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Chapter 17

Prostate Cancer, Inflammation and Antioxidants

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/53296

1. Introduction

Prostate cancer (PCa) is a long latency type of tumour that usually develops in men older than 50 years of age. Prostate epithelial neoplasia (PIN), the initial malignant lesion, progresses to invasive carcinoma over the course of years. Because of the particular features of prostate carcinogenesis, this type of tumour may represent a paradigm for cancer prevention. The lack of a comprehensive aetiology for prostate cancer and the need for an effective and inexpensive biological treatment modality, devoid of side effects, has resulted in a multitude of therapeutic trials. Present evidence suggests that chemo preventive agents may be used in cancer treatment (Tallberg et al. 2008; Crohns et al. 2009). Because they are considered pharmacologically safe and derived from natural sources, most chemo preventive agents can be used in combination with chemotherapeutic agents to enhance the effect at lower doses and thus minimize chemotherapy-induced toxicity. There are various therapies that can successfully reduce the size of tumours, however, often patients suffer a relapse and the tumour re-grows. Some researchers believe that this happens because the therapies fail to eradicate a small proportion of cells that drive tumour growth known as cancer stem cells. They believe that these are the cells that should be targeted to eliminate the tumour forever.

Today, cancer is considered to be a complex multistep disorder, the result of a combination of factors including exposure to radiation and/or carcinogens (damage to DNA), infection, genetics, aging, immune function disorders, and lifestyle factors such as smoking (Nelson et al. 2003; Mahan et al. 2004). Several clinical trials have evaluated the effect of dietary nutrients on prostate tumour development. These dietary agents may help to suppress the transformative, hyper proliferative and inflammatory processes that initiate carcinogenesis. The curative effect does not seem to involve apoptosis (Tallberg and Atroshi, 2011).

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Most human diseases are due to chronic inflammation resulting in loss of function of a joint, a blood vessel or an entire organ. In some organs, such as the heart and brain, acute inflammation can be fatal. Oxidative stress is a major by-product of cellular metabolism and its regulation is critical for preventing disease and aging. Levels of reactive oxygen species (ROS) are generally higher in proliferating tumour cells than in normal cells, and this may explain why ROS is a key component in the efficacy of chemotherapeutic drugs (Crohns et al. 2009).

This review focuses on the mechanisms of free radical formation and ROS signalling in prostate cancer on the basis of current literature. We also highlight the mechanisms by which inflammatory processes contribute to prostatic carcinogenesis and how antioxidants react to neutralize free radicals.

2. Prostate cancer as an age-related disease

Prostate cancer is the common among men in the developed world. The risk increases after the age of 50 (Sakr et al., 1994; Abate-Shen and Shen, 2000; Schaeffer, 2003; Yancik 2005). Aggressive treatment for older men is not advisable because of an increased risk of short-term and long-term treatment-related adverse effects (Lu-Yao et al. 1999). The development of cancer lesions can be in two different regions of the prostate gland, in the peripheral zone, which is most common, and the remaining lesions are found in the transition zone located in the periurethral region (McNeal, 1988). Prostatic cancer multifocality makes accurate clinical staging difficult, and repeated revisions have been undertaken in an effort to optimize prognostic accuracy (McNeal, 1988; Andreoiu and Cheng, 2010).

Normal aging is associated with changes in body composition. While treatments for the disease continue to improve with each passing decade, the disease itself has likely been around since ancient times. Recently it was documented that a mummy - thought to be a man in his 50s - had numerous sclerotic spots throughout the bones of his pelvis and lower spine that were most consistent in appearance with metastases from prostate cancer (Prates et al., 2011).

3. Risk factors for prostate cancer

The etiological factors associated with prostate cancer are poorly studied compared to other common cancers. It is suggested that diet (Fair et. 1997; Schulman et al. 2001) and environmental differences (Muir et al. 1991) play important roles (Shimizu et al., 1991; Minami et al., 1993). For example, it is not known whether decreasing fat or increasing fruits and vegetables in the diet helps to decrease the risk of prostate cancer or death from prostate cancer. High intake of fat, especially total fat and saturated fat, is a risk factor for prostate cancer (Andersson et al. 1996; Kolonel, 2001). This has been explained by the evidence indicating that fat may be mediated through endogenous hormones

(Bosland, 2000). Phytoestrogen metabolites have been studied, and dietary habits are probably an important factor contributing to the geographic variations observed in some Asian men compared to European men, which may explain the low incidence of prostate cancer in Asia (Adlercreutz et al., 1993).

4. Mechanism of prostate cancer cell

Living cells have three main systems for protection and repair under oxidative stress: (1) direct antioxidant enzymes (Superoxide dismutase (SOD), catalase, peroxidises), (2) proteases and phospholipases activated by oxidative modification of membranes, (3) lipid and water soluble antioxidants (Sies, 1997; Finkel and Holbrook, 2000). Normalization of malignant gene transcription in an organ requires dietary correction of the etiologic long-standing metabolic deficiency involving six or more inter-linked natural factors aided by hormonal equilibrium, enhanced by specific autologous immunotherapy. In bio-immunotherapy this therapeutic bio-modulation is aims to simulate specific leukaemia, adenocarcinoma or sarcoma regulatory codes, leading to cancer cure by forcing tumour cells back into healthy gene transcription, without apoptosis. According to Lukacs et al. (2010), prostate cancer can be initiated by so many different mutations, and if a key regulator of self-renewal can be found, then partially one may control the growth of the cancer, no matter what the mutation is. Their approach, which aims to attack the process that allows the cancer cells to grow indefinitely, may provide an alternative way of treating cancer by targeting the core mechanism of cancer cell self-renewal and proliferation (Lukacs et al.2010).

Cells are often exposed to a high load of oxidants and free radicals. Oxidative stress can occur as a result of increased metabolic rate, increased oxygen tension, compromise of normal cellular antioxidants and many others endogenous and exogenous factors (Figure 1). Cell motility is a complex biological process, involved in development, inflammation, homeostasis, and pathological processes such as the invasion and metastatic spread of cancer (Collins et al. 2006). Cancer metabolism is a factor that might be exploited as a potential therapeutic target for drug discovery also on how a cancer cell differs in its metabolism to that of a rapidly proliferating normal cell (Vander Heiden et al. 2009). By small interfering RNA–based functional screening of over 200 metabolic enzymes, transporters, and regulators to identify those selectively required for prostate cancer cell survival. Ros and co-workers showed that treatment with a chemical antioxidant rescued the viability of PFKFB4 (one of the genes identified) -deficient prostate cancer cells, further suggesting that PFKFB4 mediates ROS detoxification in cancer cells. Together, these findings reveal that prostate cancer cells are exquisitely sensitive to metabolic perturbations that affect the balance between glucose and the pentose phosphate pathway and implicate PFKFB4 as a potential therapeutic target (Ros et al 2012).

Under normal conditions, the antioxidant defence systems are probably capable of maintaining a low steady-state level of damage and thus protecting the cells (Zhou et al.2003). Among the risk factors for the development of prostate cancer are ageing and lifestyle. Un-

der situations of oxidative stress and with increasing age the organism may not be able to maintain homeostasis with deleterious and potentially unfortunate consequences.

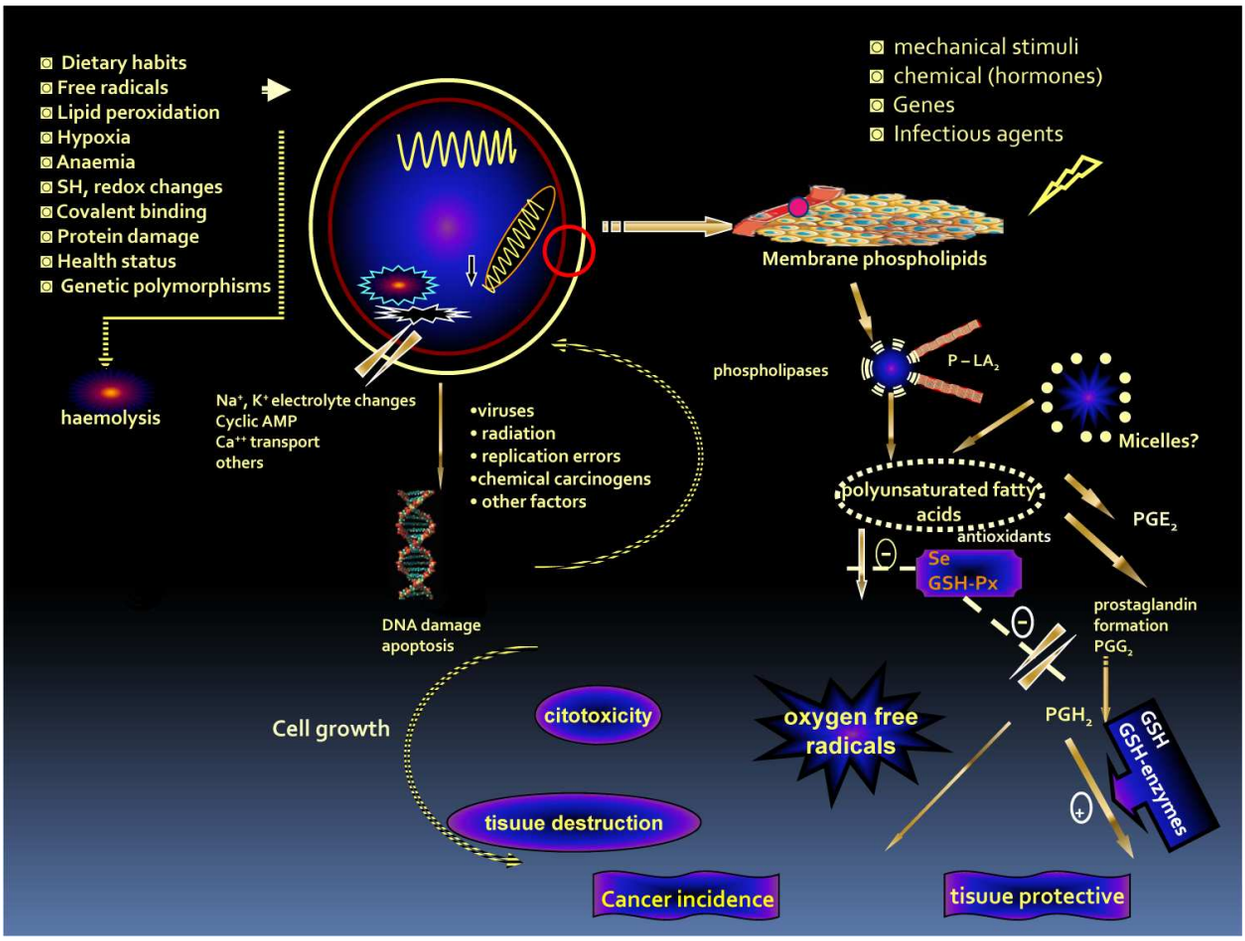


Figure 1. The prostanoid system may belong to the adaptive mechanisms by which the cell reacts to its environment. The reaction may be triggered by chemical, mechanical and other stimuli. Prostacyclin (PGI_2) and PGE_2 stimulate ATPases and the formation of intracellular cyclic AMP, which usually stabilize the cell membrane. TXA_2 among others may activate calcium-related processes which may lead to smooth muscle contraction, platelet aggregation and secretory events. PGE_2 has the capacity for both excitatory and inhibitory activities and it is often released in stressful situations. (Parantainen et al.1988)

5. Inflammation and prostate cancer

Inflammation involves the induction of complex, coordinated chemical signals and associated physiological processes following injury that promote "healing" of damaged tissues (Balkwill and Mantovani, 2001; Rakoff-Nahoum, 2006; Mantovani et al, 2008). Early responses include increases in vascular permeability and activation, together with the directed migration of leukocytes (neutrophils, monocytes and eosinophils) towards the site of injury, where the ground-work is being laid for the formation of a new extracellular matrix. The directional migration is mediated by secreted chemokines that form a concentration gradient

towards the site of inflammation (Koopmann and Krangel, 1997). The extracellular matrix provides the structure upon which cells (fibroblasts and endothelial cells) can migrate and proliferate, regenerating new tissue and a vascular network. In later stage of the inflammatory response, the macrophages are the dominant cell type, orchestrating and directing the healing process. Normally, inflammation is a self-limiting process due to the production of anti-inflammatory cytokines, which buffer the effect of pro-inflammatory cytokines. The cytokine/chemokine pattern persisting at the inflammatory site is important in the development of chronic disease. Deregulation of any of the cooperating factors can lead to prolonged inflammation with chronic exposure to cytotoxic mediators (Coussens and Werb, 2002). Chronic inflammation can be caused by a variety of factors, including bacterial, viral, and parasitic infections, chemical irritants, and non-digestible particles, but often the underlying cause is unknown. The longer the inflammation persists, the higher the risk of associated carcinogenesis (Shacter *et al.*, 2002, Coussens and Werb, 2002).

At the site of inflammation, caused by either wounding or infection, phagocytic cells (e.g. neutrophils and macrophages) generate reactive oxygen and nitrogen substances (Atroshi et al. 1988; Gallin, 1992), but these cells also synthesize and secrete large quantities of growth factors and a number of potent angiogenic factors, cytokines, and proteases, all of which are important mediators in the tissue regeneration, but can also potentiate neoplastic tumorigenesis. Prostaglandins, cytokines, nuclear factor NFkB, chemokines and angiogenic factors are the main molecular players that link inflammation to genetic alterations. However, free radical species derived from oxygen (ROI) and nitrogen (RNI) are the main chemical effectors (Jackson et al. 1997; Baron and, Sandler, 2000; Federico et al. 2007). Various carcinomas (including cancers of the liver, bladder, colon, stomach, and oesophagus) have been shown to arise from areas of infection and inflammation (Federico et al. 2007). Over 15% of all malignancies worldwide are attributable to infectious agents, and inflammation is a major component of these chronic infections (Kuper et al., 2000; Ibrahim and Makkiya, 2011). Colon cancers arising in individuals with inflammatory bowel disease (e.g. chronic ulcerative colitis or Crohn's disease) and stomach cancers caused by chronic Helicobacter pylori infection are among the most intensively studied and well established types of cancer associated with inflammation of different origins (Coussens and Werb, 2002).

6. The role of inflammation in the pathogenesis of prostate

Although it has been established that chronic inflammation plays a causative role in the development of many human cancers, the contribution of inflammatory processes to the development of prostate cancer has not been extensively studied. Bioactive food components are increasingly being evaluated as potential prostate chemopreventive agents (Barqawi et al. 2004; Chong and Rashid, 2005; Sonn, et al. 2005; Hsu et al 2010; Schellhammer, 2012). One such agent is resveratrol, a phytochemical which has been considered as a chemopreventive for human prostate cancer (Ratan et al. 2002; Stewart et al. 2003).

The contribution of inflammatory intermediates such as eicosanoids in cancer initiation and progression is another area of interest. These intermediates might form the link between in-

flammation and cancer. Interest in the relationship between chronic prostatic inflammation and prostate cancer is increasing. Proliferative inflammatory atrophy, or proliferative inflammatory atrophy (PIA), consists of lesions in the prostate characterized by atrophy of the epithelium and by an increased proliferative index (De Marzo et al. 1999). These lesions are common in older men and have been hypothesized to be a precursor of prostate cancer (Nelson et al. 2004; De Marzo et al. 2007). More knowledge about the risk factors could lead to better preventive measures together with better treatments.

Evidence suggests that inflammation is vital for the aetiology of prostate cancer and the pathogenesis of PCa reflects both hereditary and environmental components. These evidence stems from epidemiological, histopathological and molecular pathological studies (Ames et al., 1995; De Marzo et al. 1999; Coussens and Werb, 2002). More general evidence of a relationship between inflammation and prostate cancer has been provided by reports indicating that daily use of non-steroidal anti-inflammatory drugs (NSAIDs) may be associated with a reduce incidence of prostate cancer (Gupta et al. 2000). The exact mechanism whereby inflammation might act in tumour development and progression remains to be elucidated, but is likely to be complex.

Some studies have suggested that prostatitis, inflammation of the prostate gland that includes acute or chronic bacterial infection, may be linked to an increased risk of prostate cancer (Dennis et a. 2002; Roberts et al. 2004). This link was explained that chronic inflammation within the prostate due to the exposure of microbial agents stimulates the production of ROS and inflammatory cytokines leading to carcinogenesis (Coussens and Werb, 2002; De Marzo et al. 2007).

Chronic inflammation has been associated with the development of malignancy in several other organs such as the oesophagus, stomach, colon, liver and urinary bladder. Inflammation is thought to incite carcinogenesis by causing cell and genome damage, promoting cellular turnover, and creating a tissue microenvironment that can enhance cell replication, angiogenesis and tissue repair. Epidemiological data have correlated prostatitis and sexually transmitted diseases with an increased risk of prostate cancer and intake of anti-inflammatory drugs and antioxidants with a decreased risk. Evidence from genetic and molecular studies also supports the hypothesis that prostate inflammation and/or infection may be a cause of prostate cancer. In 1999 De Marzo et al proposed that proliferative inflammatory atrophy (PIA) is a precursor to PIN and cancer. Further research will provide opportunities for the discovery and development of strategies for treatment and prevention of prostate cancer (Sugar, 2006).

Accumulating epidemiologic and molecular evidence suggests that inflammation is an important component in the aetiology of prostate cancer. Supporting this hypothesis, population studies have found an increased risk of prostate cancer in men with a prior history of certain sexually transmitted infections or prostatitis. More general evidence of a relationship between inflammation and prostate cancer has been provided by reports indicating that daily use of non steroidal anti-inflammatory drugs (NSAIDs) may be associated with a lower incidence of prostate cancer. The exact mechanism whereby inflammation might act in tumour development and progression remains to be elucidated, but is likely to be complex.

http://dx.doi.org/10.5772/53296

Cancer lesions can develop in two different regions of the prostate gland, most commonly (in ~80% of cases) in the periphery zone, while most of the remaining lesions are found in the transition zone, which is located in the periurethral region (McNeal, 1968, 1988).

7. Possible interaction between prostaglandins and glutathione metabolism in prostate cancer

Prostaglandins (PGs) constitute a whole family of peroxidized lipids formed in most cells. Almost any kind of stimuli be it mechanical, chemical, physiological or traumatic, may initiate the formation of different kinds of PGs (Atroshi et al. 1986). Thus the particular importance of the local PG-impact is usually very difficult to evaluate. Some PGS, like PGEs and PGI_2 (prostacyclin), are potent triggers of inflammatory symptoms. The main roles for PGEs and PGI_2 in inflammation may in fact be in the generation of hyperalgesia, sensitization of the tissue to the irritant and pain producing activity of the amine and peptide type of mediators of inflammation (Ferreira and Nakamura, 1979; Ferreira 2002). On the other hand, these PGs have a marked tissue protective function, e.g. in preventing vasoconstriction and platelet aggregation. Other prostanoids (PG-like substances), like PGD_2, $PGF_2\alpha$ and thromboxane A_2 (TXA_2), are mostly vasoconstrictors. Their formation may be associated with allergic and other reactions of hypersensitivity, and TXA_2 is a very potent aggregator of platelets.

Prostaglandins play a role in the regulation of several important physiological and pathological processes, and evidence (Marnett, 1992; Thun et al., 1991; Taketo, 1998; Samuelsson et al., 2007) suggests that they could be involved in tumour progression. Studies have demonstrated that PGE_2 and its EP receptors are implicated in promoting carcinogenesis in different types of cancer (Wang and Klein, 2007). Arachidonic acid (AA) is the precursor for prostaglandin E_2 (PGE_2) synthesis and increases growth of prostate cancer cells (Van et al., 1998). However, the real sources of PGs are not well known and are a matter of speculation. For example we do not know for sure if the PGs originate in the blood, inflamed tissue, etc. There are several possibilities:

1. Bacterial toxins might contribute to the PG-release (figure 2). This was clearly demonstrated by Giri and coworkers (1984), and similar mechanisms might operate in the spontaneous disease as well (Liu et al. 2011; Sanz-Motilva et al. 2012).

2. The production of PGs is greatly increased by polymorphonuclear leukocytes. Neutrophil invasion is a typical feature in inflammation (Atroshi et al. 1988).

3. Changes in tissue protein and electrolyte contents are factors that have marked effects on PG-production (atroshi et al. 1988). Albumin is a typical factor increasing the formation of PGs, particularly that of $PGF_2\alpha$.

4. Inflammatory mediators are factors that might contribute to the formation of PGs. (e.g. monoamines and peptide hormones).

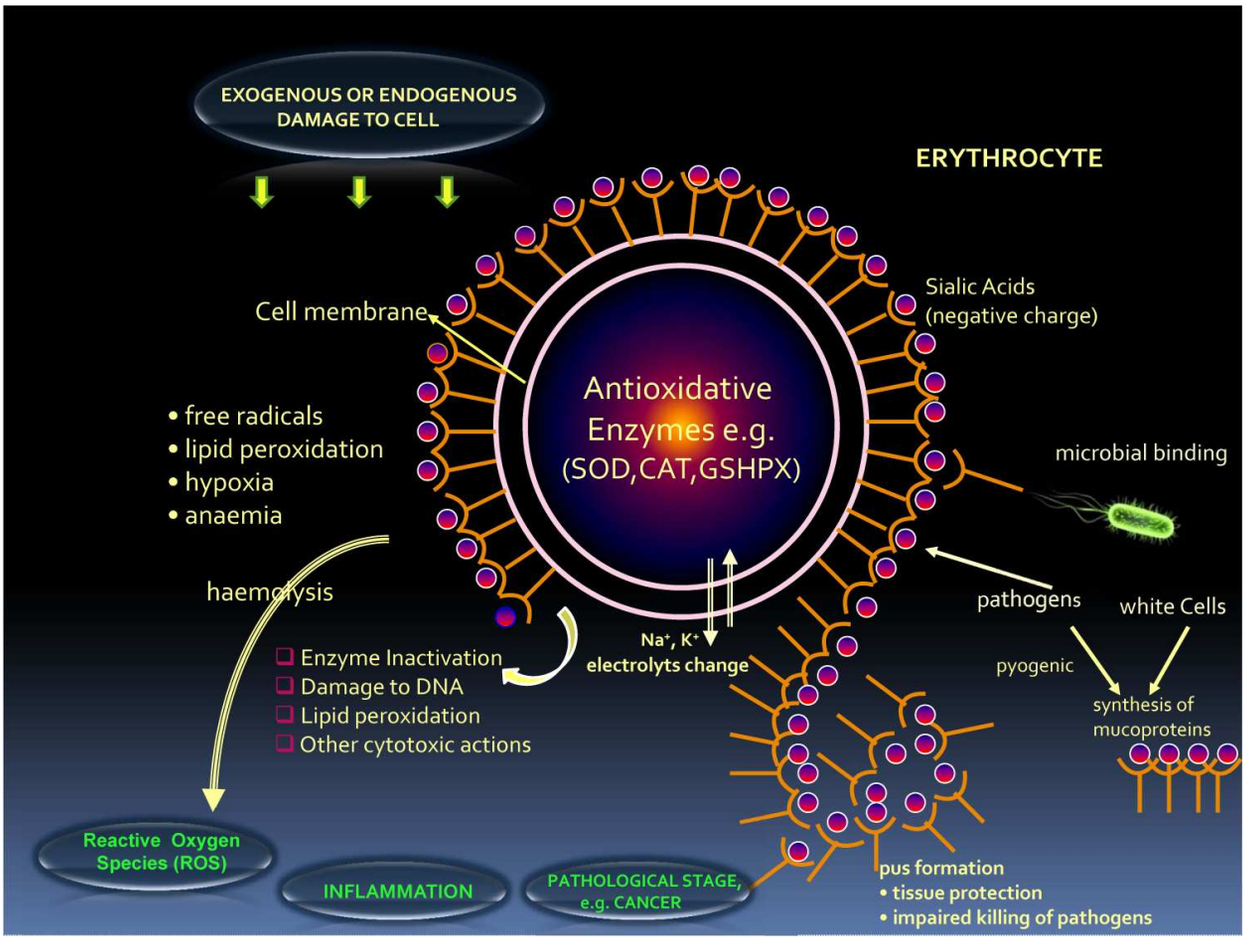


Figure 2. Possible interaction between erythrocyte and inflamed tissue during infection/inflammation. Oxygen free radicals produced by hypoxia, bacterial toxins and phagocytosis increase lipid peroxidation and peroxidative stress in the erythrocyte. Pyogenic bacteria as well as white cells may stimulate the synthesis of mucoproteins. The pus formed has antioxidant activity and the formation of oxygen free radicals is needed. GSH and other antioxidant enzymes represent the intracellular charged compounds, potential sources of reducing equivalents. The intracellular enzymes (GSH, GSHPX etc.) may greatly affected by oxygen free radicals and lipid peroxidation associated e.g. in infection, hypoxia and cancer. Destruction of erythrocytes is one possible source of GSH and other antioxidant enzymes which are elevated in the inflamed tissue. (Atroshi et al.1986)

8. Possible importance of leukotrienes

Leukotrienes (LTs) are biologically active fatty acids derived from the oxidative metabolism of arachidonic acid through the 5-lipoxygenase pathway (Matsuyama et al. 2010; Haeggström and Funk, 2011). Leukotrienes and other lipoxygenase products are synthesized from the same precursor fatty acids as PGs, and substantial changes in PG/LT balance are possible during inflammation and infection (Figure 3). LTs are highly vasoactive, and together with PGs they may contribute to the local haemodynamic changes in the inflamed tissue. Moreover, some LTs are very active leukotactic agents, and LTB_4 in particular could contribute to the massive invasion of neutrophils in the inflammatory area. PGE_2 and LTB_4 are involved

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in inflammation and carcinogenesis in several tissues. PGE_2 and inflammation may be associated to stromal benign prostatic hyperplasia whereas LTB_4 may play a role in prostate carcinogenesis; cancerous samples had higher LTB_4 levels than pericancerous samples, but there was no difference in PGE_2 levels (Larré et al. 2008).

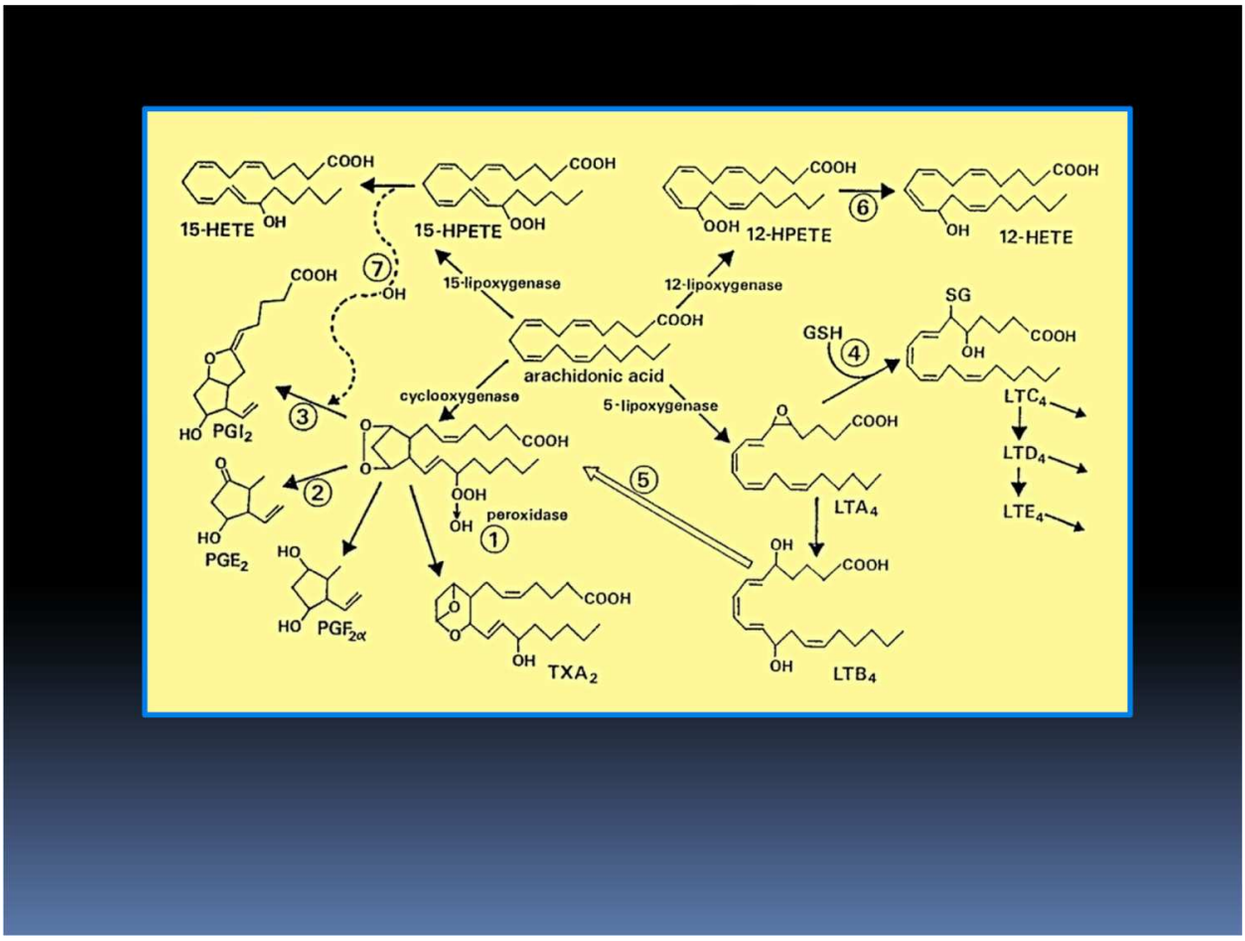


Figure 3. Enzymes with peroxidase activity are needed to reduce the endoperoxide PGG2 to PGH2 (1), and specific isomerases resembling GSH-S-transferase (2) reduce PGH2 further to PGs and prostacyclin (3). GSH and GSH-enzymes are involved in the formation of leukotrienes as well. One molecule of GSH (4) is attached to LTA 4 to form LTC4, the first of the cysteinyl leukotrienes (C, D, E). The peroxidative capacity of erythrocytes may participate in the conversion of LTA 4 to LTB4. Peroxidases are also needed to reduce other lipid hydroperoxides to corresponding alcohols (6) to prevent the enzyme destruction caused by oxygen free radicals (7). The activity of LTB4 may be mediated by PGs (5). (Atroshi et al. 1986)

Lipoxygenase-like activities are seen in the phagocytosis and bacterial killing. Lipid peroxidation as such is a source of oxygen free radicals. On the other hand, the radicals are among the most potent triggerers of lipid peroxidation. Some free radicals, particularly the hydroxyl radical (•OH) are very toxic to the tissues. During reduction of the 15-hydroperoxide, to the corresponding alcohol •OH is formed and the enzyme systems that form PGI_2 may be injured. Leukotriene B_4 (LTB_4) has been implicated in prostate and colon carcinogenesis. The anticancer effect of celecoxib is COX-2-independent in HT-29 and PC-3 cells and in HT-29

cells primarily via down-regulating LTB_4 production (Gao et al., 2010). Matsuyama and co-workers (2010) have demonstrated that CysLT1R expressed in urological cancer may play a crucial role in carcinogenesis and may therefore be a novel target in the treatment of urological cancer. An increasing body of evidence supports an acute role for 5-LO products already during the earliest stages of pancreatic, prostate, and colorectal carcinogenesis (Steinhilber et al., 2010).

9. The role of GSH-enzymes in the metabolism of arachidonic acid

The tissue content of GSH is normally very high, in some tissues the level is up to the 5 mM. The functions of GSH are often tissue protective, and there are numerous enzymes in which GSH plays a central role as a cofactor.

Typical GSH-enzymes include GSH-peroxidase (GSH-Px), located in the circulation almost exclusively in the red cells, various GSH-transferases that have peroxidise-like activity and bind chemicals and γ-glutamyl transferase which reflects the function of the liver and is involved in the transport of amino acids across the cell membrane. GSH is also consumed by some cytochromes, most notably cytochrome P-450.

Several steps in the metabolism of arachidonic acid may be normally regulated by GSH-enzymes (Rouzer et al. 1982). It was an early observation that GSH may function as a chemical cofactor or coenzyme in the formation of some PGs, particularly PGEs (Mimata et al. 1988). Specific, atypical GSH-S-transferases are needed in the isomeration of PG-endoperoxides (the intermediary step) to PGEs and PGDs (Hubatsch et al. 2002). Ghosh (2004) demonstrated that selenium significantly reduced the incidence of clinical prostate cancer. A high intake of dietary fat containing arachidonic acid or its precursor fatty acids should be administered when selenium is used for the management of prostate cancer, as it has been suggested that a combination of selenium and 5-lipoxygenase inhibitors may be an effective regimen for prostate cancer control (Ghosh and Myers, 1998; Ghosh, 2004). A low prostatic arachidonic acid level was found in patients undergoing prostate surgery for either benign or malignant disease. Showed a low prostatic arachidonic acid level, which was explained as a result of the increased use of arachidonic acid for the production of prostaglandins and/or leukotrienes (Faas et al. 2003; Tilg and Moschen, 2006; Calder 2012).

There is little data available on these parameters in the prostate. Richie et al (2012), working with age related changes in selenium and glutathione levels in different lobes of the rat prostate found an increased level of oxidative stress together with decreases in selenium and the major cellular antioxidant glutathione (GSH). They compared the levels of selenium, GSH and protein-bound GSH (GSSP) in blood and prostate tissues in rats. Their findings of age-related changes in GSSP and selenium in the DL prostate are consistent with the sensitivity of this lobe to carcinogenesis and, thus, may be playing a mechanistic role (Richie et al. 2012). Selenium is an integral part of GSH peroxidase, the enzyme that mediates antioxidants by glutathione (Parantainen et al. 1988). Studying the metabolic profiles of human prostate cancer tissues it was shown a significant decrease in reduced glutathione (GSH)

during cancer progression from low- to high-grade Gleason scores (Sreekumar et al. 2009; Pavlou and Diamandis, 2009). Some studies found a lower Se concentration in the whole blood and plasma in benign prostatic hyperplasia (BPH) patients compared to healthy controls was observed by Eichholzer et al. (2012); also they found a lower activity of erythrocyte GPx. A significant inverse association between serum Se concentrations and the risk of BPH was shown (Eichholzer et al. 2012).

The formation of PGs is a very specific form of lipid peroxidation, and in these processes GSH-Px may have a central regulatory role. Some pGs inhibit the formation of lipid peroxides, while a certain level of peroxides is needed to maintain normal PG-production (Hemler and Land, 1980; Sugino et al. 2001). Such a "peroxide tone" is a crucial factor in the regulation of the metabolism of arachidonic acid in toto. Peroxidases may have a key role in eliminating the oxygen free radical during the conversion of endoperoxides to corresponding alcohols. The hydroxyl radical formed from 15-HPETE may thus be trapped (Chance et al. 1979; Flohé and Ursini, 2008).

Considering the circulatory peroxides, the functioning of the erythrocyte GSH-Px may have a crucial role. During infection and inflammation there may be a marked reduction in the erythrocyte count. Such anaemia may be due to haemolytic processes in which lipid peroxidation and the formation of free radicals may be the key event.

In the formation of leukotrienes, the GSH-enzymes γ-GT and GSH-S-transferases have a key role. The whole group of **cysteinyl leukotrienes** are formed by adding GSH to LTA_4, which gives rise to LTC_4 and, when the GSH is split, to LTD_4, LTE_4 and LTF_4. In the formation of the other type, LTB_4, GSH does not have a direct role (Morris et al.1981). However, LTA_4 is reduced to LTB_4 on contact with erythrocytes, which points to a certain importance of the peroxidise-like mechanisms, possibly GSH-Px, so abundant in the red cell. Leukotriene B_4 (LTB_4) is a potent lipid mediator of inflammation, implicated in numerous diseases including prostate cancer. An LTB_4 tissue level was shown to play a role in in benign and cancerous prostates. Cancerous from patients' sample had higher LTB_4 than pericancerous samples (Larre et al. 2008).

10. Diet, inflammation and prostate cancer

The causes of cancer have been largely attributed to genetic and environmental factors, including lifestyle, and are generally thought of as either avoidable or unavoidable. Dietary habits have been considered for years in epidemiological and case controlled studies to have an impact on cancer development and prevention. However, this association between diet and cancer has never been as clear as the correlation between smoking and cancer. Differences in diet and lifestyle may account for the variability of prostate cancer rates in different countries (Manolio et al. 2009). Good nutrition may reduce the incidence of prostate cancer and help reduce the risk of prostate cancer progression (Miller et al 2012). Several studies suggest a relationship between diet and prostate cancer risk; however, nutritional studies are difficult to perform because of the inherent heterogeneity of any study population (Klein et al.2006), the variations in

individual lifestyles, and the quantitative and qualitative complexity in food and food products (Giovannucci et al, 1993; Huang, 2006). Therefore, randomized and carefully controlled studies can address the relation between prostate cancer and nutrition.

The importance of nutrition in disease prevention and treatment has gained much attention in recent years. Diet may represent a modifiable prostate cancer risk factor, but a vegetable-based prostate-healthy diet is a major change for most men (Carmody et al. 2008). Other study suggest that keeping the appropriate body mass and level of cholesterol by proper diet and physical exercises may be the prophylaxis of prostate cancer (Pilch et al 2012). The cancer preventive activity of vitamin E has been suggested by many epidemiologic studies. Yang and co-workers suggested that vitamin E, as ingested in the diet or in supplements that are rich in γ- and δ-tocopherols, is cancer preventive; whereas supplementation with high doses of α-tocopherol is not (Yang et al 2012). It has been suggested that intake of vegetables and fruit plays a role in protecting against prostate cancer development (Chan and Giovannucci, 2001; Key et al., 2004). Furthermore, vitamins and trace elements have been studied for their roles in prostate cancer pathogenesis (Chanand Giovannucci, 2001; Moyad et al. 2002; Tallberg and Atroshi, 2011).

In order to disentangle the association of diet and prostate carcinogenesis better understanding of the human genome will further accelerate nutrigenomics applications and the development of nutritional modifications including personalized nutrition for our well-being and will also present a strong influence on future drug discovery (Lundstrom,2012). However, antioxidant supplements so far tested seem to offer little improvement over a well-balanced diet, possibly because of the choice of the substances tested or of an excessive dosage (Fair and Wynder, 1996; Dolara et al. 2012). Future trials of nutritional medication might help to disentangle the association of diet and prostate carcinogenesis.

The effect of diet can be direct, via the cumulative effect of exposure to nutrients and carcinogens in foods; in this case, the balance of cancer-promoting and -protective substances may contribute in defining cancer risk (Antila et al. 1996; Adhami and mukhtar, 2012; Adhami et al.2012). There are also indirect ways by which diet affects the cancer process. These include the effects of diet on energy balance and risk of obesity and the hormonal and metabolic responses related to energy balance.

There is an emerging consensus that situations of acute or chronic imbalance between the antioxidative capacity of cells and tissues, and the production of pro oxidative species, is associated with the development of a number of human diseases. Despite enormous interest in the area of antioxidants as therapeutic tools, the development of foreign compounds as therapeutic antioxidants has provided little therapeutic benefit.

1. Many important physiological functions, such as the regulation of cell cycle (mitogenesis and apoptosis), are known to be tightly coupled to the induction of controlled episodes of oxidative stress in biological systems. This entails problems in terms of potential side effects for antioxidant therapy, which have been largely ignored in most clinical use of antioxidants. This may have serious implications for the choice of antioxidant principle to be used.

2. The actual choice of antioxidant therapy is it xenobiotic or endogenous, should be indicated based on sound molecular knowledge of the involvement of oxidative stress in the actual pathology.

3. Dietary habits are probably an important factor that contributes to the geographic variations in prostate cancer rates. A large number of epidemiological studies have investigated the association between dietary factors and prostate cancer. Epidemiologic studies on prostate cancer have extensively investigated dietary risk factors (Kolonel, 2001; Park et al. 2007). Suggesting that diet and environmental differences play important roles in prostate cancer (Shimizu et al., 1991; Minami et al.,1993).

11. Conclusion

Cancer is due to the accumulation of DNA mutations that confer a growth advantage and invasive properties on clones of cells. A variety of external factors including nutrients in the environment interacting with genetic susceptibility influence the accumulation of mutations in cells. Nutrition is important at every stage of carcinogenesis from initiation to promotion to progression and metastasis. In spite of the fact that prostate cancer is the most common male cancer in many countries in the developed world, little is known of risk factors and predisposing conditions.

The number of prostate cancer cases around the world is increasing. Its incidence has been associated with ageing, environmental factors and changes in lifestyle. Based on some research in animals and people, certain dietary measures have been suggested to prevent the progression of prostate cancer. However, there is no solid evidence that a healthy diet can prevent people from developing prostate cancer. The reasons that patients with prostate cancer are using the dietary supplements are to enhance their health. Such dietary elements may also limit drug efficiency.

Oxidative stress has been suggested to play a key role in carcinogenesis. Free radicals have been shown to mediate the anti-cancer actions of many chemotherapeutic regimens. Despite active investigation, knowledge is lacking concerning the local and systemic effects of free radical-generating treatments in cancer. Free radicals are among the environmental factors that might contribute to cancer process (Atroshi et al. 2010). While it has not been conclusively determined whether free radicals are a cause or an effect of prostate cancer, it is clear that characteristic types of free radical damage increase with cancer. However, understanding the nature of that particular tumour can help us to optimize therapy or to design therapeutic approaches. Recently, Maddams and co-workers have shown that a large increase in cancer can be expected in the oldest age groups in the coming decades, and therefore there is an increased demand upon the right treatment and health services (Maddams et al. 2012).

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