

Exercise and Prostate Cancer: Evidence and Proposed Mechanisms for Disease Modification

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Abstract

Exercise has many potential benefits in relation to cancer. Apart from primary prevention, these include improvement of nonspecific cancer-related symptoms, amelioration of symptoms and cardiovascular risk factors related to cancer treatment, and improvements in various quality-of-life-related factors. Increasing evidence also points toward improved cancer-free and overall survival in cancer patients who undertake regular exercise, findings which should encourage further research in this area. Obesity is known to be associated with a proinflammatory, prothrombotic humoral milieu, which may promote aggressiveness in prostate cancer through inter-

actions with NK-cell-mediated killing of circulating tumor cells, through platelet-circulating tumor cell interactions, and through alterations in adipokine and myokine profile among others. Physical activity reduces levels of systemic inflammatory mediators and so exercise may represent an accessible and cost-effective means of ameliorating the proinflammatory effects of obesity in cancer patients. This review outlines the evidence for the benefits of exercise in these patients, focusing on prostate cancer, and delineates current theories of the underlying biological mechanisms. *Cancer Epidemiol Biomarkers Prev*; 25(9); 1281–8. ©2016 AACR.

Introduction

Prostate cancer, the most frequently diagnosed male cancer in the developed world (1), is a leading cause of male cancer-related death. Although prostate-specific antigen (PSA) screening identifies many early cancers, numerous men still present with locally advanced or metastatic disease for whom radical surgery with curative intent is inappropriate. In this setting, increased disease-free and overall survival and improved quality-of-life (QoL) are the primary management objectives, and new therapies and lifestyle alterations that can assist are increasingly needed.

Exercise has well-documented benefits in improving cardiovascular risk and bone mineral density and in treating obesity and diabetes. The incorporation of exercise programs into cancer care is increasingly recognized to have beneficial effects. A systematic review of exercise interventions in cancer survivors found improvements in strength, fatigue, fitness, functional QoL, self-esteem, and anxiety (2). Much of this research relates to colon and breast cancer but increasing evidence demonstrates improvements in symptom control, all-cause mortality, and cancer-specific mortality in prostate cancer also. Improved cancer-specific mortality suggests the potential for exciting developments in our understanding of the biology and aggressiveness of prostate cancer, together with novel therapeutic opportunities.

In prostate cancer patients with potentially curable disease, obesity and its complications may make surgery impractical. Androgen deprivation therapy (ADT), the mainstay of systemic treatment for hormone-responsive advanced prostate cancer, itself causes obesity and metabolic syndrome. As medical therapy for obesity-related cardiovascular risk factors improves, aggressiveness of prostate cancer becomes more important than cardiovascular complications in determining the cause of mortality in these men. We know that obese men have a worse outlook regarding cancer-related mortality than nonobese men. The combination of an aging population with an increased prostate cancer incidence, increasing obesity prevalence, and improved management of cardiovascular risk factors means that in the future more men are going to die as a result of the deleterious effect of overweight in advanced prostate cancer.

This review will attempt to outline the observational and experimental evidence for the benefits of exercise in prostate cancer patients with particular reference to the amelioration of the negative effects of obesity. It will also delineate the current theories as to the biological mechanisms underlying these benefits.

Evidence for Benefits of Exercise in Cancer Patients

Cancer and benefits of exercise

Regular exercise is important for primary prevention of many cancers. It is associated with decreased risk of endometrial (3), colon (4), bladder (5), renal (6), gastroesophageal (7), and breast cancers, with a dose-effect relationship in the latter in some studies (8). Evidence for exercise in reduction of hematologic cancer risk is not convincing (9).

Exercise helps ameliorate nonspecific cancer-related symptoms, reduces cardiovascular risk factors (10), and improves general QoL, even without reduction in body weight. A meta-analysis (11) found moderately reduced cancer-related fatigue

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and improved symptoms of depression and sleep disturbance. A Cochrane review (12) found that "aerobic exercise can be regarded as beneficial for individuals with cancer-related fatigue during and post-cancer therapy". A separate Cochrane review (13) found improvements in body image/self-esteem, sexuality, social functioning, anxiety, and pain. These QoL indicators are particularly important in patients with advanced cancers for whom treatment with the aim of cure is inappropriate.

The emerging evidence for improved cancer-specific overall and progression-free survival in exercise therapy is exciting. While the potential benefits should not be overstated, exercise is increasingly considered an anticancer therapy in its own right. A systematic review found improved outcomes in breast and colon cancer (14), although no randomized controlled trials are available. The evidence includes the benefits of post-diagnosis physical activity (15) as well as long-term exercise participation before breast cancer diagnosis (16). Similarly, in colon cancer, there is evidence for both pre- (17) and post-diagnosis (18, 19) exercise. A supervised exercise program may be associated with improved progression-free survival in lymphoma (20).

Prostate cancer and benefits of exercise

Prostate cancer is a heterogeneous disease, and risk factor associations for total nonaggressive disease are different from aggressive/lethal disease (21). A retrospective questionnaire-based study of 988 cancer patients (T2 or greater) and 1,063 controls found that vigorous physical activity and physical activity over the first 18 years of life decreased cancer risk (22). A large prospective study found no association between occupational or leisure time activity and prostate cancer incidence (23), although occupational activity was associated with lower risks of advanced-stage prostate cancer. In the Health Professionals Follow-up Study (24), there was a lower risk of advanced, high Gleason grade, or fatal prostate cancer in men over 65 years of age undertaking the highest category of vigorous activity. There was no association with prostate cancer incidence for total, vigorous, and nonvigorous activity overall. Most other population-based studies show similar findings, with little effect of exercise on overall incidence but some association with reduced aggressive cancers (25–27). Some studies find increased risk of prostate cancer in selected groups of men undertaking exercise (28, 29), which underlines the complexity of the issues involved and the difficulty in controlling for quantity and type of exercise in large-scale observational studies.

The diagnosis of prostate cancer may provide a "teachable moment" when men are amenable to lifestyle changes. For prostate cancer patients, in whom most exercise studies assess QoL indicators, there is solid evidence that exercise (especially group exercise) improves muscular and aerobic endurance, reduces fatigue, and improves overall QoL (30). There is relatively strong evidence for improved health-related, social, and physical QoL. Exercise has specific benefits in ameliorating prostate cancer treatment side-effects, such as improved muscular strength, cardiorespiratory fitness, lean body mass, and fatigue (31). Among 66 men undergoing radiotherapy, there was significantly reduced rectal toxicity after 30 minutes of aerobic walking exercise, three times per week, for 4 weeks (32). Among 121 men receiving radiotherapy and/or androgen blockade, both resistance and aerobic exercise improved

fatigue, and resistance exercise also improved QoL, strength, triglycerides, and body fat (33). Another study found significant changes in waist circumference following a 16-week intervention, although with high drop-out rates (34).

Accumulating data suggest that exercise can modify the biology of prostate cancer, in addition to improving QoL-related parameters. In a follow-up study of 2,705 men with nonmetastatic prostate cancer who survived at least 4 years after diagnosis, vigorous exercise (cycling, swimming, jogging) for more than 3 hours weekly led to lower all-cause and cancer-specific mortality (35). Brisk walking trended towards lower cancer-specific mortality without achieving statistical significance. Another study found 57% reduced progression rates among men with clinically localized prostate cancer who walked briskly for more than 3 hours weekly. Walking pace was associated with decreased risk of progression independent of duration (36). Several more recent large follow-up studies provide further evidence for physical activity in reducing prostate cancer-specific mortality (37, 38).

Feasibility of exercise programs in cancer patients

The quality of clinical evidence for exercise programs in advanced cancer is somewhat limited by difficult accrual of participants to trials. Individual studies should be assessed critically, as the ability to undertake exercise may act as a surrogate for better performance status, which may in turn act as confounding factor. Supervised exercise programs are feasible in colon (39) and even posttreatment lung cancer (40). The PEACH trial (41) recruited a heterogeneous sample of cancer survivors for a supervised exercise intervention: 186 patients were available for recruitment, 43 (23%) of whom were randomized into the program. A common reason for exclusion was a potential participant residing too far from the study site, suggesting that recruitment from multiple clinical sites may help to achieve accrual targets.

Many PEACH trial participants were breast cancer survivors, and had a younger age profile than would be expected for a prostate cancer study. Prostate cancer patients might be less inclined to participate in moderate-to-vigorous intensity exercise than younger breast cancer patients. However, Richman and colleagues' study (36) included many participants who engaged in regular walking at a brisk pace (34.5%). Kenfield and colleagues' study (35) shows improved mortality in those who exercised for >9 MET-h/week, with approximately 75% engaging in this level of activity. The Richman and colleagues study (36) supports the hypotheses that brisk walking may elicit the same physiologic responses as more vigorous exercise does in a different man, and that moderate-to-brisk intensity walking intervention may be acceptable to a considerable proportion of prostate cancer patients. An international multicenter trial of exercise in men with advanced prostate cancer (the ExPeCT trial; ClinicalTrials.gov identifier NCT02453139) is currently underway at our institution, and participant accrual targets are being met.

Potential Mechanisms

Metabolic syndrome and systemic inflammation

Metabolic syndrome is a constellation of cardiovascular disease risk factors, including hypertriglyceridemia, hypertension, and low HDL cholesterol, with central adiposity and insulin resistance

the most important components. In the United States, more than 30% of adults are obese (42). Hypogonadism, due to androgen deprivation therapy (ADT), the mainstay of treatment for advanced prostate cancer, is an independent risk factor for the components of metabolic syndrome (43–47). Fifty-percent of men undergoing long-term ADT have metabolic syndrome (48), possibly contributing to the excess noncancer mortality in this population (49). Obesity/metabolic syndrome is associated with progression but not incidence of prostate cancer (50). Overweight and high plasma C-peptide levels predispose to cancer-related death in men subsequently diagnosed with prostate cancer (51). However, evidence for metabolic syndrome as a risk factor in development of prostate cancer is inconclusive (52, 53).

Metabolic syndrome may promote prostate cancer aggressiveness through altered insulin-like growth factor (IGF) signaling. IGF1 binds to IGF1 receptor (IGF1R), and its function can be modulated by IGF-binding proteins (IGFBP). When activated IGF1R increases proliferative and antiapoptotic activity via the RAF and PI3K pathways (54). Metabolic syndrome-associated hyperinsulinemia appears to inhibit the modulatory function of IGFBP1, increasing the concentration of nonbound bioavailable IGF1 (55). In addition to this systemic effect, the local tumor environment also leads to increased sensitivity to IGF1 through increased expression of the IGF1R receptor. (56, 57).

Metabolic syndrome is characterized by low-level chronic systemic inflammation (reviewed in ref. 58), and evidence suggests that substantial crosstalk occurs between pathways involved in inflammation, coagulation, and obesity (59). Tissue factor (TF), the principal initiator of the coagulation cascade, is also a proinflammatory mediator, triggering signaling through G-protein-coupled receptors. TF appears to have a critical role at the crossroads of obesity, inflammation, and thrombosis (60). In mice, inhibited TF-mediated signaling in hematopoietic cells reduced high-fat diet-related insulin resistance (through downregulation of TNF α and IL6 and upregulation of IL10), without impacting body weight. In adipose tissue, inhibited TF-mediated signaling led to reduced weight gain. In a seminal article, TNF α was shown to be constitutively expressed in adipose tissue and hyperexpressed in obesity (61). Other inflammatory mediators (IL6, CRP, and MIF) are also increased in obese patients. IL6 and TNF α stimulate leptin and reduce adiponectin production, and TNF α suppresses NO synthase expression. Apart from its metabolic effects, insulin mediates many other processes, including platelet inhibition by increasing NO expression, anti-inflammatory activity by decreasing NF κ B and CRP, and antithrombotic activity by reducing TF activity. In a rat model, rises in serum IL6 and TNF α were suppressed by insulin (62). Insulin resistance is characteristic of metabolic syndrome. Therefore, obese men tend to be in a proinflammatory and prothrombotic state.

There are substantial preclinical experimental data, both in prostate cancer cell culture studies and murine models, to support the hypothesis that reductions in systemic inflammatory mediators (with consequent effects on platelet adhesion) may underlie exercise-associated improved outcomes. Incubation with serum from healthy male volunteers after exercise led to 31% inhibition of growth of LNCaP prostate cancer cell lines, and preincubation of LNCaP cells before injection into immunodeficient mice led to delayed tumor formation (63).

EGF and IGFBP1 may exert inhibitory effects on postexercise serum. A similar study using serum from men undergoing a low-fat, high-fiber diet in addition to regular exercise reduced growth and increased apoptosis in LNCaP cells, associated with reductions in serum IGF1 (64). The cells also had increased p53 content (replicated elsewhere; ref. 65) and reduced NF- κ B activation. In a study of men with early-stage, low-grade prostate cancer who undertook comprehensive diet and lifestyle changes, it was found that their serum inhibited LNCaP cell growth more than the serum of a comparison group of men who did not make these changes (66). Mice injected with prostate cancer cells and randomized to voluntary exercise tended toward reduced expression of prometastatic genes, with no change in primary tumor growth rate (67). There was also improved tumor vascularization, modulated through increased HIF1 α and VEGF concentrations leading to productive (nonpathologic) angiogenesis. In a separate SCID mouse xenograft model, voluntary running wheel exercise led to suppressed PC-3 tumor growth in male mice, manifested by reduced mitosis and increased apoptosis. The regimen was associated with increased food and fluid consumption by the mice and led to reduced adiposity but no change in overall body weight (68).

There are also intriguing clinically derived data concerning the effects of exercise on systemic inflammation. In noncancer patients, physical activity reduces levels of systemic inflammatory markers (69) and so exercise may enable modification of the negative proinflammatory effects of obesity. The anti-inflammatory effect of physical activity depends on exercise volume, intensity, and type, rather than on weight loss (70). Among prostate cancer patients, decreased CRP levels were found in prostate cancer patients following a 12-week program of resistance and aerobic exercise (71), and preliminary data from the Promenadgruppen study found significant changes in concentrations of adipokines and inflammatory markers compared with a control group in patients who underwent a 10-week small group walking program (unpublished data). Both study and control groups showed similar weight loss but the study group showed a 12 mm Hg reduction in systolic blood pressure, a 33% increase in levels of HDL, and a 60% reduction in CRP.

IL6 and TNF α are both raised in the serum of patients with metastatic carcinoma, compared with patients without metastases. Both are elevated in metastatic prostate cancer in direct proportion to disease stage, and increases occur at the time of biochemical disease progression (72). TNF α enhances the invasion of prostate cancer cell lines through synthesis of selectin ligands (73).

Adipokines

The serum levels of adipokines, produced by adipose tissue and playing roles in appetite, energy balance, and insulin resistance, vary depending on adiposity. Adipokines have potentially pro-oncogenic roles in angiogenesis and cell proliferation. Adiponectin has anti-inflammatory effects and its serum concentration is inversely correlated with adiposity. It dose-dependently reduces platelet aggregation (74) and suppresses inactivation of nitric oxide (NO, an inhibitor of platelet activation). Resistin is associated with insulin resistance through AMP kinase downregulation. It upregulates proinflammatory cytokines (IL6, TNF α) which act via the NF- κ B pathway to increase proliferative, proinflammatory, and antiapoptotic protein transcription. Nuclear

expression of NF- κ B is associated with nodal metastasis in prostate cancer (75).

Immunologic impairment (NK cells)

NK-cell numbers in blood and in solid organs, together with their cytotoxicity and cytokine secretion, are reduced in obesity. Obese compared with nonobese patients have fewer circulating NK cells (76), and those with hypertension, raised fasting glucose, and unfavorable lipid profiles have less NK cells than "metabolically healthy" obese patients. Obese subjects have fewer hepatic NK cells and leptin receptor–positive cells compared with normal weight subjects (77). The NK-cell fraction of blood is sensitive to exercise (reviewed in ref. 78), and 5-fold increases in NK concentrations after exercise have been noted. Brief exercise upregulates molecular pathways in circulating NK cells associated with cancer and cell communication (79). In healthy young men, hypoxic exercise training leads to enhanced *in vitro* NK-cell cytotoxicity (80).

Obesity has substantial negative quantitative and qualitative effects on NK cells, the effector cells for killing circulating tumor cells (CTCs, see below). In addition, evidence suggests that interactions between platelets and CTCs can dramatically impair NK-cell–mediated immune editing.

Platelet cloaking of circulating tumor cells

Epithelial cells (having an EpCAM⁺, CD45[−] immunophenotype) rarely exceed one cell per 7.5 mL of blood in patients without malignancy (81). CTC enumeration, using technologies such as the FDA-approved CellSearch system or the filtration-based ScreenCell system (ScreenCell) may have a prognostic role in advanced prostate cancer. A prospective study of castration-resistant prostate cancer found that ≥ 5 CTCs per 7.5 mL of blood correlated with a poor prognosis (82). When a variety of clinical, serologic, and pathologic parameters were considered, the model best predictive of survival was based on baseline LDH, baseline CTC count, and fold change in CTC count at monthly intervals (83).

Despite the long-recognized association between cancer and thromboembolism, it has been unclear whether the thrombocytosis often seen in patients with metastases is a consequence or cause of widespread tumor dissemination. Evidence now shows that platelets support tumor metastasis by various mechanisms (84). Platelets are involved in arrest of CTCs in the vasculature and through endothelial interactions enable their extravasation. Platelets also secrete various pro-oncogenic factors including PDGF and VEGF, and mediate prosurvival signals in ovarian cancer cells (85). Platelets can adhere to CTCs ("platelet cloaking") and may thereby impair NK-cell–mediated killing.

Tumor cell–induced platelet aggregation correlates with metastatic potential, and may be due to "cloaking" of tumor cells by adherent platelets. The interaction between CTC cloaking by platelets and their killing by NK cells is incompletely understood. Thrombocytopenic mice exhibited reduced tumor metastatic burden when tumor cells were NK-cell sensitive, and *in vitro* studies demonstrated reduced NK tumorolytic activity when platelets aggregated around tumor cells (ref. 86; Fig. 1). In a mouse model, deficiency for $G\alpha_q$, a G-protein critical for platelet activation, markedly decreased experimental and spontaneous metastases (87). This effect was eliminated in NK-cell–deficient mice, further supporting the hypothesis that adherent platelets

may obstruct the direct cell–cell contact required for NK-cell killing. Our group has recently demonstrated significant reductions in NK-cell activity (using flow cytometry for CD107a) through platelet cloaking of cancer cells, which appears to be mediated by the release of activated platelets (unpublished data). Release of TGF β by adherent platelets, which downregulates the NK-cell–activating receptor NKG2D (88), may also inhibit NK-cell–tumor interactions. Platelets may enable evasion of NK-cell killing by conferring a "pseudonormal" phenotype on CTCs through high tumor cell surface expression of normal MHC class 1 antigen (89).

TF expression by tumor cells and the presence of serum factor XIII transglutaminase support metastasis by impeding NK-cell killing of CTCs (90, 91). Of note, prostasomes secreted by benign and malignant prostate cells contain high concentrations of TF, with strong procoagulant effects *in vitro* (92), suggesting a link between TF activity and platelet cloaking of CTCs.

In a murine model, platelets activated by CTC interactions release adenine nucleotides which, acting upon the endothelial P2Y2 receptor, open the endothelial barrier and facilitate trans-endothelial migration (93). An experimental antibody preferentially induces oxidative platelet fragmentation by targeting the $\beta 3$ subunit of the platelet's fibrinogen receptor, reducing metastasis (94, 95). Platelet-derived TGF β and direct platelet–tumor cell contacts activate TGF β /Smad and NF- κ B cancer cell pathways, resulting in EMT and enhanced metastasis in mice (96). All of these mechanisms require close interaction of tumor cells with platelets, interactions which can be described and quantified as platelet cloaking.

Demonstration that platelet cloaking is a mechanism by which obesity disimproves prostate cancer survival would suggest that therapies targeted at points along the pathway of platelet activation could be efficacious. For example, adiponectin supplementation or blockade of IL6 or TNF α could be useful. Comparison of the expression of lethality-associated genes between the primary site and CTCs could highlight genes which are upregulated as part of the metastatic pathway, with potential for targeted therapy.

The role of skeletal muscle

Skeletal muscle plays an important role in counteracting the proinflammatory effects of obesity. Contracting skeletal muscles release myokines which act as antagonists to the generally proinflammatory adipokines (reviewed in ref. 97). For example, although muscles produce IL6, a proinflammatory mediator which contributes to the deleterious effects of metabolic syndrome when chronically elevated, they do so in a TNF α –independent manner. Physically active people have low basal levels of IL6. High basal levels are associated with metabolic syndrome. This suggests a role for muscle-derived IL6 in metabolism rather than inflammation, and IL6 stimulates insulin-mediated glucose uptake in muscle cells *in vitro*. Other myokines include IL15, which decreases lipid deposition in pre-adipocytes, and myostatin, whose expression is reduced by aerobic and strength exercise. The overall effects of the skeletal muscle secretome involve muscle hypertrophy, adipose tissue oxidation, increasing insulin sensitivity, increasing osteogenesis, reducing inflammation, increasing antitumor activity, and increasing pancreatic function. Obese men are characterized by sarcopenic obesity, and their reduced muscle mass contributes

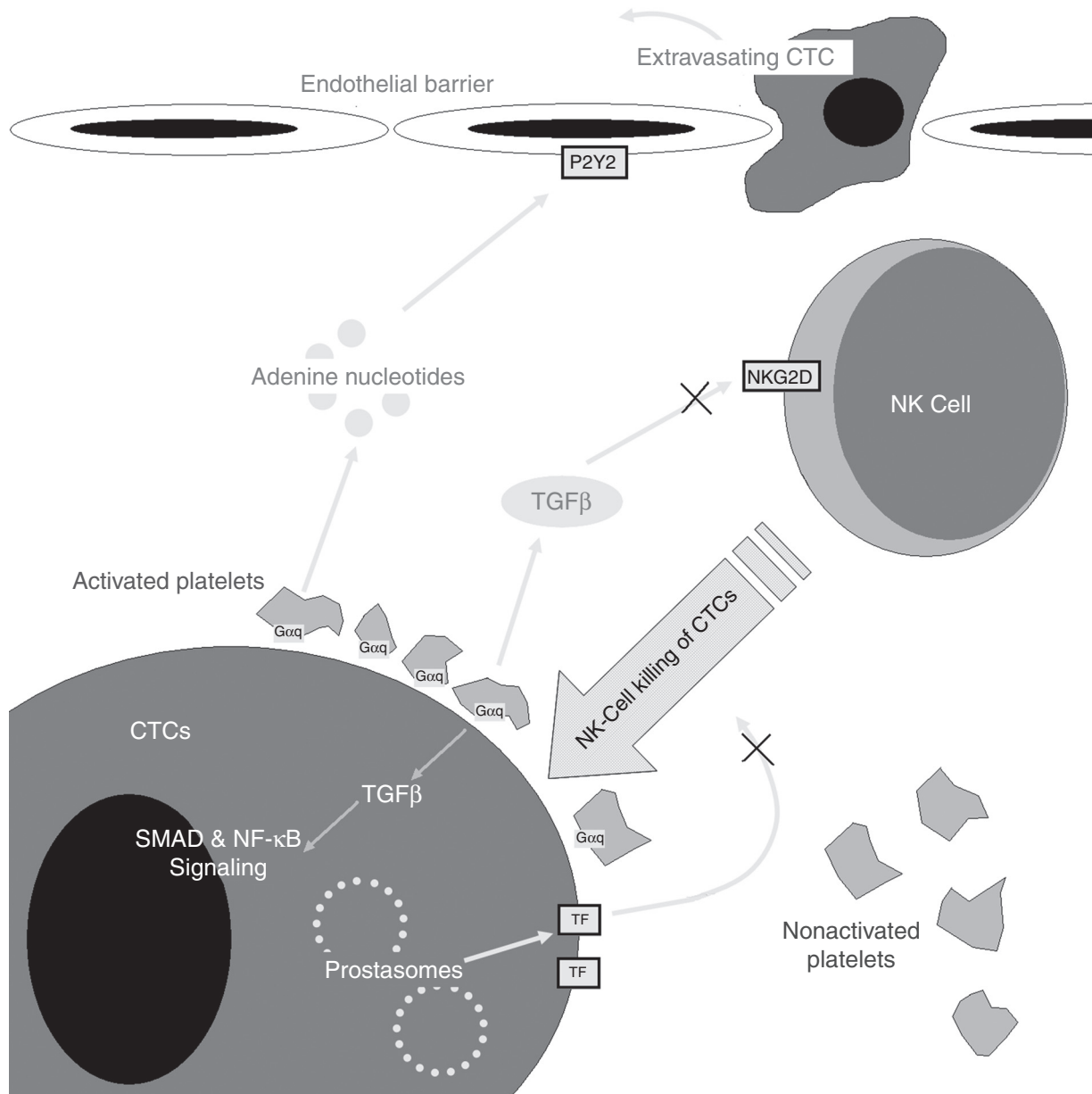


Figure 1.

Activated platelets, expressing $G\alpha_q$, adhere to prostate cancer CTCs and release TGF β , impairing NK-cell activation through NKG2D downregulation. CTC-expressed tissue factor also impairs NK-cell killing, probably by direct obstruction by the platelet cloak. Adenine nucleotides from activated platelets open the endothelial barrier via endothelial P2Y2, and epithelial-mesenchymal transition and invasiveness is promoted by platelet-derived TGF β -mediated activation of NF- κ B and SMAD pathways within CTCs.

substantially to insulin resistance and metabolic syndrome. Skeletal muscle-derived factors interact substantially with those derived from adipose tissue, and increasing skeletal muscle mass as well as reducing adiposity is likely to be of benefit in reducing platelet cloaking of CTCs. The sarcopenia caused by ADT may be responsive to antagonists of myostatin (98). Myostatin negatively regulates skeletal muscle growth and is a member of the TGF β superfamily. Chronic myostatin exposure can cause apoptosis in cancer cells, through a shift from oxidative phosphorylation to glycolysis (99).

Conclusions

Because of the combination of an aging population and rising levels of obesity, a "perfect storm" of increased incidence and aggressiveness of prostate cancer is imminent. Low-cost interventions are required which can improve QoL and modify disease biology independent of the various surgical, radiologic, and pharmacologic options already available. Although the mechanisms by which it does so are incompletely understood, the proinflammatory and prothrombotic milieu associated with obesity appears to

be the pathway through which this lifestyle-modifiable disease exerts its aggressive effects in prostate cancer. There is increasing observational and experimental evidence that exercise can modify the biology of prostate cancer and ameliorate some of the deleterious effects of obesity in these patients. Further focused research is required both to prove the disease-modifying effects of exercise and to explore the useful underlying mechanisms.

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No potential conflicts of interest were disclosed.

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