Effects of moderate and high intensity exercise on T1/T2 balance

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ABSTRACT

Type 1 (T1) and Type 2 (T2) lymphocytes promote cell-mediated immunity and humoral immunity respectively. Evidence accumulated over the past two decades has demonstrated diverse responses of T1 and T2 cells to acute exercise or long-term training at moderate and high intensities. This brief review highlights the current findings from animal and human experimental models on the relationship between the T1 and T2 cell counts and the cytokines these cells produce, in response to moderate and high intensity exercise. The potential of using the T1/T2 balance as an indicator of immune function changes in response to exercise is discussed.

Key words: T1 cell, T2 cell, interferon-γ, interleukin-4, IFN-γ/IL-4 ratio

INTRODUCTION

Cytokines produced by T lymphocytes play a critical role in the development of host immunity against infection. It has been established that intracellular pathogens initiate a strong cellular immune response resulting in the differentiation of naive $CD4^+$ and $CD8^+$ T lymphocytes into type 1 T lymphocytes (T1), which consist of T helper type 1 (Th1) and T cytotoxic type 1 (Tc1) phenotypic cells (figure 1). These cells are characterised by production of interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and interleukin (IL)-2 (28, 34). In contrast, extracellular pathogens initiate a humoral immune response resulting in the differentiation of naive $CD4^+$ and $CD8^+$ T lymphocytes into type 2 T lymphocytes (T2),

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which consists of Th2 and Tc2 phenotypic cells characterised by the production of IL-4, IL-5, IL-6, and IL-10 (figure 1) (28, 34). T1 and T2 cell responses are mutually inhibitory. T1-derived cytokines (notably IFN-γ) inhibit T2 cell development, while T2-derived cytokines (IL-4, IL-10) suppress T1 responses (15, 29). T1/T2 balance (or Th1/Th2 balance, Tc1/Tc2 balance) has been used as an indicator of the changes in immune function and has become a research focus during the past decades (23, 25, 44, 48). There is currently no consensus on the definition of T1/T2 balance in the literature. In this review T1/T2 balance refers to a dynamic change between the numbers of T1 and T2 cells or between the concentrations of cytokines secreted by T1 and T2 cells. A significant up-regulation or down-regulation of any subset of the T1 or T2 cells or their cytokines indicates T1/T2 imbalance. The T1/T2 imbalance has been reported in acute and chronic infections or several diseases in humans such as cancer and asthma (6, 13, 33, 49, 51).

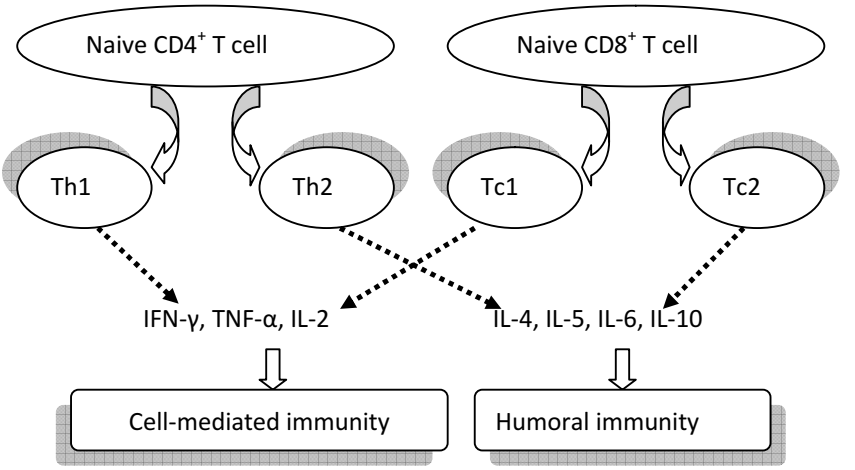

Figure 1. Development of T cells from T precursors.

In theory, T1 cells are associated with cell-mediated immunity and play a more important role in clearing infections (28), whereas T2 cells are associated with humoral immunity and play a key role in preventing infections (11). Thus, a severe depression of T1 cells caused by acute or chronic stress may lead to a failure in completely clearing viral infections, while an immune polarisation toward T1 phenotype may indicate an increased ability for clearing infections.

In the current literature the consensus is that the responses of T1 cells to infection are suppressed after high intensity exercises that may provide an explanation for the increased susceptibility to infection following prolonged high intensity exercise (18, 21, 46). In contrast, the T1 cell responses are strengthened following moderate intensity exercises which may enhance the immune responses to infectious agents (17, 19). However, these suggestions are based only on the results of

a small number of experiments. There have been no systematic investigations on the alterations of T1/T2 balance in response to exercise of various types, intensities and durations.

Given that the T1/T2 balance is considered to be closely associated with the immune function in response to different forms of exercise, the primary purpose of this brief review is to analyse the current literature regarding the specific effect of exercise intensity on T1 and T2 counts and function in humans or animals. Furthermore, acute and chronic effects of exercise on T1/T2 balance in different subject populations will be analysed. Whether the alterations in the T1/T2 balance following exercise can be used as an indicator for monitoring immune function and health of exercise participants will also be discussed.

T1 AND T2 CELLS AND THEIR CYTOKINES

The innate immune system activates T cells and induces differentiation of naive T cells into polarised subsets of effector T cells, in response to infection, disease or physical exercise (9, 31, 47). The type 1/type 2 (Th1/Th2 and Tc1/Tc2) paradigm is a good indication of T cells polarisation. In simple terms, both Th1 and Th2 cells are differentiated $CD4^+$ T cells with Th1 cells producing predominantly IFN-γ (or IL-2), and Th2 cells producing IL-4 (or IL-10), respectively (28). In theory, Th1 and Th2 cells can be differentiated functionally and phenotypically by parameters other than IFN-γ and IL-4 production (13), but the two cytokines quintessentially classify the Th1/Th2 paradigm. Similarly, $CD8^+$ T cells can also develop into IFN-γ- or IL-4-producing cells that are called Tc1 and Tc2 cells, respectively (24). In the present review, we classify IFN-γ^+CD4^+ (or IL-2^+CD4^+), IFN-γ^+CD8^+ (or IL-2^+CD8^+), IL-4^+CD4^+, and IL-4^+CD8^+ cells as Th1, Tc1, Th2 and Tc2, respectively, and define IFN-γ^+ and IL-4^+ T cells as T1 and T2 cells, respectively. In addition, the concentration of these cytokines in T cell culture supernatants after stimulation is used as an indication of the functional changes of the polarised subsets.

EFFECTS OF INFECTION FOLLOWING EXERCISE AND TRAINING ON T1/T2 CELL CONCENTRATION AND FUNCTION

Several studies have investigated the influence of viral infection such as herpes simplex virus type 1 (HSV-1) through an intranasal route, or lymphocytic choriomeningitis (LCMV) via injection following exercise on T1/T2 cells balance, using mice models (16-19). The results of these studies (table 1, see addendum) can be summarised in four points.

1) Exercise training with moderate intensity for 8 weeks up-regulated the function of both T1 and T2 cells in clearing HSV-1 in both young and older adult mice at different time points post training. This beneficial effect could last for at least 7 days.

2) Compared with the values measured 7 days after infection, both of T1 cell-derived IFN-γ, IL-2, and T2 cell-derived IL-10 concentrations increased 10 days after the infection in young adult mice, while the T1/T2 balance was still maintained.
3) In contrast, in older mice the cytokines associated with the balance of T1/T2 cells seemed heading to opposite directions at the two time points of tissue sampling after infection. The cytokine secretion patterns changed from type 1 phenotype at the 7th day post-infection to type 2 at the 10th day post-infection. In general, the change of T1/T2 balance appeared to be associated with ageing, and senescence might result in a defect in T1 cells development and a subsequent defect in cell-mediated immunity leading to an intracellular infection (1, 36). There was evidence that moderate intensity exercise training could prevent the defect from happening and maintain T1/T2 balance at the 7th day post-infection (17). However, excessive T1 cell response to viral infection might result in tissue damage (20). An elevation of T2 cell-like cytokines would then occur that would inhibit the differentiation of T1 cells through mutually inhibitory effect that would prevent further tissue damage at the 10th day post-infection.
4) High intensity exercises, either acute or chronic, could decrease the concentration of T1 cells or T1 cell-derived cytokines for clearing HSV-1 or LCMV in young adult mice. However, in older mice, high intensity exercise did not cause suppression of LCMV-specific T1 cell responses. The mechanisms underlying the differences observed in young and older mice are not clear and require further study.

EFFECTS OF EXERCISE AND TRAINING ON T1/T2 CELL CONCENTRATION AND FUNCTION

Effects of moderate intensity exercise

There have been several reports on T1/T2 balance in response to moderate intensity exercise in humans of different ages, including young adults who performed one bout of exercise and older adults who participated in exercise training (table 2, see addendum). One study demonstrated that T1 cell-derived IFN-γ increased significantly even just after a bout of moderate intensity exercise for 30 min, but none of T2 cell-derived cytokines were measured in that study (5). It was speculated that moderate intensity exercise might promote the T1-type cytokine response (5, 26).

It has been reported that long-term moderate intensity exercise training for 0.5, 2, or 4 years could all reverse age-associated reduction of T1 cells and T1 cell-derived cytokines (table 2, see addendum). There have been reports that moderate intensity exercise training was effective to improve immune function in older people, and it has been speculated that exercise-induced differentiation of naive T cells toward the type 1 phenotype is one of the mechanisms underlying the improvement (10, 30, 36).

However as demonstrated by Kohut et al. (2004), the function of both T1 and T2 cells in clearing HSV-1 were up-regulated in both young and older adult mice

after moderate intensity training (19). Therefore the T1/T2 balance may still be maintained when the T1 and T2 cells number and/or their cytokines both increase.

Effects of high intensity exercise

Acute effects of high intensity exercise

In this section, the acute effects of high intensity exercise in humans on T1 and T2 concentrations in peripheral blood (table 3, see addendum), and on the T1, T2-derived cytokine levels in T cell culture supernatants after stimulation (table 4, see addendum), are discussed, for the acute alteration of T1/ T2 distribution and function.

There has been consistent evidence that both of the distribution and function of T1 cells in the circulation are suppressed 1 h after one bout of prolonged (1 h and over) high intensity exercise, whereas no significant changes are found in the distribution and function of T2 cells (table 3, 4, see addendum). The suppression may last for more than 24 hours (5, 41). Furthermore, the trend of change in the cytokines produced by T1 and T2 cells is consistent with that of the number of the cells that produce these cytokines.

The suppression of the distribution and function of T1 cells following one bout of prolonged high intensity exercise may be associated with the changes of some hormones. In theory, glucocorticoids (GCs) act through their classic cytoplasmic/nuclear receptors on antigen presenting cells (APCs) to inhibit the production of IL-12 that is the main inducer of Th1 cells (7). IL-12 is extremely potent in enhancing IFN-γ and inhibiting IL-4 synthesis by T cells. Therefore, GCs' inhibition of IL-12 production may be a major mechanism by which GCs affect Th1/Th2 balance. Similarly, catecholamines (CAs) suppress the production of IL-12 and IFN-γ, and stimulate the production of type 2 cytokines (37). The correlation between stress hormones and T1-, T2-derived cytokines following exercise has been investigated using human models. It has been reported that the mean plasma adrenalin concentration correlated negatively with the percentage of circulating Tc1 cells at 2 h post-exercise (running at 75% $\dot{V}O_{2max}$ for 2.5 h), but plasma cortisol did not correlate with the percentage of circulating T1 cells (41). The relationship between cortisol and T1/T2 balance following exercise has not been reported and needs further investigation.

Interestingly, the changes of the polarised subsets of T cells are quite different from the changes of the cytokines secreted by these cells in the circulation within 5 min after a bout of prolonged high intensity exercise (table 3, 4, see addendum). The suppression of type 1 cytokines has been found immediately after an exercise and persisted for 24 h (22, 35, 40), but the concentration of type 1 T cells changed differently (increased, decreased or had no obvious change) immediately after or 5 min after similar or same exercise protocols (14, 21, 22, 35, 40). During a high intensity exercise, the circulating concentration of T1 cells can be affected more significantly by adrenalin and noradrenalin because there is a higher surface expression of β2-adrenergic receptors on T1 cells compared with T2 cells (27). The CAs mediate trafficking of circulating leukocytes from the spleen and lymphatic system to the circulation (positive effect for the circulating T1 cells) or

from the systemic circulation to the peripheral immune compartments such as skin, urogenital and gastrointestinal tracts (negative effect for the circulating T1 cells) (21). Therefore, the direction of the change in circulating T1 cells soon after high intensity exercise depends on the balance between the positive and negative effects under different exercise intensity and duration.

It is also interesting to find that high intensity exercise for a shorter duration (e.g. less than 30 min) did not decrease the distribution of T1 cells and inhibit the function of T1 cells in the circulation at 1 or 2 h post-exercise (40, 50). In these studies (40, 50), the changes in the distribution and function of T1 cells in the circulation immediately after exercise were also measured, but these changes were more likely having been affected by the stress hormones. With this consideration we just choose the time points at 1 or 2 hours post-exercise for discussion. Therefore, it seems that the number and function of the polarised subsets of T cells may also relate to the duration of high intensity exercise.

Chronic effects of high intensity exercise

In studies on both humans and animals, chronic and high intensity exercise training appeared to result in less T1 cell polarisation (table 5, see addendum). Furthermore, this inhibition of T1 cells could last for more than 7 days in mice (47). It is worthwhile to note that the values measured within one hour post-exercise would be more likely to reflect an acute response to the last exercise session, but not the cumulative effect of multiple bouts or days of exercise. Therefore, for a discussion of the chronic effects of exercise, the data collected at 1 h post last exercise session is not included, and the data collected next morning before exercise is used for discussion of the training effects (21) (table 5, see addendum).

To our knowledge, alteration in cytokines produced by the polarised subsets of T cells induced by chronic and high intensity exercise has not been investigated.

CONTROVERSIES AND FUTURE DIRECTIONS

The relationship between concentration and function of T1/ T2 cells

As discussed above, alterations in T1 and T2 cell concentrations in peripheral blood are not consistent with T1- and T2-derived cytokine levels in T cell culture supernatants after stimulation, following a bout of intensive exercise. This disagreement was evident even under the same experimental conditions (40). A study (40) showed that high intensity exercise induced a promotion in the concentration of circulating T lymphocytes that produce IFN-γ ($P < 0.01$) and IL-2 ($P < 0.01$) immediately post-exercise. In contrast, exercise resulted in a decrease in the levels of IFN-γ ($P < 0.01$) and IL-2 ($P < 0.01$) produced by circulating lymphocytes at the same time point. Therefore, it is still inconclusive on whether an increased number of T1 cells in circulation is beneficial for cell-mediated immunity.

The suppression in the function of T1 cells, as indicated by decreased IFN-γ, has been associated with the expression of transcriptional factors such as signal trans-

ducer and activator of transcription 4 (STAT4), Th1-specific T box transcription factor T-bet, E twenty-six (ETS)-related transcription factor ERM, interferon regulatory factor-1 (IRF-1) which are crucial for the production of IFN-γ by T1 cells (32). Therefore, the number of T1 cells with lower expression of related transcriptional factors is not a meaningful indicator of cell immune response soon after high intensity exercise because these T1 cells can not produce IFN-γ effectively. In addition, in some other experimental reports included in the present review, exercise-induced changes in the concentration of circulating T1 and T2 cells were in parallel to that in the corresponding intracellular lymphocyte cytokines at other time points (21, 22, 35). Further research is needed to examine the relationship between the number of T1 and T2 cells and the level of related cytokines produced by these cells.

The relationship between the amount of cytokines produced by circulating T1/T2 cells and the concentration of that in serum or plasma

During and after exercise, the secretion of cytokines by T1/T2 cells into the circulation is a causative mediator of exercise-induced immune perturbation (43). Whether the changes in circulating cytokines can be used as an indication of the function of T1/T2 cells is an important question. Previous studies have shown that certain cytokines such as IL-6 and TNF-α are produced directly by exercising skeletal muscle or other tissues during exercise (39, 45). Other cytokines such as IFN-γ, IL-2 are produced primarily by T and natural killer (NK) lymphocytes in response to exercise (37). Considering the function of the pro-inflammatory cytokines (IFN-γ, IL-2) and anti-inflammatory cytokines (IL-4, IL-10), it seems reasonable to speculate that the up- or down-regulation in the circulation soon after exercise are supposed to be caused by promoting the trafficking of cytokines from the circulation to the vasculature of other immune compartments (e.g. skeletal muscle, urogenital and gastrointestinal tracts), instead of a reduction of the cytokines produced by circulating T1/T2 cells. Previous study have demonstrated that exercise-induced changes in the intracellular leukocyte cytokines (IFN-γ, IL-2, IL-4, IL-10) detected immediately after exercise are not necessarily in parallel to their changes in circulation (50). In another study, the plasma concentrations of IFN-γ, TNF-α, IL-2, IL-4 did not show significant changes immediately after a bout of exhaustive exercise (42). The relationship between the amount of cytokines produced by circulating T1/T2 cells and that in the serum or plasma at various time points post-exercise is still not clear.

IFN-γ /IL-4 ratio and T1/T2 balance

$CD4^+$ T cells and $CD8^+$ T cells are classified according to their cytokine profile as type 1 (Th1/Tc1) or type 2 (Th2/Tc2) (24). In order to more effectively evaluate the balance of T1 and T2 cells differentiation in response to physical activity, the ratio between $CD4^+$ T cells or $CD8^+$ T cells expressing intracellular IFN-γ and that expressing intracellular IL-4 has been used as an indication of Th1/Th2 or Tc1/Tc2 balance (14, 30). As mentioned before, the alteration in the concentration of T1/T2 cells are not always consistent with that in the corresponding intracellular cytokines after exercise (40). So the ratio might not be synchronous with the balance of cell-mediated immunity and humoral immunity.

Type 1 and Type 2 immune responses can be induced by T1- and T2-derived cytokines respectively, but that can't be induced directly by T1 and T2 cells. Obviously, it is more meaningful to evaluate T1/T2 balance using the concentration of cytokines than using the number of cells. Among these cytokines, IFN-γ and IL-4 are respectively signature cytokines of T1 and T2 cells (8). So we speculate that the ratio between IFN-γ and IL-4 produced by $CD4^+$ T cells and/or $CD8^+$ T cells may be an alternative indicator of Th1/Th2 or Tc1/Tc2. Likewise, to determine the IFN-γ/IL-4 ratio in plasma or serum might be more practical for evaluation of this balance at some particular time points after exercise if the two cytokines produced by circulating T1/T2 cells were in parallel to the concentrations of these cells in circulation. Furthermore, the ratio of IFN-γ/IL-4 in circulation and T cell culture supernatants after stimulation has been used as an indication of T1/T2 balance in the field of medical research (12, 13).

CONCLUSIONS

Evidence accumulated over the past two decades indicates that: 1) high intensity exercise is in favour of type 2 phenotype T cells, which is one of the mechanisms underlying the down-regulation of host protection against viral infection post exercise; 2) moderate intensity exercise induces a shift of the type 1/type 2 T cell balance toward type 1 in older adults that is in the reverse of age-associated reduction of T1 cells or T1 cell-derived cytokines, and improves T1 cell function in young adults, but the effect of moderate intensity exercise on T2 cell function hasn't been clarified through experimental studies; 3) the alteration in cytokines produced by T1/T2 cells is not consistent with that in the number of cells expressing corresponding cytokines, and that of the same cytokines in the circulation in a short period of time after exercise, while the relationships in a long recovery period has not been examined; and 4) Th1/Th2 and Tc1/Tc2 ratios may be used as an indicator for T1/T2 cells differentiation but might not always represent their functional changes. The IFN-γ/IL-4 ratio in culture supernatant of stimulated T cells or in the circulation might be an effective indicator for monitoring the balance between cell-mediated immunity and humoral immunity.

ADDENDUM

Table 1. Effects of infection following exercise on T1/T2 cells and related cytokines

Reference	Subjects	Type of exercise	Level of exercise and protocol	Protocol of viral infection	Resource	post-infection
(17)	Young adult mice Older adult mice	Moderate, chronic, treadmill	Speed: 8 m/min during week one and gradually progressing to 18 m/min Duration: gradually increased during week 1–4; from week 5–8, mice ran 40–45 min per day Frequency: 5 days per week Cycle: 8 weeks	Mice were infected with HSV-1 at 24 h post-exercise	Production by stimulated spleen cells	IFN-γ↑, IL-2↑; IL-10↑ (7 days post-infection) IFN-γ↑*, IL-2↑*; IL-10↑ (7 days post-infection)
(19)	Young adult mice Older adult mice	Moderate, chronic, treadmill	Speed: 8 m/min during week one and gradually progressing to 18 m/min Duration: gradually increased during week 1–4; from week 5–8, mice ran 40–45 min per day Frequency: 5 days per week Cycle: 8 weeks	Mice were infected with HSV-1 at 24 h post-exercise	Production by stimulated spleen cells	IFN-γ↑*, IL-2↑*; IL-10↑* (10 days post-infection) IFN-γ–, IL-2–; IL-10↑* (10 days post-infection)
(16)	Young adult mice Older adult mice	Strenuous, acute, treadmill	Incremental exercise to exhaustion. Speed was increased from 4 m/min to 32 m/min by 4 m/min every minute; 13.1±4.6 min Incremental exercise to exhaustion. Speed was increased from 4 m/min to 17 m/min by 4 m/min every minute; 11.9±7.2 min	Mice were infected with LCMV immediately post-exercise	Spleen cells	T1↓* (8 days post-infection) T1– (8 days post-infection)
(18)	Young adult mice	Strenuous, acute, treadmill	Gradually increasing speeds until fatigue. Speed began at 11.5 m/min and was increased by 4–6 m/min every 25 min. The maximum speed reached was 42 m/min Duration: 2.5 h	Mice were infected with HSV-1 within 10-15 min post-exercise	Production by stimulated spleen cells	IFN-γ↓*, IL-2↓*; IL-10– (3 days post-infection)

↑ higher than that in the control group; ↓ lower than that in the control group; – no obvious change; * significantly different from the control group.

Table 2. Effects of moderate intensity exercise on T1/T2 cells and related cytokines

Reference	Subjects	Type of exercise	Level of exercise and protocol	Source	Post-exercise
(5)	Young adult human	Moderate, acute, cycling	70% of their 4-mmol/L lactic acid threshold, 30 min	Production by stimulated peripheral blood lymphocytes	IFN-γ↑ (30 min post-exercise) IFN-γ↑* (24 h post-exercise)
(10)	Older adult human	Moderate, chronic. 1.workout while marching and standing; 2. workout in low positions – in squat, on hands and knees, lying on your side, in prone position	Intensity: pulse rate ≦ 80% of the age-predicted maximum (200-age) Duration: 50 min Frequency: twice a week during 10 months of the year Cycle: 2 years	Production by stimulated peripheral blood lymphocytes	IL-2↑*, IFN-γ–; IL-4– (At least the next day after the last exercise. The exact interval was not reported in this study)
(30)	Older adult human	Moderate, chronic, walking	Intensity: equivalent to 57% $\dot{V}O_2$ peak for 30 min every day, and for one and a half hours once a week Duration and frequency: 3-5 km every day and 10 km once a week Cycle: 4 years	Peripheral blood	Th1↑*, Tc1↑; Th2↑, Tc2↑; Th1/Th2 two-fold↑, Tc1/Tc2↑ (at least 24 hours after the last exercise)
(36)	Older adult human	Moderate, chronic, cycling and resistance training	Intensity and duration: part 1 (endurance training) was a cycle-ergometer exercise (30 min) at 80% work rate of the DPBP▲. Part 2 (endurance training) requires their muscles to work against gravity by moving their own weight up and down, which comprised three sets of seven exercises (10 repetitions). Frequency: 5 days a week Cycle: 6 months	Peripheral blood	Th1↑*; Th2↓ (at least 24 hours after the last exercise)

↑ higher than pre-exercise or that in the control group; ↓ lower than that in the control group; – no obvious change; * significantly different from the control group.
▲DPBP (double-product break-point) is the point of accelerating double product (heart rate × systolic blood pressure), which has been shown to have strong positive correlations with the lactate and ventilatory thresholds.

Table 3. Acute effects of high intensity exercise on T1/T2 cells

Reference	Subjects	Type of exercise	Intensity	Duration	Source	Immediately post-exercise	1-2 h post-exercise	1 d post-exercise
(41)	Endurance-trained male runners	Treadmill	75% $\dot{V}O_{2max}$	2.5 h	Peripheral blood	Th1↓*, Tc1↓*; Th2–, Tc2–	Th1↓*, Tc1↓*; Th2–, Tc2– (2 h post-exercise)	Th1↓*, Tc–; Th2–, Tc2–
(22)	Moderately to well endurance-trained men	Cycle	65% $\dot{V}O_{2max}$	2.5 h	Peripheral blood	Th1–, Tc1↑*; Th2–, Tc2–	Th1↓*, Tc1↓*; Th2–, Tc2– (2 h post-exercise)	
(21)	Endurance-trained male cyclists	Cycle	Exercise to exhaustion at ~63% Wmax (~74% $\dot{V}O_2$ max)	107±7 min	Peripheral blood	T1↓*; T2–	T1↓*; T2– (1 h post-exercise)	
(14)	Healthy men	Treadmill, 5% downhill incline	75% $\dot{V}O_{2max}$	1.5 h	Peripheral blood	Th1↑, Tc1↑; Th2↑, Tc2↑; Th1/Th2↑, Tc1/Tc2↑	Th1↓, Tc1↓; Th2↑, Tc2↑; Th1/Th2↓, Tc1/Tc2↓ (2 h post-exercise)	
(35) ▲	Male volunteers with several years of rowing experience	Rowing on a rowing ergometer	The highest possible power output (Average % of $\dot{V}O_2$ peak: 73.2±4.0) that could be maintained for 1 h	1 h	Peripheral blood	Th1–, Tc1– (5 min post-exercise)	Th1↓*, Tc1↓ (1 h post-exercise)	
(40)	Endurance-trained men	Supine bicycle	78 ± 3% $\dot{V}O_2$ peak	19±1 min	Peripheral blood	T1↑*	T1– (2 h post-exercise)	

↑ higher than pre-exercise; ↓ lower than pre-exercise; – no obvious change; * significantly different from pre-exercise.

▲ IL-2$^+$CD4$^+$ cells and IL-2$^+$CD8$^+$ cells were classified as Th1 and Tc1 respectively because IFN-γ$^+$CD4$^+$ cells and IFN-γ$^+$CD8$^+$ cells were not measured in this study.

Table 4. Acute effects of high intensity exercise on T1, T2-derived cytokines

Reference	Subjects	Type of exercise	Intensity	Duration	Source	0-30 min post-exercise	1-24 h post-exercise
(22)	Moderately to well endurance-trained men	Cycle	65% $\dot{V}O_{2max}$	2.5 h	Production by stimulated peripheral blood CD4+ T cells	IFN-γ↓*, IL-4– (immediately after exercise)	IFN-γ↓*, IL-4– (2 h post-exercise)
					Production by stimulated peripheral blood CD8+ T cells	IFN-γ↓*; IL-4– (immediately after exercise)	IFN-γ↓*; IL-4– (2 h post-exercise)
(2)	Male cyclist	Cycle	90% of the anaerobic threshold	6 × 20 min	Production by stimulated peripheral blood cells	IFN-γ 16% ↓, TNF-a 26%↓, IL-2 35%↓; IL-4 35.5%↓ (immediately after exercise)	
(21)	Endurance-trained male cyclists	Cycle	Exercise to exhaustion at ~63% Wmax (~74% $\dot{V}O_{2max}$)	107±7 min	Production by stimulated peripheral blood CD3+ T lymphocytes	IFN-γ↓*; IL-4– (immediately after exercise)	IFN-γ↓; IL-4– (1 h post-exercise)
(5)	Healthy people	Cycle	100% of their 4-mmol/L lactic acid threshold	90 min	Production by stimulated peripheral blood cells	IFN-γ↓ (30 min post-exercise)	IFN-γ↓ (24 h post-exercise)
(35)	Male volunteers with several years of rowing experience	Rowing on a rowing machine	The highest possible power output (Average % of $\dot{V}O_2$ peak: 73.2±4.0) that could be maintained for 1 h	1 h	Production by stimulated peripheral blood cells	IFN-γ–, IL-2↓* (5 min post-exercise)	IFN-γ↓*, IL-2↓* (1 h post-exercise)
(3)	Elite male triathletes	Swimming, cycling, and running	São Paulo International Triathlon	?	Production by stimulated peripheral blood cells	IFN-γ 35.1% ↓, TNF-a 16.9%↓ (15 min post-exercise)	
(4)	Elite male triathletes and marathoners	Running or swimming, cycling, and running	São Paulo International Triathlon or running 30 km in 2 h	?	Production by stimulated peripheral blood cells	IFN-γ 27% ↓, TNF-a 19%↓; IL-4 18.7%↓ (15 min post-exercise)	
(50)	Healthy males	Cycle	80% of the peak $\dot{V}O_2$	30 min	Production by stimulated peripheral blood cells	IFN-γ↑, IL-2↑*, TNF-a↑*; IL-4↑* , IL-10↑*, IL-6↑ (immediately after exercise)	IFN-γ↓, IL-2↑, TNF-a↓; IL-4↓, IL-10↓, IL-6↓ (1 h post-exercise)
(38)	Well trained competitive oarsmen	Rowing on a rowing machine	Incremental exercise to exhaustion. Male: $\dot{V}O_{2max}$ was 135.8±6.6% predicted; Females: $\dot{V}O_{2max}$ was 138.4±12.3% predicted	Male: 16.0±0.92 min; Females: 15.5±0.0 min	Production by stimulated peripheral blood cells	IFN-γ↓*, TNF-a↓*; IL-6↓*, IL-10↓ (20 min post-exercise)	
(40)	Endurance-trained men	Supine bicycle	78 ± 3% $\dot{V}O_2$ peak	19 ±1 min	Production by stimulated peripheral blood cells	IFN-γ↓*, IL-2↓* (immediately after exercise)	IFN-γ↓, IL-2↓ (2 h post-exercise)

↑ higher than pre-exercise; ↓ lower than pre-exercise; – no obvious change; * significantly different from pre-exercise.
? duration was not reported in the study.

Table 5. T1/T2 cell changes after long-term high intensity exercise

Reference	Subjects	Type of exercise	Level of exercise and protocol	Source	Within 36 h post-exercise	7 d post-exercise
(21) ▲	endurance-trained male cyclists	Cycle	Intensified training period for 7 days	Peripheral blood	T1↓*; T2– (next morning to the last exercise)	
(47)	Female rats	treadmill	Progressive load training period for 9 weeks (6 days a week) week 1: 15 m/min × 40 min at 2% (grade) week 2: 20 m/min × 60 min at 10% (grade) week 3: 25 m/min × 90 min at 10% (grade) week 4: 30 m/min × 120 min at 5% (grade) week 5: 30 m/min × 120 min at 5% (grade) week 6: 30 m/min × 120 min at 8% (grade) week 7: 35 m/min × 120 min at 10% (grade) week 8: 35 m/min × 120 min at 15% (grade) week 9: 35 m/min × 120 min at 15% (grade)	Spleen cells	T1↓; T2↑ (36 h post-exercise)	T1↓*; T2↑*

↑ higher than that in the control group; ↓ lower than pre-exercise or that in the control group; – no obvious change; * significantly different from pre-exercise or that in the control group.

▲ The blood samples were collected before, immediately after and 1 h after the first exercise and last exercise of 8 days training period which consists of 2-day of VO_{2max} tests (exercise to exhaustion at ~74% VO_2 max) and 6-day intensified training period in the experiment. But we regard the samples collected at the time point of pre-exercise on the 8^{th} day training in order to differentiate from the acute effect of exercise in the present article.

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