

# Hematopoiesis with Obesity and Exercise: Role of the Bone Marrow Niche

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## ABSTRACT

*Hematopoietic stem and progenitor cells (HSPC), the most primitive cells of the hematopoietic system responsible for maintaining all mature blood cells, display the hallmark characteristics of self-renewal and multi-potent differentiation into mature cell lineages. HSPC activity is directed by the bone marrow niche, a complex environment composed of heterogeneous cell populations that regulate HSPC function through the secretion of a wide array of cytokines and growth factors. Diet induced obesity results in a dramatic remodeling of the bone marrow niche, skewing HSPC function resulting in a compromised immune system. Exercise is a viable treatment option for deficits imposed by obesity and to combat immune dysfunction; however, the impact of exercise on the bone marrow niche is not well defined. This review summarizes the available information on how obesity disrupts the normal bone marrow niche and HSPC function. In addition, we review the limited data available detailing how exercise may be used to combat obesity induced bone marrow dysfunction, and discuss future directions for research in this field.*

**Keywords:** Exercise training, MSC, HSC, diet-induced obesity

## INTRODUCTION

Physical inactivity and a sedentary lifestyle along with caloric over-consumption are major contributors to the global obesity epidemic. The World Health Organization estimates that obesity rates have rapidly increased in recent decades, resulting in 39% of adults being classified as overweight and 13% as obese in 2014 (181). The obesity epidemic is even more prevalent in more developed countries. For example, over 36% of adults in the United States are obese (109). Obesity is associated with an increased risk of health complications including type II diabetes (25, 157), cancer (21, 96, 124), and cardiovascular disease (118, 124). In addition, obese individuals are more susceptible to infection (94, 112, 141, 154) and

have worse disease prognosis (147); suggesting impaired immune competence results from obesity. Indeed, obesity is characterized by an increased quantity of innate immune cells (42), and decreased repertoire of functional adaptive immune cells (57) resulting in decreased immune surveillance. Interestingly, these changes to the hematopoietic system mirror the phenotype observed with aging suggesting that obesity may be inducing a premature aging phenotype. The altered production of mature immune cells in obesity merits closer investigation into the precursors of leukocytes: hematopoietic stem and progenitor cells (HSPCs).

HSPCs are the most primitive cells of the hematopoietic system from which all cells in the myeloid, lymphoid, and erythroid lineages are derived. The bone marrow is the primary site of HSPC maintenance and differentiation. Within the bone marrow, the “stem-cell niche” or bone marrow niche is characterized as a specialized microenvironment that maintains HSCs throughout the lifespan (131). The bone marrow niche tightly regulates HSC function through direct cell to cell contact, sympathetic stimulation, and the secretion of autocrine and paracrine factors. Chronic disease states, such as obesity and cardiovascular disease, as well as advancing age, dramatically remodel the bone marrow microenvironment and corresponding milieu resulting in altered HSC function (34, 35, 110, 136, 169). The increasing number of individuals becoming obese and entering advanced age necessitates further investigations into interventions aimed at attenuating or mitigating detrimental changes to the hematopoietic system.

Exercise bestows numerous benefits that extend the quality and quantity of life in both healthy and diseased individuals. For instance, exercise has been demonstrated to reduce the accumulation of body fat (158), mitigate low-grade chronic inflammation (161), improve cognitive function in healthy (10, 28) and diseased individuals (62, 72), and increase bone density (107). While the complete pleiotropic impacts of physical activity and exercise in healthy and diseased populations are still being determined, it nevertheless remains a low cost, easily implementable, and effective method for attenuating deficits resulting from disease states such as obesity. Although exercise does appear to be a promising therapy, a paucity of data exists examining the impact of exercise on HSPCs and the bone marrow niche. Thus, the purpose of this review will be to unravel how the combination of obesity and exercise impact the hematopoietic system via modulation of the HSPC niche. The following sections will define HSPCs and their regulation by the bone marrow niche, the impact of

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obesity and exercise on HSPCs and the bone marrow niche, and describe possible mechanisms responsible for altered hematopoietic function.

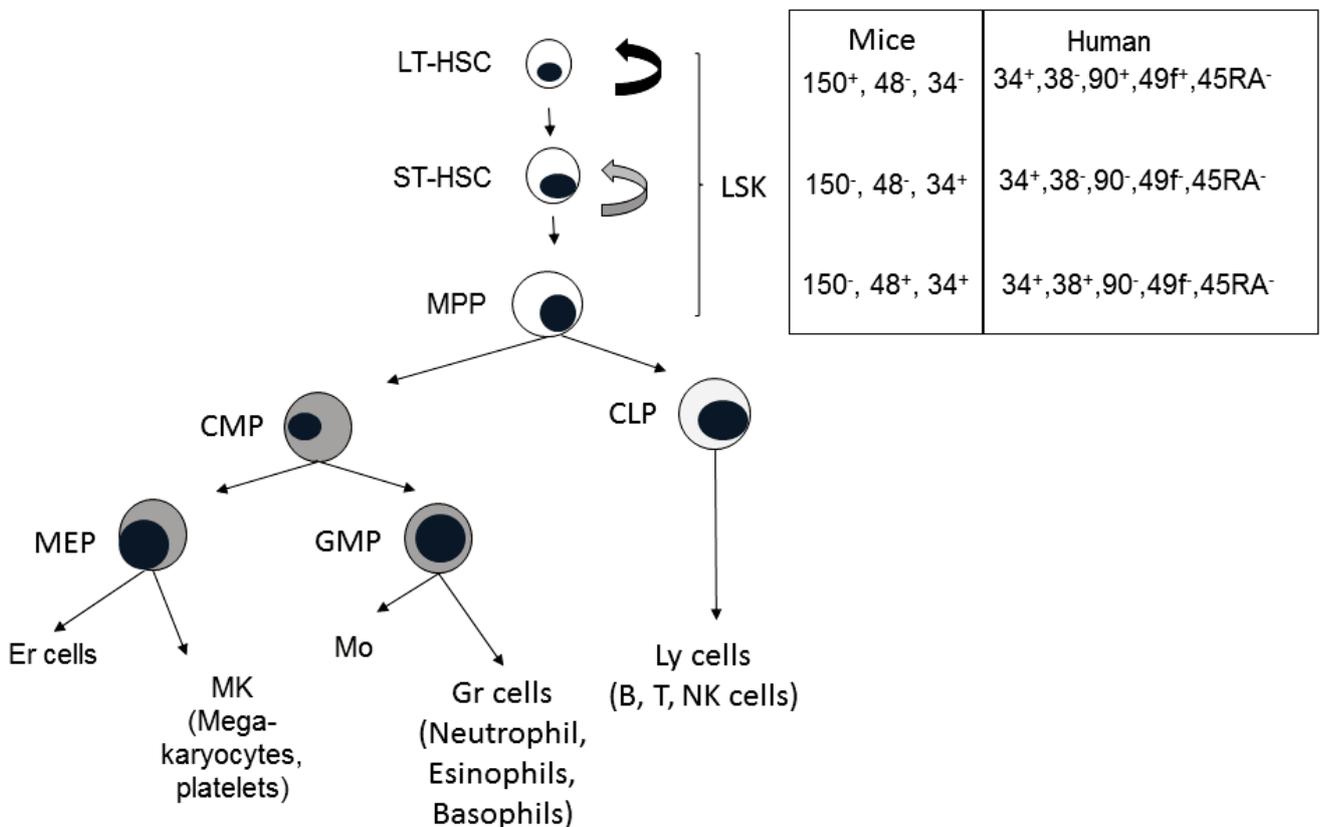
**Defining HSPCs**

HSPCs are the pluripotent precursors to all mature cells of the hematopoietic system. HSPCs constitute a small fraction, <0.001%, of the total bone marrow cell population, and yet maintain the entirety of the hematopoietic system by undergoing self-renewal divisions to maintain the more primitive populations and differentiation to lineage committed cells (15). HSPC migration, proliferation and fate decisions are regulated by autocrine and paracrine factors from within the bone marrow, as well as systemic cues. Indeed, HSPC mobilization and function is affected by circadian rhythms (91), acute infection (71), psychological stress (125), ischemia (129), tissue damage (114), and energy status (30, 88). The hematopoietic system turns over between  $10^{11}$  –  $10^{12}$  cells daily. To maintain this constant demand throughout the lifespan, a portion of HSPCs remain quiescent for protection against DNA damage or premature exhaustion while more differentiated progenitors maintain mature lineages (69, 100, 146).

Characterization of distinct HSPC populations remains difficult due to a lack of specific known markers. Additionally,

difficulty in obtaining HSPC samples from humans has led to most functional research being conducted in murine models. While the murine model is efficient for modeling HSPCs and the bone marrow niche, special considerations must always remain due to differences between species. Indeed, human and murine HSPCs exhibit different cell surface phenotypes. Within mice, the broad HSPC pool is identified by the expression of surface antigens cKit and Sca-1 while lacking the expression of committed lineage markers (LSK) (48). The identification of the SLAM family allowed for phenotypic characterization of HSPC sub-populations that related to reconstitution ability in serial transplant assays (77). Similar HSPC populations have been determined in humans based upon the expression of CD34 (33, 153) and CD38 (152). Traditionally, HSPCs have been divided into different sub-populations of long-term hematopoietic stem cells (LT-HSC), short-term hematopoietic stem cells (ST-HSC), and multi-potent progenitors (MPP) before terminally committing to myeloid and lymphoid lineages (63, 83) (Figure 1). Functionally, the self-renewal capacity is highest among the primitive LT-HSCs while the proliferative capacity is highest among the more differentiated multi-potent progenitors.

Currently, technical challenges make determination of self-renewal and proliferative capacity of HSCs difficult. The



**Figure 1.** Traditional view of hematopoietic stem and progenitor cell (HSPC) hierarchy. HSPCs have the capacity to self-renewal to maintain primitive cell populations or differentiate into mature hematopoietic cells. The lineage- Sca-1 cKit<sup>+</sup> (LSK) phenotypic markers are used to identify the whole stem cell pool within mice. Additional phenotypic markers are outlined that identify distinct HSPC subpopulations in humans and mice. Abbreviations: Long-Term (LT), Short-Term (ST), Hematopoietic Stem Cell (HSC), Multi-Potent Progenitor (MPP), Common Myeloid Progenitor (CMP), MEP (Megakaryocyte/Erythroid Progenitor), GMP (Granulocyte/Macrophage Progenitor), Erythroid (Er), MegaKaryocyte (MK), Mo (Monocyte), Granulocyte (Gr), Common Lymphoid Progenitor (CLP), Lymphocyte (Ly).

“gold standard” for measuring HSPC functionality relies on the serial transplant assay, whereby bone marrow cells are serially transplanted into lethally irradiated mice to determine reconstitution potential (122). This is a time-consuming assay that lasts at least 8 months. Additionally, transplantation into lethally irradiated recipients may not be directly related to HSPC functionality in steady state conditions. Similarly, due to the lack of single, specific markers for tracing HSPC subpopulations, HSPC proliferation and the relative contribution of each subpopulation to steady state hematopoiesis remains challenging. Recent techniques permitting HSPC lineage tracing via “barcoding” (146), and the development of artificial 3-dimensional bone marrow niches for the evaluation of HSPC self-renewal and differentiation *in vitro* over a much shorter timespan (31) will allow for significant advancements in our understanding of HSPC biology.

### Obesity, Exercise, and HSPCs

The process of hematopoiesis produces all blood and immune cells and occurs within the bone marrow and, under certain conditions, in peripheral tissue compartments such as the spleen throughout the lifespan (8, 166). Diseases associated with chronic inflammation, including obesity, cancer, heart disease, and other chronic inflammatory conditions, such as the late effects of cancer therapy, have all been linked to alterations in immune function (108, 120, 164). Moderate intensity exercise has been shown to be a powerful mediator of immune function (180). Acute exercise increases the quantity of circulating monocytes and induces an acute inflammatory response that is dependent on exercise intensity (105, 113). Exercise training increase erythrocyte content within peripheral circulation (61), is generally thought to be anti-inflammatory, and enhances tissue regeneration (116, 160). However, the effect of obesity and exercise on hematopoiesis itself remains less well-characterized.

#### Obesity and HSPCs

Obesity is well documented to increase the quantity of circulating white blood cells in humans (46, 103, 119, 167) and mice (149). Within the bone marrow, diet-induced obesity (DIO) causes an expansion in bone marrow cellularity and mature immune cells (22, 35, 155). This expansion is likely due to the activation and increased cycling of HSPCs. Mice fed a 60% high fat diet (HFD) for 12 weeks experienced an increase in the number of HSPCs and monocyte progenitors (135). This differentiation bias towards myelopoiesis was also observed in a serial transplantation assay (135). Similarly, a shift towards increase myeloid cells and reduction in lymphoid cells was observed in mice after 6 weeks of consuming a 60% HFD (2). On the other hand, mice fed a 45% HFD for 18 weeks experienced a decrease in the most primitive HSPCs and increase in MPPs (14). Additionally, serially transplanted HSPCs displayed a reduced capacity for hematopoietic reconstitution (14). While differences in fat content of the diets used (45% vs 60%) may influence the degree of phenotypic response, the available data suggests DIO stimulates hematopoiesis with a bias towards myelopoiesis, and cycling of HSPCs with exhaustion of the most primitive population. Indeed, DIO appears to stress the HSPC populations risking premature exhaustion and is similar to the phenotype observed in aging.

#### Acute Exercise and HSPCs

Currently, only a few studies have examined the effects of acute exercise on hematopoiesis. Acute aerobic exercise stimulates HSPCs in the bone marrow as evidenced by an increase in cycling HSPCs and colony forming-unit (CFU) capacity (50, 90, 97). Mooren and Kruger observed an increase in progenitor cells 24 hours following a novel bout of treadmill exercise in sedentary mice while exercised mice experienced no change in HSPCs (97). Together, these data suggest that an acute bout of exercise is a potent physiological stressor, which induces proliferation of the HSPC populations. The effects of acute exercise on hematopoiesis in humans is lacking due to the difficulty of sampling bone marrow tissue. Nevertheless, Wu and colleagues did examine the amount of hematopoietic cells from bone marrow aspirates after an acute bout of exercise in bone marrow donors (171). The authors found that following exercise, while the volume of bone marrow aspirate, number of collections required, and collection pain were improved in the exercise group, no differences were seen in the relative proportion of CD34+ cells (171). However, the total quantity of HSPCs was not evaluated, and more specific markers of HSPCs were not used. Additionally, Wu and colleagues collected bone marrow aspirate 15 minutes after the exercise bout, rather than previous rodent studies that have analyzed bone marrow 24-48 hours after exercise. Together, these data suggest that an acute bout of exercise is sufficient to stimulate proliferation of HSPCs; however, it may take 24-48 hours for changes in HSPC content to be detected.

A larger body of human data exists detailing the mobilization of HSPCs into circulation following acute exercise (39, 49). While the majority of these studies suggest that exercise increases HSPC mobilization in humans, a couple of recent studies have shown that colony forming capacity is decreased in the peripheral blood following acute exercise suggesting decreased function. Kroepfl *et al* (78) showed that HSPCs collected 10 minutes post exercise had a decreased functional capacity, and confirmed these results in a later study investigating the relationship between HSPCs and exercise-induced norepinephrine increase (78). It is possible that during or after acute exercise, more differentiated HSPCs are recruited to peripheral tissues, such as muscle, to participate in tissue repair (114). The mechanisms responsible for acute exercise-induced HSPC mobilization remain to be elucidated. Acute exercise results in an acute inflammatory response that may contribute to the mobilization of HSPCs from the bone marrow. G-CSF and IL-6 have been observed to increase following acute exercise and may influence HSPC mobilization (17, 148, 163, 173). However, no correlations between mobilized HSPC content and cytokines concentrations have been determined following acute exercise (17). This suggests that circulating cytokines may not be the primary signal inducing HSPC mobilization from the bone marrow in response to exercise. Our lab recently observed an increase in G-CSF, SCF, IL-3 and thrombopoietin from bone marrow stromal cells after an acute exercise bout in mice that may contribute to shuttling HSPCs into peripheral circulation (50). Furthermore, vascular endothelial growth factor- $\alpha$  (VEGF- $\alpha$ ) has been observed to be elevated following exercise in circulation (17) and skeletal muscle (50), suggesting that tissue damage or ischemia may play a role in homing HSPCs to peripheral

tissues. Taken together, these data suggest that tissue damage or local factors within the bone marrow are primarily responsible for mobilizing HSPCs following acute exercise.

#### *Exercise Training and HSPCs*

Similar to acute exercise, little data exists examining the effects of prolonged exercise training on hematopoiesis. Chronic exercise training increases blood volume, red cell volume, blood hemoglobin content, and immune function. Additionally, some studies have shown that exercise trained individuals have increased amounts of HSPCs at rest in both the bone marrow and peripheral blood (8, 17, 38). Baker and colleagues investigated HSPC content using CFU assays following chronic exercise training and found that increased hematopoiesis was apparent in both the peripheral blood and the bone marrow (8). These data were confirmed and extended by De Lisio and colleagues who demonstrated that progressive treadmill exercise training increase HSPC content collected from the central bone marrow cavity (or “vascular niche”) but not the quantity of HSPCs associated with the inner lining of the bones (the “endosteal niche”) (38). Importantly, no difference in the repopulating ability of HSPCs was detected between exercise trained and sedentary mice in a bone marrow transplantation assay (38), suggesting that benefits to HSPCs from exercise training may be due to cell-extrinsic factors, possibly due to alterations in the bone marrow niche. In summary, both acute and chronic exercise seem to stimulate hematopoiesis. More research is needed to fully characterize the effects of exercise on hematopoiesis, as well as to delineate the potential mechanisms responsible for these effects. Additionally, future research is necessary to determine if exercise can offset phenotypic skewing within HSPC populations that occurs in chronic diseased states such as obesity and aging.

#### **The Bone Marrow Niche**

The concept of a niche, or distinct microenvironment specialized to support the maintenance and differentiation of HSPCs during steady-state or stress hematopoiesis, was first introduced by Schofield in 1978 (131). Since then, important discoveries by a variety of groups have increased our understanding of the cell-types and molecular signals comprising the HSPC niche within the bone marrow. Several excellent reviews have been recently published outlining the cellular and molecular components of the HSPC niche, and the reader is directed to these reviews for a more comprehensive overview of the niche (4, 16, 58). The bone marrow is comprised of multiple, distinct niches that regulate HSPC function and are continuously being redefined with the advent of more precise visualization and identification techniques. Previous data indicated two main stem cell niches within the bone marrow: the endosteal and perivascular niches (77, 137, 172). The endosteal niche was viewed as a site for quiescent HSPCs due to increased homing following transplantation experiments and because osteoblasts were shown to secrete growth factors that regulate HSPC quiescence (5, 142, 172, 178). However, repeated experiments finding low associations of HSPCs contacting osteoblasts and conditional depletion of mature osteoblasts not effecting HSPC quantity have questioned the essential role of the endosteal niche under homeostatic conditions (further reviewed in (98)).

The conditional deletion of stem cell factor (SCF) from endothelial cells which decreased HSPC quantity and the frequent association of HSPCs with blood vessels and sinusoids within the bone marrow shifted the focus to the perivascular niche (77, 142). Furthermore, subsequent reports emphasized perivascular and endothelial cells as the primary site for modulating HSPC quiescence via CXCL12, SCF, and notch ligands (20, 45, 67, 142). Recently, several studies further refined the perivascular niches and observed quiescent HSPC are localized closely to arterioles while more active HSPCs are located near sinusoidal openings (66, 79). The hypoxic nature of the arteriole niche, due to low perfusion (165) and increased vascular wall integrity of arterioles, results in decreased generation of reactive oxygen species (ROS) within HSPCs (66). Furthermore, the hypoxic nature also implicates hypoxic inducible factor-1 (HIF-1) in maintaining HSPC quiescence as increased oxygen content increases stem cell proliferation and mitotic activity (51). Indeed, HIF-1 expression which is upregulated in ischemic tissues partially regulates CXCL12 expression in these tissues, and may be involved in drawing progenitor cells into peripheral tissues (24). Hypoxic culture maintains HSPC reconstitution potential *in vitro* (68), and conditional deletion of HIF-1 $\alpha$  within HSPCs results in decreased ability to fully regenerate the hematopoietic system in serial transplant assays (150). The most primitive HSPCs are maintained near the endosteum where HIF-1 expression is the highest (82) whilst its expression is lower the central marrow cavity (77). While this lends credence to the hypothesis that HIF-1 may be leading to increased HSPC retention within the bone marrow, Levesque et al observed an increase in HIF-1 $\alpha$  and VEGF-a within bone marrow lysates following G-CSF mediate mobilization of HSPCs (82). Given they used whole bone marrow lysates, it is impossible to determine which specific cell population was responsible for increased HIF-1, and whether HIF-1 directly resulted in HSPC mobilization, or if it worked indirectly via increasing VEGF-a which is a potent mobiliser of HSPCs (82). Overall, these data demonstrate that increased HIF-1 is necessary for long term maintenance of HSPCs *in vivo* and *in vitro*, however, the role in mobilization still needs further delineation. Conversely, HSPCs located near “leaky” sinusoids have an increased production of ROS, are actively cycling, and are readily able to enter peripheral circulation in response to signals from circulation (66). Likewise, HSPCs have been observed to localize near megakaryocytes (19, 179) while erythropoiesis occur in erthroblastic islands (80, 123).

In addition, a variety of stromal cell populations have been identified using genetic labeling approaches that express either leptin receptor (44, 45) Prx1 (55) nestin (64, 92), platelet derived growth factor receptor- $\alpha$  (117) or CXCL12 (111, 143). All of these cell populations are enriched to varying degrees for osteogenic and adipogenic differentiation capacity and contain fibroblast colony forming cells suggesting they consist of mesenchymal stromal cells (MSCs), and that these populations overlap to some yet unknown extent. These MSC populations have all been shown to directly associate with HSPCs and to secrete paracrine factors that regulate HSPC cell fate decisions (16, 58). Thus, through their capacity to signal directly to HSPCs, or to form mature cellular components of the HSPC niche such as osteoblasts and adipocytes

via their differentiation, MSCs are an important, heterogeneous cellular component of the HSPC niche. Taken together the localization of HSPCs impacts their functional status, and disruption of niche homeostasis can disrupt normal hematopoiesis.

### **Obesity and Exercise Induced Remodeling of the HSPC Niche**

The architecture of the bone marrow influences HSPC activity as the bone marrow niche tightly regulates HSPCs in a dynamic balance between quiescence, self-renewal, and differentiation. MSCs, and their progeny, are particularly important modulators of HSPC function. MSCs contribute to bone turnover by differentiating into osteoblasts and remodel the central marrow cavity through adipogenic differentiation in addition to secreting growth factors to support HSPC maintenance (55, 111). Recent evidence suggests a reciprocal relationship between osteogenic and adipogenic differentiation of MSCs. In mice, diet induced obesity (DIO) disrupts the bone marrow compartment, skewing MSC differentiation towards adipogenic lineages resulting in increased marrow adipose tissue (MAT). This reciprocal relationship is also supported by the accumulation of MAT in both obese humans and mice. In humans, increased MAT is negatively correlated with bone density (168), bone mineral density, and bone formation (134). In mice, 8 weeks of 45% HFD induction led to an increase in MAT and decrease in trabecular bone density (35). Similar results were observed in mice fed similar HFD for 6 (2, 139, 140), 12 (47), 18 weeks (176), or 6 months; however, not all studies have observed a concurrent decrease in bone density (47, 139, 140). The differential response of bone mineral density is likely due to different study designs as Styner and colleagues used a 45% HFD for 6 weeks in female mice (139, 140) compared to a 60% HFD for 6 weeks in 8 week old male mice (47). Thus, the relative proportion of fat in the diet may impact observed results in bone marrow remodeling. MAT accumulation negatively impacts the bone marrow compartment as adipocytes will physically occupy red marrow space and MAT potently secretes pro-inflammatory cytokines, such as IL-6, and TNF- $\alpha$ , as well as free-fatty acids, affecting cells throughout the bone marrow including HSPCs (56). Indeed, MAT is a negative regulator of hematopoiesis as the quantity and repopulating capacity of HSPCs collected from areas of high MAT were decreased compared to HSPCs collected from areas of low MAT (104). The skewed MSC differentiation towards the adipogenic lineage, and increased MAT in obese mice and humans mirror changes to the bone marrow compartment observed with aging (101), suggesting that obesity causes a premature aging phenotype in the bone marrow compartment.

The effect of exercise on the bone marrow niche is less well investigated. Forced treadmill the exercise training was demonstrated to remodel the bone marrow by decreasing MAT, and possibly priming MSC towards the osteogenic lineage (8, 159). Mice exercised via wheel running also experience a decrease in bone marrow adiposity even in the presence of a high fat diet (140) or in the presence of PPAR $\gamma$  agonist (139), emphasizing that both forced (8, 36, 159) and voluntary (139, 140) exercise attenuate the accumulation of MAT within the bone marrow. Furthermore, chronic exercise

improves the bone architecture via increased mineral density in combination with decreasing MAT (133, 140), supporting the hypothesis that exercise directs MSCs down osteogenic lineages and a more healthy bone marrow environment (104). Interestingly, exercise training donor mice prior to bone marrow transplant (BMT) did not impact homing, engraftment, or reconstitution in recipient mice (38), suggesting that “preconditioning” HSPCs within donors does not have a large impact on the hematopoiesis upon transplantation. However, HSPC transplant into exercise trained recipient mice resulted in increased reconstitution without affecting homing (36). De Lisio and colleagues also demonstrated decreased MAT accumulation, and decreased apoptosis within the bone marrow after recipients were preconditioned with exercise with no enhanced preservation of CD45<sup>+</sup> hematopoietic cells suggesting enhanced survival of non-hematopoietic cells in the bone marrow with exercise were contributing to enhanced reconstitution (36). The decreased apoptosis following BMT observed by De Lisio and colleagues, could be due to an increased production of antioxidant enzymes in the marrow in response to exercise (40). These data suggest that the effects of exercise on HSPCs are likely cell non-autonomous versus cell-autonomous.

### **Potential Mechanisms Regulating Bone Marrow Remodeling in Obesity and Exercise**

The effects of obesity and exercise on the bone marrow microenvironment are likely not due to one specific mechanism, but rather a multitude of changes to systemic and bone marrow environments with the respective conditions. Several signaling pathways have been implicated in the reciprocal differentiation of MSCs towards osteogenic or adipogenic lineages that may contribute towards age and chronic disease related deficits to bone density (12, 13, 26, 59, 99, 138, 174). Cytokines secreted by the bone marrow stroma including transforming growth factor  $\beta$  (TGF- $\beta$ ), bone morphogenetic proteins (BMPs), insulin-like growth factor (IGF), and fibroblast growth factors activate transcription factors Runx2 and Osterix, increasing osteogenic differentiation (81, 95, 102, 177). On the other hand, adipogenic differentiation is supported by the transcription factors CCAT/enhancer binding protein alpha (C/EBP $\alpha$ ) and PPAR $\gamma$  (32, 75). The following sections will discuss the research available pertaining to how exercise and obesity impact the bone marrow architecture.

### **Pro-inflammatory cytokines**

Obesity is characterized by systemic low grade inflammation, and an increase in the circulating levels of leptin (52), IL-1 $\beta$  (130), Tumor Necrosis Factor  $\alpha$  (TNF $\alpha$ ) (56, 151), IL-6 (9, 56), and monocyte chemoattractant protein-1 (MCP-1) (73), all of which may have implications on bone marrow homeostasis. TNF $\alpha$  has been previously been demonstrated to inhibit osteoblastic differentiation of MC3T3-E1 pre-osteoblastic and fetal calvaria precursor cells (53). Additionally, TNF $\alpha$  has been observed to activate NF- $\kappa$ B which prevents osteogenic differentiation via the subsequent inhibition of Runx2 and Osterix (74, 86, 87). Furthermore, TNF $\alpha$ -/- mice displayed increased femoral bone density and decreased MAT following an 18 week 60% HFD. Together, these data suggest an integral role for TNF $\alpha$  signaling and pre-osteoblast cell differentiation. IL-1 $\beta$  and MCP-1 have also been demonstrat-

ed to reduce the osteoblastic differentiation potential of MSCs and decrease bone density (144, 145). These data support the potential role of inflammatory cytokines on skewing MSC differentiation from osteogenic towards adipogenic lineages. IL-6 and TNF $\alpha$  have also been implicated to increase osteoclastogenesis, increasing bone breakdown and inhibiting osteoblastogenesis (1, 170, 175). Within the bone marrow, HFD increases the expression of pro-inflammatory cytokines TNF $\alpha$ , IL-1 $\beta$ , and IL-6 in whole mouse bone marrow isolates (14, 56) and isolated rat MSCs (35). Overall, the available data suggests that both systemic and bone marrow specific elevations in inflammatory cytokines results from obesity. Given the role inflammatory cytokines have in directing MSC differentiation, it is likely these cytokines are contributing to the increases in MAT and subsequent bone marrow niche remodeling observed with obesity.

Chronic exercise training is generally considered anti-inflammatory. Exercise training has been shown to decrease the expression of TNF $\alpha$ , IL-1 $\beta$  while increasing the expression of anti-inflammatory cytokine IL-10 in obese rats and mice (18, 54, 85). Additionally, exercise stimulates the release of IL-10 and IL-1Ra, which have been observed to decrease IL-1 $\beta$  and TNF $\alpha$  production (3, 120). Currently, there is limited research available investigating the role of inflammatory cytokines in response to exercise and obesity in the bone marrow. We have previously observed an acute bout exercise alters the secretome of bone marrow stromal cells (50). Other disease models, such as osteoporosis in rats, have observed an increase in bone mineral density following exercise via wheel running (84). Exercised OVX rats also had decreased levels of IL-1 $\beta$  and IL-6 within bone marrow cells compared to sedentary rats (84). These data support the notion that exercise training may mitigate disease associated decreases in osteoblastogenesis, bone mineral density, and the increase in pro-inflammatory cytokines. However, further research is necessary to define the relationship between exercise and inflammatory cytokine mediated remodeling of the bone marrow architecture, and its role in hematopoiesis. Additionally, studies specifically characterizing changes to the MSC secretome following exercise training in the presence and absence of obesity are needed.

### Oxidative Stress and Reactive oxygen species (ROS)

Reactive oxygen species (ROS) are formed during cellular respiration and are mainly produced by the mitochondria. Physiological levels of ROS play a key role in regulating stem cell fate decisions. Obesity has been associated with increased oxidative stress and the generation of ROS (60). MSC are particularly sensitive to the presence of supra-physiological levels of ROS as seen in chronic inflammation and diseased states (further reviewed in (6)). Several studies have indicated that increased presence of ROS inhibits markers of osteogenic differentiation, increases DNA damage, and spurs adipocyte differentiation of MSCs *in vitro* (7, 121, 132). Indeed, the increased presence of ROS has been observed to shift MSC differentiation towards adipogenic lineages in advanced aging (70, 76). In addition to their effects on MSCs which likely have indirect effects on hematopoiesis, ROS have also been shown to directly influence HSPC function. Increasing endogenous ROS production in HSPCs by TNF- $\alpha$  exposure decreased the reconstitution ability in serial transplant assays

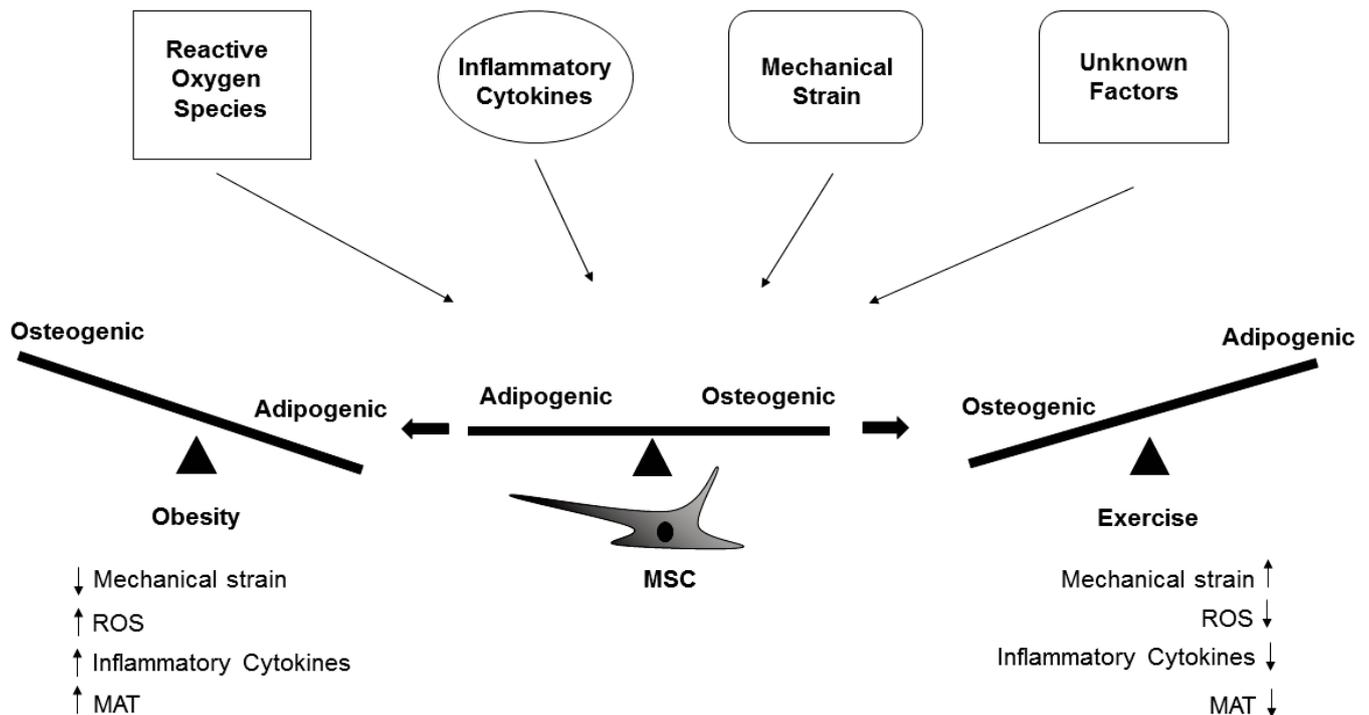
that was recovered by blocking ROS production (65). Whole body radiation *in vivo* has been shown to have negative long-term effects on primitive HSCs by decreasing their content and colony forming capacity *in vitro* (27). These effects may be due to increased HSPC senescence (93) induced by persistent oxidative stress (162). Together, ROS may negatively impact hematopoiesis indirectly by promoting MSC adipogenic differentiation, or directly by inducing HSC senescence and prolonged oxidative stress.

Few studies exist characterizing the impact of exercise and the generation of ROS within the bone marrow. De Lisio and colleagues observed exercise training reduced DNA damage and apoptosis signaling within the bone marrow of mice exposed to an acute challenge radiation exposure (40). These results suggest that exercise training confers protection within the bone marrow to the exogenous generation of ROS. These results are further supported by increased protection of circulating lymphocytes to irradiation from exercise trained individuals (156) and skeletal muscle of exercise trained mice (37). While it is tempting to speculate that exercise training may stimulate the production of anti-oxidant enzymes within the bone marrow similar to that seen in skeletal muscle (37), no data are available to confirm this hypothesis. However, the reduction of DNA damage within the bone marrow of exercise trained mice following irradiation does support this hypothesis and may contribute to exercise induced MSC biasing towards osteoblast lineages. Further research will be needed to fully characterize this response.

### Other Potential Factors

Exercise and obesity may also influence cell-intrinsic mechanisms regulating MSC differentiation. PPAR $\gamma$  signaling promotes MSCs differentiation down the adipogenic lineage. Mechanical strain induced by exercise has been observed to decrease PPAR $\gamma$  expression in MSCs, favoring osteogenesis over adipogenesis *in vivo* (89) and *in vitro* (23, 29, 127, 133). PPAR $\gamma$  expression is activated by long-chain fatty acids (126), suggesting that hyperlipidemia induced by high fat diet stimulates MSCs adipogenesis. Interestingly, these signals seem to be overridden by exercise in the presence of a PPAR $\gamma$  agonist (139). Metabolic stress has been linked to changes within the bone marrow stromal tissues. Bone marrow stromal cells incubated in the serum of overweight individuals promoted adipogenic differentiation over osteoblastic differentiation (43). While the underlying mechanism remain undetermined, this does suggest that unknown circulating factors may be influencing MSC fate determination within the bone marrow MSCs.

Overall, obesity and exercise seem to elicit functionally opposite results within the bone marrow (Figure 2 see next page). Obesity skews MSCs towards adipocyte lineages, increases the accumulation of MAT, and creates a more pro-inflammatory phenotype similar to aging. These changes in the niche are associated with altered HSC differentiation that favors increased myeloid biased progenitors, increased HSPC cycling, and mobilization leading to exhaustion of primitive HSPC populations (11, 106, 135, 155). Exercise and physical activity decrease the accumulation of MAT even in the pro-adipogenic conditions, suggesting that exercise may be a



**Figure 2.** Factors influencing mesenchymal stromal cell differentiation (MSC). Systemic and bone marrow specific factors influence the differentiation of MSCs down adipogenic or osteogenic lineages. Obesity is associated with an increase in bone marrow adiposity likely due to increases of these factors. Exercise decreases marrow adipose tissue and increase bone marrow density, indicating that MSCs may be stimulated down an osteogenic lineage by decreasing reactive oxygen species and inflammatory cytokines while increasing mechanical strain within the bone marrow. Abbreviations: Mesenchymal stromal cell (MSC), Reactive oxygen species (ROS), and Marrow adipose tissue (MAT).

potent therapy to combat obesity induced changes to the bone marrow environment. However, further investigations are needed to fully delineate the multi-faceted responses of exercise in the context of the bone marrow stroma. Only a few studies have elucidated the impact of exercise on the HSPC populations (36, 38), none exist characterizing the impact on changes in MSCs, endothelial cells, or HSPC localization.

### Conclusion and Future Directions

Obesity has a direct impact on the fate of the hematopoietic system (135), distressing normal immunological function (112) and phenotype (103). This dysfunction extends to HSPCs resulting in expansion of the less primitive progenitor cell pool, at the cost of self-renewal leading to premature exhaustion. The altered phenotype and function of HSPCs is likely due to modulations within the bone marrow niche. HSPC function is carefully regulated by niche localization, and disruption of cellular constituents can disrupt HSPC homeostasis. Although evidence does suggest that bone marrow niche disruption contributes to altered HSPC function in obesity, the systemic disruptions including elevated levels of pro-inflammatory cytokines associated with obesity, negates the ability to definitively characterize the primary suspect in altered HSPC function.

Chronic exercise directly combats the systemic effects of obesity by improving body composition (41), improving immune function (115), and decreasing chronic low grade inflammation (128). The pleiotropic responses of exercise extend to the

bone marrow, inducing beneficial bone marrow remodeling and expanding the HSPC pool without compromising self-renewal. Although these preliminary data are promising, many questions remain unanswered pertaining to the mechanisms responsible for the effects of exercise on the bone marrow compartment and HSPC function. An in-depth analysis determining the extent to which exercise expands the whole HSPC pool or specific sub-populations still does not exist. In addition, although exercise has been identified to decrease overall bone marrow adiposity and alter the inflammatory status of the bone marrow; alterations in the individual cell populations making up distinct niches within the bone marrow still needs to be characterized. Furthermore, defining the molecular pathways by which exercise influences HSPCs, MSCs, and the bone marrow niche may highlight potential therapeutic pathways to combat obesity and hematological malignancies. Overall, the effects of exercise on the hematopoietic system need further characterization; however, exercise still remains a viable and feasible method of combatting obesity induced changes to the hematopoietic system.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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