The Role of Exercise and Hyperlipidaemia in Breast Cancer Progression

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ABSTRACT

Exercise reduces the risk of breast cancer development and improves survival in breast cancer patients. However, the underlying mechanisms of this protective effect remain to be fully elucidated. It is unclear whether exercise can attenuate or modify the pro-tumour effects of obesity and related conditions, such as hyperlipidaemia. This review summarises how hyperlipidaemia and exercise contribute to or reduce breast cancer risk and progression, respectively, and highlights the possible mechanisms behind each. In particular, the effects of exercise and hyperlipidaemia on the immune microenvironment of tumours is analysed. The potential value of commonly investigated circulating factors as exercise-modulated, prognostic biomarkers is also discussed. We propose that exercise may alleviate some of the pro-tumorigenic effects of hyperlipidaemia through the reduction of blood lipid levels and modulation of cytokine release to induce beneficial changes in the tumour microenvironment.

Key words: Breast cancer, cholesterol, physical activity, immunity, tumour microenvironment

INTRODUCTION

Breast cancer is a global health concern. It is the most common cancer diagnosed in women (193) and the fifth largest contributor to cancer deaths worldwide (23). As such, understanding the underlying mechanisms of disease progression is vital to providing better therapies and prevention.

The purpose of this review is to explore the association between exercise and (breast) cancer progression, and to highlight potential mechanisms underlying the exercise-prognosis relationship. Types of exercise include resistance training, aerobic exercise and training that includes a mindfulness component such as Tai chi or yoga. The role of obesity and associated hyperlipidaemia (abnormal elevation of serum lipid levels) in breast cancer risk and progression will be examined, and the value of some commonly investigated circulating factors as exercise-modulated, prognostic biomarkers will be discussed.

OBESITY, HYPERLIPIDAEMIA AND BREAST CANCER

Obesity is an increasing health problem in developed countries worldwide. It has been associated with an increased risk of developing breast cancer, as well as with a poorer prognosis (11, 141, 158). It has been shown that adipocytes in the immediate vicinity of the tumour (cancer associated adipocytes) interact with breast cancer cells, causing them to become more invasive and providing them with metabolites (145). In addition, obese adipose tissue is characterised by chronic, low-grade inflammation. Hypertrophic adipocytes in obese adipose tissue can grow to a size of 150-200 μm in diameter, thus reaching or exceeding the maximum oxygen diffusion distance (192). This results in a hypoxic state, leading to the activation of hypoxia inducible factors (HIF), subsequent tissue fibrosis and the increased secretion of inflammatory adipokines, as well as macrophage infiltration (192). This low-grade, chronic inflammatory state has been associated with further metabolic dysregulation (192).

Hyperlipidaemia is commonly comorbid with obesity, but its implications as an independent risk or prognostic factor in breast cancer are much less clear. Preclinical studies show that hyperlipidaemia increases breast tumour growth rate, incidence and metastasis (3, 100, 112, 153, 163). In addition, breast tumours from hyperlipidaemic mice are more proliferative (100, 153, 163), have reduced apoptosis (153) and show increased microvessel density (100, 112, 153).
However, epidemiological studies have produced contradictory results regarding the effect of hyperlipidaemia, particularly hypercholesterolaemia, on breast cancer risk and progression, with some studies showing that hyperlipidaemia increases risk and/or progression (10, 43, 97, 101, 157, 164), and others showing that it reduces or does not change risk and/or rate of progression (42, 58, 65, 177, 183). In connection with this, the role of statins and other lipid lowering drugs on breast cancer risk and progression is unclear (26, 42, 97, 104, 138, 159, 186). However, two recent meta-analyses of observational studies found that statin use was associated with reduced breast cancer recurrence and/or mortality (121, 204). These discrepancies may be due to the inherent limitations of epidemiological studies, as well as differences in methodology, influences of different cancer treatments and possible differ-

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ences in the roles of high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C). Indeed, a recent study found that breast cancer patients with pre-operatively high levels of serum HDL-C had improved overall survival, while abnormal LDL-C and total cholesterol were not significantly correlated with prognosis (107). Furthermore, serum cholesterol may be reduced in cancer patients, as it is rapidly utilised by proliferating tumour cells (37, 63). It is also possible that some results from studies examining the role of serum cholesterol in breast cancer risk may be confounded by undiagnosed malignancies (83). Hence, the role of hyperlipidaemia and specifically the role of different types of cholesterol in breast cancer patients requires further investigation.

Proposed Molecular Mechanisms of Cholesterol in Cancer

A number of mechanisms to explain the observed pro-tumorigenic effect of hyperlipidaemia in rodent studies have been proposed, mainly focussing on the effect of hypercholesterolaemia (Figure 1). Firstly, Alikhani *et al.* demonstrated that

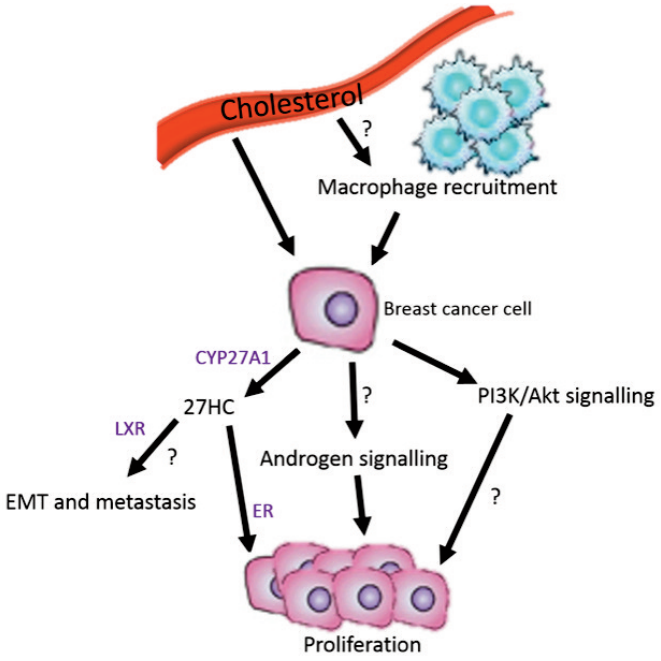

Figure 1: Potential Mechanisms of Cholesterol in Breast Cancer Progression.
It has been postulated that cholesterol exerts a pro-tumorigenic effect in a number of ways. It promotes proliferation through the action of its metabolite, 27-hydroxycholesterol (27HC), on the estrogen receptor (ER). In addition, it may increase macrophage recruitment, activate the liver X receptor (LXR) through 27HC, induce androgen signalling and/or induce PI3K/Akt signalling. ? denotes unverified or, in the case of PI3K/Akt signalling, potentially non-physiological mechanisms; CYP, cytochrome P450 enzyme; EMT, epithelial to mesenchymal transition. Schematic summarises findings or hypotheses of published works (3, 143, 153).

cholesterol induces protein kinase B (Akt) signalling, and suggested that cholesterol-mediated activation of the phosphatidylinositol-3-kinase (PI3K)/Akt pathway may be causative for the increased proliferation of breast tumour cells (3). Secondly, it has been reported that 27-hydroxycholesterol (27HC), an abundant primary cholesterol metabolite generated by the cytochrome P450 oxidase, sterol 27-hydroxylase (CYP27A1), exerts pro-tumorigenic effects (40, 142). Two independent studies have shown that 27HC promotes MCF-7 breast cancer cell xenograft growth in mice (143, 194). Two mechanisms have been proposed to explain this. First, 27HC can function as an oestrogen receptor (ER) agonist (41). ER signalling is an important driver of ER-positive breast cancer growth, and as such activation of this pathway by 27HC could provide an explanation for the increased growth rate of ER-positive breast tumours in a hyperlipidaemic environment (41). Second, Nelson *et al.* postulate that 27HC stimulates liver X receptor (LXR) signalling, thereby promoting epithelial–mesenchymal transition (EMT) and metastasis (143). However, their data is inconclusive (and as yet unconfirmed), as a synthetic LXR agonist did not promote metastasis to the same extent as 27HC in ER-negative breast tumour xenografts (143). In addition, 25HC has been implicated in a similar way to 27HC in increasing breast cancer cell proliferation through the activation of ER-signalling (105).

The ER-mediated effect of 27HC and 25HC does not provide an explanation for the observed pro-tumorigenic effect of cholesterol on ER-negative breast tumours (153). The authors of that study suggest that cholesterol-induced tumour progression could be mediated by androgen signalling or monocyte/macrophage recruitment (153); however both hypotheses are yet to be validated.

Taken together, 27HC-mediated ER-signalling provides the most solid mechanism for increased proliferation of ER-positive breast tumour cells in a hyperlipidaemic environment, but does not explain cholesterol-mediated proliferation of ER-negative breast tumour cells. Thus, further studies are necessary to elucidate the mechanism(s) behind the more rapid tumour growth and increased metastasis occurring in a hyperlipidaemic host.

Hyperlipidaemia and Immunity

The impact of hyperlipidaemia on host immunity is complex, with studies indicating both an impairment of immunity resulting in increased susceptibility to infection (102, 114), and a reduction in tolerance through reduced functionality of regulatory T cells (T_{reg} cells) (9). Oxysterols, formed during cholesterol metabolism, are well known to play a role in regulating immune responses and can also directly act on tumour cells to influence tumour cell growth (reviewed in (184)). However, work to date has focussed on tumour-derived oxysterols and *in vitro* experiments with synthetic oxysterols. It is therefore unknown what effect hyperlipidaemia has on the abundances of oxysterols in the cancer setting, and what the impact of hyperlipidaemia on the intratumoral immune phenotype may be.

Hyperlipidaemia is often characterised by high levels of LDL-C (144). Oxidised LDL can bind to toll-like receptors (TLR) on macrophages and other phagocytes, initialising a pro-inflammatory signalling cascade (74). Thus, an abnormal elevation of LDL-C can lead to chronic inflammation and the development of atherosclerosis through TLR signalling on macrophages (74). Moreover, chronic inflammation has been linked to cancer development and progression (17), while

exercise has been shown to reduce chronic inflammation (110). In this regard, exercise may inhibit cancer progression and development in hyperlipidaemic individuals through the reduction of chronic inflammation.

EXERCISE AND CANCER

Physical activity is important for physical and mental well-being. It can prevent excess weight gain or aid in weight loss and reduce the risk of cardiovascular disease (140). In addition, it can lower serum lipid levels (120). As hyperlipidaemia, and high cholesterol in particular, promote breast tumour growth and progression (discussed in the previous section), this lowering of serum lipids by exercise is likely to slow tumour growth. Furthermore, exercise is increasingly recognised as an effective, well-tolerated adjunct to cancer therapy (15). It has been associated with reduced breast cancer risk and improved survival of breast cancer patients (11, 141). In addition to survival benefits, exercise can improve the quality of life of breast cancer patients by attenuating or inhibiting cachexia, fatigue, cardiotoxicity of chemotherapy, weight gain, bone loss and by improving mental health (reviewed in (2)).

Exercise has a role to play in all phases of breast cancer evolution, including prevention, treatment and aftercare. The exercise-induced reduction in the risk of developing breast cancer ranges from 15-80% (134). During treatment, exercise may be beneficial both by alleviating chemotherapy side effects (reviewed in (2)) and by altering the tumour microenvironment to improve drug delivery and reduce tumour aggressiveness (discussed in detail in the following sections). Finally, mental and physical quality of life can be significantly improved by exercise in breast cancer survivors during aftercare (reviewed in (2)). Furthermore, exercise may help to prevent disease recurrence (25, 73).

Epidemiological Studies

Numerous epidemiological studies have investigated the association between exercise and cancer prognosis (including breast, colorectal, prostate, ovarian, non-small cell lung cancer and glioma), with the majority reporting that exercise improves survival (14, 25, 72, 73, 77, 78, 91, 99, 128-131, 136, 137, 156, 162, 166, 176). Two studies showed no association (19, 31). The magnitude of this decrease in mortality ranged from 15-57% for all-cause mortality and 20-67% for cancer-specific mortality. Both studies that found no association between exercise and survival were observational studies (19, 31), which are prone to bias by over-reporting of exercise frequency/intensity (20); this may have skewed the results. In addition, the volume and intensity of physical activity required for the improved prognosis vary between studies. As such, the optimal therapeutic 'exercise dose' remains to be elucidated and may vary according to cancer type, although a recent meta-analysis suggests that the current WHO guidelines of at least 2.5 hours of moderate intensity exercise or 1.25 hours of vigorous intensity exercise per week (3-6 metabolic equivalents of task (MET)) are sufficient to improve survival by 24% for breast cancer (106). Survival was further improved with increasing level of exercise and up to 40% survival improvement at 20 MET-h/week, at which point no further survival benefit was seen with increasing exercise levels (106). With respect to exercise type, resistance and aerobic training have been shown to have quality of life benefits in breast cancer patients, both when used separately (32, 49, 149) or together (49, 133).

Pre and post-diagnosis exercise have both been shown to have survival benefits for breast cancer patients (25, 72, 73, 77, 78, 113). It seems that post-diagnosis exercise has a larger effect on survival than pre-diagnosis exercise, although the wide range of reported values makes it difficult to say with certainty (pre-diagnosis: 12-39% improved survival, post-diagnosis: 20-67%) (25, 72, 73, 77, 78, 113). However, it may be important to maintain pre-diagnosis exercise levels, as decreased physical activity after diagnosis was associated with a four-fold greater risk of death (78).

Emerging evidence indicates that cardiorespiratory fitness (CRF) may be an important prognostic marker (34, 89, 91, 93, 96, 166). A single study has specifically investigated the CRF-prognosis relationship in breast cancer patients, using VO_{2peak} which is the maximum rate of oxygen consumption during exercise (89). This study reported a non-significant improvement in survival in patients with metastatic disease with $VO_{2peak} > 1.09$ L/min compared to those with $VO_{2peak} < 1.09$ L/min (89). Multiple studies have found that breast cancer patients have reduced CRF compared to healthy individuals, placing them at increased risk of cardiovascular disease (reviewed in (152)). Moreover, CRF can be improved by exercise training, thereby reducing this risk (152). Therefore, it seems clear that improvement of CRF by exercise training can improve survival by reduction of the risk of cardiovascular events, but the relationship between CRF and breast cancer-specific mortality warrants further research.

Exercise Biomarkers in Cancer Patients

Exercise is known to modulate levels of blood-based biomarkers. As such, it is of interest whether an association can be found between biomarkers modulated by exercise and cancer prognosis. A number of studies have found changes in the levels of metabolic and/or inflammatory biomarkers in breast cancer survivors following exercise training, as discussed below.

The main metabolic biomarkers that have been investigated to date are factors of the insulin-glucose axis. Insulin-like growth factor 1 (IGF-1) has mitogenic and anti-apoptotic effects, while IGF binding protein 3 (IGFBP-3) regulates the activity and bioavailability of IGF-1 (170). As such, high serum levels of IGF-1 and/or low levels of IGFBP-3 have been associated with an increased risk of developing breast cancer, as well as aiding breast cancer progression (22, 62, 181). Therefore, modifying levels of these factors could be important for cancer outcome. Studies investigating the effect of exercise on levels of these factors have indicated that exercise reduces serum IGF-1 and/or increases IGFBP-3 in breast cancer patients (44, 76, 79, 85), but some studies reported opposite effects or no change in one or both markers (76, 79, 171). Nevertheless, a meta-analysis of randomised controlled trials in breast cancer survivors concluded that exercise was

significantly associated with a reduction in circulating IGF-1 levels (49), despite non-significant results in some of the primary studies. In addition, high levels of IGF-1 and an increased IGF-1:IGFBP-3 ratio (indicative of bioavailable IGF-1) have been correlated with decreased survival in breast cancer patients (39, 60). Conversely, in healthy individuals, exercise can increase serum IGF-1 levels, although this is not consistently reported (reviewed in (52)). In addition, a recent study suggests that elevated serum IGF-1 improves overall survival of breast cancer patients (180). Taken together, the effect of exercise on IGF-1 levels remains unclear, although the vast majority of studies indicate that high levels of serum IGF-1 are associated with poor prognosis in breast cancer patients.

Total serum IGF-1 has been negatively associated with hyperlipidaemia (119). In addition, human growth hormone (hGH) has been shown to lower plasma cholesterol and increase IGF-1 in hyperlipidaemic patients (168). This may be mediated by IGF-1 and hGH dependent stimulation of macrophages to take up LDL (66). Together, this suggests that the exercise-mediated reduction of plasma lipids may be mediated, at least in part, through an exercise-induced increase in IGF-1. In the context of cancer, this relationship may be more complex due to the mitogenic effect of IGF-1 on cancer cells.

Leptin is another metabolic biomarker that has been shown to be modulated by exercise. Leptin is an adipokine that has a wide array of physiological roles and is secreted by white adipose tissue, which functions as an energy storage site and endocrine organ (170). Leptin is present in higher levels in obese or overweight individuals (76, 86, 172). High levels of leptin are associated with an increased breast cancer risk (146, 170). In addition, leptin has been shown to promote breast cancer cell growth both *in vitro* and *in vivo* (38, 202). A number of studies have found that exercise decreases circulating leptin levels in breast cancer survivors (13, 76, 172, 187). However, some studies have found no reduction from baseline in circulating leptin levels following an exercise intervention (108, 165, 179). This could be explained by no or only a small decrease in body mass index (BMI), suggesting that weight loss rather than exercise itself is more important for the reduction of serum leptin. This is supported by a significant decrease in circulating leptin in three studies where weight loss was the goal (13, 86, 187). In addition, a recent study has demonstrated that alteration of leptin levels by exercise training is dependent on changes in body fat (178).

C reactive protein (CRP) is a common marker of systemic inflammation and is associated with an increased risk of cardiovascular disease (132). In addition, CRP has been associated with decreased overall and disease-free survival in breast cancer patients (154). The majority of studies investigating the effect of exercise on CRP levels in breast cancer survivors found a decrease in CRP levels in exercise groups (45, 53, 56, 59, 155, 187). Two studies found no difference, but of these one had a baseline level of CRP comparative to that of healthy individuals (179), suggesting that CRP levels may not have been sufficiently elevated for exercise to cause a reduction, and the other suggested that their exercise dose may not have been high enough to elicit a response (94). Taken together, there is evidence that exercise reduces CRP in breast cancer survivors, and therefore, that CRP may be an important prognostic biomarker modulated by exercise training.

Interleukin 6 (IL-6) is a myokine released from skeletal muscle during exercise, resulting in up to a 100-fold increase in its serum levels (150). It is postulated to mediate some exercise-induced anti-inflammatory effects by inhibiting tumour necrosis factor α (TNF-α) and IL-1 production, as well as inducing IL-1 receptor antagonist (IL-1ra) and IL-10 (150). On the other hand, increased serum IL-6 has also been associated with a poor prognosis in breast cancer (109). Studies investigating the effect of exercise on serum IL-6 levels in breast cancer survivors have reported no significant changes (59, 85, 94, 165, 179, 187). Two recent meta-analyses have investigated the effect of exercise on serum IL-6 in breast cancer survivors (95, 127). One of these indicates that exercise reduces serum IL-6 (127), despite non-significant results in a number of the initial studies, while the other shows no change (95). Taken together, the association between exercise, breast cancer and IL-6 is unclear, making it unlikely to have a use as an exercise-modulated prognostic biomarker.

Monocyte chemoattractant protein 1 (MCP-1), also known as CC chemokine ligand 2 (CCL2), is the primary chemokine responsible for attracting monocytes and immature macrophages to peripheral sites (36). As such, it plays an important role in the recruitment of monocytes and macrophages to the tumour, where they are programmed by factors in the microenvironment to take on either a pro-tumour M2 phenotype or an anti-tumour M1 phenotype (54). In general, a large number of tumour associated macrophages (TAMs) is associated with poor prognosis in breast cancer as the tumour microenvironment promotes an M2 phenotype (54). Similarly, intratumoral MCP-1 expression is linked to increased macrophage infiltration and poor prognosis (reviewed in (175)). Data on serum MCP-1 levels are inconclusive, with some reporting an increase in breast cancer patients and others reporting no change (reviewed in (175)). However, recent preclinical mouse studies indicate that serum MCP-1 is significantly elevated in tumour-bearing animals compared to non-tumour-bearing controls (139, 195) and exercise may attenuate this increase (139). To our knowledge, no epidemiological studies have investigated the influence of exercise on serum levels of MCP-1 in breast cancer patients. Taken together, preliminary data suggest that MCP-1 shows promise as a prognostic biomarker that may be modulated by exercise, but further studies, in both animal models and humans, are required to confirm this.

The abovementioned biomarkers are among those most commonly investigated with regards to exercise and cancer, and may prove to be of prognostic value. However, none of these were robust predictors of survival, and as such it would be of value to identify other biomarkers that are regulated by exercise and also play a role in breast cancer outcome.

Effect of Exercise on Tumour Growth in Preclinical Studies

Numerous preclinical studies have attempted to elucidate the role of exercise in tumour progression and the impact on the tumour microenvironment. However, these studies have pro-

duced conflicting results with regards to the effect of exercise on tumour growth, with some reporting inhibited tumour growth (12, 16, 55, 64, 70, 80, 151, 173, 203, 205), some reporting mixed results (118, 185, 206) and others reporting no inhibition of growth (24, 28, 46, 48, 88, 90, 92, 124, 125, 167, 188). These discrepancies may be explained by differences in animal model (immunocompetent versus immunodeficient), mode of exercise (forced versus voluntary), and other confounding factors, such as stress caused by individual housing or excessive tumour burden.

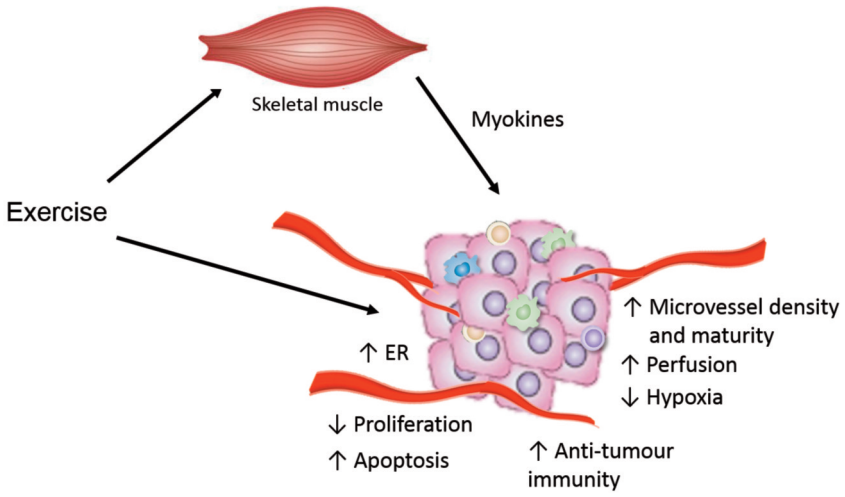

Figure 2: Proposed Mechanisms for the Effects of Exercise on the Tumour Microenvironment.
Exercise has been reported to have multiple effects on tumour growth and the tumour microenvironment. It induces increased perfusion through increased microvessel density and maturity, which results in decreased hypoxia and a less aggressive tumour as well as improved drug delivery. In addition, it promotes anti-tumour immunity and stimulates the release of myokines from skeletal muscle. This reduces proliferation and increases apoptosis of tumour cells. Moreover, exercise may upregulate the estrogen receptor (ER). Taken together, exercise induces favourable effects in the tumour microenvironment, resulting in inhibited tumour growth and metastasis. Figure summarises results from published studies (16, 46, 71, 122, 151).

Forced exercise paradigms, such as treadmill running, have been identified as a source of stress for rodents, increasing levels of corticosteroids and changing normal circadian rhythm (7, 21, 98, 196). This may be a confounding factor in studies investigating the effect of exercise on tumour progression. Indeed, of the 14 studies using forced exercise (12, 28, 46, 70, 80, 90, 118, 124, 126, 167, 173, 185, 188, 206), only 4 reported an inhibition of tumour growth (12, 70, 80, 173), whereas of the 10 studies using voluntary exercise (16, 28, 48, 55, 64, 88, 92, 151, 203, 205), 6 reported an inhibition of tumour growth (16, 55, 64, 151, 203, 205).

The majority of the abovementioned studies have investigated exercise as a monotherapy. The discrepant results in these studies suggest that the ability of exercise on its own to limit tumour growth is relatively small. However, it may reduce the incidence of metastasis (88, 200) and induce changes in the tumour microenvironment resulting in a less aggressive tumour phenotype (discussed in detail below). Furthermore, in a clinical setting, exercise would be utilised as an adjuvant therapy to surgery, chemotherapy, radiation and/or targeted therapies. It is therefore important that future exercise oncology studies include these aspects of cancer treatment and investigate how exercise influences tumour growth in conjunction with standard therapy.

Effect of Exercise on the Tumour Microenvironment

Despite the discrepant results regarding tumour growth, progress has been made towards determining changes in the tumour microenvironment following exercise training (Figure 2). The tumor microenvironment is the cellular, chemical and physical environment within the tumour, which includes immune and stromal cells, acidification due to increased glycolysis, and an aberrant blood supply leading to areas of low oxygen (hypoxia).

Jones *et al.* have shown that exercise increases intratumoral perfusion (16, 88, 92) and reduces hypoxia (16), thereby normalising the tumour microenvironment. Normalisation is here defined as remodelling of the microenvironment to more closely resemble that of normal tissue, and perfusion refers to blood flow, which should result in improved delivery of oxygen and therapeutics. Perfusion results were consistent across different cancer types (breast and prostate), immunocompetent and immunodeficient mice, and despite varying impact on tumour growth (16, 88, 92). In addition, McCullough *et al.* have reported increased intratumoral perfusion in prostate tumours of Copenhagen rats during acute exercise (126). However, in another study by the same group, tumours from rats that had been treadmill-trained for 5-7 weeks and sacrificed 48 h after the last exercise bout showed no increase in perfusion (125). Despite this lack of change in intratumoral perfusion, they observed a significant decrease in hypoxia in tumours from exercising compared to sedentary animals. Together, this suggests that even a transient increase in perfusion may aid in reducing hypoxia and in reducing an aggressive tumour phenotype (189).

The effect of exercise on intratumoral perfusion may differ depending on tumour location. Garcia *et al.* conducted a recent study in which they compared the effect of exercise on intratumoral blood flow in orthotopic (correct anatomical site) and ectopic (subcutaneous) prostate tumours, and found directly opposing effects in that blood flow was increased to the orthotopic tumour, but decreased to the ectopic tumour, during exercise (51). Indeed, blood flow to the skin and subcutaneous adipose tissue was also reduced during exercise (51). This raises important considerations for the study design of preclinical exercise studies, as results from studies using subcutaneous models may not reflect true physiological results.

Increased perfusion should lead to a reduction in hypoxia and an associated reduction in hypoxia factors, including the transcription factor hypoxia inducible factor-1 (HIF-1). However,

two studies by the same group have shown an increase in HIF-1α protein levels in tumours of exercising animals (88, 92), while a further study from a different group indicates a decrease in intratumoral HIF-1α mRNA following exercise training (80). Unfortunately, none of these studies measured intratumoral hypoxia directly, and as such it cannot be conclusively stated that the expression of HIF-1α reflected tumour hypoxia, as HIF-1α expression can also be regulated independently of oxygen tension (27). As such, the effect of exercise training on intratumoral hypoxia and HIF-1α expression remains to be confirmed.

Other modifications of the tumour microenvironment caused by exercise training include increased apoptosis and increased microvessel density and maturity, providing potential mechanisms for reduced tumour growth and improved perfusion, respectively (16, 64, 88, 118). One study reports contradictory results, showing a reduction in apoptosis and blood vessel density in the tumours of exercising mice (206). However, this study used forced treadmill running to exhaustion in order to investigate the effect of intense, prolonged exercise on tumour growth and the tumour microenvironment, and the method of detection of apoptosis and vessel density was suboptimal (quantification of haematoxylin and eosin (H&E) stained slides without a specific marker for the structures of interest). Thus, these results may not accurately reflect the effect of therapeutic exercise on the tumour microenvironment.

A recent study in Sprague-Dawley rats has found that exercise increases expression of the oestrogen receptor in breast tumours (46). The authors suggest that this may be a favourable change as it would make tumours easier to treat (via endocrine therapy). However, this is an isolated report that requires validation and further research into its implications.

Secretion of exercise-induced myokines from skeletal muscle may impact tumour growth (Figure 2). It has been demonstrated that a number of different myokines reduce tumour growth or tumour cell proliferation by as yet unidentified mechanisms (5, 50, 71), which include secreted protein acidic and rich in cysteine (SPARC), oncostatin M (OSM) and irisin.

Taken together, exercise impacts the tumour microenvironment in a number of ways: by increasing intratumoral perfusion, increasing vessel patency and reducing hypoxia, which leads to increased apoptosis and reduced proliferation of tumour cells. This may be mediated through the release of myokines. However, a number of questions remained unanswered. It is not known whether these effects are true for all cancer types, whether location on/in the body plays a role, or how these microenvironmental effects may change with chemotherapy, radiation or targeted therapies.

Effect of Exercise on the Immune Tumour Microenvironment

Exercise is known to influence immunity. In the context of cancer, increasing evidence over the last few years indicates that exercise induces a favourable change in the immune microenvironment of the tumour, making it less immunosuppressive and enhancing anti-tumour immunity (Figure 3; (4, 55, 123, 151, 199)). Key immunological cell types that are known to influence tumour progression include tumour associated macrophages (TAMs), natural killer (NK) cells and T cells.

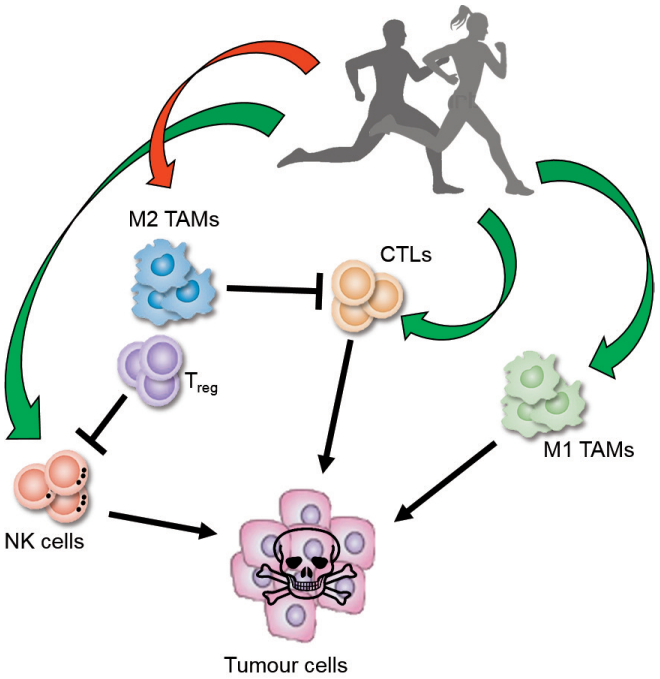

Figure 3: Overview of Exercise-Mediated Effects on the Immune Tumour Microenvironment.
Exercise has been reported to enhance anti-tumour immunity by alleviating the immunosuppressive microenvironment found within tumours and by enhancing the cytotoxic capabilities of tumour-killing cell types. Specifically, exercise increases cytotoxic activity of natural killer (NK) cells, induces a phenotypic shift from M2 to M1 macrophages and may alter proportions of T cells to include more cytotoxic T-cells (CTLs) and fewer regulatory T (T_{reg}) cells. Together, this results in improved killing of tumour cells. Green arrows denote stimulation and red arrow denotes inhibition. Figure summarises results from published studies (54, 55, 123, 151).

NK cells are the immune cells that respond most strongly to acute exercise, and as such they may be among the most important initial responders in the exercise-mediated anti-tumour response (75). It was first shown by Hoffman-Goetz *et al.* that NK cells from moderately exercised mice showed enhanced anti-tumour cytotoxicity against transformed fibroblasts, lymphoma cells and breast tumour metastases (67-69, 84, 116, 117). This has been substantiated by more recent publications in mice (151) and clinical studies ((18), reviewed in (103)). Pedersen *et al.* showed that exercise increases NK cell mobilisation to the tumour site, which was mediated by epinephrine (151). Idorn and Hojman suggest that it is this epinephrine-mediated mobilisation that is key, and that as long as exercise intensity is sufficient to elicit an epinephrine response, the duration of exercise is less important (75). In addition to their cytotoxic capabilities, NK cells influence the activity of many other immune cell types, including T cells, B cells and dendritic cells (30, 82, 87).

Macrophages can be broadly classified into two main phenotypic subtypes: M1 and M2. M1 macrophages are inflammatory, and responsible for the elimination of pathogens by

phagocytosis and the stimulation of adaptive immunity by the secretion of pro-inflammatory cytokines (81). M2 macrophages are immunoregulatory and play a role in wound healing (81). TAMs generally exhibit an M2 phenotype, which promotes tumour progression through the inhibition of cytotoxic immune cells and the secretion of angiogenic factors (191). Because of this, high numbers of TAMs have been associated with a poorer prognosis in breast cancer patients (57, 198, 201). Studies have shown that exercise training may cause a phenotypic shift in TAMs from a pro-tumour M2 to an anti-tumour M1 phenotype (reviewed in (54)). This is demonstrated by the increased secretion of M1-associated cytokines from *ex vivo* stimulated peritoneal macrophages from exercising compared to sedentary mice bearing mammary tumours (1), increased cytotoxicity/phagocytosis of macrophages from exercising mice (33, 174) and decreased expression of M2-associated genes (123). Therefore, some of the anti-tumour effects of exercise are likely mediated through the repolarisation of TAMs.

The adaptive immune system also plays an important role in the tumour microenvironment. T cells in the lymph nodes must be activated by antigen-presenting cells holding tumour-specific antigens, following which they travel to the site of the cancer and infiltrate the tumour (29). Cytotoxic T cells (CTLs) are responsible for tumour cell killing; however, their response can be switched off by inhibitory molecules on the tumour cell surface (29). In addition, T_{reg} cells and other immunoregulatory cell types can suppress CTL-mediated cell killing through the secretion of inhibitory cytokines, cytolysis and metabolic disruption (190). Exercise may increase the proportion of intratumoral CTLs and reduce T_{reg} cells, as evidenced by increased *Cd8* and reduced *Foxp3* gene expression in mucosal scrapings from a transgenic mouse model for colorectal cancer, the $Apc^{Min/+}$ mouse (123). However, the immune microenvironment in the gut is unique in that it tends to be highly immunosuppressive due to the need for tolerance to food and commensal microbiota-derived antigens, and thus these results may not be translatable to other cancer types. In breast cancer, it has been shown that exercise decreases intratumoral gene expression of *Ccl22*, a chemokine known to attract T_{reg} cells (55). However, none of these studies have investigated the functionality of intratumoral T cell subtypes following exercise, which would be an important next step in determining how exercise affects T cell immunity in tumours.

The role of hypoxia in anti-tumour immunity is fairly well established, in that it inhibits anti-tumour immune responses and promotes immunosuppression (6, 148). Specifically, hypoxia has been shown to decrease tumour cell susceptibility to CTL and NK cell mediated lysis (47, 61, 147, 169), increase T_{reg} cell attraction, induction and immunosuppressive function (35, 111, 160), and promote an immunosuppressive phenotype in myeloid cells (reviewed in (148)). Furthermore, a recent study has demonstrated that type 1 T helper (T_H1) cells can contribute to intratumoral vessel normalisation (182). On the other hand, T_{reg} cells and M2 macrophages can induce (pathological) angiogenesis (160, 161). Therefore, exercise-induced modulation of the immune phenotype within the tumour may be a contributing factor to the vessel normalisation and reduced pathological angiogenesis seen in some of the studies discussed in previous sections.

Although much progress has been made over the last few years in determining the effects of exercise on the immune microenvironment of the tumour, much is still unknown. The bulk of research thus far has focussed on NK cells and macrophages, with some work beginning to emerge on T cells. Future work will focus on how exercise affects other immune cell types within the tumour microenvironment (and systemically), such as B cells and neutrophils, as well as specific subtypes (e.g. T helper cell subtypes such as T_H1, T_H2 and T_H17).

Taken together, current data shows that exercise increases anti-tumour immunity and alleviates the immunosuppressive microenvironment found in solid tumours, which may also improve vessel patency and reduce hypoxia.

INTERPLAY OF HYPERLIPIDAEMIA AND EXERCISE IN BREAST CANCER PROGRESSION

Hyperlipidaemia is an inflammatory disease. This is at least partly attributable to the activation of TLR signalling by oxidised LDL, which induces a pro-inflammatory phenotype in innate immune cells (74). In turn, chronic inflammation has a well-established pro-tumour effect (17). Thus, we propose that hyperlipidaemia contributes to breast cancer progression through the induction of chronic inflammation. Conversely, exercise can reduce chronic inflammation (110, 197). This is likely through the action of anti-inflammatory myokines (197). In addition, exercise has been shown to reduce TLR expression on monocytes and reduce the number of circulating pro-inflammatory monocytes (197). Therefore, exercise may inhibit breast cancer progression in hyperlipidaemic individuals by dampening TLR activation and by the action of anti-inflammatory myokines, thereby reducing chronic inflammation.

Hyperlipidaemia is characterised by elevated serum cholesterol levels. This increase in serum cholesterol should result in an increased exposure of tumour cells to cholesterol. As cholesterol and some of its metabolites have been shown to directly increase breast cancer cell proliferation *in vitro* and breast tumour growth *in vivo* ((3, 143), reviewed in (8)), it is likely that hyperlipidaemia also exerts pro-tumour effects through the direct effect of cholesterol. On the other hand, exercise can lower serum lipid levels, possibly by augmenting the ability of skeletal muscles to utilise lipids rather than glycogen or by increases in lecithin-cholesterol acyltransferase and lipoprotein lipase activity (reviewed in (120)). Therefore, a further mechanism by which exercise may inhibit tumour growth in hyperlipidaemic individuals is the reduction of blood cholesterol, thereby reducing the amount of cholesterol that tumour cells are exposed to.

Taken together, exercise may inhibit breast cancer progression in hyperlipidaemic individuals by reducing hyperlipidaemia-

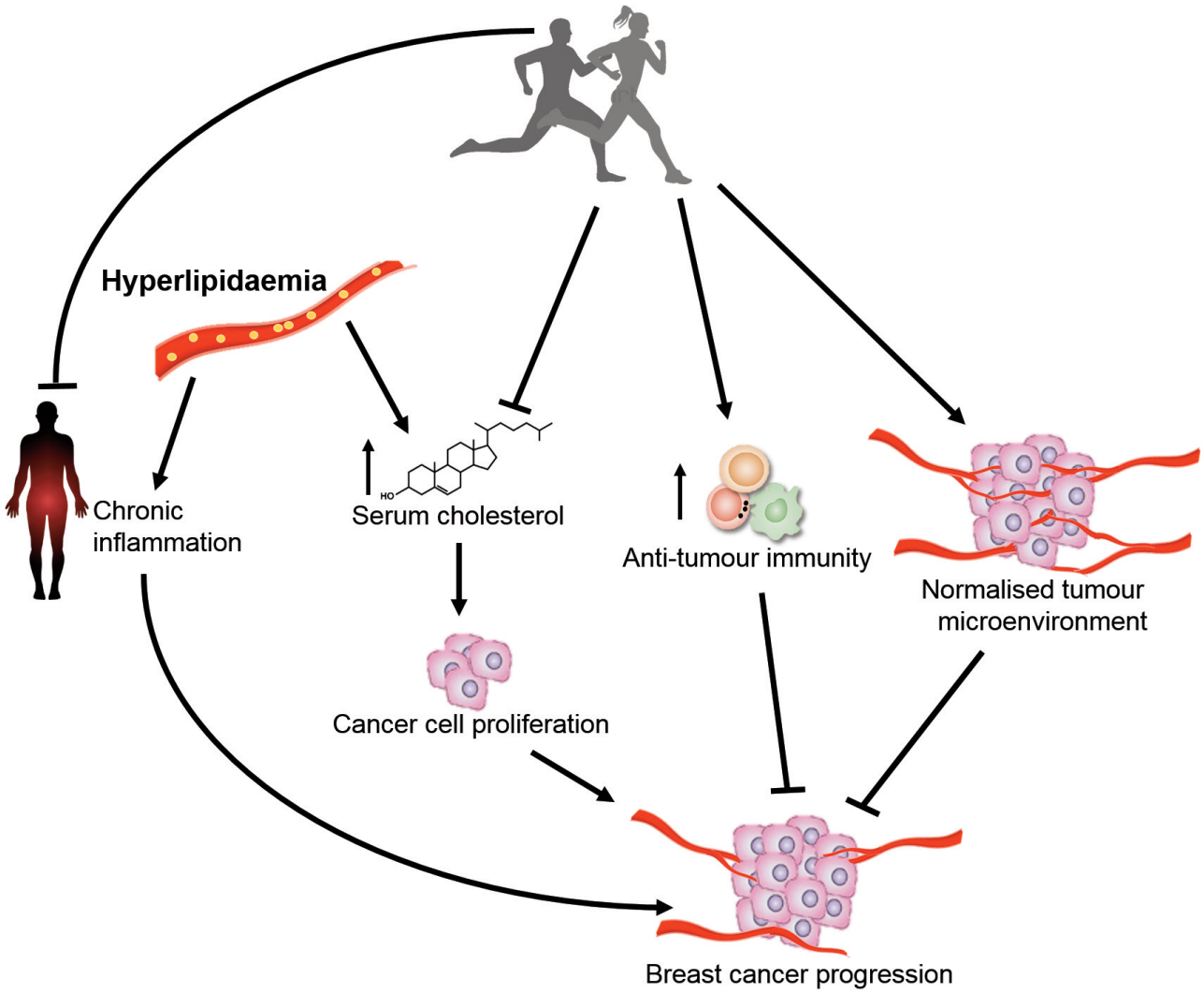

Figure 4: Hypothesised interplay of exercise and hyperlipidaemia in breast cancer progression.
Hyperlipidaemia can promote breast cancer through the induction of chronic inflammation and the mitogenic action of cholesterol on tumour cells. Exercise may work against the pro-tumour effect of hyperlipidaemia by reducing chronic inflammation, lowering serum lipids, increasing the ability of the immune system to recognise and destroy tumour cells and by normalising the vascular network of the tumour, thereby reducing hypoxia.

associated chronic inflammation, by lowering serum cholesterol and thereby reducing the exposure of tumour cells to cholesterol, by enhancing anti-tumour immunity and by normalising the tumour vasculature (Figure 4, discussed in the previous section).

CONCLUSION

Obesity-associated hyperlipidaemia and exercise have opposing effects on breast cancer growth and development, and as such it is possible that exercise could be utilised in hyperlipidaemic patients to lower lipid levels and mitigate the pro-tumour effect of hyperlipidaemia. To our knowledge, no published work is available which specifically investigates this issue. To date, substantial clinical and preclinical work has been undertaken separately to investigate the effects of hyperlipidaemia and exercise on breast cancer. However, it is unknown how hyperlipidaemia influences the anti-tumour immune response and the immune microenvironment of the tumour.

In terms of exercise, the optimal therapeutic 'dose' of exercise remains unclear, as few studies are available which specifically investigate this. It seems likely that a minimum level is required (it has been shown that the current WHO guidelines appear to be adequate (106)), and that excessive exercise may be detrimental, as overtraining is known to weaken the immune system in healthy individuals (115).

Furthermore, most studies to date have focussed on exercise as a monotherapy, whereas in the clinic it would function as an adjunct to surgery, chemotherapy, radiation and/or targeted therapies. Therefore, it is essential that future work determines how exercise and other therapies together influence tumour growth and the tumour microenvironment. In addition, it is unknown whether the effects of exercise on the tumour microenvironment differ according to tumour type and location. It needs to be further explored how exercise modulates perfusion to the skin and internal organs, and how this can have different effects on different cancer types. In this context, a recent study investigating the association between cancer risk and leisure time physical

activity in over one million adults reported that exercise was associated with decreased risk of developing lung cancer, but increased risk of developing melanoma (135).

Further work on the immune microenvironment of the tumour is also required to determine how cell types or subsets, such as neutrophils or T helper cell subsets, are affected by exercise. Functionality assays on T cell subsets would provide information as to whether exercise alters the cytotoxic or immunosuppressive activity of these cells, or whether it only influences recruitment to the tumour site.

In summary, work to date indicates that exercise can slow tumour growth and effect changes in the tumour microenvironment which make it less aggressive, more susceptible to treatment and more likely to be recognised and attacked by the immune system. In contrast, obesity-associated hyperlipidaemia makes tumours more aggressive. Joint analysis of diet and exercise will provide further insight into how the two modalities, which are two of the largest lifestyle factors responsible for a person's individual health and well-being, can affect the progression of cancer. We suggest that exercise may alleviate some of the pro-tumorigenic effects of hyperlipidaemia through the reduction of chronic inflammation, blood lipid levels and by exerting specific anti-cancer effects on the tumour microenvironment.

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