Biochim Biophys Acta* **1768,** 167–174, 2007.