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REVIEW ARTICLE

Exercise-induced stem cell activation and its implication for cardiovascular and skeletal muscle regeneration

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Abstract

A number of publications have provided evidence that exercise and physical activity are linked to the activation, mobilization, and differentiation of various types of stem cells. Exercise may improve organ regeneration and function. This review summarizes mechanisms by which exercise contributes to stem cell-induced regeneration in the cardiovascular and the skeletal muscle system. In addition, it discusses whether exercise may improve and support stem cell transplantation in situations of cardiovascular disease or muscular dystrophy.

Key words: *Exercise, stem cells, satellite cells, angiogenesis, VEGF*

Introduction

A number of studies have shown that exercise improves the function and regeneration of the cardiovascular system and skeletal muscle by activating and mobilizing organ-resident stem cells (1–3) or by recruiting blood-circulating stem or progenitor cells (4–7). However, the types of stem cells (or progenitor cells) and the mechanisms by which these cells are activated to induce regeneration or growth differ depending on the respective organ or tissue. Exercise provokes a number of stimuli: Mechanical, metabolic and hypoxic. It also induces the release of various growth factors, cytokines and hormones. Physical activity results in the induction of molecular adaptations that improve physical performance, fitness and/or health whether under power sport conditions or situations of leisure sport, prevention or rehabilitation. This implies growth processes must occur for both heart and skeletal muscle cells. This in turn depends on the formation of new blood vessels and the repair or replacement of cells that were physically stressed so much they are damaged or undergo cellular apoptosis. This review focuses on the mechanisms that may be responsible for the exercise-induced improvement of cellular stem cell support and repair in the cardiac, vascular and skeletal muscle system. A knowledge of these mechanisms can help to develop approaches for stem cell therapies and to evaluate the potential of supporting physical exercise to increase the efficiency of stem cell application.

Do stem cells contribute to the exercise-induced improvement of cardiac function?

Physical exercise improves cardiac function. This improvement of cardiac function has been shown to be attributed at least partially to an increase in cardiac hypertrophy (for review see (8–10)) and an improvement in cardiac capillarisation (11,12). The mechanisms involved in exercise-induced muscle angiogenesis are discussed in detail below. Regarding the development of cardiac hypertrophy, recent research has shown that exercise-induced cardiac hypertrophy involves several signaling pathways, including those mediated by Akt (13,14).

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In the last few years evidence has emerged that the heart is not a terminally differentiated organ but has an intrinsic regenerative potential. The replacement of cardiac cells (cardiomyocytes, fibroblasts, endothelial and vascular cells) seems to take place by an activation of cardiac-resident stem cells, which are located in cardiac stem cell niches (15–19), or by a recruitment of blood circulating progenitor cells (4–7). Resident cardiac stem cells have been identified as cells that are positive for various stem or progenitor cell markers (e.g. Kit, Sca-1, Isl-1), and Side Population (SP) properties (17,20). Cardiac stem cells have been described to divide symmetrically and asymmetrically with the symmetric division to predominate. Thus the replicating cardiac stem cell gives rise to one daughter and one daughter committed cardiac stem cell. By this mechanism of growth kinetics, the pool of primitive cardiac stem cells is preserved, and a myocyte progeny is generated together with endothelial and smooth muscle cells (19). To date nothing has been written on whether physical activity may improve or influence the cardiac stem cell pool.

Although further research on the self-renewing capacity of the heart is still lacking, the self-repair capacity of the cardiac muscle seems to be limited. In most cases the damage to cardiomyocytes resulting from ischemic injury is irreversible and leads to the development of progressive heart failure, which is characterized by the loss of functional cardiomyocytes. In these cases, cell-based transplantation therapy provides a potential alternative approach for replacing damaged myocardial tissue and restoring cardiac function (17). There is evidence that physical activity increases the number of circulating bone-marrow-derived progenitor cells (4–6) and also improves their migratory capacity in patients after myocardial infarction (21), and that short intensive exercise can increase the migratory activity of mesenchymal stem cells (Schmidt et al. in press). It has not been shown whether this improvement of the stem/progenitor cell activation may be attributed to an increased homing, transmigration and –differentiation of the circulating progenitor cells into cardiomyocytes.

In conclusion, although evidence exists for a self-renewing capacity of the cardiac muscle by resident as well as circulating stem cells, the mechanisms underlying these processes have to be further investigated. Moreover, while preliminary evidence suggests physical activity can be involved in stem cell mediated myocardial adaptation and repair, further research is necessary to evaluate the role of physical activity in detail.

Exercise, stem cells and skeletal muscle

Regeneration and growth of skeletal muscle are mainly managed by resident stem cells, the so called 'satellite cells'. Satellite cells occupy a sublaminar position between the basal lamina and sarcolemma (22). In contrast to adult stem cells, which by definition are multipotent cells, with considerable proliferative potential, satellite cells only have a limited capacity for self-renewal. This means that under pathological conditions skeletal muscle degenerates. Quiescent satellite cells have a high nuclear-to-cytoplasmic volume ratio with few organelles and a small nuclear size. Molecular regulation of satellite cells involves a series of transcriptional networks that lead to myogenic commitment, cell-cycle entry, proliferation, and terminal differentiation. A scheme of these processes is presented in Figure 1.

Satellite cells are marked by the expression of Pax7, and in many muscles also of Pax3. Pax3 and Pax7 regulate the entry of the satellite cells into the myogenic programme via the activation of the myogenic regulatory factors (MRF). Pax3 and Pax7 lie genetically upstream of both MyoD and Myf5, which determine the skeletal muscle fate of these cells (23). Myoblast terminal differentiation is characterized by the upregulation of myogenin and MRF4. Upon activation, satellite cells increase their cytoplasm content and the numbers of organelles and reduce the amount of heterochromatin. Skeletal muscle satellite cells supporting growth or regeneration are thought to be activated and incorporated into growing myofibers by endocrine and locally expressed autocrine and paracrine growth factors, the latter being load sensitive, e.g. VEGF (24), IGF (25), nitric oxide and hepatocyte growth factor (26), fibroblast growth factor (27) (Figure 1). Very interestingly, many of these autocrine/paracrine factors are also systemically increased in situations of enhanced exercise and thus may contribute to an activation of the satellite cells. They may also initiate or activate other stem cell-dependent regeneration processes, e.g. vascular development (see below).

Special attention should be drawn to the release of insulin-like growth factor-I (IGF-I) regarding muscle regeneration (28). It seemed relevant to measure expression levels of two insulin-like splice variants following imposed local damage. These were the systemic IGF-IEa and an autocrine splice variant produced by muscle. The latter was recently cloned from stretched, stimulated muscle. Because of this, and since it has a different sequence to systemic IGF-I, it has been called mechanogrowth factor (MGF). IGF-I is reportedly involved in satellite cell activation (29), although these *in vitro* studies may not accurately reflect what is happening

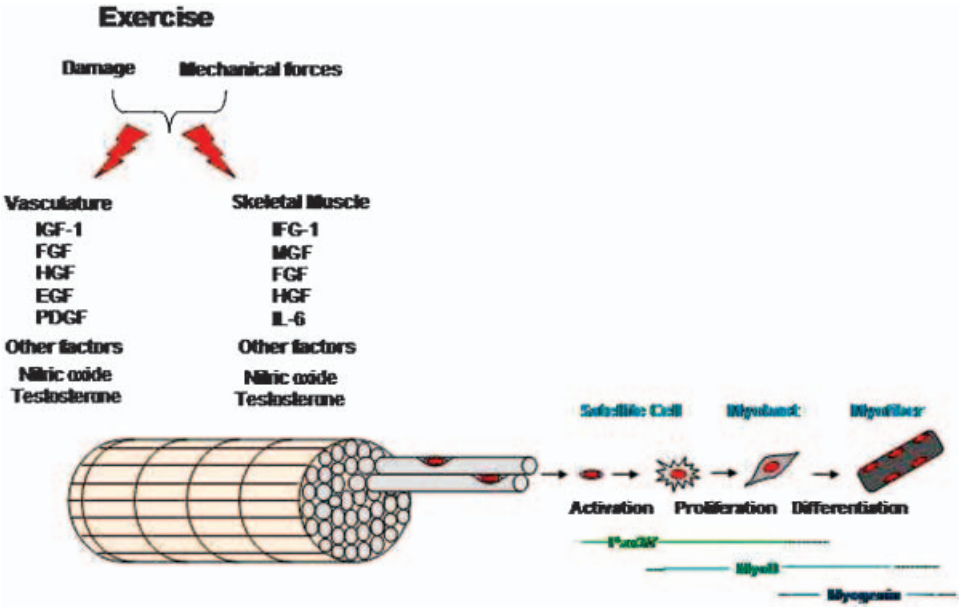

Figure 1. **Scheme for the mechanisms underlying exercise-induced activation of skeletal muscle satellite cells.** By mechanical stress and by damage of the skeletal muscle fibers, exercise induces the release of various growth factors and other signaling molecules (e.g. nitric oxide, NO) in an autocrine and paracrine fashion from the vasculature as well as from the skeletal muscle cells. The factors induce an activation and differentiation of the quiescent satellite cells.

in vivo, particularly in mature muscle when subjected to damage. Recent *in vivo* studies have indicated that MGF has different expression kinetics than IGF-IEa (30). This and other studies (31) suggest they have different modes of action.

Satellite cells have only a limited capacity for self-renewal, which means that under pathological conditions skeletal muscle degenerates. The origin of satellite cells is unclear. They express M-cadherin (M-cad) and N-CAM (32–34) and co-express myogenic factors including those mentioned above. They also express some endothelial cell markers (35). It has been shown that a stem cell fraction in bone marrow can provide skeletal muscle progenitors (36), although the efficiency of this process is very low. Adult skeletal muscle of the limb also contains a so-called stem cell population which can be separated on similar criteria to those applied to bone marrow stem cells (37) with which they have markers in common. These cells also appear to be able to contribute to muscle and blood. It is not clear whether they give rise to satellite cells or integrate muscle fibres through another route. Again this is a rare event. The origin of the so-called muscle stem cells is unknown; perhaps they arise from blood vessels/blood cells or from connective tissue (38) within the muscle.

There are several reports that indicate that exercise activates satellite cells in mature skeletal muscle cells and induces their differentiation, leading to muscle hypertrophy (39–41). Exercise also activates myogenin protein expression (41). This exercise-induced activation of satellite cells seems to be specifically attributed to eccentric exercise, i.e. to a situation when the muscle is activated while it is stretched. It is interesting to note that the forces generated by activation combined with stretch exceed even those of maximal isometric contraction. In the muscle fibres involved, the sarcomeres may be pulled out to such a degree that there is no longer any overlap of the actin and myosin filaments, thus causing damage (42).

However, exercise-induced activation of satellite cells seems to be age and gender-dependent. It was recently reported that myofiber hypertrophy with resistance training is superior in young men compared to young women and older adults (43). In another study it was shown that a single bout of maximal eccentric exercise increases satellite cell numbers in young and old men, with a significantly greater response among the young men (3). Taken together these data suggest that age-related changes in satellite cell recruitment may contribute to muscle regeneration deficits among the elderly. This issue should be taken into account when thinking of age-related rehabilitation and prevention programs.

Exercise-induced mechanisms underlying vessel formation in muscular tissue

There is clear evidence that exercise improves the blood perfusion of cardiac and skeletal muscle

(44–46). Angiogenesis (the sprouting of new vessels from existing vessles) and intussusceptions (the division of existing vessels) are mechanisms which are generally accepted to take place in the adult organism. There is an ongoing discussion whether vasculogenesis, i.e. the de novo formation of blood vessles, is a process which takes place in adults (47).

Whereas muscle regeneration and new formation under physiological conditions seem to be mainly dependent on the presence of resident stem cells, they are critically dependent on the presence and the function of bone-marrow derived circulating stem and progenitor cells. Exercise induces several stimuli which have a close relationship to the mechanisms involved in the (new) formation of vascular vessels. Physical activity is therefore known to induce several adaptation processes (48,49).

Hypoxia and ischemia initiate a number of angiogenic and vasculogenic processes including the release of growth factors and the release of progenitor cells. Several studies have reported the contribution of bone marrow-derived endothelial progenitor cells (EPC) to neovascularization in ischemic muscle, the influence of hypoxia on EPC (4,7,50–54), upregulation of adhesion molecules and chemoattractant molecules and changes in proliferation and differentiation of progenitor cells.

Bone marrow (BM) is the major reservoir for adult stem cells (Figure 2). Stem cells are localized in a microenvironment known as the stem cells ''niche'', where they are maintained in an undifferentiated and quiescent state (55,56). Under ''steady-state-conditions'' the normal oxygen tension in bone marrow is hypoxic, leading to a constitutive expression of stromal cell-derived factor-1 (SDF-1), which provides a strong binding of progenitor cells to their niche (57). Stem cells remain in the G0 phase of the cell cycle and are in contact to BM stromal cells (56). If required stem cells are released into peripheral circulation, which is regulated by a variety of growth factors, enzymes, ligands and surface receptors.

After an ischemic or hypoxic event, growth factors/cytokines, such as SDF-1, vascular endothelial growth factor (VEGF), erythropoietin (EPO) (all regulated by the O_2-dependent transcription factor hypoxia-induced factor (HIF-1)) are released by tissue and stimulate the mobilization of progenitor cells from bone marrow (57–61) (Figure 2). Several studies have shown that EPO significantly increases the number of EPCs in the bone marrow and peripheral blood. It enhances EPC differentiation and proliferation, and increases ischemia-induced neovascularization (62–65). Similar results were shown for VEGF, which augments the number of circulating EPCs and enhances EPC proliferation, adhesion and incorporation into endothelial monolayers (66–68). Sweeney et al. showed that SDF-1 is a potent factor to mobilize progenitor cells from bone marrow, to attenuate EPC apoptosis and to increase vasculogenesis by augmenting EPC recruitment (69).

The cytokines (VEGF, SDF-1) released by ischemic tissue stimulate the expression of matrix metalloproteinase-9 (MMP-9) in the bone marrow. The upregulation of the extracellular proteinase MMP-9 results in an increased bioavailability of soluble Kit-ligand (sKitL). sKitL is expressed as a membrane form (membrane Kit-ligand; mKitL) and can be cleaved by MMP-9 to the soluble form sKitL.

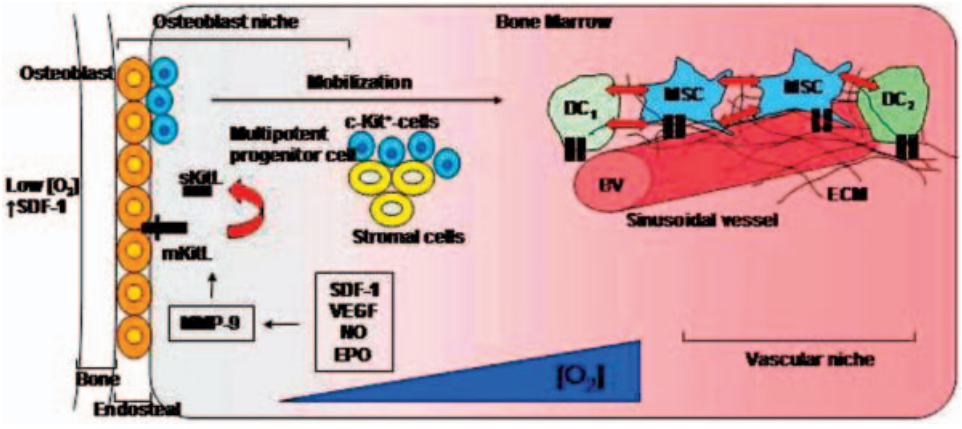

Figure 2. **Bone marrow (BM) – the reservoir for adult stem cells.** The bone marrow is a major reservoir for adult stem cells. Under steady-state conditions most stem cells are in contact with bone marrow stromal cells including osteoblasts. Upon activation stem cells are shifted to the vascular niche. The equilibrium between these two compartments is dictated by stem cell active cytokines bound to the ECM or tethered to the membrane of stromal cells.

KitL, a stem cell active cytokine, conveys signals that modulate survival, adhesion (to stromal cells), recruitment and motility of c-Kit$^+$-cells (c-Kit is the receptor for KitL, expressed on a variety of stem cells including cardiac, endothelial, epithelial and hematopoietic progenitor cells). In its soluble form KitL enhances the mobility of stem cells, translocating them into a vascular-enriched niche favoring differentiation and mobilization to peripheral circulation (56,70). In one of our studies, we showed that exercise significantly increased the MMP-9 serum concentration, possibly affecting the mobilization of stem cells (71).

After the release of progenitor cells from bone marrow, cells home to ischemic/hypoxic or damaged regions via alterations of the affected tissue. Tepper et al. demonstrated that EPC adhesion was significantly increased in hypoxic endothelium (54). This homing process is highly regulated by a variety of adhesion molecules (intercellular adhesion molecule-1 (ICAM-1), E-selectin, P-selctin, vascular cell adhesion molecule-1 (VCAM-1), platelet-endothelial cell adhesion molecule-1 (PECAM-1)) and chemoattractant factors (SDF-1, VEGF) which are also effected by hypoxia/ischemia (54,57,72–76).

SDF-1, a member of the chemokine family, and its receptor CXCR4, are known to play a critical role for stem cell homing and mobilization, which may be influenced by exercise-induced hypoxia and mechanical strain. Several progenitor cells express the CXCR4 receptor which mediates their homing to tissues expressing SDF-1 (72). Ceradini et al. showed that the SDF-1 promotor contains a hypoxia-responsive element binding the HIF-1 (57). Using an animal model, they demonstrated that SDF-1 expression in endothelial cells was directly proportional to reduced oxygen tension. The HIF-1-induced expression of SDF-1 led to an increase in adhesion, migration and homing of CXCR4 positive cells. This suggests that the SDF-1/CXCR4-system is a critical mediator for ischemia-specific recruitment of circulating progenitors (57). The SDF-1 expression of endothelial cells may be a signal indicating tissue hypoxia that helps recruit released progenitor cells from circulation in the ischemic tissue (“conditional niche”) (77).

Ischemia in muscle tissue also selectively increased the expression of ICAM-1, an important adhesion molecule. EPCs expressed ß$_2$-integrins, the ligand of ICAM-1, suggesting that ICAM-1/ß2-integrin binding plays an important role in homing of EPCs to ischemic tissue (75,78). Radisavljevic et al. showed that the expression of ICAM-1 is controlled by VEGF and nitric oxide (NO), both increased during hypoxia and exercise (79).

After adhesion, adherent progenitor cells egress into the tissue where they are themselves exposed to hypoxia. The microenvironment – including contact with surrounding cells, the extracellular matrix, the local milieu as well as growth factors – is likely to play a key role in determining stem cell differentiation (55). Akita et al. reported that hypoxic preconditioned EPCs showed a greater migratory activity and contributed to a higher extent to neovascularization (50). These hypoxic conditions stimulate EPC proliferation/differentiation and the organization of cell clusters. The clusters align in the direction of the ischemic gradient and form vascular-like cords (54). The differentiation of EPCs to mature endothelial cells (EC) may be caused by local factors released from ischemic tissue or in an autocrine fashion. It was shown that hypoxia augments the VEGF production and release in EPCs during differentiation (50). The ability of EPCs, but not mature endothelial cells, to proliferate in hypoxic conditions, underlines their important role in the neovascularization of ischemic tissue (54). In addition to the metabolic stimulus of hypoxia, Hristov et al. were able to show that the differentiation of EPCs was stimulated by apoptotic bodies from mature endothelial cells, suggesting that local tissue damage may also influence progenitor cell differentiation (80).

Exercise-induced ‘angiogenic’ mechanotransduction

Tissues and cells in the body are continuously exposed to a mechanical environment which is highly influenced and changed by exercise training. Contraction of the skeletal muscle leads to mechanical forces acting on the tissue.

It is well accepted that the microenvironment of stem cells, mediated by growth factors and cytokines as previously described, has significant influence on the differentiation and phenotypic expression of progenitor cells. Now direct and indirect evidence shows that mechanical signals may regulate stem cell fate as well.

Because HIF-1 is not only stabilized by hypoxia, but also by mechanical stimuli (e.g. exercise-induced increases in blood flow causing shear stress to the vascular endothelium) it seems that HIF-1-regulated cytokine/growth factor expression (SDF-1 and VEGF) may be important in several adaptation and regeneration processes (72,81,82). Stretching cells in culture upregulates VEGF (mRNA and protein), leads to enhanced endothelial cell migration and tube formation, activates membrane type 1 matrix metalloproteinase (MT1-MMP), and

upregulates angiopoietin (Ang2) and Tie2 expression (49,83–85).

Blood vessels are constantly subjected to hemodynamic stresses, such as shear stress due to increased blood flow and radial wall stress because of internal pressure. The pulsatile nature of blood flow results in a cyclic mechanical strain in the vessel walls which increases during physical activity (48,49,86).

This hemodynamic stress increases the endothelial NO production/bioavailability, which has been shown to be essential for the mobilization of stem and progenitor cells (87). eNOS expressed by bone marrow stromal cells influences recruitment of EPCs and hematopoietic stem cells (87). The effect of physical activity on EPCs is markedly reduced after inhibition or deletion of eNOS, which suggests an NO-dependent increase of EPCs in response to exercise. It has been suggested that statin treatment upregulates EPCs, potentially by an NO-mediated pathway, supporting the importance of NO for EPC regulation. MMP-9, which is required for stem cell mobilization, and VEGF are reduced in the bone marrow of mice deficient in eNOS (5,87).

During adhesion and incorporation, circulating progenitor cells are exposed to fluid shear stress that modulates gene expression, proliferation and differentiation. Yamamoto et al. demonstrated that shear stress applied to EPCs increased the percentage of cells in the S and G2 phases of the cell cycle, which indicates augmented proliferation. EPCs exposed to shear stress elongated, showed increased expression of EC-specific markers (KDR, Flt-1) and formed tube-like structures (88). Additionally, increases in the NO expression and production of EPCs were observed, which may further contribute to the beneficial effects of exercise training on the vasculature (89). The bioavailability of NO is further augmented by increases of Cu/Zn SOD activity and its expression in EPCs, which prevents the interaction with O_2^- (90).

Exercise-induced stem cell mobilization and its therapeutic option for noninvasive, minimal therapy

The exogenous application of stem cells represents a new therapeutic option for the treatment of cardiac and skeletal muscle diseases as well as for the treatment of vascular impairment. Although less is known about the influence of physical activity on the self-renewing capability of cardiac muscle, it seems possible that, similar to what has been described in skeletal muscle, physical activity may contribute to an increased pre-differentiation of resident cardiac stem cells. It has been described e.g. that transplantation of normal muscle precursor cells is a potential approach to restore dystrophin expression within dystrophin deficient mdx mice, a model of Duchenne Muscular Dystrophy (91). In the same study it was shown that exercise-induced fiber breaks, which improved muscle progenitor cells recruitment and fusion and increased long-term graft success and also transverse and longitudinal distribution of hybrid fibers (91). In a very recent study it was demonstrated that exercise training for three weeks after acute myocardial infarction leads to a significant mobilization and increase in functional activation of bone marrow-derived circulating progenitor cells in humans (21). Hypoxia, shear stress and strain may represent first-line mediators of complex pathways in exercise-induced stem cell tissue replacement. In addition, exercise may support stem cell-induced regeneration by preconditioning/optimizing the microenvironment (e.g. pH alterations or a processation of the extracellular matrix). A better understanding of these mechanisms may make physical activity a useful tool for the regulation of stem cell proliferation and differentiation also in minimally invasive stem cell transplantation therapy.

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List of abbreviations

Ang2	Angiopoietin
BM	Bone marrow
BV	Blood vessel
CXCR4	SDF-1 receptor
DC	Differentiated cell
EC	Endothelial cell
ECM	Extracellular matrix
EGF	Epidermal growth factor
eNOS	Endothelial NO-Synthase
EPC	Endothelial progenitor cell
EPO	Erythropoietin
FGF	Fibroblast Growth Factor
HGF	Hepatocyte growth factor
HIF-1	Hypoxia-induced factor
ICAM-1	Intercellular adhesion molecule-1
IGF-1	Insulin-like growth factor
IL-6	Interleukin-6
M-cadherin	Calcium-dependent intercellular adhesion molecule
MGF	Mechano growth factor
mKitL	Membrane Kit-ligand
MMP	Matrix metalloproteinase
MRF	Myogenic regulatory factor
MSC	Mesenchymal stem cell
NO	Nitric oxide
PDGF	Platelet-derived growth factor
PECAM-1	Platelet-endothelial cell adhesion molecule-1
SDF-1	Stromal cell-derived factor-1
sKitL	Soluble Kit-ligand
SOD	Superoxide dismutase
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor