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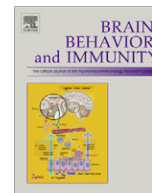

Latent Cytomegalovirus infection amplifies CD8 T-lymphocyte mobilisation and egress in response to exercise

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ABSTRACT

Exercise induces mobilisation of $CD8^+$ T lymphocytes (CD8TL) into the peripheral blood. This response is largely confined to effector-memory CD8TLs: antigen experienced cells which have a strong tissue-homing and effector potential. This study investigated whether effector-memory cells also account for the CD8TL egress from peripheral blood following exercise. As latent Cytomegalovirus (CMV) infection is associated with a robust expansion in the number and proportion of effector-memory CD8TLs, we also investigated if CMV serostatus was a determinant of the CD8TL responses to exercise.

Fourteen males (Mean age 35, SD ± 14 yrs), half of whom were CMV seropositive (CMV^+), ran on a treadmill for 60 min at 80% $\dot{V}O_2$ max. Blood was collected at baseline, during the final minute of exercise, and 15 min and 60 min thereafter. CD8TL memory subsets were characterised by flow cytometry, using the cell-surface markers CD45RA, CD27, and CD28.

The results confirmed that CD8TLs with an effector-memory phenotype ($CD27^-CD28^-CD45RA^{+/-}$) exhibited the largest increase during exercise (+200% to +250%), and also showed the largest egress from blood 60 min post-exercise (down to 40% of baseline values). Strikingly, the mobilisation and subsequent egress of total CD8TLs was nearly twice as large in CMV^+ individuals. This effect appeared specific to CD8TLs, and was not seen for $CD4^+$ T lymphocytes or total lymphocytes. This effect of CMV serostatus was largely driven by the higher numbers of exercise-responsive effector-memory CD8TLs in the CMV^+ participants.

This is the first study to demonstrate that infection history is a determinant of immune system responses to exercise.

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1. Introduction

All mammals, including humans, have a remarkable capacity to acutely change the cellular composition of peripheral blood in response to psychological and physiological stressors (Dhabhar, 2000). For example, strenuous exercise causes a near-immediate mobilisation of lymphocytes into the blood, a process referred to as lymphocytosis (Gleeson and Bishop, 2005; McCarthy and Dale, 1988). This phenomenon is particularly marked for lymphocytes with a cytotoxic potential, such as Natural Killer cells, γδ T lymphocytes, and $CD8^+$ T lymphocytes (CD8TLs) (Anane et al., 2009). These subsets exhibit a high adrenergic receptor density and sensitivity, which in turn, regulates their detachment from vascular endothelium and release into the blood (Anane et al., 2009; Benschop et al., 1994; Dimitrov et al., 2010). Indeed, there is now conclusive evidence that stress and exercise-induced lymphocytosis is under the control of the sympathetic nervous system and the concomitant release of catecholamines (Benschop et al., 1994; Dimitrov et al., 2010; Elenkov et al., 2000).

One to two hours after high-intensity exercise, the lymphocytosis is followed by a lymphocytopenia whereby the numbers of circulating lymphocytes fall below baseline level (Gleeson and Bishop, 2005; McCarthy and Dale, 1988). Experimental studies in rodents suggest that this lymphocytopenia reflects extravasation to selected peripheral tissues, such as the lungs, presumably to enhance immunosurveillance in front-line tissues (Krüger et al., 2008; Krüger and Mooren, 2007). Consistent with this model, recent studies in humans have shown that exercise preferentially mobilises a subset of memory CD8TLs that have a strong tissue migrating potential and the capacity to induce rapid effector responses (e.g., target killing) (Campbell et al., 2009; Simpson et al., 2008, 2007a). It might therefore be predicted that these tissue-migrating memory cells would preferentially egress from peripheral blood post-exercise, but there is currently no data to support this contention.

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Subsets of CD8TLs have been identified on the basis of the combined expression of cell-surface markers such as CD45RA, CD27, and CD28 (Appay et al., 2002, 2008; Hamann et al., 1997; Romero et al., 2007) (see Table 1). In our study we used two phenotypic profiles to define effector memory sub-populations; comparing CD45RA and CD27 expression, or CD27 and CD28 expression (see Table 1). CD45RA is one of the isoforms of the leukocyte surface protein CD45. This RA isoform is present on naïve T cells and replaced by the isoform CD45RO after antigenic recognition. However, CD45RA is re-expressed on a subset of so-called 'revertant' memory cells, and this $CD45RA^{+}CD27^{-}$ phenotype is known to exhibit strong effector potential (such as the ability for rapid target killing, inflammatory cytokine production, and tissue migration, see Table 1). CD27 and CD28 are co-stimulatory and survival molecules that are co-expressed on naïve and early memory populations. However, during differentiation (i.e., a process characterised by the accumulation of effector functions), these markers are gradually lost and a $CD27^{-}CD28^{-}$ phenotype defines a population of late-differentiated effector-memory cells. $CD45RA^{+}CD27^{-}$ cells are themselves largely $CD28^{-}$ and there is therefore considerable overlap between these phenotypic profiles (Appay et al., 2008; Hamann et al., 1997; van Lier et al., 2003).

Individual differences in the proportions and numbers of the various CD8TL memory subsets are to a considerable extent determined by infection history (Chidrawar et al., 2009; Khan et al., 2002). For example, infection with Cytomegalovirus (CMV) causes a robust accumulation of late-differentiated effector-memory CD8TLs, which are characterised by loss of CD27 and CD28 expression, as well as frequent 'reversion' to expression of the naïve CD45RA isoform (Appay et al., 2002; van Lier et al., 2003). CMV is an endemic herpes virus which infects approximately 60% of western populations (Lubeck et al., 2010; Staras et al., 2006). In healthy individuals infection with CMV is usually asymptomatic and the virus remains latent in the body, but is believed to undergo intermittent reactivation (Stowe et al., 2007; Zanghellini et al., 1999). In view of research showing a selective mobilisation of effector-memory CD8TLs with exercise (Campbell et al., 2009), we investigated if CMV seropositive individuals demonstrated an exaggerated CD8TL exercise-response as a consequence of the accumulation of late-differentiated/effector-memory CD8TLs.

The aim of the current study was therefore to determine the pattern of egress of discrete CD8TL memory subsets following exercise and to compare this to the profile of mobilisation during exercise. Secondly, we aimed to determine if infection history is a determinant of this immune cell redistribution, with the specific aim to investigate if CMV serostatus influences the magnitude and kinetics of CD8TL mobilisation.

2. Methods

2.1. Participants

Participants were fourteen healthy non-smoking men (mean age = 35, SD ± 14; BMI; 24 ± 3 kg m^{-2}), who were accustomed to vigorous endurance exercise and had a cardio-respiratory fitness ($\dot{V}O_2$ max) within the 90th percentile for their age (Whaley et al., 2006). Participants provided informed consent, and the study was approved by the School of Sport and Exercise Sciences research ethics committee, of the University of Birmingham.

2.2. Procedures

Participants visited the laboratory to undergo two graded exercise tests on a treadmill. The first exercise test measured $\dot{V}O_2$ max by running to volitional exhaustion, to enable the intensity of the exercise trial to be prescribed relative to the fitness of each participant (i.e., 80% of $\dot{V}O_2$ max). A second test assessed the relationship between oxygen consumption ($\dot{V}O_2$) and four sub-maximal running speeds (range 8.2–11.6 km h^{-1}) to calculate the speed to elicit 80% of $\dot{V}O_2$ max, using linear regression. Breath-by-breath measurements were recorded every 5 s throughout both tests (Oxycon Pro, Jaegar, Germany), with heart rate monitored (RS200, Polar, Finland) and ratings of perceived exertion (RPE) (Borg, 1973) recorded during the final minute of each stage. In addition, participants had leisure time physical activity assessed using the international physical activity questionnaire (IPAQ) (Craig et al., 2003). IPAQ data was expressed as MET-minutes per week, where 1 MET (metabolic equivalent) is equal to resting metabolic rate (Ainsworth et al., 1993).

2.3. Exercise trial

One week after the preliminary tests, participants visited the laboratory for an exercise trial. Participants were instructed to refrain from exercising and drinking alcohol or caffeine during the day prior to the trial. After an overnight fast, participants reported to the laboratory between 06:00 and 07:00. Following a 15 min rest, a baseline blood sample (Pre) was collected from forearm vein by an indwelling catheter, which was kept patent by flushing regularly with saline.

The baseline sample was followed by the exercise trial, which consisted of treadmill running at a speed to elicit 80% of $\dot{V}O_2$ max for 60 min. Breath-by-breath measurements, heart rate and RPE were recorded for periods of 5 min at regular intervals. Blood samples were collected during the final minute of exercise (Ex60), and again 15 min (Post15) and 60 min (Post60) post-exercise. To address possible confounding of exercise results by diurnal variation in lymphocyte counts, seven participants also completed a control trial which involved sitting in the same room for 2 h, with all measures collected in an identical manner to the exercise trial. The order of the two trials was counterbalanced.

2.4. Flow cytometry

Blood was collected in ethylene-diamine-tetra-acetic acid (EDTA) vacutainer tubes (Becton–Dickinson, Oxford, UK) and samples were prepared within 3 h of collection. Briefly, whole blood was incubated with the following monoclonal antibodies for

Table 1
Phenotypic identification and functional properties of CD8TL ($CD3^{+}CD8^{+}$) subsets.

Cell description	Identification	Migration preference	Effector potential	Reference
Naïve	$CD45RA^{+}CD27^{+}$	Lymphoid tissue	–	Hamann et al. (1997), Romero et al. (2007)
Central memory (CM)	$CD45RA^{+}CD27^{-}$	Lymphoid tissue	–	Hamann et al. (1997), Romero et al. (2007)
Effector memory (EM)	$CD45RA^{-}CD27^{-}$	Peripheral tissue	+	Hamann et al. (1997), Romero et al. (2007)
$CD45RA^{+}$ effector memory (RAEM)	$CD45RA^{+}CD27^{-}$	Peripheral tissue	++	Hamann et al. (1997), Romero et al. (2007)
Early	$CD27^{+}CD28^{+}$	Lymphoid tissue	–	Appay et al. (2002)
Inter mediate (Inter)	$CD27^{+}CD28^{-}$	Peripheral tissue	+	Appay et al. (2002)
Late	$CD27^{-}CD28^{-}$	Peripheral tissue	++	Appay et al. (2002)

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