Position Statement
Part one: Immune function and exercise

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CONSENSUS STATEMENT

An ever-growing volume of peer-reviewed publications speaks to the recent and rapid growth in both scope and understanding of exercise immunology. Indeed, more than 95% of all peer-reviewed publications in exercise immunology (currently >2, 200 publications using search terms "exercise" and "immune") have been published since the formation of the International Society of Exercise and Immunology (ISEI) in 1989 (ISI Web of Knowledge^{SM}). We recognise the epidemiological distinction between the generic term "physical activity" and the specific category of "exercise", which implies activity for a specific purpose such as improvement of physical condition or competition. Extreme physical activity of any type may have implications for the immune system. However, because of its emotive component, exercise is likely to have a larger effect, and to date the great majority of our knowledge on this subject comes from exercise studies.

In this position statement, a panel of world-leading experts provides a consensus of current knowledge, briefly covering the background, explaining what we think we

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know with some degree of certainty, exploring continued controversies, and pointing to likely directions for future research. Part one of this position statement focuses on 'immune function and exercise' and part two on 'maintaining immune health'. Part one provides a brief introduction and history (Roy Shephard) followed by sections on: respiratory infections and exercise (Maree Gleeson); cellular innate immune function and exercise (Jeffrey Woods); acquired immunity and exercise (Nicolette Bishop); mucosal immunity and exercise (Michael Gleeson and Nicolette Bishop); immunological methods in exercise immunology (Monika Fleshner); anti-inflammatory effects of physical activity (Charlotte Green and Bente Pedersen); exercise and cancer (Laurie Hoffman-Goetz and Connie Rogers) and finally, "omics" in exercise (Hinnak Northoff, Asghar Abbasi and Perikles Simon).

The focus on respiratory infections in exercise has been stimulated by the commonly held beliefs that the frequency of upper respiratory tract infections (URTI) is increased in elite endurance athletes after single bouts of ultra-endurance exercise and during periods of intensive training. The evidence to support these concepts is inconclusive, but supports the idea that exercised-induced immune suppression increases susceptibility to symptoms of infection, particularly around the time of competition, and that upper respiratory symptoms are associated with performance decrements. Conclusions from the debate on whether sore throats are actually caused by infections or are a reflection of other inflammatory stimuli associated with exercise remains unclear.

It is widely accepted that acute and chronic exercise alter the number and function of circulating cells of the innate immune system (e.g. neutrophils, monocytes and natural killer (NK) cells). A limited number of animal studies has helped us determine the extent to which these changes alter susceptibility to herpes simplex and influenza virus infection. Unfortunately, we have only 'scratched the surface' regarding whether exercise-induced changes in innate immune function alter infectious disease susceptibility or outcome and whether the purported anti-inflammatory effect of regular exercise is mediated through exercise-induced effects on innate immune cells. We need to know whether exercise alters migration of innate cells and whether this alters disease susceptibility. Although studies in humans have shed light on monocytes, these cells are relatively immature and may not reflect the effects of exercise on fully differentiated tissue macrophages. Currently, there is very little information on the effects of exercise on dendritic cells, which is unfortunate given the powerful influence of these cells in the initiation of immune responses.

It is agreed that a lymphocytosis is observed during and immediately after exercise, proportional to exercise intensity and duration, with numbers of cells (T cells and to a lesser extent B cells) falling below pre-exercise levels during the early stages of recovery, before returning to resting values normally within 24 h. Mobilization of T and B cell subsets in this way is largely influenced by the actions of catecholamines. Evidence indicates that acute exercise stimulates T cell subset activation *in vivo* and in response to mitogen- and antigen-stimulation. Although numerous studies report decreased mitogen- and antigen-stimulated T cell proliferation following acute exercise, the interpretation of these findings may be confounded by alterations in the relative proportion of cells (e.g. T, B and

NK cells) in the circulation that can respond to stimulation. Longitudinal training studies in previously sedentary people have failed to show marked changes in T and B cell functions provided that blood samples were taken at least 24 h after the last exercise bout. In contrast, T and B cell functions appear to be sensitive to increases in training load in well-trained athletes, with decreases in circulating numbers of Type 1 T cells, reduced T cell proliferative responses and falls in stimulated B cell Ig synthesis. The cause of this apparent depression in acquired immunity appears to be related to elevated circulating stress hormones, and alterations in the pro/anti-inflammatory cytokine balance in response to exercise. The clinical significance of these changes in acquired immunity with acute exercise and training remains unknown.

The production of secretory immunoglobulin A (SIgA) is the major effector function of the mucosal immune system providing the 'first line of defence' against pathogens. To date, the majority of exercise studies have assessed saliva SIgA as a marker of mucosal immunity, but more recently the importance of other antimicrobial proteins in saliva (e.g. α-amylase, lactoferrin and lysozyme) has gained greater recognition. Acute bouts of moderate exercise have little impact on mucosal immunity but prolonged exercise and intensified training can evoke decreases in saliva secretion of SIgA. Mechanisms underlying the alterations in mucosal immunity with acute exercise are probably largely related to the activation of the sympathetic nervous system and its associated effects on salivary protein exocytosis and IgA transcytosis. Depressed secretion of SIgA into saliva during periods of intensified training and chronic stress are likely linked to altered activity of the hypothalamic-pituitary-adrenal axis, with inhibitory effects on IgA synthesis and/or transcytosis. Consensus exists that reduced levels of saliva SIgA are associated with increased risk of URTI during heavy training.

An important question for exercise immunologists remains: how does one measure immune function in a meaningful way? One approach to assessing immune function that extends beyond blood or salivary measures involves challenging study participants with antigenic stimuli and assessing relevant antigen-driven responses including antigen specific cell-mediated delayed type hypersensitivity responses, or circulating antibody responses. Investigators can inject novel antigens such as keyhole limpet haemocyanin (KLH) to assess development of a primary antibody response (albeit only once) or previously seen antigens such as influenza, where the subsequent antibody response reflects a somewhat more variable mixture of primary, secondary and tertiary responses. Using a novel antigen has the advantage that the investigator can identify the effects of exercise stress on the unique cellular events required for a primary response that using a previously seen antigen (e.g. influenza) does not permit. The results of exercise studies using these approaches indicate that an acute bout of intense exercise suppresses antibody production (e.g. anti-KLH Ig) whereas moderate exercise training can restore optimal antibody responses in the face of stressors and ageing. Because immune function is critical to host survival, the system has evolved a large safety net and redundancy such that it is difficult to determine how much immune function must be lost or gained to reveal changes in host disease susceptibility. There are numerous examples where exercise alters measures of immunity by 15-25%. Whether changes of this magnitude are sufficient to alter host defence, disease susceptibility or severity remains debatable.

Chronic inflammation is involved in the pathogenesis of insulin resistance, atherosclerosis, neurodegeneration, and tumour growth. Evidence suggests that the prophylactic effect of exercise may, to some extent, be ascribed to the anti-inflammatory effect of regular exercise mediated via a reduction in visceral fat mass and/or by induction of an anti-inflammatory environment with each bout of exercise (e.g. via increases in circulating anti-inflammatory cytokines including interleukin (IL)-1 receptor antagonist and IL-10). To understand the mechanism(s) of the protective, anti-inflammatory effect of exercise fully, we need to focus on the nature of exercise that is most efficient at allieviating the effects of chronic inflammation in disease. The beneficial effects of endurance exercise are well known; however, the anti-inflammatory role of strength training exercises are poorly defined. In addition, the independent contribution of an exercise-induced reduction in visceral fat versus other exercise-induced anti-inflammatory mechanisms needs to be understood better. There is consensus that exercise training protects against some types of cancers. Training also enhances aspects of anti-tumour immunity and reduces inflammatory mediators. However, the evidence linking immunological and inflammatory mechanisms, physical activity, and cancer risk reduction remains tentative.

In the very near future, genomics, proteomics, and metabolomics may help exercise immunologists to better understand mechanisms related to exercise-induced modulation of the immune system and prevention (or reduced risk) of diseases by exercise training. In addition, these technologies might be used as a tool for optimizing individual training programmes. However, more rigorous standardization of procedures and further technological advances are required before practical application of these technologies becomes possible.

Key Words: exercise; sport; training; immune; pathogen; infection; innate; acquired; mucosal; saliva; leukocyte; monocyte; neutrophil; granulocyte; lymphocyte; immunoglobulin; method; cytokine; interleukin; inflammation; cancer; genomics; proteomics; metabolomics

INTRODUCTION AND HISTORY

Two recent papers have summarized the scientific history of exercise immunology (263) and its development as a specific discipline (264) with its own international society and a dedicated journal. Exercise immunology has quite a short history relative to many branches of the exercise sciences, the modern era of careful epidemiological investigations and precise laboratory studies beginning in the mid 1980s. However, an ever-growing volume of peer-reviewed publications speaks to a rapid growth in both scope and understanding of the topic since that date. In addition to enquiries into many areas of intrinsic scientific interest, exercise immunologists have found diverse applications for their talents in augmenting population health and maintaining high performance athletes in peak physical condition.

From early during the 20th century, clinicians had pointed to what seemed adverse effects of prolonged heavy exercise upon both resistance to and the course of various viral and bacterial diseases (25, 261). These concerns were seemingly sub-

stantiated by a 2-6 fold increase in the reported symptoms of upper respiratory infection (URTI) for several weeks following participation in marathon or ultra-marathon events (200, 224). The influence of exercise on the risks of URTI is discussed in the following section. A transient fall in the circulating natural killer (NK) cell count following a sustained bout of vigorous exercise (270) seemed to offer a mechanism explaining the increase in risk; the temporary lack of NK cells and killer cell activity offered an "open window," a period when a reduced resistance to viral infections allowed easier access to infecting micro-organisms. Innate immunity is discussed in detail later in this part of the position statement. In one report, the reduction in NK cell count persisted for seven days following exercise (259), but in most studies, circulating NK cell numbers and activity have been described as being depressed for only a few hours, raising doubts as to whether the "window" was open long enough to account for the increased vulnerability to infection. Moreover, technical advances (particularly in automated cell counting and identification) (85) have underlined that exercise does not destroy NK cells; rather, they are temporarily relocated to reservoir sites such as the walls of peripheral veins in response to the exercise-induced secretion of catecholamines and activation of adhesion molecules (266). A more plausible explanation for the reported increase in URTI during heavy training and following participation in long-distance events appeared as attention shifted to immunoglobulins in general, and in particular to a depression of front-line defences through a decrease in the mucosal secretory functions of the nose and salivary glands (152, 298). The influence of exercise on mucosal immunity is discussed in more detail later in this part of the position statement.

The hypothesis of a U-shaped relationship between physical activity and resistance to disease, although based on a relatively limited amount of laboratory and epidemiological data (202, 267), has made intuitive sense, jibing with the more general belief that although regular moderate doses of physical activity have beneficial effects on health, excessive amounts or intensities of physical activity have negative consequences. In the case of the immune system, one suggestion has been that an excess of physical activity provokes something analogous to clinical sepsis, with tissue destruction from an excessive inflammatory reaction (260). Although initially conceived simply in the context of URTI (201), the concept of a U-shaped response has now been extended to cover the effects of physical activity upon a variety of clinical disturbances of immune function. In terms of cancer prevention and therapy (268), regular moderate physical activity has been shown to reduce the risk of developing certain forms of the disease (265); it also limits the risk of metastasis, at least in experimental animals (156). Exercise and cancer is discussed in more detail in this part of the position statement. On the other hand, excessive exercise has been shown to cause DNA damage and apoptosis (176, 186). Ageing is increasingly considered in part as an expression of disturbed immune function; high concentrations of pro-inflammatory cytokines are seen in the elderly, and seemingly contribute to such problems of ageing as sarcopenia, neural degeneration and Alzheimer's Disease. Moreover, appropriate amounts of physical activity can control levels of pro-inflammatory cytokines, and appear to have a beneficial effect on these manifestations of ageing (188). Certain autoimmune conditions also respond to carefully regulated physical activity programmes, although it has yet to be established clearly whether benefit occurs

through some direct modulation of cell counts and cytokines, or through changes in the activity of transcription factors for pro-inflammatory cytokines (9).

Developments in fluorescent antibodies have allowed exercise immunologists to identify an ever-growing number of cell sub-types and receptors. At the same time, new cytokine identification kits and methods in molecular technology (173) have allowed the examination of humoral factors that are present in the body for very short periods and in extremely low concentrations; an increasingly complex range of pro- and anti-inflammatory cytokines has been revealed. The exercise immunologist seems drawn into the main streams of sports medicine, physiology and even psychology. A fascinating cascade of cytokines is now thought to have an important role not only in controlling exercise-induced inflammation, but also in regulating the release and necessary flow of metabolites (221). Development of the sub-discipline of psycho-neuroimmunology (141) has emphasized that vigorous exercise should be considered as but one example of the body's reaction to a variety of stressors (221), with an important two-way communication between peripheral immunocytes and hypophyseal centres, involving a wide variety of hormones and autonomic pathways (157). A section in the second part of the position statement deals with stress and immune function.

On the sports field, exercise immunologists are increasingly asked to develop procedures to detect such abuses as blood doping (185) and gene transfer (11) (see "Omics" section in this part of the position statement). However, attempts to pinpoint immunological markers of over-training have as yet proved inferior to traditional indices such as mood state and physical performance (as discussed in the second part of this position statement). A variety of nutritional supplements to date seem to have had only limited success in blunting the immune impairment associated with heavy exercise (as discussed in the second part of this position statement).

These are a few of the important topics on which a panel of world experts provide a succinct consensus of current knowledge, briefly covering the relevant background, exploring continued controversies, and pointing to likely directions of future research.

RESPIRATORY INFECTIONS AND EXERCISE

Background

There are more uncertainties than evidence based facts on the nature of upper respiratory tract infections (URTI) associated with exercise, particularly in high performance athletes. Although URTI or 'sore throats' are the most common reason for presentation of elite athletes to a sports medicine clinic (62, 77, 80), the debate on whether sore throats are actually caused by infections, or are a reflection of other inflammatory stimuli associated with exercise remains unclear (48, 106, 242).

The costs associated with identification of the underlying causes of upper respiratory symptoms (URS) and the delay in obtaining results of investigative tests

means that infections are not usually verified by pathology examinations. Physician confirmation of an infective cause of the symptoms, based on clinical signs and symptoms, has until recently been considered the 'gold standard' for exercise studies, but the involvement of physicians in assessments and diagnosis is not common in research settings. Recently, the 'gold standard' of physician verified diagnosis of URTI has also come under scrutiny, and been found less than ideal (48). Very few studies have examined the underlying causes of URS and extensive clinical investigations of athletes are rare (48, 242).

The focus on respiratory infections in exercise has been stimulated by the commonly held beliefs that the frequency of URTI is increased in elite endurance athletes and that their incidence is associated with more intensive training (201). The evidence to support these concepts is inconclusive, but does, support the idea that exercised-induced immune suppression increases susceptibility to symptoms of infection and that URS are associated with performance decrements.

Evidence based consensus and uncertainties

Over the past thirty years, there have been numerous investigations examining the association between changes in immune parameters and the risk of URTI in athletic and non-exercising populations. The only immune measures to date to show consistent relationships with URS in exercising populations have been changes in salivary IgA concentrations and secretion rates (19, 89, 263). A section focusing on exercise and mucosal immunity appears later in this part of the position statement.

Altered mucosal immunity and risk of symptoms of URTI

The inverse relationship between salivary IgA concentrations and risk of URTI in exercising and non-exercising populations has demonstrated differences between these two populations (76, 89, 98, 232). The different population risk profiles are predominantly due to differences in the levels of intensity and quantum of exercise undertaken by very fit elite athletes and non-elite exercising or sedentary populations. The impact of exercise intensity on salivary IgA concentrations and secretion rates has demonstrated greater decreases in salivary IgA associated with prolonged high intensity exercise, whereas moderate increases in salivary IgA occur in response to short duration moderate intensity exercise (6, 19, 23, 98, 129, 148, 163, 232).

Although study populations vary, the association of an increased risk of URS and/or URTI with lower concentrations of salivary IgA and secretion rates has been consistent for high-performance endurance athletes undertaking intensive training (64, 91, 92, 95, 97, 148, 187, 195-198, 201, 320). Similarly, the increases in salivary IgA observed after moderate exercise training may contribute to the reduced susceptibility to URTI associated with regular moderate exercise (3, 129).

Symptoms and frequency

Although there are many anecdotal reports that URTIs are more common in elite athletes, there is very little reported evidence to support this commonly held belief. This uncertainty is compounded by the current uncertainty around whether the URS are due to infections or other inflammatory stimuli mimicking URTI (48, 242).

Retrospective and prospective longitudinal studies have identified that the majority of elite athletes experience symptoms of URTI at a rate similar to the general population (48, 78, 234). However, the episodes of URS in elite athletes do not follow the usual seasonal patterns of URTI observed in the general population, but rather occur during or around competitions (97, 160, 198, 224). Symptoms occur more frequently during the high intensity training and taper period prior to competitions in some sports, such as swimming (79, 89, 91), but in other endurance sports, such as long distance running, URS appear more frequently after a competition (49, 198, 224). Illness-prone athletes may also be susceptible to URS during regular training periods or following increases in training load (80). The commonly reported short-term duration of URS (1-3 days) in most studies suggests that in most instances a primary infection is unlikely and the symptoms may be due to viral reactivation (97, 242) or other causes of exercise-induced inflamma-

Table 1. Pathogens identified and the number of cases in comprehensive prospective studies of athletes presenting with symptoms of upper respiratory infections in 1) a cohort of high performance triathletes during training and competitions (282); 2) a study of elite athletes from a variety of sports undertaking routine training presenting to a sports clinic with URS (48); and 3) a cohort of elite athletes experiencing recurrent episodes of URS associated with fatigue and performance decrements (242). Where investigations were not performed this is recorded as (-).

Pathogen identified by microbial and viral investigation	Triathletes (n=63) undertaking routine training and competitions Spence et al. (282)	Elite athletes (n=70) presenting to a sports clinic Cox et al. (48)	Elite athletes (n=41) with persistent fatigue and poor performance Reid et al. (242)
Rhinovirus	7	6	-
Influenzae (A & B)	7	1	-
Parainfluenzae (1, 2 & 3)	4	3	-
Adenovirus	0	2	-
Coronavirus	2	0	-
Metapneumovirus	1	0	-
Epstein Barr virus (primary infection)	1	1	3
EBV reactivation	-	1	8
Cytomegalovirus	0	0	5
Herpes simplex virus (types 1 & 2)	0	-	-
Ross River virus	-	-	1
Toxoplasmosis	-	-	1
Mycoplasma pneumoniae	0	1	1
Streptococcus pneumonia	2	1	-
Staphylococcus pyogenes	0	1	-
Haemophilus influenzae	0	0	-
Moraxella catarrhalis	0	0	-
Enterococcus spp	0	0	-

tion. The evidence that URS are associated with poor performance is also limited. In the month prior to an international competition URS have been associated with decrements in performance in elite swimmers (235), suggesting that regardless of whether the URS are due to infections or other inflammatory stimuli, they can impact on performance at an elite level. However, a small proportion of high-performance endurance athletes experience recurrent episodes of URS at significantly higher rates than the incidence in the general population (92, 234), and in these athletes the URS are associated with significant persisting fatigue and poor performance (79, 91, 93, 242).

Infections versus inflammation

The few studies that have undertaken pathology testing to identify infectious from non-infectious causes of the episodes of URS in high-performance athletes have revealed that bacterial infections account for about 5% of the episodes (48, 94, 242, 282). Most episodes of URS with an identified infectious cause are of viral origin, but these account for only about 30-40% of the episodes in each study (48, 282). The bacterial and viral pathogens identified in these comprehensive studies indicate that the infections are caused by the usual respiratory pathogens associated with URTI (246) in the general population (Table 1).

However, the profile of infections in a study of elite athletes experiencing recurrent URS associated with long-term fatigue and poor performance identified a high percentage as having herpes group viruses (e.g. cytomegalovirus) or evidence of Epstein Barr Virus (EBV) reactivation (242) (Table 1). Epstein Barr viral reactivation has also been demonstrated in association with URS in some endurance sports (97, 242), which may account for the short duration of the symptoms reported in most studies, resulting from viral reactivation rather than primary infection. However, in a study examining the prophylactic use of an antiviral treatment in elite runners, it was shown that not all episodes of URS were associated with EBV expression (50) and that the frequency of EBV expression differed between sports (50, 97). Although an anti-herpes virus treatment was effective in reducing EBV expression in elite long-distance runners, it was not effective in reducing the frequency of episodes of URS, once again suggesting other non-infective causes for the URS in elite athletes (50).

Physician diagnosis of infections as the cause of the URS has recently come under scrutiny (48) and in conjunction with a previous study by Reid et al. (242) has identified that elite athletes suffering recurrent episodes of URS need more exhaustive clinical assessments to exclude non-infectious yet treatable causes of the symptoms, such as asthma, allergy, autoimmune disorders, vocal cord dysfunction and unresolved non-respiratory infections. In these studies, other diseases with an inflammatory basis accounted for 30-40% of episodes of URS in elite athletes. These studies identified that URS were divided into approximately one-third proportions as having an infectious cause, non- infectious medical cause and an unknown aetiology. The speculative causes of the ‘unknown-aetiology’ group could include physical or mechanical damage such as drying of the airways (16); asthma and allergic airway inflammation (106); psychological impacts of exercise on membrane integrity and immunity (22); and the migration

to the airways of inflammatory cytokines generated during damage to muscles susained in eccentric exercise (214, 222). Multiple stressors experienced by athletes, biological, physical and psychological, are likely to induce neurological and endocrine responses in addition to alterations in immune parameters; these share common exercise-induced pathways (207) that may result in URS. However, there is currently little direct evidence to support any of these mechanisms being associated with URS, respiratory infections or susceptibility to infections in athletes.

Cytokine regulation

Cytokine responses to exercise (particularly those associated with micro-trauma and or glycogen depletion of muscle tissue (27, 214, 222, 294)) are reasonably well characterised (as discussed in the section on anti-inflammatory effects of physical activity later in this part of the position statement). They are likely to play an important role in modulating post-exercise changes in immune function that increase the risk of infection or the appearance of inflammatory symptoms (294). The pro-inflammatory responses to exercise have the potential to be involved in expression of URS that mimic URTI. A study comparing cytokine responses to exercise in illness-prone distance runners demonstrated impaired anti-inflammatory cytokine regulation compared to runners who did not suffer frequent episodes of URS (51). A recent cytokine gene polymorphism study by Cox et al. (47) identified an underlying genetic predisposition to high expression of the pro-inflammatory interleukin-6 in athletes prone to frequent URS. These studies add further weight to the evidence that suggests infections are not the only cause of the symptoms of 'sore throat'. They are supported by studies examining the prophylactic use of topical anti-inflammatory sprays to prevent URS in long-distance runners which demonstrate a reduction in the severity of the symptoms but not the frequency of episodes following marathon races (49, 257).

Conclusions and future directions

Interpreting the findings of studies on the role of respiratory infections in exercise is often limited by the lack of pathogen identification. Regardless of the underlying stimulus for the inflammatory symptoms the implications of the upper airway symptoms for athletes may be the same. However, unless the symptoms are confirmed as infections, reference to symptoms as URS rather than as infections or URTI should become the accepted reporting standard, particularly when there is no physician assessment.

The current consensus is that the cause of URS in athletic populations is uncertain. Physician identification can no longer be considered the gold standard and symptoms should only be referred to as infection if a pathogen has been identified. Although diagnostic pathology is rarely performed, in the few studies that have examined pathology, the infections identified in most athletes have been the common respiratory pathogens observed in the general population.

Inflammation from non-infective causes is common among athletes and many will have underlying treatable conditions. As differentiation between the inflammatory causes of URS is currently not feasible in most research settings, appro-

priate treatments are difficult to prescribe universally. Athletes with recurrent URS associated with long-term fatigue and poor performance do, however, warrant more exhaustive clinical investigations, including assessment for possible involvement of the herpes group viruses. Identifying athletes with an underlying genetic predisposition to pro-inflammatory responses to exercise may be useful in managing the training regimens of elite athletes, particularly those who suffer recurrent episodes of URS associated with fatigue and poor performance.

The two main questions to be resolved about the relationship between respiratory infections and exercise are: 1) whether the upper respiratory tract symptoms are actually infections and if so whether they can be prevented or treated; and 2) if the symptoms are not due to infections can the different causes of the inflammation be segregated in the complex paradigm of elite training to optimise the illness-prone athlete's training and performance.

CELLULAR INNATE IMMUNE FUNCTION AND EXERCISE

Background

Innate immunity is our first line of defence against infectious pathogens and is intimately involved in tissue damage, repair and remodeling. The major difference between innate immune responses and adaptive responses is that innate responses do not strengthen upon repeated exposure (there is no memory function). In addition, innate responses are less specific in terms of pathogen recognition. So, whereas innate responses recognize classes of pathogens (e.g. gram-negative bacteria) through toll-like receptors (TLRs), lymphocytes exhibit exquisite specificity for epitopes of individual pathogens (e.g. influenza virus). The innate branch of the immune system includes both soluble factors and cells. Soluble factors include complement proteins which mediate phagocytosis, control inflammation and interact with antibodies, interferon α/β which limits viral infection, and anti-microbial peptides like defensins which limit bacterial growth. Major cells of the innate immune system include neutrophils which are first line defenders against bacterial infection, dendritic cells (DCs) which serve to orchestrate immune responses, macrophages (Mϕ's) that perform important phagocytic, regulatory and antigen presentation functions, and natural killer (NK) cells which recognize altered host cells (e.g. virally infected or transformed). However, many host cells, not just those classified as innate immune cells, can initiate responses to pathogenic infection. Although partitioning the immune system into innate and adaptive systems makes the system easier to understand, in fact, these branches are inextricably linked with each other. For example, the innate immune system helps to develop specific immune responses through antigen presentation, whereas cells of the adaptive system secrete cytokines that regulate innate immune cell function. This section will focus on the influence of acute and chronic exercise on cellular components of innate immunity (Figure 1). A later section in this part of the position statement will focus on exercise and inflammatory cytokines which constitute the products of innate immune and other cells.

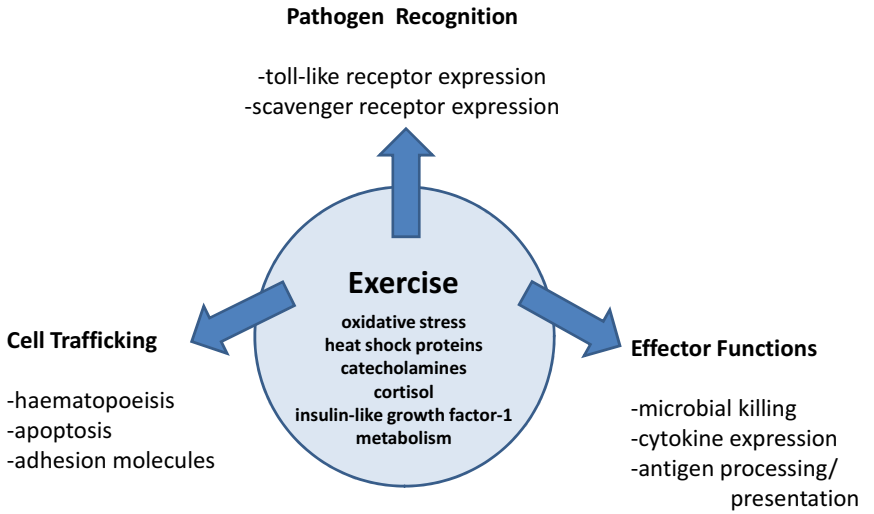

Figure 1. Potential mechanisms whereby acute/chronic exercise affects innate immunity. Exercise-induced factors such as oxidative stress, increased metabolic rate, heat shock proteins, catecholamines, cortisol and insulin-like growth factor can influence: pathogen recognition by altering expression of recognition molecules such as toll-like or scavenger receptors; cell trafficking by altering haematopoieisis, cell death and adhesion molecule expression; and effector functions like oxidative burst, cytokine expression and antigen processing and presentation. This list of potential mechanisms is not all-inclusive and very few have been definitively tested.

Consensus

Acute exercise and cellular innate immune function

Neutrophils

Acute exercise results in a first, rapid and profound neutrophilia (increase in blood neutrophil number) followed by a second, delayed increase in blood neutrophil count a few hours later, the magnitude of which is related to both the intensity and duration of exercise (216, 247). The initial increase is likely due to demargination caused by shear stress and catecholamines, whereas the later increase may be due to cortisol-induced release of neutrophils from the bone marrow (162). Unstimulated neutrophil degranulation, phagocytosis and oxidative burst activity are increased by an acute bout of exercise but there is a reduced degranulation and oxidative burst in response to bacterial stimulation that can last for many hours (215, 216, 247). This indicates that although exercise may mobilize highly functional neutrophils into the circulation, in recovery, their ability to respond to exogenous stimuli may be diminished. Marginated neutrophils are more mature than recently released neutrophils and this likely has implications for the study of exercise on neutrophil function, although this does not appear to influence respiratory burst activity (276).

Monocytes/Macrophages

Many studies have examined the influence of acute exercise on human $CD14^+$ blood monocytes (Mo's) which are relatively immature cells destined to become

tissue Mϕ's. Acute exercise results in a transient (~2 h) monocytosis and most likely represents a shifting of Mo's from the marginated to the circulating pool (206). This could occur as a result of haemodynamic and/or cortisol or catecholamine-induced release from the vascular endothelium (136). Indeed, administration of the beta-blocker propranolol can reduce exercise-induced monocytosis (2) and adrenaline (epinephrine) administration causes monocytosis (307). There are also reports that exercise can affect Mo phenotype, cell surface protein, and cytokine expression. For example, in response to acute exercise, there is a preferential mobilization of $CD14^+/CD16^+$ expressing Mo's (115, 289) that exhibit a pro-inflammatory phenotype relative to $CD14^+/CD16^-$ classical Mo's. It may be that these marginated cells have a more mature inflammatory function for entry into tissues and are knocked off the endothelium in response to exercise. Interestingly, the percentage of these $CD14^+/CD16^+$ cells is reduced in recovery, perhaps indicating remarginalization or tissue recruitment (272). Acute exercise also reduces expression of TLRs 1, 2 and 4 on $CD14^+$ Mo's (140). However, the extent to which these changes reflect a true decrease versus Mo population shifts is unclear. In an attempt to reconcile this, Simpson et al. (272) examined cell surface proteins on Mo subpopulations in response to acute exercise. They found that TLR4 and HLA.DR (major histocompatibility molecule II important in antigen presentation) expression were altered on total $CD14^+$ Mo's but also on individual Mo populations, indicating that changes in cell surface expression are not influenced solely by exercise-induced changes in Mo subpopulations in blood. Several studies have examined Mo cytokine production after acute exercise, finding that, although spontaneous cytokine levels in $CD14^+$ cells change little (245, 285), acute exercise reduces TLR ligand-stimulated interleukin (IL)-6, IL1-α, and tumour necrosis factor-alpha (TNF-α production (140, 286), perhaps as a consequence of reduced TLR expression. Further studies regarding the effects of acute exercise on Mo TLR signaling may clarify these observations.

Because Mo's are relatively immature, exercise-induced changes in their function may not reflect actual tissue Mϕ function which is central to inflammation and immune responses. For this reason, animal studies have examined the influence of exercise on tissue Mϕ number and function. Both moderate and intense acute exercise have potent stimulatory effects on phagocytosis (210), anti-tumour activity (52, 327, 328), reactive oxygen and nitrogen metabolism (327, 328), and chemotaxis (206, 209). However, not all functions are enhanced by exercise. We have documented prolonged exercise-induced reductions in Mϕ MHC II expression (325) and antigen presentation capacity (35, 36). Some effects may be dose-dependent as exhaustive exercise was shown to decrease alveolar Mϕ anti-viral function; this effect was correlated with increased susceptibility to Herpes simplex virus (HSV)-1 infection (133, 134) and related to increased release of adrenal catecholamines, but not corticosterone (133). Thus, it appears that exercise, perhaps dependent on dose with respect to some functions, can affect tissue Mϕ's and, in some studies, disease outcomes in animals. Whether these same effects can be generalized to humans is unknown.

Dendritic cells

The effect of acute exercise on DCs has received little attention despite the important emergent role of these cells in the initiation of immune responses. There are

only two studies reporting that exercise can increase circulating numbers of DCs (59, 109) and, to our knowledge, nothing is known about acute effects of exercise on DC function.

Natural killer (NK) cells

There is a vast literature on the acute effects of exercise on circulating NK ($CD3^{-}CD16^{+}CD56^{+}$) cells, perhaps because of their ease of study and large magnitude change in response to exercise. Like other blood leukocytes, NK cells are rapidly mobilized into the circulation in response to acute exercise, most likely by increased shear stress and catecholamine-induced down-regulation of adhesion molecule expression (15, 122, 301). There appears to be a differential mobilization such that $CD56^{bright}$ NK cells are less responsive than $CD56^{dim}$. Perhaps this indicates a reduced ability to defend against pathogens during acute exercise, as $CD56^{bright}$ cells are more cytotoxic. However, the health significance of exercise-induced changes in circulating NK cells, like other leukocytes, remains unknown. After prolonged exercise, the numbers of circulating NK cells are reduced in blood (87), perhaps as a consequence of remarginalization or tissue migration, but there is a relative increase in the $CD56^{bright}$ subset (302).

NK cell cytotoxicity (NKCC) is a major functional measure of NK activity. Early studies demonstrated that unstimulated NKCC was dependent upon the intensity and duration of the exercise bout (87). Immediately after a single bout of moderate or exhaustive exercise there is a 50-100% increase in human peripheral blood NKCC (87, 329). The exercise-induced increase in NKCC is largely due to an increase in the absolute number and percentage of blood NK cells (87). NKCC expressed on a per cell basis does not appear to change much after acute exercise unless the bout is intense and prolonged, in which case NKCC can be depressed for several hours, possibly indicating an enhanced period of susceptibility to infection (90). Only a few studies have examined whether NK cells mobilized into the circulation in response to exercise have altered sensitivity to stimulating agents like interferon-α or IL-2 (68, 329); however, like unstimulated NKCC, these effects are likely mediated by distributional shifts in NK cell subsets and should not necessarily be interpreted as altered NK cell function on a per cell basis.

Exercise training and cellular innate immune function

Neutrophils

Regular exercise training does not appear to alter blood leukocyte counts, including neutrophils appreciably (90). However, there are a few reports that exercise training reduces blood neutrophil counts in those with chronic inflammatory conditions or neutrophils in sites of chronic inflammation (171) raising the possibility that such exercise acts in an anti-inflammatory fashion in those with inflammation. This effect could be beneficial or deleterious, dependent upon the context. Although there is little known about the influence of exercise training on neutrophil function, regular exercise, especially heavy, intense training, may attenuate neutrophil respiratory burst (103, 233). This could reflect a sustained effect of previous acute exercise, as attenuation of respiratory burst has been documented to last several days post-exercise (295).

Monocytes/Macrophages
Both longitudinal exercise training and cross-sectional studies have shown that physically active people exhibit reduced blood Mo inflammatory responses to lipopolysaccharide, lower TLR4 expression, and a lower percentage of $CD14^+/CD16^+$ 'inflammatory' Mo's (73, 165, 166, 273, 290, 300). The extent to which these effects on the relatively small blood Mo pool contribute to the anti-inflammatory effect of exercise training is unknown. In contrast, animal studies have demonstrated that exercise training can increase induced inflammatory responses of peritoneal Mϕ's (128, 151, 292), indicating a possible difference between the effects of training on blood Mo's when compared with differentiated tissue Mϕ's. Animal studies have the potential to shed additional light on the source of the anti-inflammatory effect of regular exercise, especially in populations that exhibit inflammation. Indeed, in two recent studies, we have shown that exercise training, with or without a low fat diet, reduces visceral adipose tissue (e.g. Mϕ infiltration and pro-inflammatory cytokine gene expression) and systemic inflammation in high fat diet-fed mice (309, 310). Regular exercise may also reduce Mϕ infiltration into other sites of chronic inflammation, including growing tumours (336), and this could be interpreted as a benefit given the tumour supporting role of these cells. In contrast, reduced infiltration of Mϕ's into sites of chronic infection could lead to morbidity, although this has not been demonstrated. In fact, Mϕ's appear to play a definitive role in mediating the beneficial effects of regular moderate exercise as it relates to intranasal infection with HSV-1 in mice (181).

Dendritic cells
There are two reports from the same group demonstrating an effect of exercise training on rat dendritic cells. Liao et al. (147) reported that dendritic cell number increased after training, with no difference in costimulatory molecule (CD80 or CD86) expression, while Chiang et al. (40) found that MHC II expression, mixed leukocyte reaction and IL-12 production were increased in DCs from exercise trained rats. Clearly, given the importance of DCs in early immune regulation, this is an area ripe for investigation.

Natural killer (NK) cells
Despite much research regarding the effects of exercise training on NK cell number and function, there appears to be much controversy regarding its effect. Early cross-sectional or intervention studies with limited subject numbers reported modest increases in NKCC after moderate exercise training in previously sedentary subjects (167, 194, 202, 223, 269, 326). In larger trials, one study (65) found that 15 weeks of moderate exercise training increased NKCC compared with sedentary controls, while another 12-month trial found no change in NKCC in 115 post-menopausal women (31). However, intense training has been shown to alter NK cell subsets and reduce NKCC (93, 293). Studies in animals have demonstrated that regular exercise can increase *in vivo* cytotoxicity (119, 120, 155); however, the specific contribution of NK cells in mediating this exercise effect is unclear (119).

Controversies

Based upon the body of literature, it appears that both acute and chronic exercise have the potential to alter both the number and function of cells of the innate immune system (Figure 1). A limited number of animal studies have helped us determine the extent to which these changes alter susceptibility to herpes simplex (181) and influenza virus (149, 150, 271) infection. Unfortunately, we have only 'scratched the surface' regarding whether exercise-induced changes in immune function alter infectious disease susceptibility or outcome. In addition, although some progress has been made, we know relatively little about how acute and chronic exercise affect innate immune cell trafficking. We need to determine whether exercise alters migration of these cells and whether this alters disease susceptibility. Given the important role of innate immune cells in inflammatory states and the relationship between inflammation and chronic disease, we need to clarify whether the purported anti-inflammatory effect of regular exercise is mediated through exercise-induced effects on innate immune cells. In this regard, it is of interest to know whether exercise affects Mϕ phenotype (e.g. classical versus alternative). Although studies in humans shed light on Mo's, these cells are relatively immature and may not reflect the effects of exercise on fully differentiated tissue Mϕ's. Lastly, there is very little information on the effects of exercise on DCs, which is unfortunate given the powerful influence of these cells early in immune responses.

ACQUIRED IMMUNITY AND EXERCISE

Background

Acquired immunity (also known as adaptive or specific immunity) is designed to combat infections by preventing colonisation of pathogens and destroying invading micro-organisms. With only a few exceptions, it is initiated by the presentation of antigen to T helper ($CD4^+$) lymphocytes within the peptide binding groove of major histocompatibility complex class II molecules on antigen presenting cells $CD4^+$ T cells form a key part of the cell-mediated immune response, since they orchestrate and direct the subsequent response. Helper T cell clones can be divided into two main phenotypes, type 1 (Th1) and type 2 (Th2) cells, according to the cytokines that they produce and release. Th1 cells play an important role in defence against intracellular pathogens, e.g. viruses, the release of the cytokines interferon-γ (IFN- γ) and interleukin-2 (IL-2) stimulating T cell activation and proliferation of clones of effector cells. Memory T cells are also generated, allowing a rapid secondary response upon subsequent exposure to the same antigen. Th2 cells release IL-4, IL-5, IL-6 and IL-13 and appear to be involved in protection against extracellular parasites and stimulation of humoral immunity (production of antibody and other soluble factors that circulate in the blood and other body fluids). Therefore, cytokines released from Th2 cells can activate B lymphocytes, leading to proliferation and differentiation into memory cells and plasma cells (although some antigens can activate B cells independently of $CD4^+$ cells). Plasma cells are capable of secreting vast amounts of immunoglobulin (Ig) or antibody specific to the antigen that initiated the response. The binding of Ig to its target antigen forms an antibody-antigen complex and both free Igs and anti-

body-complexes circulate in the body fluids. $CD8^+$ cells can also be classified into type 1 (Tc1) and type 2 (Tc2) cells according to their cytokine profiles, as described above, but the functional significance of these cells is at yet unclear. A further set of T-cells, the naturally-occurring regulatory T-cells (Tregs) express the phenotype CD4+CD25+ and can suppress the functional activity of lymphocytes by mechanisms that most likely involve secretion of cytokines including IL-10 and TGF-β1.

Consensus: acute exercise and acquired immune function

T and B cell number

Acute exercise elicits characteristic transient biphasic changes in the numbers of circulating lymphocytes. Typically, a lymphocytosis is observed during and immediately after exercise, with numbers of cells falling below pre-exercise levels during the early stages of recovery, before steadily returning to resting values. This pattern of mobilisation is observed for T cells (and T cell subpopulations) and to a lesser extent, B cells. Changes are proportional to exercise intensity and duration, although the effect of intensity is more marked (161, 258). Insufficient recovery between prolonged exercise bouts appears to exaggerate the biphasic response (251). Mobilization of T and B cell subsets in this way is largely influenced by the actions of adrenaline (epinephrine) both directly on the expression of cell adhesion molecules particularly those of the integrin and selectin families, and indirectly via sympathetically mediated influences on cardiac output and the

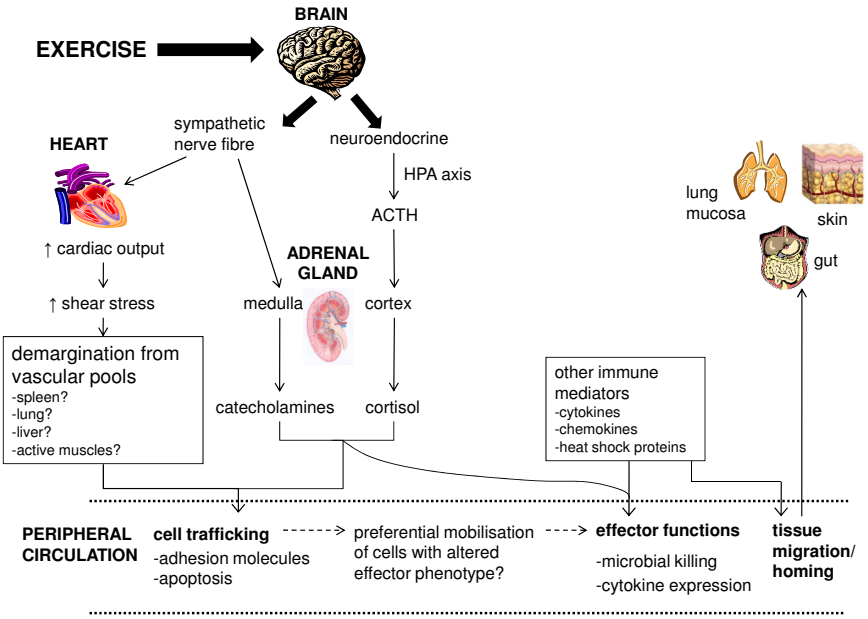

Figure 2. Potential mechanisms by which acute and chronic exercise affects acquired/adaptive immunity. HPA = hypothalamic pituitary adrenal; ACTH = adrenocorticotropic hormone.

subsequent increase in shear stress associated with enhanced blood flow (262) (Figure 2). Lymphocytes express a high density of β_2-adrenergic receptors and the density of these receptors increases with both exercise and exposure to catecholamines (262). The greatest expression of these receptors is found on the surface of NK cells, with fewer on $CD8^+$ and B cells and least of all on $CD4^+$ cells; the differing effects of intense exercise on the relative magnitude of mobilization of the lymphocyte subsets reflects this differential density of adrenergic receptor expression. The decrease in T cell number following exercise is largely due to a decrease in type 1 T cells, since intensive physical activity decreases the percentage of circulating Type 1 T cells but has little effect on the percentage of circulating Type 2 T cells (118, 287). It is unclear whether these changes are due to apoptosis or, as seems more likely, a redistribution of cells to other compartments. A decrease in the percentage of type 1 $CD4^+$ and $CD8^+$ T cells alone does not necessarily indicate that defence against intracellular pathogens such as viruses is suppressed; cytokine production is just one step of the multi-stage process that ultimately leads to lymphocyte proliferation or cytotoxicity. It is possible that any increase or decrease in cell number is countered by a diminished or enhanced response of other aspects of immune cell function. Moreover, the addition of a subpopulation of cells from the marginated pool into the circulation in response to exercise may influence lymphocyte function simply because the mobilized cells may have different functional abilities to those already in the circulation (Figure 2).

T and B cell function

T cells play a fundamental role in the orchestration and regulation of the cell-mediated immune response to pathogens. One important consequence of a defect in T cell function is an increased incidence of viral infections (63). With this in mind, it has been speculated that the apparent increased susceptibility of sportsmen and women to upper respiratory tract infections may be due to exercise-induced decreases in T cell function.

There is evidence that acute exercise stimulates T cell subset activation *in vivo* and in response to mitogen- and antigen-stimulation, as assessed by expression of cell surface markers of T cell activation, including CD69, CD25, the HLA-DR antigen, CD45RO and CD45RA (84, 86, 100). It is not clear whether such increases in activation are due to the recruitment of activated cells into the circulation, or are an effect on the state of activation of individual cells themselves. Most likely it is a combination of both. Numerous studies report decreased mitogen- and antigen-stimulated T cell proliferation following acute exercise, but interpretation of these findings may be confounded by the presence of NK cells and B cells within the cell cultures; alterations in relative numbers of T, B and NK cells in blood samples obtained before and after exercise may affect the proportion of cells that can respond to stimulation in a given volume of blood or number of peripheral blood mononuclear cells (102). Furthermore, *in vitro* stimulation with mitogen does not necessarily reflect the more subtle responses of cells following a specific antigen encounter within the body (20). Moreover, exercise may alter T cell function *in vitro* through an increase in the rate of apoptosis in cell culture rather than a decrease in T cell proliferation rate (101).

Upon stimulation, B cells proliferate and differentiate into memory cells and plasma cells, with plasma cells localised primarily in lymphoid or mucosal tissue and able to produce and secrete vast amounts of Ig (or antibody) specific to the antigen that initiated the response. The binding of Ig to its target antigen forms antibody-antigen complexes; Ig and antibody-antigen complexes circulate in the body fluids. The effect of exercise on humoral immune function has been assessed through measurements of serum and mucosal Ig concentration *in vivo* and serum Ig synthesis following *in vitro* mitogen-stimulation. Serum Ig concentration appears to remain either unchanged, or slightly increased, in response to either brief or prolonged exercise (184, 203, 229). Mitogen-stimulated IgM concentration appears to increase in response to exercise independently of changes in T or B cell number, although there are contrasting findings concerning IgA and IgG (258, 306).

Consensus: exercise training and acquired immune function

In the true resting state (i.e. more than 24 h after their last training session) circulating lymphocyte numbers and functions of athletes appear to be broadly similar to those of non-athletes (192). Longitudinal studies in which previously sedentary people undertake weeks or months of exercise training fail to show any marked changes in T and B cell functions, provided that blood samples are taken at least 24 h after their last exercise bout. In contrast, T and B cell functions appear to be sensitive to increases in training load in well-trained athletes undertaking a period of intensified training, with decreases in circulating numbers of Type 1 T cells, reduced T cell proliferative responses and falls in stimulated B cell Ig synthesis reported (7, 139, 308). This suggests that athletes engaging in longer periods of intensified training can exhibit decreases in T cell functionality. The cause of this depression in acquired immunity appears to be related to elevated circulating stress hormones, particularly cortisol, and alterations in the pro/anti-inflammatory cytokine balance in response to exercise (Figure 2). This appears to result in a temporary inhibition of Type 1 T cell cytokine production, with a relative dampening of the Type 1 (cell-mediated) response.

Conclusions

Acute intensive exercise elicits a depression of several aspects of acquired immune function. This depression is transient and cell numbers and functions usually return to pre-exercise values within 24 h. If recovery between exercise sessions is insufficient, as during prolonged periods of intensified training in elite athletes, this temporary decrease in cell function can become a chronic depression of acquired immunity. Although not clinically immune deficient, it is possible that the combined effects of small changes in several aspects of host defence may compromise resistance to minor illnesses, such as respiratory infections. The clinical significance of these alterations requires more detailed investigation.

MUCOSAL IMMUNITY AND EXERCISE

Background
Mucosal surfaces such as those in the gut, urogenital tract, oral cavity and respiratory system are protected by a network of organised structures known as the Common Mucosal Immune System (96). These structures include Peyer's patches and isolated lymphoid follicles in gut-associated, nasal-associated, and bronchial/tracheal-associated lymphoid tissues and salivary glands. The production of immunoglobulin A (IgA), specifically secretory IgA (SIgA), is the major effector function of the mucosal immune system, SIgA together with innate mucosal defences such as α-amylase, lactoferrin and lysozyme, provides the 'first line of defence' against pathogens present at mucosal surfaces. In addition, secretory IgM and locally produced IgG play a less significant role in protection of mucosal surfaces (96). The transepithelial transport of the polymeric Ig receptor (pIgR)-IgA complex into secretions such as saliva affords three potential ways in which IgA provides an effective defence against microbial pathogens: through prevention of pathogen adherence and penetration of the mucosal epithelium, by neutralising viruses within the epithelial cells during transcytosis and by excretion of locally formed immune complexes across mucosal epithelial cells to the luminal surface (138).

Consensus
A high incidence of infections is reported in individuals with selective deficiency of SIgA (105) or very low saliva flow rates (75). Moreover, high levels of saliva SIgA are associated with low incidence of URTI (252) and low levels of saliva SIgA in athletes (64, 95) or substantial transient falls in saliva SIgA (187) are associated with increased risk of URTI.

Levels of saliva SIgA vary widely between individuals. Although some early studies indicated that saliva SIgA concentrations are lower in endurance athletes compared with sedentary individuals (304), the majority of studies indicate that there are no differences between athletes compared with non-athletes except when athletes are engaged in heavy training (19, 96).

Falls in saliva SIgA concentration can occur during intensive periods of training (4, 32, 64, 93, 95, 97, 187, 303, 304) and some studies (32, 64, 93, 95, 187), though not all (4, 303, 320) have observed a negative relationship between saliva SIgA concentration and occurrence of URTI. Several of the above cited studies examined changes in saliva SIgA during intensive periods of military training (32, 303, 320). However, this often involves not only strenuous physical activity, but also dietary energy deficiency (see section on nutritional countermeasures in part two of the position statement), sleep deprivation (see section on sleep disruption in part two of the position statement) and psychological challenges (see section on the effects of stress on immune function in part two of the position statement). These multiple stressors are likely to induce a pattern of immunoendocrine responses that amplifies the exercise-induced alterations (207).

Increases in saliva SIgA have been observed after a period of regular moderate exercise training in previously sedentary individuals and may, at least in part, con-

tribute to the apparent reduced susceptibility to URTI associated with regular moderate exercise (3, 129).

The saliva SIgA response to acute exercise is variable and may be influenced by exercise mode, intensity and duration as well as the fitness of the subjects, unstimulated versus stimulated saliva collection methods, how saliva SIgA is expressed (e.g. absolute concentration, as a secretion rate or as a ratio to total protein or osmolality) and other factors that may be present such as reduced food intake, dehydration, sleep deprivation, altitude, and psychological stress (19). Levels of saliva SIgA are generally unchanged with resistance exercise sessions (130) and moderate aerobic exercise lasting less than 1 h (19).

The saliva SIgA response to exercise is generally not affected by environmental temperature (116, 137, 312), short periods (<24 h) of fasting (5) or food restriction (207), carbohydrate intake during exercise (18, 146, 199), up to 30 h of sleep deprivation (243), or by time of day (4, 57, 145).

Salivary α-amylase is another antimicrobial protein (317) and its secretion is stimulated by increased activity of the sympathetic nervous system (37), with the majority of this protein produced by the parotid gland (281). In accordance with this, several studies have found that exercise increases the α-amylase activity of saliva in a manner that is dependent on exercise intensity (6, 18, 145, 317).

Controversies

Secretion of saliva and its constituent proteins is regulated by the autonomic nervous system. The secretion of SIgA in rats can be increased by both parasympathetic and sympathetic nerve stimulation and adrenaline has recently been shown to increase the transport of human IgA into saliva by rat salivary cells via increased mobilisation of the pIgR (33, 34). Since intensive exercise is associated with enhanced sympathetic nervous system activation, it seems surprising that some studies report a decrease in saliva SIgA concentration following a bout of high intensity exercise (>80%$\dot{V}O_2$max) that recovers to resting levels within 1 h of exercise completion (154, 164). Other studies have reported either no change (163, 243, 299) or increases (6, 23, 313) in saliva SIgA concentration after single or repeated bouts of high intensity exercise.

Saliva SIgA concentration (or secretion rate) in response to prolonged (>1.5 h) moderate intensity exercise (50-75%$\dot{V}O_2$max) is more consistently reported to decrease (153, 199, 213, 288, 304) or remain unchanged (23, 116, 163, 195, 255). Different methods of saliva collection and differences in hydration status of subjects may contribute to the discrepancies in the literature (19, 144, 207, 291).

A few small-scale studies have reported that female athletes have lower saliva SIgA concentration (95) and secretion rate (4, 5) compared with their male counterparts, but confirmation of this possible gender difference is required in a larger subject population.

There is little data available regarding changes in salivary lysozyme and lactoferrin concentrations with acute or chronic exercise, although intense and exhaustive

exercise of both short and long duration is associated with increases in salivary lysozyme (6, 316, 317) and lactoferrin secretion (316). These effects also appear to be dependent on exercise intensity, since no change was seen following ~20 min of cycling at 50%$\dot{V}O_2$max (6). Prolonged cycle ergometer exercise at 60%$\dot{V}O_2$max caused a significant increase in salivary α-defensin concentrations and secretion rates (53).

The mechanisms by which exercise influences salivary responses remain to be fully elucidated (Figure 3). The rate of secretion of saliva SIgA is dependent on the production of IgA by the plasma cells in the submucosa and/or the rate of IgA transcytosis across the epithelial cell which is determined by the availability of the pIgR (24). The time-course (minutes) of the alterations in saliva SIgA secretion that are observed in response to acute exercise suggest that this is the princi-

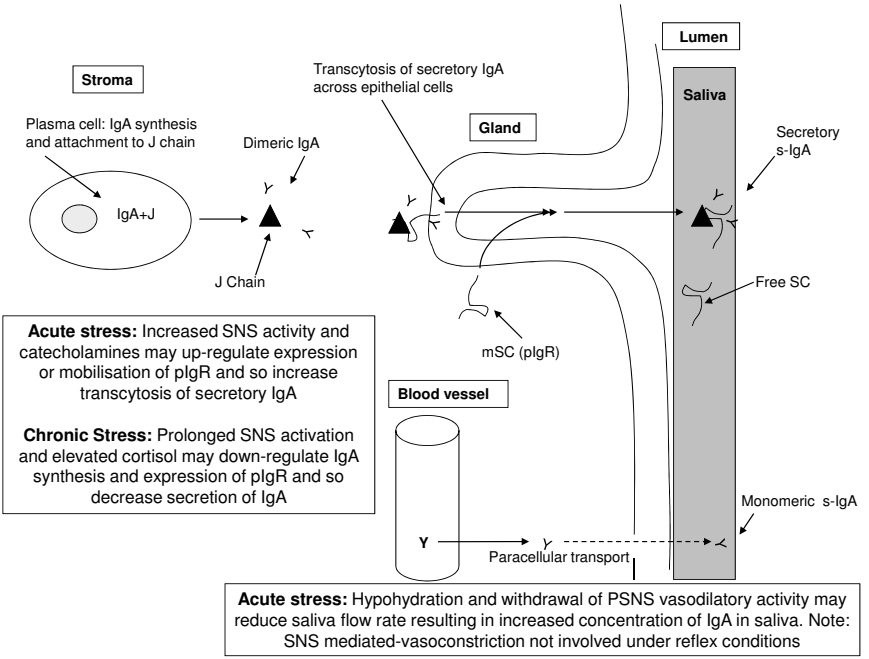

Figure 3. Effects of acute and chronic stress on receptor-mediated transport of locally produced dimeric IgA and paracellular transport of serum derived monomeric IgA into saliva. mSC = membrane secretory component; pIgR = polymeric Ig receptor; SNS = sympathetic nervous system; PSNS = parasympathetic nervous system.

pal mechanism by which acute intensive exercise influences saliva SIgA secretion. In anaesthetised rats, acute stimulation of β-adrenoreceptors above a certain threshold increases saliva SIgA secretion in a dose-independent manner via elevated transcytosis from the glandular pool (230) and this is associated with increased availability of the pIgR (34). Although such a mechanism has not yet

been demonstrated in humans, the finding that increases in saliva SIgA secretion rate are associated with elevations in plasma adrenaline following caffeine ingestion lends some support to this suggestion (21).

Although enhanced IgA transcytosis probably accounts for elevations in saliva SIgA secretion observed after exercise, it cannot account for the findings of either no change or decreases in saliva SIgA secretion rate with intense physical activity. The observation that increased mobilisation of the pIgR only occurred above a certain threshold frequency of stimulation (230) could account for the finding of little change in saliva SIgA levels at more moderate intensities of exercise. However, the finding of decreased concentrations of saliva SIgA in response to acute exercise is harder to explain. Nevertheless, a study in rats demonstrated that following a prolonged treadmill run to exhaustion, decreases in saliva SIgA concentration were associated with a decline in pIgR mRNA expression (127). Although highly speculative, this might imply that there is a second critical threshold (or duration) of stimulation, above which pIgR expression becomes downregulated.

It is unlikely that cortisol plays a major role in the regulation of saliva SIgA secretion in response to acute exercise, because changes in both saliva SIgA concentration and secretion rate have been observed in the absence of any alterations in plasma or salivary cortisol (6, 145, 146, 256, 299) and there appears to be no correlation between saliva SIgA and cortisol responses to exercise (164).

Modification of IgA synthesis could play a major role in the changes in saliva SIgA secretion observed in response to long term intensive training and chronic psychological stress (19, 24, 226). In addition, it may be that repeated mobilisation of the pIgR could deplete the available formed IgA pool, leading to decreases in saliva SIgA output. However, to date there is scant research in either animals or humans to support these speculations.

Conclusions

To date the majority of exercise studies have assessed saliva SIgA as a marker of mucosal immunity but more recently the importance of other antimicrobial proteins in saliva including α-amylase, lactoferrin and lysozyme has gained greater recognition. Acute bouts of moderate exercise have little impact on mucosal immunity, but very prolonged exercise and periods of intensified training can result in decreased saliva secretion of SIgA. Mechanisms underlying the alterations in markers of mucosal immunity with acute exercise are probably largely related to the activation of the sympathetic nervous system and its associated effects on salivary protein exocytosis and IgA transcytosis. Depressed secretion of SIgA into saliva during periods of intensified training and chronic stress are likely linked to altered activity of the hypothalamic-pituitary-adrenal axis, with inhibitory effects on IgA synthesis and/or transcytosis. There is reasonable evidence to indicate that reduced levels of saliva SIgA are associated with increased risk of URTI.

IMMUNOLOGICAL METHODS IN EXERCISE IMMUNOLOGY

Background

There are many examples in the literature and reviewed in this consensus paper that acute exercise and exercise training can alter host defence, leading to changes in disease susceptibility and severity. One important mechanism for such changes is alterations in *immune function*. Herein lies a primary challenge for exercise immunologists; how does one measure immune function in a meaningful way? The immune system is comprised of a large variety of cells, occurs in diverse tissues (i.e., lymph node, Peyer's patches, spleen and liver), and involves the orchestration of hundreds of soluble and cell membrane associated proteins. Successful host defence is the end product of these responses.

Consensus

Exercise immunology experiments test the impact of acute exercise and/or regular exercise training on a number of measures of the immune system. The types of immunological assessments most commonly reported, especially in the human exercise studies involve analyses of blood borne circulating immune proteins (e.g., interleukin (IL)-6, IL-1β, C-reactive protein, IL-8, tumour necrosis factor alpha (TNFα) chemokines), circulating blood leukocytes (e.g., CD4+ T cells, CD8+ T cells, Th1, Th2, Th17, Treg, B cells, neutrophils, monocytes), and salivary/plasma antibody or immunoglobulin (Ig) concentrations. Some studies document dynamic changes in the composition of blood leukocyte populations (e.g., decreases in peripheral blood CD4+ T cells and increases in neutrophils), and some studies isolate the peripheral blood leukocytes and put them in culture with various exogenous stimuli, such as mitogens, that stimulate large populations of immune cells to produce immune products. Using these types of measures, there are many reported examples of robust dynamic changes produced both with acute exercise and after exercise training. As discussed in other sections of this position statement, the nature of the reported changes measured depends on a number of variables that include the training status of the individual, the intensity of the exercise bout, the nutritional status of the individual, the timing of the blood/saliva sample collection and the nature of the specific immunological measure. Due to the reported dynamic changes in such blood borne and salivary measures, it is essential that multiple samples are taken, including pre-, during-, and post- exercise timepoints. Non-exercised, time-matched controls must also be sampled to control for circadian, seasonal, and environmental changes in these dynamic measures. The majority of studies in exercise immunology are sensitive to these aspects of experimental design, making these methodological features strengths of the field.

Another approach to assessing immune function extends beyond blood or salivary soluble proteins, circulating cells, total Ig or *in vitro* stimulated responses. It involves challenging experimental subjects with antigenic (immune stimulating, not disease capable) or pathogenic (immune stimulating, possible disease producing) stimuli and assessing relevant antigen-driven responses including antigen specific cell-mediated delayed type hypersensitivity (DTH) responses or antibody responses and in some instances, changes in disease susceptibility, duration, and

severity. This approach allows assessment of *in vivo* immune function and has several advantages over the previously described measures. Firstly, the generation an antigen specific Ig response reflects a functionally important end product of a multicellular *in vivo* immunological response. For example, the generation of a primary antibody response to a novel antigen like keyhole limpet haemocyanin (KLH) requires antigen presentation (likely by a B cell given KLH is a low dose soluble protein) to CD4+ T cells. KLH specific T cells then provide T cell help in the form of both co-stimulation and cytokines to KLH specific B cells to stimulate the production of anti-KLH IgM and promote isotype switching to anti-KLH IgG1 (driven by Th2 cytokines) and IgG2a (driven by Th1 cytokines). If an acute exercise bout or exercise training impacts *in vivo* immune function, then changes in the generation of KLH specific Ig will be detected. In addition, if there are selective changes in isotype switching, for example an impact on anti-KLH IgG1 and not on anti-KLH IgG2a, or *vice versa*, this suggests selective effects on Th1 and Th2 responses (70, 88, 159, 177). This approach has been successfully used in both humans (274, 275, 278) and animals (55, 69, 71, 82, 179, 311).

The results of the exercise immunology studies that measure *in vivo* anti-KLH Ig responses support the general conclusion that an acute bout of intense exercise suppresses anti-KLH Ig production (178), however, moderate exercise training can restore optimal antibody in the face of stressors (69, 72) and ageing (99, 277). Interestingly, the majority of studies using this measure rarely demonstrate an *increase* in the anti-KLH Ig response with exercise training in **young healthy adults.** This is likely due to the fact that young healthy sedentary and physically active organisms already possess excellent immune responses, and elevating that response further is not necessarily a good thing. Too much immunity is just as detrimental as too little (Figure 4). In other words, the positive effects of exercise training on immune function and host defence may be most readily revealed when *in vivo* immune function is sub-optimal consequent to ageing, stress, or other factors. In fact there are several papers that demonstrate that regular physical activity reduces incidence of illness only if people report high levels of stress (26, 74).

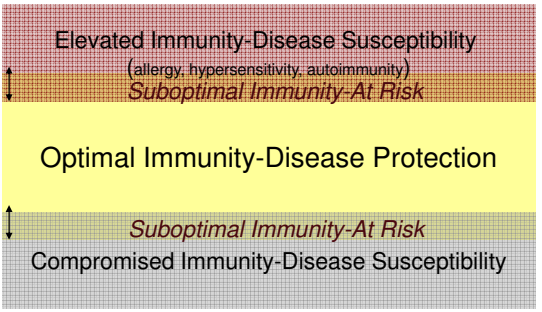

Figure 4. Exercise associated changes in immune function have greatest effects on host defence and disease susceptibility/severity, if the individual has suboptimal immune function due to ageing, stress or other factors.

A related approach that also measures *in vivo* immune function, and is reported in the exercise immunology literature is to inject **not a novel** antigen, such as KLH, but rather a mixture of antigens using influenza vaccine or tetanus vaccine that usually contain a subset of repeated antigens that have been "seen" by people before (30, 60, 61). The advantage of this approach, especially when studying humans, is that people are

willing to receive such injections because they produce useful immunity against influenza and/or tetanus. The disadvantage of this approach is that the subsequent antibody response is a mixture of primary, secondary and tertiary responses. This makes it difficult to accomplish the following: 1) measure group changes in isotypes (very little IgM is detectable in secondary and tertiary versus primary responses); 2) compare concentrations of antigen specific antibody (secondary and tertiary responses characteristically produce higher levels of IgG than primary responses); and 3) make inferences about cellular mechanisms for any detected changes (unique cellular and co-stimulatory signals are required for primary versus secondary and tertiary responses)(70). Thus the assessment of an antigen-specific immune response following vaccination yields important information about *in vivo* immune responses that are superior to measuring dynamic circulating protein or cell changes, but suffers some interpretive limitations not found after primary antigenic challenge.

An additional methodological and interpretation challenge when studying exercise-induced changes in immune responses is to determine if the measured changes in immunity are sufficient to alter host defence or disease susceptibility/severity. This is a complex challenge. It involves issues associated with immune safety net and redundancy (Figure 4) and immune response specificity relative to host disease defence. Because immune function is critical to host survival, the system has evolved a large safety net and redundancy such that it is difficult to determine how much immune function must be lost or gained to incur changes in host disease susceptibility. Studies on human immunodeficiency (HIV) patients offer insight into the issue. It is commonly reported that patients with HIV must lose at least ~50-60% of their total circulating CD4+ T cells before an increase in the incidence of opportunistic infection occurs (182). There are numerous examples of exercise altering circulating cell numbers and other measures of immunity, often by 15-25%. Whether changes of this magnitude are sufficient to alter disease susceptibility or severity likely depends on the state of the host. If, for example, immune function was optimal or functioning at 100% then ± 15-25% change may not impact host defence in a clinically significant way, because the safety net for immune function is great. If instead immune function was suboptimal due to ageing, stress or other factors placing host immunity in the "at risk zone", then a 15-25% change in immune function could have significant consequences for host defence (Figure 4). A second issue to consider when interpreting the functional significance of changes in immune measures for host defence is response specificity. That is, what specific types of pathogens or disease states could be impacted by changes in the aspects of immunity measured? For example, how would transient changes in circulating T cell numbers influence anti-viral host defence? This issue is especially challenging for human research. There are, however, several rodent disease models that establish clear links between changes in specific immune responses and corresponding changes in host defence and disease severity. Work by Shamgar Ben-Eliyahu is one example (12). Although he is not specifically testing the impact of exercise, he is exploring the impact that other stressors (i.e., surgery, drugs etc.) have on immune function and host defence. A strength of his model is that he both demonstrates stress-associated suppression in NK cell tumour killing *ex vivo* and stress-associ-

ated increases in tumour load *in vivo* (14). Furthermore he has verified that the tumour tested in these studies is primarily killed by NK cells and **not** CD8+ T cells (13). Thus using this type of approach one can measure immune function and verify relevance for host defence and disease susceptibility/severity.

A second approach used in immunology research involves challenging animals with pathogens that require specific and well-characterized immunological responses for survival. *Leishmania major*, for example, requires a Th1 dominant response for effective host defence (43). If one blocks the development of Th1 responses, the animal will die. This is a useful experimental model, because one can link changes in specifically Th1 responses (cytokines, clonal expansion, Th1 differentiation or activation, etc.) with corresponding changes in *Leishmania* disease susceptibility, severity and host survival. This type of model could be implemented in exercise immunology studies.

Controversies and future directions

Most studies in exercise immunology are conducted in humans and are usually limited to immune measures derived from the blood, such as soluble immune proteins, cell numbers, *in vitro* cellular responses to mitogen and total Ig concentrations. As previously discussed, it is difficult to determine how such changes could impact host defence, disease susceptibility or severity. Although persistent or chronic elevations in blood concentrations of inflammatory proteins may be reflective of changes in inflammatory processes, it is possible that dynamic, short-lived changes in blood borne immune factors offer little insight into how the *in vivo* immune function and/or host defence is altered. In addition, increases in concentrations of blood borne soluble proteins such as IL1β, IL8, and TNF-α that classically play a role during local tissue inflammation, likely are not related to tissue inflammation. There is no evidence that the acute increases in circulating concentrations of these proteins produced by stressors or exercise function to modulate any inflammatory process, especially in an otherwise healthy host. More likely, the acute elevations in IL-6 and IL1-β found after exercise may be more important for the *metabolic* rather than the *immunological*, responses to exercise.

Given the pleiotropic and context dependent nature of cytokines/chemokines, perhaps we should revise our thinking when trying to interpret acute and dynamic effects of exercise. Firstly, we need to consider any change in cytokine concentration within the context of the cytokine network (180). In other words, the contextual dependence of cytokines cannot be ignored. A nice immunological example of contextual dependence is the effect of transforming growth factor (TGF)-β on CD4+ T cell differentiation. Based on the 3-signal model of T cell activation and differentiation (45), cytokines play a pivotal role in CD4+ T cell differentiation after activation from Th0 (non-polarized) to Th1, Th2, Treg etc. TGF-β plus IL6, for example, drives the differentiation of the Th0 toward a Th17 cell. In contrast, TGF-β in the absence of IL-6 drives the differentiation of the Th0 toward a Treg cell. A second example of cytokine networks and context dependence can be found in the exercise immunology literature, where increases in circulating IL-6 in the presence of TNF-α is indicative of inflammation, whereas increases in cir-

culating IL-6 in the absence of TNF-α may be indicative of increased energy demand (217, 219)(Figure 6).

In conclusion, there are clear effects of both acute exercise and exercise training on measures of immune products and function. Exercise training effects on immune function and host defence are especially demonstrable when immune function is not optimal due to ageing, stress or other factors. Exercise immunology researchers are faced with challenges associated with both the immune measures and the interpretation of changes in such measures. *In vivo* antigen specific immune function can be measured by injecting subjects (both people and animals) with novel antigens and vaccination antigens; assessment of antigen specific immunoglobulin and T cell (by DTH tests) responses is a strong approach. The ability to predict if any change in antibody titre or T cell function is sufficient to alter host defence, specific disease susceptibility or disease severity however, remains debatable.

ANTI-INFLAMMATORY EFFECTS OF PHYSICAL ACTIVITY

Chronic inflammation is involved in the pathogenesis of insulin resistance, atherosclerosis, neurodegeneration, and tumour growth. Evidence suggests that the protective effect of exercise may, to some extent, be ascribed to the anti-inflam-

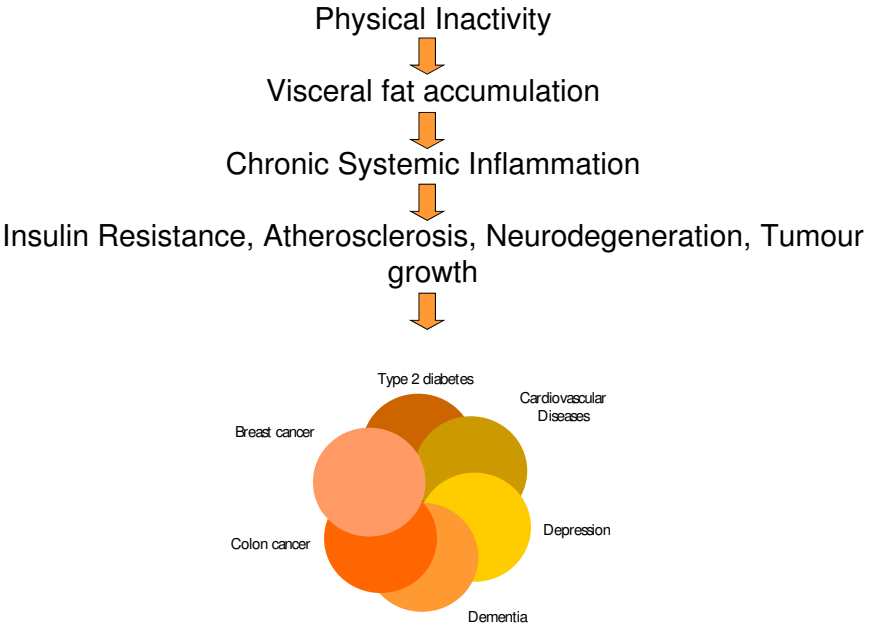

Figure 5. Hypothesis: Physical inactivity leads to accumulation of visceral fat and consequently to the activation of a network of inflammatory pathways, which promotes development of insulin resistance, atherosclerosis, neurodegeneration, and tumour growth, leading to the development of "the diseasome of physical inactivity".

matory effect of regular exercise, mediated via a reduction in visceral fat mass and/or by induction of an anti-inflammatory environment with each bout of exercise.

Background

It is well-established that physical inactivity increases the risk of type 2 diabetes (305), cardiovascular diseases (204), colon cancer (322), breast cancer (175), dementia (253) and depression (211). Physical inactivity leads to the accumulation of visceral fat and consequently the activation of a network of inflammatory pathways. Chronic inflammation promotes the development of insulin resistance, atherosclerosis, neurodegeneration, and tumour growth (104), and subsequently the development of a number of diseases associated with physical inactivity (218) (Figure 5).

The protective effect of exercise against chronic inflammation associated diseases may, to some extent, be ascribed to an anti-inflammatory effect of regular exercise. Several studies show that markers of inflammation are reduced following longer-term behavioural changes involving reduced energy intake and increased physical activity (reviewed in (225)). We suggest that the long-term anti-inflammatory effects of exercise may be mediated both via a reduction in visceral fat mass and the establishment of an anti-inflammatory environment with each bout of exercise.

Consensus

We have suggested that cytokines and other peptides that are produced, expressed, and released by muscle fibres and exert paracrine or endocrine effects should be classified as "myokines" (218). Such myokines may exert a direct effect on fat metabolism and thereby result in indirect anti-inflammatory effects. Moreover, myokines may exert direct anti-inflammatory effects or stimulate the production of anti-inflammatory components.

It is suggested that contracting skeletal muscles release myokines, which work in a hormone-like fashion, exerting specific endocrine effects on visceral fat and other ectopic fat deposits. Other myokines work locally within the muscle via paracrine mechanisms, exerting their effects on signalling pathways involved in fat oxidation.

The first identified and most studied myokine is the gp130 receptor cytokine, interleukin (IL)-6. A number of studies during the past decade have revealed that both type I and type II muscle fibres express the myokine IL-6 in response to muscle contractions. Subsequently IL-6 exerts its effects both locally within the muscle (e.g. through activation of 5' adenosine monophosphate activated protein kinase, AMPK) and, when released into the circulation, in a hormone-like fashion in a number of organs. Within skeletal muscle, IL-6 acts locally to signal through a gp130Rβ/IL-6Rα homodimer resulting in activation of AMPK and/or phosphatidylinositol-3-kinase (PI3K) to increase fat oxidation and glucose uptake (219). Although it has not been demonstrated that IL-6 has specific effects on visceral fat mass, it does appear to play an important role in lipid metabolism. IL-15 is expressed in human skeletal muscle and has been identified as an anabol-

ic factor in muscle growth. In addition to its anabolic effects on skeletal muscle *in vitro* and *in vivo*, IL-15 appears to play a role in lipid metabolism (191). Therefore, IL-15 has been suggested to be involved in muscle – fat cross talk. IL-15 mRNA levels are upregulated in human skeletal muscle following a bout of strength training (190), suggesting that regular training may lead to IL-15 accumulation within muscle. Interestingly, we demonstrated a decrease in visceral fat mass, but not subcutaneous fat mass, when IL-15 was overexpressed in murine muscle (189).

The cytokine response to exercise differs from that elicited by severe infections (Figure 6). Classical pro-inflammatory cytokines, tumour necrosis factor alpha (TNF-α) and IL-1β, in general do not increase with exercise, indicating that the cytokine cascade induced by exercise is markedly different from the cytokine cascade induced by infections, (reviewed in (219)).

To study whether acute exercise induces an acute anti-inflammatory response, a model of "low grade inflammation" was established in which a low dose of *E. coli* endotoxin was administered to healthy volunteers, randomised to either rest or exercise prior to endotoxin administration. In resting subjects, endotoxin induced a 2 to 3 fold increase in circulating levels of TNF-α. In contrast, when the subjects performed 3 h of ergometer cycling and received the endotoxin bolus at 2.5 h, the TNF-α response was totally blunted (284). This study provides some evidence that acute exercise may inhibit TNF-α production.

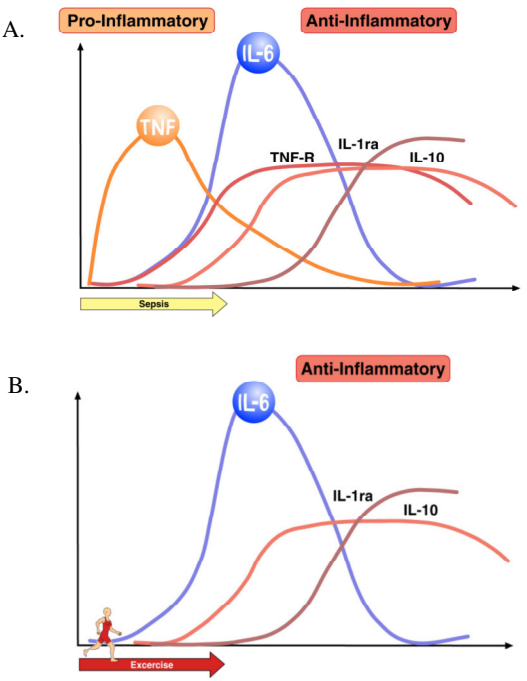

Figure 6. Comparison of sepsis-induced (A) versus exercise-induced (B) increases in circulating cytokines. During sepsis, there is a marked and rapid increase in circulating TNF-α, which is followed by an increase in IL-6. In contrast, during exercise the marked increase in IL-6 is not preceded by elevated TNF-α (220).

Typically, IL-6 is the first cytokine released into the circulation during exercise. The level of circulating IL-6 increases in an exponential fashion (up to 100 fold) in response to exercise and declines in the post-exercise period. The circulating levels of well-known anti-inflammatory cytokines such as, IL-1ra and IL-10, also increase after exercise. However, the

appearance of IL-6 in the circulation is by far the most marked and its appearance precedes that of the other cytokines. A number of studies have demonstrated that contracting skeletal muscle fibres per se produce and release IL-6. Of note, IL-6 infusion totally mimics the acute anti-inflammatory effects of a bout of exercise both with regard to induction of IL-1ra and IL-10 and with regard to suppression of endotoxin-stimulated increases in TNF-α levels. During acute exercise there is also a marked increase in adrenaline (epinephrine), cortisol, growth hormone, prolactin, and other factors that have immunomodulatory effects (104, 193). Taken together, it appears that each bout of exercise induces an anti-inflammatory environment.

Controversies
Patients with chronic inflammatory diseases such as type 2 diabetes are often prescribed exercise to improve quality of life; however, the use of exercise as a treatment for these diseases remains controversial. A systemic review has highlighted that acute and chronic exercise may elicit different responses in patients with chronic inflammatory disease when compared with healthy controls (227). For example, it has been reported that in patients with chronic obstructive pulmonary disease plasma TNF-α levels were abnormally increased compared with healthy controls following moderate-intensity exercise (236). Therefore, more needs to be understood about the nature of exercise that has anti-inflammatory effects in patients with chronic inflammatory diseases without increasing the underlying inflammatory pathology of the disease.

Future directions
To understand the mechanism of the protective, anti-inflammatory effect of exercise fully, we need to focus on the nature of exercise that is most effective at allieviating the effects of chronic inflammation in disease. The beneficial effects of endurance exercise are well known; however, the anti-inflammatory role of strength training exercises is poorly defined and remains an area for future investigation. In addition, the independent contribution of an exercise-induced reduction in visceral fat versus other exercise-induced anti-inflammatory mechanisms needs to be better understood.

EXERCISE AND CANCER

Background
Exercise can have a beneficial role in cancer prevention and therapy. Determining if regular physical activity reduces cancer risk through immunological mechanisms is of public health relevance and could lead to tailored and novel exercise prescriptions.

Consensus
The incidence of several types of cancer is reduced by regular physical activity. Comprehensive reviews by the International Agency for Research on Cancer (17) and the World Cancer Research Fund (330) identified an independent protective effect of physical activity on colon and postmenopausal breast cancer risk. Evi-

dence is also mounting that physical activity reduces risks of endometrial, lung, and pancreatic cancers.

Physical activity has a therapeutic effect in cancer patients by reducing cancer recurrence, enhancing health outcomes, and increasing survival. Women who exercised moderately prior to (81), and after a breast cancer diagnosis, had significant improvements in overall and disease-specific survival and quality of life compared to sedentary counterparts (280, 318). Protective effects of physical activity have also been observed for colorectal cancer patients (169).

There are fewer reports on exercise and neoplasia in animals with chemically-induced, transplantable, or spontaneous tumours (111). These studies describe exercise protecting against intestinal tumour incidence or number, although results with Apc^{min} mice, which develop intestinal tumours spontaneously, have been less consistent (10). A beneficial effect of exercise on mammary tumour incidence, multiplicity, growth rate and/or survival has also been reported (249).

Controversies

The biological mechanisms relating exercise and cancer are not well understood. Potential mediators include reductions in body mass and/or adiposity, decreases in reproductive hormone levels, altered growth factor milieu, enhanced antioxidant defence mechanisms, and changes in immune function, including reduced inflammation and enhanced anti-tumour immunity. Mechanisms studied in detail in humans have not been studied in animal models, and vice versa. Therefore, the relative contribution of these mechanisms in specific cancer types remains unknown. With respect to the hypothesis that exercise induces alterations in immune mediators, more is known about exercise-induced changes in inflammatory mediators than about changes in specific anti-tumour mechanisms; however, controversies exist for both hypotheses.

The association between chronic inflammation and cancer is well established (46). Human cross-sectional studies demonstrate an inverse relationship between regular physical activity and inflammatory biomarkers, including C-reactive protein (CRP), tumour necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) (123, 225). Reductions in CRP levels with exercise training have also been reported (123). Although exercise may reduce inflammatory biomarkers, clinical trials indicate variable outcomes, with an effect of exercise on CRP in some but not all studies (231). Less work has been done with IL-6 in humans, but again there are conflicting results (319). Finally, a recent randomized trial on markers of inflammation following a 12-month exercise intervention reported no change in participant colonic prostaglandin levels (1).

Animal studies demonstrate an anti-inflammatory role of exercise via multiple pathways. Exercise normalized the elevated levels of TNF-α in soluble TNF-receptor knock-out mice (126). Freewheel training lowered TNF-α expression and increased expression of antioxidant enzymes in mouse intestinal T lymphocytes (112, 113) and decreased prostaglandin E_2 level in the serum and polyps from Apc^{min} mice (121). Treadmill exercise decreased the number of

macrophages in polyps from Apc^{min} mice (8), and swimming exercise in rats reduced COX-2 positive cells in colonocytes (54). Taken together, several inflammatory pathways may be altered by exercise, but it is unclear to what extent and under what physiological conditions these changes occur.

Macrophages and natural killer (NK) cells have been studied in both tumour-bearing and healthy subjects following exercise. Collectively, animal model data show a positive effect of exercise on macrophage function, with enhanced clearance of lung metastases (324). Additionally, training results in greater *in vitro* NK cell cytotoxicity (221, 248), enhanced *in vivo* mechanisms of natural immunity and reduced pulmonary tumour metastases in mice (155, 221); however, these effects are small and modified by exercise intensity and timing. No change in NK cell cytotoxicity was observed following a 12-month walking intervention in healthy postmenopausal women (31). There are fewer studies on exercise and antigen-specific T cell functions. Moderately active older adults have higher influenza-specific *in vitro* peripheral blood mononuclear cell proliferation (132) and greater *in vivo* delayed type hypersensitivity (DTH) responses (277) compared with sedentary individuals. Moderate exercise also enhances antigen-specific T-cell mediated cytokine production and proliferation following vaccination (131, 250). Exercise improves antigen-specific T cell function, which may translate into better protection from infectious agents and greater immunosurveillance. Clinical and epidemiological studies show that the incidence of upper respiratory tract infections is lower in moderately active individuals compared with their sedentary counterparts (42). Although no T cell responses were measured, adequate adaptive immune responses play a critical role in the clearance of viral infections of the respiratory tract (323). The potential importance of adaptive immune responses in relation to exercise and virally-induced cancers cannot be overstated. For example, cervical cancer of which nearly all cases are due to human papillomavirus (HPV) is one of the leading causes of cancer death among women worldwide. However, no studies have examined the effect of exercise on the generation of HPV-specific T cells or the role of exercise in minimizing the immunosuppressive environment created by the presence of the tumour.

If an exercise-induced enhancement of anti-tumour mechanisms occurs, protection should be evident for lymphomas, due to the greater role of immune mediation. Only three studies have examined the relationship between physical activity and Hodgkin's and non-Hodgkin's lymphomas (HL, NHL, respectively). Participation in collegiate sports was associated with a trend to reduced risk of HL, although this did not reach statistical significance (212). Women who participated in strenuous physical activity at various time points in adult life had a lower risk of HL (125). Yet, a case-control study on NHL and occupational physical activity (measured as energy expenditure or sitting time) found no significant association (333).

The hypothesis that exercise-mediated changes in immunity contribute to a reduction in cancer risk is prevalent. For example, women participating in a US national sample believed the causes of breast and colon cancers were due to changes in one's immune system (60% of the sample) and lack of exercise (35-45% of the

sample) (314). Nevertheless this hypothesis is based on limited evidence (168) and many studies have significant methodological limitations (283).

Future directions

Physical activity is beneficial in preventing some cancers, and in decreasing recurrence, increasing survival, and improving quality of life for cancer patients. Multiple biological pathways may be involved, including a reduction in inflammation and an enhancement of anti-tumour immunity. Neither of the aforementioned mechanisms has been studied in adequate detail to gain a full understanding of their role in cancer prevention and therapy with respect to exercise. Inflammatory mediators have many physiological, metabolic and immunological roles and are produced in many tissues. Numerous cell types of the innate and adaptive immune system work in partnership to generate anti-tumour host responses. Additional studies will be needed to determine a) which inflammatory mediators and anti-tumour immune mechanisms are most sensitive to exercise, b) the dose, duration and frequency of exercise needed to achieve anti-inflammatory or anti-tumour effects, and c) the timing of sample collection with respect to the exercise bout to adequately capture appropriate levels of anti-inflammatory mediators and anti-tumour immune mechanisms.

Several technical limitations also need to be addressed. We suggest that the development of more sophisticated animal models is required. Although carcinogen-induced tumours have provided valuable insights, they are limited in that these carcinogens induce mutations at multiple genetic loci (117) and trigger both inflammation and immunosuppression (296). In contrast, spontaneous tumour models which 'mimic' human cancers are often limited to single mutations/pathways (i.e., ras, p53, APC, Wnt) and do not reflect complex multi-gene-environment (exercise) interactions. Additionally, many functional immunoassays require fresh cells and hours of assay preparation. Such immune readouts are difficult in epidemiological studies; while cryoprotectants allow freezing of immune cells for later analysis, viability comparisons to fresh cells are often not performed. Functional immunoassays could be conducted using lymphoid tissue harvested from animals, but relevant preclinical immunogenic tumour models would be required.

Concluding position

There is consensus that exercise training protects against some types of cancers. Training also enhances aspects of anti-tumour immunity and reduces inflammatory mediators. However, the data linking immunological and inflammatory mechanisms, physical activity, and cancer risk reduction remains tentative.

"OMICS" IN EXERCISE

Background and consensus

"Omics" is the circumspanning word for technologies which try to analyze an entire biologic field or large parts of it, using high throughput laboratory methods and correspondingly complex, high end- statistics. Accordingly, analysis by the "Omics approach" is often hypothesis free (non-targeted), and provides extremely

detailed and dense information, with a good chance of detecting unexpected responses or biological pathways. Exercise immunologists hope that "omics" will help them to gain a better understanding of mechanisms related to talent identification, exercise-induced disorders, modulation of the immune system by exercise, and prevention of diseases by exercise training. They also hope that "omics" can be used as a tool for optimizing individual training programmes.

Genomics, proteomics, and metabolomics, the classical three, appeared in this order according to the availability of high-throughput/ high-sensitivity methods. There is also diversification and refocusing into transcriptomics, spliceomics, lipoproteomics, pharmacoproteomics, interactomics, and, notably, exerciseomics. Targets of analysis are the genome itself (alleles, single nucleotide polymorphisms, methylations), gene expression (transcription), post-transcriptional regulation (microRNAs), abundance of proteins or metabolites and isomeric shifts and post-translational modifications.

Results on genome-wide screening for allotypes and single nucleotide polymorphisms associated with performance, fitness, or proneness to disease cannot be considered extensively here. Of special interest for exercise immunology are results on diabetes type-2, where at least 11 genes have been associated with the condition, including peroxisome proliferator-activated receptor delta, which is responsive to types/levels of lipids, and the fat mass and obesity associated (FTO) risk allele, which may not be responsible for reduced physical activity, but effects of which can be attenuated by exercise (see reviews (67, 241)).

To our knowledge, gene expression profiling was applied to exercise first in 2002, with work on rat muscle (39), hippocampus (174), and heart (56). A number of genes related to cell growth, signal transduction, calcium-flux, synaptic trafficking, or myosin light chains were found to be altered, some were new, some corresponding to previous findings, some were contradictory.

In humans, Mahoney et al. (158) defined a row of genes associated with muscle growth, remodeling and stress management following eccentric exercise (sterol and lipid metabolism, insulin and calcineurin pathways, c-myc and jun-D). Thalacker-Mercer et al. (297) exposed young and old adults to moderate exercise-induced muscle damage, and found vast differences in transcript activation, alluding to an undue inflammatory response in older subjects.

As first proposed by Fehrenbach et al. (66), many studies have now used peripheral blood gene expression fingerprinting/clustering for analysis of the effects of exercise. Types of exercise ranged from 30 min at 80% $\dot{V}O_2$max (44) to a half-marathon (334, 335) and heat injury in exercising military recruits (279). Time points chosen and platforms used for analysis also varied widely.

Special questions addressed by intervention or design were the effects of different workloads (29, 124), cell fractionation (183, 239), gender and age (205, 237, 238), as well as comparisons of immune suppressed patients versus healthy individuals (135), with every paper using different challenges and time kinetics.

Genes that were activated or suppressed showed remarkably little overlap between studies and between different times. Nevertheless, a number of pathways involved were identified albeit in different composition. They were related to stress genes and heat shock proteins (29, 44, 205, 279, 335), interferon (279), signal transduction (279, 334, 335), pro- and anti-inflammation (29, 44, 110, 135, 205, 237, 239, 279, 297, 334, 335), anti-oxidative system (334, 335), cell growth and wound healing (44, 237, 239, 297), apoptosis (29, 135, 237-239) and necrosis (297), neurotransmitters (124), immunity with natural killer cell activity (183, 237, 238), antigen processing and receptor signaling (239), asthma (107, 205, 237, 239) and arthritis (239).

MicroRNAs (miRNAs) are a large family of 21-22 nucleotide non-coding RNAs with presumed post-transcriptional regulatory activity. miRNA genes were formerly misperceived as junk-DNA, but are now recognized as important regulators of translation. Drummond et al. (58), Safdar et al. (254), and Radom-Aizik et al. (240) all found a number of miRNAs were increased following exercise and linked to adjustment of inflammation (240, 254). They also found dysregulation of exercise reactive miRNA (primary miRNA up, mature down) in aged subjects (58). An overview is given in Exercise Immunology Review, volume 16 (315).

Proteomics were applied to analyze the effects of exercise on rat heart (28), rat infarcted cerebellum (172), human muscle (108, 114), human plasma (332) and pig lipoproteins (244). Changes in expression of myofibrillar proteins, fatty acid metabolism, novel phosphorylation sites (28), and isoelectric species (114) were identified, shedding new light on the role of post-translational modification of proteins. Anti-inflammatory modification of serum complement through moderate exercise was shown (332), and a novel theory of lipoprotein structure including novel markers for vascular disease was proposed (244).

A rapidly increasing number of studies have analyzed the metabolome in relation to exercise - with circumstantial and limited relations to exercise immunology. Potential biomarkers of strenuous exercise and a strategy for analysis of complex data sets were proposed by Pohjanen et al. (228). Evaluating the effects of nutritive interventions in relation to exercise, subjects could be separated according to type of beverage, training, fitness stage and signs of insulin resistance (41, 142, 170, 331). Dampening of exercise-induced oxidative stress in human erythrocytes by administration of N-acetyl cysteine was shown (142). Finally, a role for endogenous medium chain acylcarnitines in lipid oxidation was proposed (143).

Consensus: "omics" in exercise

- There is a rapid activation and deactivation of genes in peripheral blood even after a short bout of exercise (44).
- Clustering is possible and cellular shifts due to exercise are reflected by the changes in the gene expression profile when using whole blood or peripheral blood mononuclear cells (66, 135, 183, 334).
- Gene expression is workload dependent; a secondary response by different genes is detected up to 24 h following exhaustive exercise only (29, 124, 208).
- Expression is influenced by age, and menstrual cycle (205, 237, 238, 297).

- Gene expression profile differences are in line with pathophysiological findings that could explain exercise-induced asthma (107).
- Immuno-suppressed (renal transplant recipient) patients can perform extensive, exhaustive exercise, showing very restricted gene expression changes (metabolism only), at the same time (135).
- Although gene expression profiling gives valuable information, the effects of miRNAs need to be evaluated (58, 315).
- Proteomics and metabolomics have started to shed new light on the role of isomeric forms and post-translational modification of proteins.
- Metabolomics can identify individuals at risk for diabetes, effects of nutrition and effects of exercise (38, 244, 331).

Controversies and future directions

The "omics" approach so far has had a major impact on knowledge about physiological and pathological processes associated with exercise. An enormous amount of new data has been generated, many pathways involved have been identified, new isoforms detected, and multiple candidates for biomarkers found.

Considering the vast amount of data and the high complexity of analysis applied, it is astonishing and potentially disappointing how little- if any- practical application of "omics" technology exists. There is no doubt that "omics" is generating huge steps in scientific advancement (for example detection of new proteins and metabolites, including isoforms related to lipid metabolism, diabetes type-2, and lipoprotein structure, as well as new biological pathways and gender/menstrual phase dependent gene expression). Practical applications will arise from this, but direct application of "omics" technologies for routine practical purposes (e.g., optimization of individual training/treatment programmes) will require one or more further quantum leaps of technology and yet further increased complexity of analysis. These advances need to be such that they re-simplify proceedings, and analysis will have to integrate knowledge from different levels.

In terms of genome screening for talent and for susceptibility to injury, advances may result from technological developments that will allow easier methods of purification or whole genome sequencing. These technological advances will facilitate access to instructive and sensitive personal data. It is unclear so far how the enormous danger of misuse will be handled. Determination of single factors like alpha actinin (ACTN3) variants – even if used commercially – is largely inefficient. Interaction of many different genes in optimal composition is probably required to make an athletic talent, and at this point, research is only starting. So far, it seems highly unlikely that genomics alone will have the predictive power to screen for gifted athletes (321).

At the level of gene expression, an enormous amount of knowledge about new pathways and marker molecules involved in adaption to exercise has been generated – but as yet there is no assay to answer practical questions (concerning type, intensity and duration of activity for adaptation to specific exercise) during training. Although the technology of gene expression profiling is quite advanced and can be handled in many places, practical application of these technologies is not

thinkable without rigorous standardization procedures and further technological advances (e.g. isothermic amplification). The flow of up- and down-regulation of genes in relation to exercise is so dependent on type, intensity, and duration of exercise and nutritional and conditional factors including gender, that it is highly doubtful if any experiment can ever be repeated by a different lab with identical results – even when using the same platform. So, hotspots and time lines have to be identified in order to make reliable predictions from such data, including integration of, and validation by regulatory mechanisms (miRNA) and post-translational modification, thus requiring proteomics and metabolomics.

The latter two technologies, as powerful as they already seem to be, are only just now starting to explore the potential they really have. At present, exceptionally well-equipped laboratories and highly specialized and experienced experts must meet to enable meaningful proteomics and metabolomics studies. But as the power and potential of this approach emerges, advancements of technologies can be expected in the very near future. They will be combined with genomic and gene expression data and resulting networks will then open new levels of meta-analysis for interpretation. First steps are underway (108), although up to now, a handy little tool for talent search or for individually optimized forms of training, using "omics" type analysis, is not available.

Finally, the "omics" approach on all three classical levels will probably be helpful in identifying misuse of substances or genetic interventions for doping purposes, even though direct or specific detection procedures are often preferred in the fight against doping (11). Work paving the way for "dopeomics" is underway (83, 337).

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