T cell homing and exercise

K. Krüger, F.C. Mooren

Department of Sports Medicine, Institute of Sports Sciences, Justus-Liebig-University, Giessen, Germany

Keywords: Lymphocytes, cell trafficking, surface receptors, chemokines, catecholamines, stress

ABSTRACT

Lymphocytes recirculate between the blood and lymph moving by routes that take them through various lymphoid and non-lymphoid organs in order to search for their cognate antigen. Naïve and effector/memory T cells provide distinct repertoires of receptors and ligands that constitute their ability to interact with the microvessels of different anatomical compartments and, consequently, have distinct patterns of migration. Lymphocyte migration from vascular to extravascular sites is a tightly controlled cascade of events, initiated by tethering and rolling interactions of lymphocytes on the endothelial surface. Local chemokines initiate in the activation of integrin adhesiveness, followed by firm arrest and endothelial transmigration.

Environmental stress induces a substantial re-distribution of T-cells within lymphoid and non-lymphoid organs. A uniform response pattern seems to exist with a decrease in lymphocyte numbers in the spleen which is accompanied by an increase in lymphocytes in lung, bone marrow and Peyer's patches. The alterations of the migration properties could be partially explained by adrenergic mechanisms which influence surface expression of adhesion molecules. Furthermore exercise and environmental stress result in a decreased expression of adhesion molecules, which might be the result of a selective mobilization of cells.

In conclusion, exercise stress induces a substantial re-distribution of T-cells within lymphoid and non-lymphoid organs. It can be hypothesized that these stress-induced effects on lymphocyte trafficking might enhance immune surveillance and vigilance. However, further investigations are crucially needed to gain more insights into the underlying mechanisms.

Address for correspondence
Prof. Dr. Frank C. Mooren, Department of Sports Medicine
Justus-Liebig University Giessen, Kugelberg 62, 35394 Giessen
Tel: 49-641-9925210, Fax: 49-641-9925219
e-mail: frank-christoph.mooren@sport.uni-giessen.de

INTRODUCTION

Exercise is known to induce characteristic alterations of blood lymphocyte counts. An initial lymphocytosis during exercise is followed by a lymphocytopenia in the recovery phase after exercise (Nieman et al. 1991). The initial rise of blood lymphocytes is supposed to reflect cell mobilization both from the marginal pool and from peripheral lymphoid organs (Gabriel and Kindermann, 1998, Hay and Andrade, 1998, Krüger et al. 2007). However, it remains unclear which mechanisms are responsible for the decrease of blood lymphocyte in the post-exercise period. Some studies presented evidence in which apoptosis plays a role in the post-exercise lymphopenia. Most investigators, however, have only found rather small apoptosis levels in the peripheral circulation suggesting that programmed cell death may not play the predominant role (Mars et al. 1998; Mooren et al. 2002, Steensberg et al. 2002, Mooren et al. 2004). Therefore, other processes, like lymphocyte trafficking and redistribution, which may be involved in the quantitative changes of blood lymphocytes during and after exercise stress, have to be considered as well.

Lymphocyte trafficking describes the movement and migration of lymphocytes throughout the various lymphoid and non-lymphoid compartments on their search for pathogens or antigens. It is a highly regulated process which is determined by tissue-specific guidance signals expressed by the endothelial cells of postcapillary venules, combined with counterreceptors expressed by the circulating lymphocytes. The expression of these signals and receptors is, in turn, dependent on activation status and is orchestrated by a number of different signalling molecules such as hormones, cytokines and chemokines (Stefanski et al. 2003, Kunkel et al. 2003, Krüger et al. 2007).

Within this review we will give (i) an overview about routes and migration pathways of lymphocytes, (ii) how lymphocyte trafficking and homing is regulated, (iii) and how exercise and exercise associated signalling mechanisms affect lymphocyte recirculation and homing.

Lymphocyte recirculation

Lymphocyte trafficking between the blood and the tissues is pivotal for normal immune responses. It allows highly efficient contacts between the lymphocytes and pathogen-derived antigens, which may enter the body via a variety of routes (Ebert et al. 2005). These antigens are invariably delivered to the secondary lymphoid tissues, such as the lymph nodes (LNs), Peyer's patches (PPs), and spleen, where they are detected by recirculating lymphocytes. A coordinated course of the immune response is initiated by following specific cell-cell contacts with antigen-presenting cells as well as cell-matrix interactions (Mackay, 1991, Butcher and Picker 1996, Sallusto et al. 2000, Moser et al. 2001).

Thereby, lymphocyte traffic seems to occur on different routes and the respective pathway a single T cell uses for migration depends on maturation and activation status. Naïve and effector/memory T cells express a distinct pattern of receptors and ligands which influence their trafficking routes. It has recently been suggested that the pattern of expression of the receptors CCR7 and CD45RA divides human T cells into distinct subsets (Sallusto et al. 1999). The naïve T cells (T_N) express both CCR7 and CD45RA and preferentially migrate to secondary

lymphoid organs like the LNs, the PPs and the spleen (Fig. 1). These organs represent the sites where antigen-loaded dendritic cells (DCs) present antigen-peptide-MHC-complexes to naïve T-cells and provide appropriate co-stimulatory signals for immune response initiation (Ebert et al. 2005). Once their cognate antigen is presented, T-cells become activated and differentiate into memory/effector T-cells.

Antigen-experienced T cells are more diverse than naïve T cells with respect to their migratory properties. In particular, these cells can be subdivided as either central memory cells (T_{CM}), effector memory cells (T_{EM}) or effector T cells (T_{EFF}). T_{CM} cells lack immediate effector functions, whereas they can rapidly respond to antigens upon re-encounter. Regarding their homing properties, T_{CM} cells are $CD45RA^-$ and $CCR7^+$ and preferentially migrate into the secondary lymphoid organs and the bone marrow. Lymphocyte access to most secondary lymphoid organs is tightly controlled by specialized vessel walls, the high endothelial venules (HEVs). HEVs are present in the LNs, the PPs, the tonsils, the appendix and bronchus and nasal-associated lymphoid tissues. The lumen of HEVs is lined by tall and cuboidal endothelial cells with an irregular surface which contributes to turbulent blood flows within the vascular microdomains, thereby promoting margination of lymphocytes along the vessel wall. HEVs share common features with ordinary venules except for expressing tissue-specific adhesion molecules for naïve lymphocytes (Streeter et al. 1988). HEVs in peripheral lymph nodes (pLNs) express peripheral lymph nodes addressins (PNAd), whereas those in the PPs express mucosal addressin cell adhesion molecule-1 (MAdCAM-1) (Streeter et al. 1988, Nakache et al. 1989).

In contrast to T_{CM} cells, T_{EM} and T_{EFF} cells are $CCR7^-$ and cannot efficiently recirculate through the LNs or the PPs. Instead, both cell types migrate to peripheral and non-lymphoid tissues where they can provide an efficient cytotoxic activity (Fig. 1) (Masopust et al. 2001, Weninger et al. 2001). Major T_{EFF} and T_{EM} subsets show a remarkable migratory selectivity for certain tissues like the gut or the skin depending on their receptor expression. The site of antigen entry strongly influences the trafficking properties of T_{EFF} and T_{EM} cells. Therefore, these T cell subsets are thought to be the only cell types which show a peripheral tissue tropism depending on the origin of the presented antigens (Mora and van Adrian 2006).

Accordingly, lymphocyte trafficking is a highly subset specific process and is based on the expression of multiple "address codes" on migrating T cells as well as on stationary endothelial cells that allow the extravasation through the vessel wall. This process includes a number of different steps which are under the control of specific adhesion molecules, including selectins, integrins and addressins, corresponding vascular ligands as well as the large family of chemokines and their receptors (Ebert et al. 2005).

Regulation of lymphocyte trafficking: The homing process

A number of well characterized signalling events serve as mediators of the lymphocyte-endothelium interaction thereby promoting the lymphocyte entry into lymphoid and non-lymphoid tissues. The site-specific transmigration through the endothelium includes a cascade of several steps, which start with the tethering and rolling of circulating lymphocytes at the vessel walls of target tissues. The

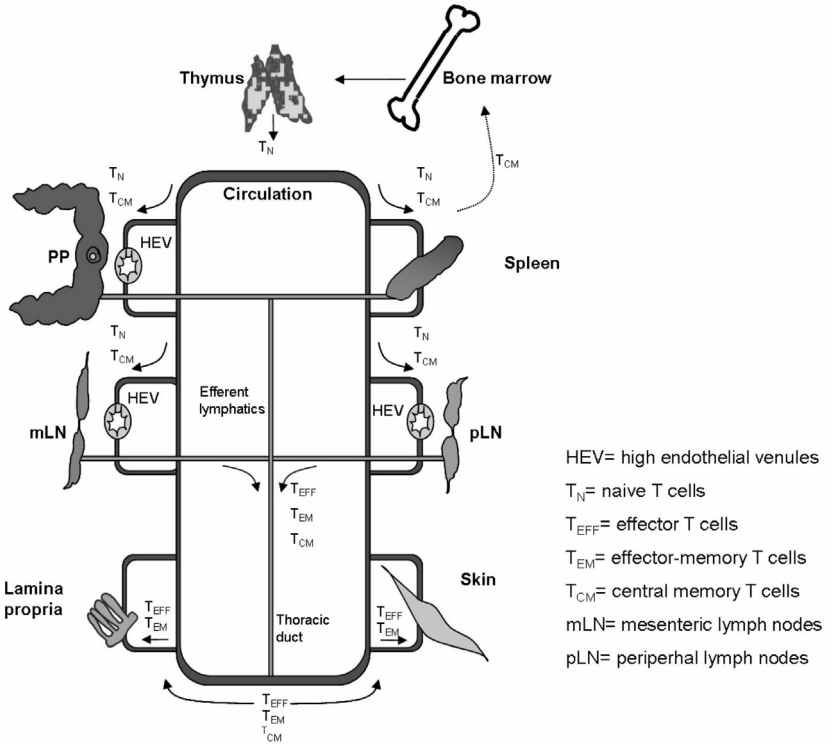

Fig. 1:
Trafficking routes of different T lymphocyte subsets through the lymphoid and non-lymphoid organs. Naïve T cells (T_N) preferentially migrate to secondary lymphoid organs like Peyer's patches (PP), spleen, mesenteric and peripheral lymph nodes (pLN and mLN). When entering lymph nodes and the PPs, T_N transmigrate through specialized vessels, the high endothelial venules (HEVs). The secondary lymphoid organs are places where T cells first meet their cognate antigen.
Migration properties of antigen-experienced T cells are more diverse and depend on the subtypes. Central memory T cells (T_{CM}) efficiently migrate into secondary lymphoid organs similar to T_N. In contrast, effector memory cells (T_{EM}) and effector T cells (T_{EFF}).migrate to a greater extent to non-lymphoid tissues like skin or lamina propria.

reversible step of rolling is mediated primarily by the three members of the selectin family, known as E-, P- and L-selectin (CD62E, CD62P and CD62L). L-selectin is expressed on the surface of lymphocytes whereas E- and P- selectin are expressed on endothelial cells (Fig. 2) (Kansas 1996). P-selectin glycoprotein ligand 1 (PSGL1) is the dominant ligand for all three selectins. Selectins are the most effective molecules which promote tethering and rolling likewise during conditions of higher fluid shear stress. In addition to PSGL1, E selectin also binds to CD44 (Hidalgo et al. 2007). CD44, the hyaluronan receptor, has been shown to function primarily by supporting lymphocyte rolling at inflammatory sites (Stoop et al. 2002).

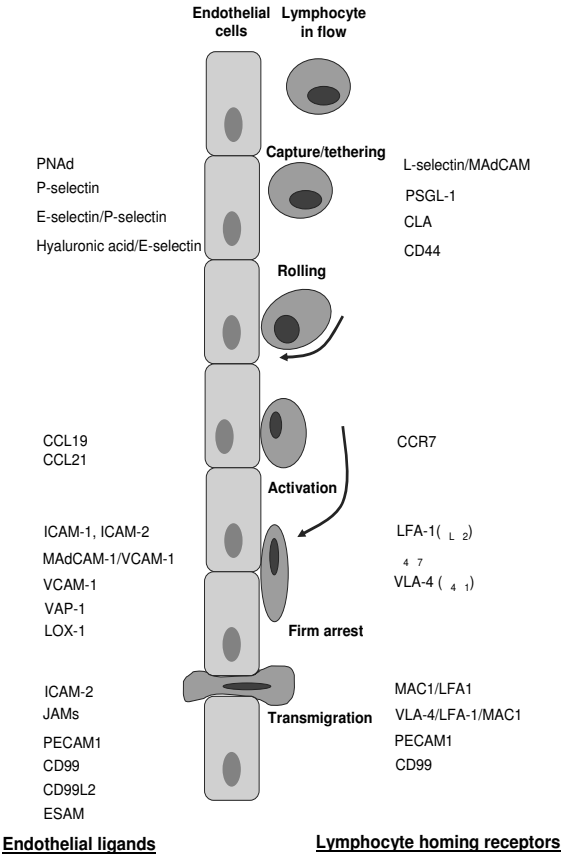

Fig. 2:
Lymphocyte recruitment from the blood stream requires adhesion and transmigration through the vessel walls. The site specific interaction with the endothelium depends on a cascade of events starting with capture, tethering and rolling of lymphocytes at the vessel wall. A number of well characterized adhesion molecules and their ligands serve as mediators of these processes. L-, E- and P-selectins and their interactions with PNAd, CLA and PSGL-1 are the most effective homing receptors and ligands which induce tethering and rolling of lymphocytes in flow. Lymphocyte firm arrest is rapidly triggered by chemokines and mediated by immunoglobulin superfamily members, such as ICAM1 and VCAM, expressed by endothelial cells. Transendothelial migration is the final step of lymphocyte migration. It is suggested, that ICAMs and junctional adhesion molecules (JAMs) are involved.

Next, integrins $\alpha_4\beta_7$, VLA-4 and LFA-1 mediate rolling and firm adhesion of lymphocytes (Chan et al. 2001). Among the integrins, $\alpha_4\beta_7$ and LFA-1 mediate rolling which is performed with the former molecule with relatively high efficiency, whereas the latter one has limited capacity. VLA-4 mediated rolling is optimal only after prior activation (Sigal et al. 2000, Grabovsky et al. 2000).

Lymphocyte activation and arrest is rapidly triggered by chemokines and mediated by the binding of the integrins VLA-4 and LFA-1 to intracellular adhesion molecule-1 (ICAM1) and vascular cell-adhesionmolecule 1 (VCAM-1) on endothelial cells (Fig.2) (Chan et al. 2004). Chemokines are the master controllers of lymphocyte migration. They are primarily secreted proteins of 67-127 amino acids which are grouped into two major subfamilies according to the arrangement of two NH2-terminal Cys residues, which are either separated by a single amino acid (CxC) or are in adjactent positions (CC). Functionally,

chemokines can be devided into three goups, inflammatory, homeostatic and dual-function chemokines, which participate in both tasks. In this review we will focus on homeostatic chemokines, which navigate lymphocytes during hematopoesis, initiation of an adaptive immune response and in immune surveillance. CXCR4 is the only chemokine receptor with ubiquitous expression in precursor and mature leukocytes suggesting a general function in leukocyte homeostasis. T cell associated chemokines are CCR7 and on subsets CXCR3, CXCR6, CXCR7, CCR9 and CCR5. Some of their ligands include CCL16, CCL19, CCL21 and CXCL13 (Moser et al. 2004). Chemokines are the most relevant physiological activators of integrin mediated adhesion and can rapidly regulate integrin avidity (Constantin et al. 2000). Transmigration through the venular walls is the final step of the process of lymphocyte emigration into secondary lymphoid organs or extra-lymphoid tissues. It involves a penetration of the endothelial-cell barrier and its associated basement membrane and occurs with a minimal disruption of the barriers structure. The exact molecular mechanisms of transendothelial migration in HEVs are not fully understood. It is suggested, that molecules including ICAMs and junctional adhesion molecules (JAMs), located in interendothelial junctions, are involved (Fig. 2) (Engelhardt and Wolburg, 2006).

Some of these homing receptors mediate tissue-specific lymphocyte homing. L-selectin seems to be predominantly involved in homing to the LNs. L-selectin is characteristically expressed by naïve lymphocytes and T_{CM} cells which continuously migrate through the secondary lymphoid organs until antigen exposure. Accordingly, L-selectin ligands are constitutively expressed on HEVs. One of the most important ligands is the peripheral lymph node addressin (PNAd), which is permanently expressed on HEVs and ensures the homing of naïve T cells and T_{CM} to LNs. In addition, L-selectin can bind to mucosal vascular cell-adhesion molecule-1 (MAdCAM-1), which is expressed on HEVs in the GALT and also contributes to the migration of lymphocytes to the gut (Mora et al. 2006). In contrast to naïve lymphocytes and T_{CM}, expression of L-selectin is typically lower on T_{EM} and T_{EFF} cells. Instead, these cells express high levels of $\alpha_4\beta_7$, which has been identified for mediating homing to the gut-associated lymphoid tissues (GALT) via binding to the endothelial ligand MAdCAM-1 (Streeter 1988).

The chemokines CCL19 and CCL21 are constitutively expressed in secondary lymphoid tissue and mediate the recruitment of naïve lymphocytes and T_{CM} cells to these sites (Cyster, 1999, Campbell and Butcher, 2000, Von Andrian and Mempel, 2003). CCL21 chemokine is displayed on the luminal surfaces of HEVs and interacts with CCR7 chemokine receptors expressed on naïve lymphocytes and T_{CM} cells. CCR9 is prominently present on small intestinal T cells which are recruited by its ligand CCL25. Furthermore, chemokine activation increases the affinity of LFA-1 for the endothelial ligands ICAM-1 and ICAM-1, which have a redundant function during trafficking across the HEVs (van Andrian & Mempel 2003).

Influence of environmental stress on lymphocyte recirculation

Since there are just a few studies available on the effects of exercise stress on lymphocyte recirculation, we expanded the scope of this section to other forms of stress such as psychological or thermal stress. This seems to be an appropriate approach because it is well known that organisms respond to various forms

of stress in a stereotype manner. One reason could be that many physical stressors, like surgery, burn, trauma and sepsis, induce a pattern of hormonal responses which are similar to that of exercise (Hoffman-Goetz and Pedersen 1994).

At first recent study by Atanackovic et al. (2006) showed that acute psychological stress induces a decrease in the peripheral numbers of T_N and T_{CM} –cells. In contrast, a prolonged increase in T_{EM} cells was observed. Therefore, the mobilized cells seem to be primarily antigen-experienced cells which might have an important impact on the recirculation-pattern of T cells during stress. Furthermore, acute stress seems to promote the retention of less mature T cells within the lymphoid organs.

Many studies consistently show that the spleen acts as a donor organ by releasing lymphocytes during stress. Dominguez-Gerpe et al. (2001) used immobilization stress to determine stress-induced lymphocyte redistribution. They detected a decreased cellularity in the spleen. Krynicki & Olszewksi (1989) used thermal stress to provoke changes in lymphocyte migration patterns. They also found significantly less lymphocytes in the spleen. Stefanski et al. (2003) used models of social stress to affect the migration of blood T cells into lymphoid organs. The social stress was induced by placing male rats into the home cage of a resident opponent, which was followed by a decrease of ^{51}Cr labelled blood T cells in the spleen and in the mesenteric and cervical LNs.

Information about exercise induced changes of lymphocyte numbers in lymphoid organs is still limited. Nielsen et al. (1997) showed an impaired T cell mobilization into the blood in splenectomised subjects during endurance exercise. In contrast, Iversen et al. (1994) observed that splenectomy was without effect on the increase of most leukocyte subtypes after short-lasting exercise (Iversen et al. 1994). Although we hypothesize that the spleen is a source of mobilized lymphocytes during exercise. Using the mouse model we could demonstrate an intensity-dependent decrease of lymphocytes in the spleen after treadmill exercise. Furthermore, this decrease was accompanied by an increase of lymphocyte numbers in the blood (Fig. 3, Krüger et al. 2007).

Bone marrow seems to be a place for lymphocytes to accumulate during stress. In the social stress model an increase of T cells in the bone marrow was detected, which was confirmed by Krynicki and Olszewski (1989) using the thermal stress model. Similarly, we could define the bone marrow as an acceptor region for lymphocytes during exercise (Fig. 3, Krüger et al. 2007). It has been observed, that immobilization stress in mice triggers specialized T-cell regulators of erythro-, granulo- and monocytopoiesis to accumulate in the bone marrow (Dygai et al. 1988, Goldberg et al. 1990). Therefore, the interaction of T cells with the hematopoietic tissue in the bone marrow might be an important prerequisite for the production of granulocytes and erythrocytes (Shakhov et al. 1988). As hypothesized by Cohen and Crnic (1984), migration of T cells in the bone marrow could be an adaptive mechanism in stressful conditions in order to stimulate the production of granulocytes and erythrocytes.

In addition we could show that exercise stress induced a redistribution of lymphocytes into the lung (Fig. 3, Krüger et al. 2007). This might be an adaptation to increased ventilation during exercise which means an enhanced probability of contacting numerous potentially harmful agents. Therefore, the exercise

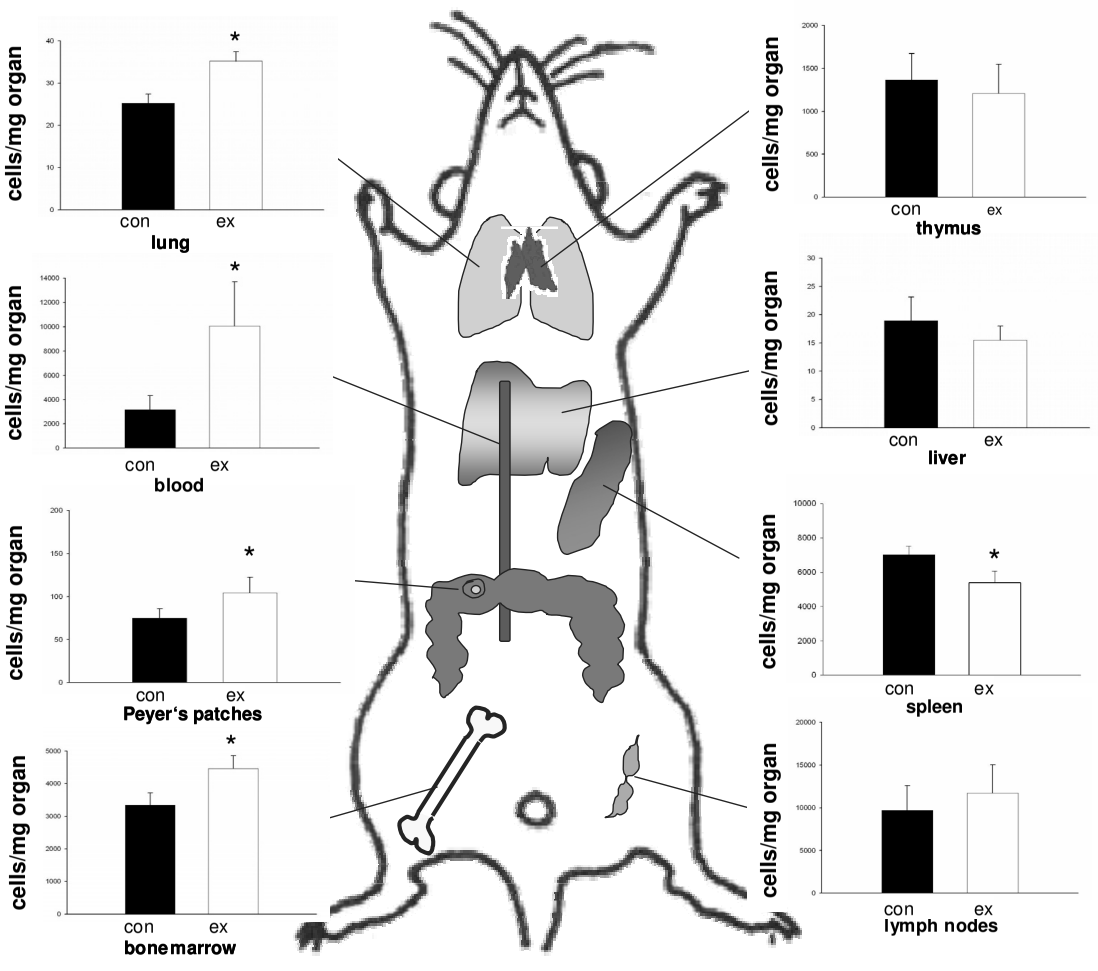

Fig. 3:
Effect of exercise on the distribution pattern of labelled T cells in lung, blood, PPs, bone marrow, thymus, liver, spleen and LNs. Mice performed an intensive running test at 80%VO_{2max} until exhaustion Using fluorescent cell tracking and flow cytometry we observed a release of T-cells from the spleen, while lung, bone marrow and Peyer's patches served as target organ. * indicates significant differences compared to control animals ($P \leq 0.05$). Data from Krüger et al. 2007.

stimulus might induce an enhanced activation of T cells followed by an amplified trapping of lymphocytes within the lung (Hamann et al. 2000).

Finally, the PPs seem to be another acceptor region for lymphocytes after environmental stress (Fig. 3, Krüger et al. 2007). Conditions of febrile temperature, as usually associated with infection or inflammation, are followed by an increased lymphocyte entry into secondary lymphoid organs (Chen et al. 2006). If mice or cancer patients are exposed to whole body hyperthermia (WBH) a decrease of blood lymphocytes has been observed (Kraybill et al. 2002, Evans et al. 2001). In mice these alterations were associated with an accumulation of T cells in the PPs (Evans et al. 2001). Similar shifts were provoked in our mice exercise model (Krüger et al. 2007). Since exercise can induce a 1-4°C increase in body temperature through an increased metabolic heat production, similar mechanisms might be operating (Brenner et al. 1998). Recently, it was shown that hyperthermia as well as exercise heat stress produce a gastrointestinal barrier dysfunction and an increase of gastrointestinal permeability (Lambert, 2004). This may allow endotoxin to enter the internal environment and causing local and even systemic immune responses (Sakurada and Hales, 1998).

As a conclusion, the redistribution of T cells into the target organs lung and PPs might increase the capacity of the immune system in immune compartments, which serve as major defence barriers of the body (Dhabhar et al. 1995). During psychological stress, effector -type T cells are primarily mobilized in order to rapidly migrate into these tissues (Atanackovic et al. 2006). Stress researchers hypothesize a rapid but transient redistribution of leukocytes to enhance immune surveillance. This would help stressed individuals to accumulate a greater number of antigene- experienced lymphocytes at sites of potential immune challenge even before the challenge is administered. In psychological stress models this activation of the sympathetic nervous system and its crosstalk to the immune system metaphorically means that the organism is preparing for “flight and fight”. A similar meaning could be true for exercise. Especially in the early response to an attack, activation of the immune response and redistribution of cells seems to be an adaptive change that might guarantee the survival of an individual (Engler et al 2004).

Signalling mechanisms during stress alter lymphocyte trafficking and homing

Lymphocyte trafficking is under the control of a network of surface ligands and receptors as described above (Butcher and Picker, 1996). Recent observations of lymphocyte distribution patterns during environmental stress suggest that signalling molecules of the autonomous nervous system and the endocrine system also play an essential role in the regulation of lymphocyte homing (Dhabhar et al. 1995, Engler et al. 2004). This includes catecholamines acting via α- and β- adrenoceptors which are also expressed by lymphocytes. During environmental stress the plasma concentrations of epinephrine and norepinephrine increase substantially in an intensity dependent manner (Mastorakos et al. 2005). Numerous studies have shown that numbers of lymphocyte subsets can be dramatically altered by catecholamines (Mills et al. 1995, Murray et al. 1992).

A peripheral rise of catecholamines during acute stress is accompanied by dose-dependent increases of circulating lymphocyte counts (Bosch et al. 2003,

Stefanski et al. 2000). Moreover, adrenalectomy has been shown to virtually eliminate the stress-induced redistribution of blood leukocytes in rats (Dhabhar et al. 1996). A few studies have investigated the influence of catecholamines on lymphocyte numbers in lymphoid organs. Madden et al. (1994) showed an enhanced lymphocyte homing to pLNs in catecholamine depleted mice. Kradin et al. (2001) and our group observed reduced numbers of lymphocytes in the spleen after application of both epinephrine (Kradin et al. 2001) and norepinephrine (Krüger et al. 2007). Furthermore, we were able to show that the application of adrenergic-receptor antagonists nadolol and phentolamine attenuates the exercise-induced mobilization of splenic lymphocytes in mice (Krüger et al. 2007).

In contrast, some exercise-induced changes of lymphocyte redistribution do not seem to be influenced by catecholamines. Neither applications of epinephrine nor norepinephrine could mimic the exercise-induced increase of lymphocytes in the PPs and the bone marrow (Krüger et al. 2007). This suggests that alternative signalling mechanisms, such as glucocorticoids, are at work. Atanackovic et al. (2006) observed a higher expression of glucocorticoid receptors on $CCR7^-$ -cells compared to $CCR7^+$ -cells on RNA level. Thus, glucocorticoids might play a role in the selective increase in effector T cells during stress. The role of glucocorticoids has been the objective of a recent study of Sudo et al. (1997). They observed a stress-induced increase in numbers and proportions of T-lymphocytes in the bone marrow after restraint stress, which could partly be blocked by RU486, a glucocorticoid receptor antagonist. Since cortisol is known to increase during prolonged intensive exercise, a mechanism such as this might be operative during exercise, too (Urhausen and Kindermann, 1987).

A major mechanism by which hormonal mediators might affect lymphocyte homing could be the alteration of homing receptors and adhesion molecules expression. The action of catecholamines is thought to change the surface density or avidity state of these specific molecules, thereby modulating adhesion forces and promoting the detachment of previously adherent cells. There is evidence that catecholamines influence the surface expression of adhesion molecules through the cyclic-adenosine-monophosphate (cAMP) second messenger system (Levitzki et al. 1988, Shephard 2003), whereas it is currently unknown which adhesion receptors are targeted by this mechanism. However, the detection of surface receptor expression provides some methodological pitfalls. Expression changes of surface receptor and adhesion molecules during environmental stress could reflect several processes such as shedding of molecules, selective apoptosis or differential mobilization and trafficking of cells with a particular phenotype. Furthermore, effects from mechanical deformation or changes in the induction of adhesion molecules might influence surface expression. Accordingly, a simple measurement of surface markers provides limited information.

There is evidence that during exercise specific lymphocyte phenotypes are mobilized which are characterized by specific sets of adhesion molecules. It is assumed that exercise mobilizes predominantly cells which express high levels of LFA-1 and low levels of CD62L. Furthermore, following exercise there seems to be a selective removal of the same cells (Gabriel et al. 1994, Kurokawa et al. 1995, Gannon et al. 2004). In addition, Nielsen et al. (2004) observed a decreased percentage of CD62L expression after marathon and half marathon

run. This decrease was accompanied by an increase in levels of soluble CD62L which indicates a shedding of adhesion molecules. Furthermore, similar changes in L-selectins were observed after acute psychological stress (Redwine et al. 2003).

Surface expression of ICAM-1 increased in most studies immediately after exercise. A significant decrease of cells expressing ICAM-1 was observed later in the post-exercise period, suggesting an extravasation of these cells out of the blood (Gannon et al. 2001, Jilma et al. 1997, Nielsen et al. 2004, Simpson et al. 2006). Additionally, levels of soluble ICAM-1 levels were elevated immediately after exercise and returned to baseline values after 1h of rest, too (Rehman et al. 1997). The treatment with the β-adrenergic receptor antagonist propranolol reduces the exercise induced increase in soluble ICAM-1 -levels. This suggests that catecholamines modify binding kinetics of ICAM-1 during exercise and lead to a shedding of this adhesion molecule, resulting in a detachment of lymphocytes (Rehman et al. 1997). During thermal stress, Chen et al. (2006) observed an increased vascular density of ICAM-1, which augmented the capture efficiency of HEVs and increased the entry of lymphocytes into lymphoid organs. Accordingly, they identified the HEVs as potentially thermally sensitive alert system.

Furthermore, during the past decade, the important role of vascular adhesion molecules in artherosclerosis has been discovered and it is now recognized as a critical factor in disease initiation and progression (Galkina et al. 2007). In this connection some studies investigated the impact of regular exercise training of adhesion molecules and endothelial function. In obese men and diabetics a reduction of sICAM-1 was found after daily aerobic training (Roberts et al. 2006). Furthermore, Schumacher et al. (2006) found inverse correlation of physical fitness with levels of sICAM-1 and sVCAM-1. These observations provide evidence for the beneficial antiatherogenic effect of regular exercise.

Finally, the role of constitutive homeostatic chemokines and their influence on lymphocyte trafficking during environmental stress should be addressed, although there are only limited data available. Most studies so far reported on exercise induced changes of inflammatory chemokines such as interleukin-8, MCP-1 or RANTES, for which the interested reader is referred to some recently published excellent reviews (Suzuki EIR 2002). In a recent study Okutsu et al. (2005) showed that cortisol augments CXCR4 expression on T lymphocytes. This observation suggests that endogenous glucocorticoids induced by exercise or stress may modify lymphocyte trafficking by up-regulating the level of chemokine receptor CXCR4 on T-cells. Another factor responsible for a change of CXCR4 expression might be oxygen tension. Recently, it could be demonstrated that CXCR4 is up-regulated after ischemic or subischemic training programs. It remains to be shown, whether these regulations of CXCR4 might be involved in the mechanisms responsible for post-exercise lymphopenia (Okutsu et al. 2005).

As a conclusion, environmental stress influences redistribution and homing of specific lymphocyte phenotypes. The expression of specific adhesion molecules and surface receptors is critical for selective trafficking of lymphocytes and might be at least partially influenced by adrenergic mechanisms. There is emerging evidence for specific distribution patterns of cells during exercise stress. Cells

seemed to be primarily released by donor organs such as spleen and on the other hand accepted in target organs such as bone marrow, lung and PPs. In conclusion, exercise stress induces a substantial re-distribution of T-cells within lymphoid and non-lymphoid organs. It can be hypothesized that these stress induced effects on lymphocyte trafficking might enhance immune surveillance and vigilance. However, further investigations are crucially needed to gain more insights into the underlying mechanisms.

REFERENCES

Atanackovic D, Schnee B, Schuch G, Faltz C, Schulze J, Weber CS, Schafhausen P, Bartels K, Bokemeyer C, Brunner-Weinzierl MC, Deter HC. Acute psychological stress alerts the adaptive immune response: stress-induced mobilization of effector T cells. J Neuroimmunol. 176(1-2):141-52, 2006.

Bosch J.A., Berntson G.G., Cacioppo J.T., Dhabhar F.S., Marucha P.T.Acute stress evokes selective mobilization of T cells that differ in chemokine receptor expression: a potential pathway linking immunologic reactivity to cardiovascular disease. Brain Behav Immun. 17(4):251-9, 2003.

Brenner, I., Shek, P.N., Zamecnik, J., Shephard; R.J.Stress hormones and the immunological responses to heat and exercise. Int. J. Sports Med. 19(2), 130-43, 1998.

Butcher, E.C., Picker, L.J.. Lymphocyte homing and homeostasis. Science. 272, 60-6, 1998.

Campbell J.J., Butcher E.C.. Chemokines in tissue-specific and microenvironment-specific lymphocyte homing. Curr Opin Immunol. 12(3):336-41, 2000.

Chan J.R., Hyduk S.J., Cybulsky M.I. Chemoattractants induce a rapid and transient upregulation of monocyte alpha4 integrin affinity for vascular cell adhesion molecule 1 which mediates arrest: an early step in the process of emigration. J Exp Med. 21;193(10):1149-58, 2001.

Chen Q, Fisher DT, Kucinska SA, Wang WC, Evans SS.Dynamic control of lymphocyte trafficking by fever-range thermal stress. Cancer Immunol Immunother. 55(3):299-311, 2006.

Cohen, J.J., Crnic, L.S. Behaviour, stress, and lymphocyte recirculation. In: Cooper, E.L.: Stress, Immunity, and Aging, Immunology Series, vol. 24. Marcel Dekker, New York, pp. 73-80, 1984.

Constantin G., Majeed M., Giagulli C., Piccio L., Kim J.Y., Butcher E.C., Laudanna C. Chemokines trigger immediate beta2 integrin affinity and mobility changes: differential regulation and roles in lymphocyte arrest under flow. Immunity. 13(6):759-69, 2000.

Cyster J.G.. Chemokines and cell migration in secondary lymphoid organs. Science 286(5447):2098-102, 1999.

Dhabhar, F.S. Stress, leukocyte trafficking, and the augmentation of skin immune function. Ann. N. Y. Acad Sci. 992, 205-17, 2003.

Dhabhar F.S., Miller A,H,, McEwen B,S,, Spencer R,L.Stress-induced changes in blood leukocyte distribution. Role of adrenal steroid hormones. J Immunol. 15;157(4):1638-44, 1996.

Dhabhar, F.S., McEwen, B.S. Enhancing versus suppressive effects of stress hormones on skin immune function. Proc. Natl. Acad. Sci U S A. 96, 1059-64, 1999.

Dhabhar, F.S., Miller, A.H., McEwen, B.S., Spencer, R.L.Effects of stress on immune cell distribution. Dynamics and hormonal mechanisms. J Immunol 15;154(10):5511-27, 1995.

Domínguez-Gerpe L, Rey-Méndez M. Alterations induced by chronic stress in lymphocyte subsets of blood and primary and secondary immune organs of mice. BMC Immunol. 2:7, 2001.

Dygai, A.M., Mikhlenko, A.V., Shakhov, V.P. The role of T-lymphocytes in regulating the processes of proliferation of the cellular elements in erythro- and granulocytopoiesis in stress. Patol Fiziol Eksp Ter. 2, 48-51, 1988.

Ebert, L.M., Schaerli, P., Moser B. Chemokine-mediated control of T cell traffic in lymphoid and peripheral tissues. Mol Immunol. 42(7):799-809, 2004.

Engelhardt B., Wolburg H. Mini-review: Transendothelial migration of leukocytes: through the front door or around the side of the house? Eur J Immunol. 34(11):2955-63, 2004.

Engler H., Bailey M.T, Engler A., Sheridan J.F. Effects of repeated social stress on leukocyte distribution in bone marrow, peripheral blood and spleen. J Neuroimmunol. 148(1-2):106-15, 2004.

Evans, S.S., Wang, W.C., Bain, M.D., Burd, R., Ostberg, J.R., Repasky, E.A.. Fever-range hyperthermia dynamically regulates lymphocyte delivery to high endothelial venules. Blood 97, 2727–2733, 2001.

Gabriel H. H., and W. Kindermann. Adhesion molecules during immune response to exercise. Can J Physiol Pharmacol. 76(5):512-23, 1998.

Galkina E, Ley K. Vascular adhesion molecules in atherosclerosis. Arterioscler Thromb Vasc Biol. 27(11):2292-301, 2007.

Gannon GA, Rhind SG, Shek PN, Shephard RJ. Differential cell adhesion molecule expression and lymphocyte mobilisation during prolonged aerobic exercise. Eur J Appl Physiol.84(4):272-82, 2001.

Goldberg, E.D., Dygai, A.M., Zakharova, O., Shakhov, V.P.The modulating influence of enkephalins on the bone marrow haemopoiesis in stress. Folia Biol. (Praha). 36, 319-31, 1990.

Grabovsky V, Feigelson S, Chen C, Bleijs DA, Peled A, Cinamon G, Baleux F, Arenzana-Seisdedos F, Lapidot T, van Kooyk Y, Lobb RR, Alon R. Subsecond induction of alpha4 integrin clustering by immobilized chemokines stimulates leukocyte tethering and rolling on endothelial vascular cell adhesion molecule 1 under flow conditions. J Exp Med. 21; 192(4):495-506, 2000.

Hamann A., Klugewitz K., Austrup F., Jablonski-Westrich D. Activation induces rapid and profound alterations in the trafficking of T cells.Eur. J. Immunol. 30, 3207-18, 2000.

Hay J.B., and W.N. Andrade. Lymphocyte recirculation, exercise, and immune responses. Can J Physiol Pharmacol. 76(5):490-6, 1998.

Hidalgo A., Frenette P.S. Leukocyte podosomes sense their way through the endothelium. Immunity. 26(6):753-5, 2007.

Hoffman-Goetz L, Pedersen BK. Exercise and the immune system: a model of the stress response? Immunol Today 15(8):382-7, 1994.

Iversen PO, Arvesen BL, Benestad HB. No mandatory role for the spleen in the exercise-induced leucocytosis in man. Clin Sci (Lond) 86(5):505-10, 1994.

Jilma B., Eichler H.G., Stohlawetz P., Dirnberger E., Kapiotis S., Wagner O.F., Schütz W., Krejcy K. Effects of exercise on circulating vascular adhesion molecules in healthy men. Immunobiology. 197(5):505-12, 1997.

Kansas G.S.. Selectins and their ligands: current concepts and controversies. Blood. 1996 Nov 1;88(9):3259-87, 1996.

Kradin R., Rodberg G., Zhao L.H., Leary C.Epinephrine yields translocation of lymphocytes to the lung. Exp Mol Pathol. 70(1):1-6, 2001.

Kraybill, W.G., Olenki, T., Evans, S.S.,Ostberg, J.R., O'Leary, K.A., Gibbs, J.F., Repasky, E.A.. A phase I study of fever-range whole body hyperthermia (FR-WBH) in patients with advanced solid tumours: correlation with mouse models. Int. J. Hyperthermia 18, 253–266, 2002.

Krüger K., Lechtermann, A., Fobker, M., Völker K, Mooren F.C.Exercise-induced redistribution of T lymphocytes is regulated by adrenergic mechanisms. Brain Behav Immun. 29, 2007

Krynicki, M., Olszewski, W.L., Influence of thermal stress on lymphocyte migration pattern in rats. Arch. Immunol. Ther. Exp. (Warsz). 37, 601-7, 1989.

Kunkel, E.J., Campbell, D.J., Butcher, E.C.. Chemokines in lymphocyte trafficking and intestinal immunity. Microcirculation. 10(3-4):313-23, 2003.

Kurokawa Y., Shinkai S., Torii J., Hino S., Shek P.N. Exercise-induced changes in the expression of surface adhesion molecules on circulating granulocytes and lymphocytes subpopulations. Eur J Appl Physiol Occup Physiol. 71(2-3):245-52, 1995.

Lambert G.P.Role of gastrointestinal permeability in exertional heatstroke. Exerc. Sport Sci. Rev. 32, 185-90, 2004. .

Levitzki A. From epinephrine to cyclic AMP. Science. 12;241(4867):800-6, 1988.

Madden K.S., Felten S.Y., Felten D.L., Hardy C.A., Livnat S.Sympathetic nervous system modulation of the immune system. II. Induction of lymphocyte proliferation and migration *in vitro* by chemical sympathectomy. J Neuroimmunol. 49(1-2):67-75, 1994.

Mars, M., Govender, S., Weston, A., Naicker, V., Chuturgoon A.High intensity exercise: a cause of lymphocyte apoptosis? Biochem. Biophys. Res. Commun. 249, 366-70, 1998.

Masopust D., Vezys V., Marzo A.L., Lefrançois L. Preferential localization of effector memory cells in nonlymphoid tissue. Science. 23;291(5512):2413-7, 2001.

Mastorakos G., Pavlatou M., Diamanti-Kandarakis E., Chrousos G.P.Exercise and the stress system. Hormones (Athens). 4(2):73-89, 2005.

Mills P.J., Berry C.C., Dimsdale J.E., Ziegler M.G., Nelesen R.A., Kennedy B.P.Lymphocyte subset redistribution in response to acute experimental stress: effects of gender, ethnicity, hypertension, and the sympathetic nervous system. Brain Behav Immun. 9(1):61-9, 1995.

Mooren, F.C., Bloming, D., Lechtermann, A., Lerch, M.M., Volker, K. Lymphocyte apoptosis after exhaustive and moderate exercise. J. Appl. Physiol. 93, 147-53, 2002.

Mooren F.C., Lechtermann A., Völker K. Exercise-induced apoptosis of lymphocytes depends on training status. Med Sci Sports Exerc. 36(9):1476-83, 2004.

Mora J.R., Cheng G., Picarella D., Briskin M., Buchanan N., von Andrian U.H.Reciprocal and dynamic control of CD8 T cell homing by dendritic cells from skin- and gut-associated lymphoid tissues. J Exp Med. 17;201(2):303-16, 2005.

Mora JR, von Andrian UH. T-cell homing specificity and plasticity: new concepts and future challenges. Trends Immunol. 27(5):235-43, 2006.

Moser B, Wolf M, Walz A, Loetscher P.Chemokines: multiple levels of leukocyte migration control. Trends Immunol. 25(2):75-84, 2004.

Murray D.R., Irwin M., Rearden C.A., Ziegler M., Motulsky H., Maisel A.S. Sympathetic and immune interactions during dynamic exercise. Mediation via a beta 2-adrenergic-dependent mechanism. Circulation. 86(1):203-13, 1992.

Nakache M., Berg E.L., Streeter P.R., Butcher E.C.The mucosal vascular addressin is a tissue-specific endothelial cell adhesion molecule for circulating lymphocytes. Nature. 12;337(6203):179-81, 1989.

Nielsen H.B., Secher N.H., Kristensen J.H., Christensen N.J., Espersen K., Pedersen B.K. Splenectomy impairs lymphocytosis during maximal exercise. Am J Physiol. 272(6 Pt 2):R1847-52, 1997.

Nielsen H.G., Lyberg T. Long-distance running modulates the expression of leucocyte and endothelial adhesion molecules. Scand J Immunol. 60(4):356-62, 2004.

Nielsen, H.B., Pedersen, B.K. Lymphocyte proliferation in response to exercise. Eur. J. Appl. Physiol. Occup. Physiol. 75(5), 375-9, 1997.

Nieman, D.C., Nehlsen-Cannarella S.L., Donohue K.M., Chritton, D.B., Haddock, B.L., Stout R.W., and J.W. Lee. The effects of acute moderate exercise on leukocyte and lymphocyte subpopulations.Med Sci Sports Exerc. 23(5):578-85, 1991.

Okutsu M., Ishii K., Niu K.J., Nagatomi R. Cortisol-induced CXCR4 augmentation mobilizes T lymphocytes after acute physical stress. Am J Physiol Regul Integr Comp Physiol. Mar;288(3):R591-9, 2005.

Pedersen, B.K. and H.. Ullum. NK cell response to physical activity: possible mechanisms of action. Med Sci Sports Exerc. 26(2):140-6, 1994.

Redwine L., Snow S., Mills P., Irwin M. Acute psychological stress: effects on chemotaxis and cellular adhesion molecule expression. Psychosom Med.;65(4):598-603, 2003.

Rehman J., Mills P.J., Carter S.M., Chou J., Thomas J., Maisel A.S.Dynamic exercise leads to an increase in circulating ICAM-1: further evidence for adrenergic modulation of cell adhesion.Brain Behav Immun. 11(4):343-51, 1997.

Roberts C.K., Won D., Pruthi S., Lin S.S., Barnard R.J.Effect of a diet and exercise intervention on oxidative stress, inflammation and monocyte adhesion in diabetic men. Diabetes Res Clin Pract. 73(3):249-59, 2006.

Roberts C.K., Won D., Pruthi S., Kurtovic S., Sindhu R.K., Vaziri N.D., Barnard R.J.. Effect of a short-term diet and exercise intervention on oxidative stress, inflammation, MMP-9, and monocyte chemotactic activity in men with metabolic syndrome factors. J Appl Physiol c100(5):1657-65, 2006.

Sakurada S., Hales J.R. A role for gastrointestinal endotoxins in enhancement of heat tolerance by physical fitness. J. Appl. Physiol. 84, 207-14, 1998.

Sallusto F., Lanzavecchia A.. Understanding dendritic cell and T-lymphocyte traffic through the analysis of chemokine receptor expression. Immunol Rev. 177:134-40, Science. 10;286(5447):2098-102, 1999.

Schumacher A., Peersen K., Sommervoll L., Seljeflot I., Arnesen H., Otterstad J.E.. Physical performance is associated with markers of vascular inflammation in patients with coronary heart disease. Eur J Cardiovasc Prev Rehabil. 13(3):356-62, 2006.

Shakhov V.P.[The role of hematopoietic islands in the development of the phenomenon of the stimulation of bone marrow hematopoiesis under stress] Gematol Transfuziol. 33(5):19-21.

Shephard R.J. Adhesion molecules, catecholamines and leucocyte redistribution during and following exercise. Sports Med. 33(4):261-84, 2003.

Sigal A, Bleijs DA, Grabovsky V, van Vliet SJ, Dwir O, Figdor CG, van Kooyk Y, Alon R.The LFA-1 integrin supports rolling adhesions on ICAM-1 under physiological shear flow in a permissive cellular environment. J Immunol. 1;165(1):442-52, 2000.

Simpson R.J., Florida-James G.D., Whyte G.P., Middleton N., Shave R., George K., Guy K. The effects of marathon running on expression of the complement regulatory proteins CD55 (DAF) and CD59 (MACIF) on red blood cells. Eur J Appl Physiol. 99(2):201-4, 2007.

Simpson, R.J., Florida-James, G.D., Whyte, G.P., Black, J.R., Ross, J.A., Guy, K. Apoptosis does not contribute to the blood lymphocytopenia observed after intensive and downhill treadmill running in humans. Res Sports Med.15(3):157-74, 2007.

Steensberg A, Morrow J, Toft AD, Bruunsgaard H, Pedersen BK. Prolonged exercise, lymphocyte apoptosis and F2-isoprostanes. Eur J Appl Physiol. 87(1):38-42, 2002.

Stefanski H.E., Jameson S.C., Hogquist K.A.Positive selection is limited by available peptide-dependent MHC conformations. J Immunol.164(7):3519-26, 2000.

Stefanski, V., Peschel, A., Reber, S. Social stress affects migration of blood T cells into lymphoid organs. J. Neuroimmunol. 138, 17-24, 2003.

Stoop R, Gál I, Glant TT, McNeish JD, Mikecz K.Trafficking of CD44-deficient murine lymphocytes under normal and inflammatory conditions. Eur J Immunol. 32(9):2532-42, 2002.

Streeter P.R., Rouse B.T., Butcher E.C. Immunohistologic and functional characterization of a vascular addressin involved in lymphocyte homing into peripheral lymph nodes. J Cell Biol. 107(5):1853-62, 1988.

Sudo N., Yu X.N., Sogawa H., Kubo C. Restraint stress causes tissue-specific changes in the immune cell distribution. Neuroimmunomodulation. 4(3):113-9, 1997.

Suzuki K, Nakaji S, Yamada M, Totsuka M, Sato K, Sugawara K. Systemic inflammatory response to exhaustive exercise. Cytokine kinetics. Exerc Immunol Rev.8:6-48, 2002.

Urhausen A., Kindermann W. Behaviour of testosterone, sex hormone binding globulin (SHBG), and cortisol before and after a triathlon competition. Int J Sports Med8(5):305-8, 1987.

von Andrian U.H., Mempel T.R. Homing and cellular traffic in lymph nodes. Nat Rev Immunol. 3(11):867-78, 2003.

Warnock, R.A., Askari, S., Butche,r E.C., von Andrian, U.H. Molecular mechanisms of lymphocyte homing to peripheral lymph nodes. J Exp Med. 19;187(2):205-16, 1998.

Weninger W., Crowley M.A., Manjunath N., von Andrian U.H. Migratory properties of naive, effector, and memory CD8(+) T cells. J Exp Med. 1;194(7):953-66, 2001.