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Training status and sex influence on senescent T-lymphocyte redistribution in response to acute maximal exercise

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ABSTRACT

Purpose: Investigate training status and sex effects on the redistribution of senescent and naïve T-lymphocytes following acute exercise.
Methods: Sixteen (8 male, 8 female) trained (18.3 ± 1.7 yr) soccer players (Tr) and sixteen (8 male, 8 female) untrained (19.3 ± 2.0 yr) controls (UTr) performed a treadmill running test to volitional exhaustion. Blood lymphocytes were isolated before (Pre), immediately post, and 1-h post-exercise for assessment of cell surface expression of CD28 and CD57 on $CD4^+$ and $CD8^+$ T-lymphocyte subsets. Plasma was used to determine cytomegalovirus (CMV) serostatus.
Results: Exercise elicited a redistribution of T-lymphocyte subsets. Senescent $CD4^+$ and $CD8^+$ T-lymphocytes increased by 42.4% and 45.9% respectively, while naïve $CD4^+$ and $CD8^+$ T-lymphocytes decreased by 8.7% and 22.5% respectively in response to exercise. A main effect ($P < 0.05$) of training status was observed for senescent $CD4^+$, $CD8^+$ and naïve $CD8^+$ T-lymphocytes: UTr had a higher proportion of senescent and a lower proportion of naïve $CD8^+$ T-lymphocytes than Tr. A main effect ($P < 0.05$) of sex was observed in senescent $CD4^+$, $CD8^+$ and naïve $CD4^+$, $CD8^+$ T-lymphocytes. Males had a higher proportion of senescent and lower proportion of naïve T-lymphocytes than females. A sex-by-training status interaction ($P < 0.05$) was observed for the senescent and naïve $CD4^+$ T-lymphocytes (but not $CD8^+$) with the highest percentage of senescent and lowest percentage of naïve T-lymphocytes observed in UTr males. CMV exerted a significant main covariate effect ($P < 0.05$) in the senescent and naïve ($P < 0.05$) $CD8^+$ T-lymphocytes but not in the senescent and naïve $CD4^+$ T-lymphocytes.
Conclusion: This study highlights important sex and training status differences in the senescent and naïve T-lymphocyte redistribution in response to exercise that warrants further investigation.
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1. Introduction

T-lymphocytes that fail to divide in response to antigenic stimulation are considered senescent (Brenchley et al., 2003). Despite this loss of novel antigen defence, senescent T-lymphocytes retain immediate effector functions, such as recognition and killing of virally infected cells (Effros, 2004). Antigen-experienced $CD4^+$ and $CD8^+$ effector and memory T-lymphocytes with a senescent phenotype (Table 1) undergo preferential mobilisation into the peripheral blood circulation followed by a subsequent egress from the circulation in response to exercise (Campbell et al., 2008; Simpson et al., 2007, 2008; Turner et al., 2010). This preferential influx of cytotoxic senescent $CD8^+$ T-lymphocytes to the peripheral tissues with retained effector killing functions following exercise is considered important for immunosurveillance. A model proposed by Dhabhar et al. (2012) suggests that in response to a stressor naïve T-lymphocytes traffic to lymph nodes where they come into contact with novel antigens. Concomitantly antigen-experienced effector and memory T-lymphocytes traffic to peripheral tissues like the skin, lung or mucosal lining of the gut where they encounter familiar antigens. In agreement with this model Bosch et al. (2003) observed a selective mobilisation of T-lymphocytes primed for inflammation in response to an acute stressor (Bosch et al., 2003).

The percentage of circulating T-lymphocytes with a senescent phenotype at rest is known to be influenced by body composition (Tchkonia et al., 2010), age (Tchkonia et al., 2010; Yan et al., 2010), maximal aerobic capacity (Spielmann et al., 2011), sex (Yan et al., 2010) and latent CMV infection (Pawelec et al., 2009; Turner

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et al., 2013). Recently, we demonstrated that one week of high-intensity exercise training resulted in a blunted mobilisation of effector memory $CD8^+$ T-lymphocytes compared with normal-intensity training in trained cyclists (Witard et al., 2012). Given that the trafficking pattern of lymphocytes is very sensitive to acute exercise training, characterising how training status, as opposed to an acute bout of high-intensity exercise impacts exercise-induced changes in senescent T-lymphocyte redistribution warrants investigation. Given that senescent T-lymphocytes accumulate at rest in CMV^+ individuals (Pawelec et al., 2009; Turner et al., 2013), and the response of lymphocytes, particularly $CD8^+$ T-lymphocytes, to exercise is influenced by CMV infection history (Turner et al., 2010), it is important to consider CMV serostatus when investigating differences between groups for senescent T-lymphocyte responses to exercise. Although total lymphocyte counts at rest are similar between sexes (Giltay et al., 2000), the percentage of T cells is lower in males (Bouman et al., 2004). However, it remains unknown whether sex alone or in combination with training status influences the redistribution of senescent T-lymphocytes in young adults.

Thus, the primary aim of this study was to characterise the effect of training status and sex on the senescent T-lymphocyte response to an acute bout of intense exercise. In addition, we simultaneously characterised the redistribution of naïve T-lymphocytes into or out of the blood compartment. In accordance with Spielmann et al. (2011), we hypothesized that the redistribution of senescent T-lymphocytes into or out of the blood compartment would be blunted in trained individuals. Given that previous work reported a greater age-related increase in effector memory cells in males vs. females (Yan et al., 2010), we hypothesized that a higher proportion of senescent T-lymphocytes would be observed in males vs. females at rest and in response to exercise.

2. Methods

2.1. Participants

Sixteen well-trained soccer players (eight male [mean ± SD age: 17.8 ± 0.7 yr, height: 180.4 ± 5.3 cm, mass: 74.5 ± 6.0 kg, body fat: 10.7 ± 1.5%] and eight female [age: 18.9 ± 2.3 yr, height: 166.0 ± 8.3 cm, mass: 61.8 ± 7.8 kg, body fat: 18.2 ± 3.4%]) were compared to a group of 16 age-matched untrained controls (eight male [age: 19.4 ± 2.3 yr, height: 180.1 ± 4.2 cm, mass: 74.4 ± 11.7 kg, body fat: 10.7 ± 4.3%] and eight female [age: 19.1 ± 1.8 yr, height: 169.0 ± 5.3 cm, mass: 59.9 ± 4.2 kg, body fat: 17.5 ± 3.8%]). All participants were non-smokers who were not taking any medication and were free from infectious illness for 6 week prior to the study. Each participant completed a pre-participation health screen questionnaire and provided their written informed consent. Ethical approval was granted by the University of Stirling Research Ethics Committee. To be included in the study, it was important that untrained active controls were not exercising any more than the UK department of health recommended healthy living guidelines of 2–3 h/week (Department of Health, Reducing Obesity and Improving Diet, 2011).

2.2. Experimental protocol

Participants arrived at the laboratory in the morning (between 7:30–9:30 am) after a >10 h fast and after 24 h of rest and were instructed to rest supine on a treatment couch for approximately 5 min. Next, a cannula was inserted into a forearm vein connected with cannula extension tube (Becton Dickson, Oxford, UK). After returning to a seated position, a baseline 10 mL blood sample was collected in a K_2EDTA blood collection tube (Becton Dickson, Oxford, UK) that was placed horizontal on a mixer at room temperature for later separation of cells.

Participants then completed an incremental exercise test to volitional exhaustion on a motorised treadmill (Powerjog G100). Starting speed was 10 km/h for trained males and 8 km/h for trained females, untrained males and untrained females. These starting speeds elicited similar relative exercise intensities for all participants in an attempt to match total exercise duration between groups. The incline of the treadmill was set at 1% to best simulate outdoor running conditions (Jones and Doust, 1997). Treadmill speed was increased by 1 km/h at 3 min increments. Heart rate (HR) during the test was recorded using Polar RS200sd HR monitors (Finland). Rating of perceived exertion (RPE) also was recorded at the end of each increment using the category-ratio Borg (CR10) scale (Borg, 1982a,b). Participants were verbally encouraged to run to volitional exhaustion. At exhaustion, participants straddled the running belt and treadmill speed was decreased to 3.5 km/h for a short recovery walk (2 min) whilst a second 10 mL blood sample was collected. A final 10 mL blood sample was collected 1-h post-exercise. Participants were allowed to consume water *ad libitum* during the test.

2.3. Peripheral blood mononuclear cells (PBMC) isolation

The methods used to isolate peripheral blood mononuclear cells (PBMCs) from whole blood have been described elsewhere (Simpson et al., 2006). The isolated PBMCs were then stored in 70%

Table 1
Surface phenotypic identification of T-lymphocyte subsets.

T-lymphocyte subset	Surface phenotype	References
Naïve T-lymphocytes	$CD57^-/CD28^+$ $KLRG1^-/CD28^+$	Appay et al. (2002) and Koch et al. (2007)
Senescent T-lymphocytes[a]	$KLRG1^+/CD27^-$ $KLRG1^+/CD28^-$ $CD57^+/CD28^-$	Voehringer et al. (2002), Brenchley et al. (2003) and Appay et al. (2002, (2008)
Memory T-lymphocytes	$CD45RA^+/CD28^+$ $KLRG1^+/CD57^-/CD28^+$	Ibegbu et al. (2005)
Central memory T-lymphocytes	$CD45RA^-/CD27^-$ $KLRG1^+/CD57^-/CD28^+$	Koch et al. (2007) and Romero et al. (2007)
Early effector-memory T-lymphocytes	$KLRG1^+/CD57^-/CD28^+$	Koch et al. (2007)
Effector-memory T-lymphocytes	$CD45RO^+/CD27^-$ $CD45RA^-/CD27^-$	Appay et al. (2002) and Romero et al. (2007)
'Reverent' effector memory T-lymphocytes (EMRA)	$CD45RA^+/CD28^-$ $CD45RA^+/CD27^-$	Appay et al. (2002) and Romero et al. (2007)

[a] Phenotype $KLRG1^+/CD28^-$ has been used to identify senescent T-lymphocytes. However under certain circumstances proliferative capabilities may be restored (Akbar and Henson, 2011). Therefore in the present study $CD57^+/CD28^-$ was chosen to identify senescent T-lymphocytes.

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