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Neural regulation of bone, marrow, and the microenvironment

Jonathan Canaani[1,2], Orit Kollet[1], Tsvee Lapidot[1]

[1]Department of Immunology, Weizmann Institute of Science, Rehovot 76100, Israel, [2]Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 64239

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1. ABSTRACT

Bone marrow niches are specialized microenvironments comprising a heterogeneous population of cells that support and regulate hematopoietic stem and progenitor cells. Considerable advances made in the field of hematopoiesis reveal a cross talk between cells, cytokines and neurotransmitters of the hematopoietic, immune and skeletal systems. Dynamic modulation and regulation of stem cells and their niches in response to internal and external stimuli are essential for homeostasis**,** host defense and repair. This review presents evidence to substantiate stem cell regulation via the "brain-bone-blood triad" beginning at the embryonic stage and continuing to adulthood.

2. INTRODUCTION

Hematopoietic stem and progenitor cells (HSPC) are essential players in a dynamic and robust system aimed at supplying the organism with an adequate number of mature blood cells of all lineages during homeostasis and at an amplified and accelerated mode during times of stress (typified by bleeding, sepsis etc). In adult mammalian species this rare population of undifferentiated cells mostly reside in the bone marrow (BM)**.** Ever since Schofield conceptualized the idea of the stem cell niche (1), namely the stromal region in the BM that supports and regulates HSPC in their basic functions of self-renewal, differentiation or apoptosis, the niche has been the focus of active research. An extensive body of literature extending from invertebrates to mammals indicates that the basic

paradigm of the niches involves: First, a tight regulation of the number of stem cells in their niches. Second, the constituents of the niche secrete factors that either stimulate or inhibit stem cell number and function and lastly physical interactions among different types of cells are important for the maintenance of the stem cell state (reviewed in (2)). This complex microenvironment comprises a heterogeneous population of regulatory cells (located in spatially discrete locations in the marrow) including stroma cells, for example bone lining osteoblasts, bone degrading osteoclasts, and other cell types which interact with them. These cells regulate HSPC through adhesion interactions, and close range signaling by secreted cytokines, chemokines, proteolytic enzymes and calcium (reviewed in (3)). This local control is supplemented with systemic control afforded by the vasculature providing factors that regulate both HSPC and their dynamic BM niches. For example, parathyroid hormone (PTH) was shown to increase HSPC number coupled with an increased number of osteoblasts (4). Additional, yet to be defined systemic factors, were recently investigated in a study showing that these factors regulate the dysfunctional hematopoiesis associated with aging through stroma components of the osteoblast lineage (5).

The dynamic nature of the hematopoietic niches is accentuated when compared for example with stem cells of the central nervous system. The latter have a static location in the lateral ventricle subventricular zone and hippocampus (6, 7) while HSPC cycle between the endosteum, sinusoids, the blood circulation and peripheral organs such as the spleen and liver. A recent study underscores the dynamic theme of the niches demonstrating that some niches are empty even under steady state conditions with a daily egress to the circulation of up to 5% of the total HSPC population (8).

The immune and nervous systems share a common trait- they must act in a quick and vigorous manner to address external and internal challenges throughout the body. Whereas the nervous system relies on input through nerves the immune system utilizes peripheral immune cells and possibly also HSPC in immune surveillance (9). It is becoming increasingly clear that a mutual cross talk exists between these two systems manifested by shared signaling molecules and receptors (10-12), anatomical proximity and common pathologies. For example aging is associated with deteriorating immunity, including reduced functionality of HSPC, coupled with Osteoporosis and cognitive decline. The emerging picture within the field suggests a bi-directional hierarchy where the immune system is under control of the nervous system but is capable of modulating the former. The convergence of the systems takes place at the bone hosting the bone marrow niches.

In this review, we consider the experimental data substantiating the existence of a “brain-bone-blood triad” focusing on the roles of neurotransmitters in HSPC development, bone remodeling, and circadian rhythms.

3. INTERACTIONS BETWEEN HSPC AND THE NERVOUS SYSTEM DURING EMBRYONIC DEVELOPMENT

The life course of an adult HSPC is characterized mostly by a stationary existence at the bone marrow with only very low levels of HSPC in the circulation. These progenitor cells are awaiting to be recruited to the circulation at times of stress as part of host defense and repair response. These processes are mimicked during clinical mobilization procedures, in which HSPC are harvested for bone marrow transplantation protocols**.** On the other hand, the main motif during the life of embryonic HSPC is migration. Indeed, mice deficient in Stromal Cell-Derived Factor 1 (SDF-1), a stroma produced chemokine essential for HSPC migration, survival, anchorage and quiescence, have multiple defects which are lethal, including impaired HSPC colonization of the bone marrow during ontogeny (13). In a succession of passages occurring during the first two embryonic weeks the HSPC will migrate between the yolk sac, aorta-gonad-mesonephros (AGM) region of the embryo, placenta, liver, thymus, spleen, and finally will colonize the bone marrow just before birth (reviewed in (14)). It is currently believed that the same HSPC migrate along the path described above with the respective niches supporting their proliferation rather than a genesis of new HSPC at each supportive organ (reviewed in (15)). However, the first definitive murine HSPC is identified only at embryonic day 10.5 at the AGM region and in the vitelline and umbilical arteries (although some HSPC may appear even earlier in the yolk sac area) (16). The distinction between this bona fide definitive HSPC and the other classes of HSPC generated during fetal hematopoiesis is functionally important because only definitive HSPC when transplanted into an irradiated adult mouse would be capable of generating a complete multilineage bone marrow.

Focusing on the AGM region of the murine embryo, several interesting observations associated with the nervous system and HSPC regulation were made. First, Similar to the bone marrow milieu, where nerves, blood vessels and HSPC are intimately close, the AGM region contains neural crest derived tissue destined to develop into the sympathetic ganglia and the adrenal gland (17). Next, beta Nerve Growth Factor (beta-NGF), a neurotrophic factor, was suggested as a candidate HSPC-regulatory molecule, stemming from the fact that exogenous administration of beta-NGF to cultures of murine AGM derived stromal cell lines caused an almost two fold increase in the repopulating activity of HSPC (18). Finally, A recent study by the same group demonstrated in AGM upregulated expression of nearly one hundred genes known to be involved in neuron development and differentiation and in development of the nervous system, thus suggesting neural regulation of the AGM region, which holds a major role in fetal hematopoiesis (19).

Further, research on zebrafish has revealed that exposure to alpha and beta adrenoreceptor blockers, namely sympathetic nervous system antagonists, increased embryonic HSPC formation while the opposite effect was

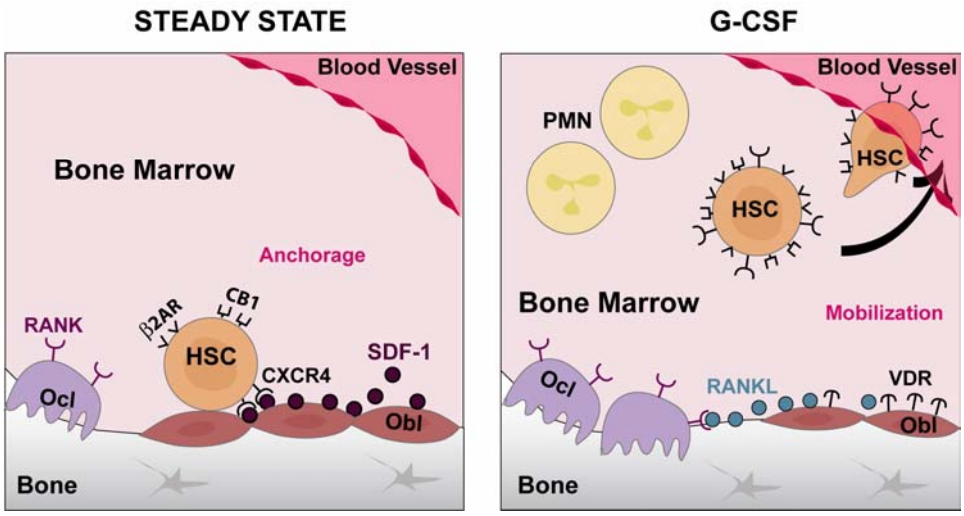

Figure 1. HSC retention in the bone marrow and mobilization to the circulation are regulated by the joint actions of chemokines, hormones, neurotransmitters and osteoclast-osteoblast interactions. During steady state conditions HSC are anchored to the endosteum via SDF-1/CXCR4 interactions. Upon G-CSF stimulation upregulation of adrenergic, endocannabinoid receptors and CXCR4 takes place on HSC coupled with upregulation of VDR on bone lining osteoblasts. Osteoblast presented RANKL activates osteoclasts which subsequently degrade SDF-1 and other stem cell niche components (not illustrated) resulting in the mobilization of HSC from the bone marrow to the peripheral blood.

seen with agonists (20). While the author's conclusions were relating the effects of these drugs to embryonic blood flow (which was increased with these drugs), one cannot exclude the possibility that blocking sympathetic output, also resulted in the increase of HSPC activity. Interestingly, exposure to an angiotensin-converting enzyme (ACE) inhibitor which regulates blood pressure decreased HSPC numbers, an observation in line with previous studies demonstrating a role for ACE in avian (21) and human hematopoiesis (22).

Further insight into the mechanistics of niche development was provided in a study showing that the formation of an intact HSPC supporting bone marrow requires the bone to undergo endochondral ossification, the process by which a cartilage template is gradually replaced by a bone matrix via the combined actions of osteoblasts and osteoclasts (23-24); this process may be regulated by the nervous system as may be inferred from the fact the chondrocytes express the (parasympathetic) nicotine receptor alpha7 nAChR which when stimulated was shown to inhibit endochondral ossification (25). Notably, the transcription factor Sox9, known to play a role in the development of most neurons and glia of the peripheral nervous system (PNS) (26) was also shown to have an essential role in chondrogenesis, and osteo-chondroprogenitor cells are derived from Sox9 expressing precursors (27).

Finally, we note the dual role in hematopoietic and nerve cells of two transcription factors (TF). Runx-1, involved directly in normal hematopoiesis and in leukemogenesis is also expressed in both the central and peripheral nervous systems of mouse embryos (reviewed in (28)), and promotes axonal growth in murine neural crest derived sensory neurons (29). Additionally, murine Mouse Mll-1, a chromatin modifying enzyme indispensable for embryonic hematopoiesis, is also required for neurogenesis in the mouse postnatal brain (30).

Albeit scattered, the data above may support a role for the nervous system in modulation of the hematopoietic niches during development, alternatively it may be deduced that these two pivotal homeostatic systems share common biological mechanisms. Elucidating regulatory pathways in HSPC development in adult mice will require further studies employing conditional knockout or knockdown of key neural genes.

4. REGULATION OF THE ADULT BONE, BONE MARROW AND HEMATOPOIETIC STEM CELLS BY THE NERVOUS SYSTEM

To fulfill its role as a dynamic reservoir of the immune and hematopoietic systems, the bone marrow has to adapt quickly and robustly to different stimuli during both homeostasis and stress situations. This vocation is met by tight regulation and mutual interplay between the nervous and immune systems and various cells constituting the supporting stroma of the bone marrow niches. Current evidence suggests that neural control over hematopoiesis is maintained both directly on HSPC and indirectly via the stromal components of the niches and mature leukocytes. Others and we have previously established that human and murine HSPC express catecholamine receptors, i.e. dopamine and beta 2 adrenergic, and that administration of catecholamines resulted in increased proliferation, colony formation potential and increased engraftment. Treatment with the mobilization myeloid cytokines G-CSF and GM-CSF upregulated the expression of catecholamines receptors on immature human CD34+ HSPC (31, 12, Figure 1).

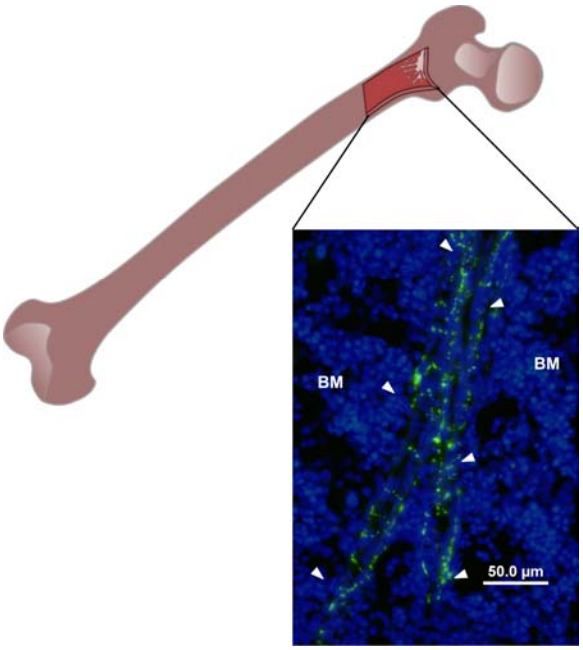

Figure 2. Immunofluorescent staining of nerve fibers in a mouse femur. Blue staining indicates BM cells. Green staining indicates expression of Tyrosine Hydroxylase, typical for sympathetic nerve fibers (white arrowheads) that are observed surrounding BM blood vessels.

Evidence from the clinic demonstrates that mind and bone being associated is more than a metaphor as is apparent from the observation that major depression is a risk factor for low bone mineral density (32). Both of which can be rectified by anti depressant pharmacotherapy (33)**,** leading to the suggestion that osteoporosis is a neuroskeletal disease (34). In addition, peripheral neuropathy, being nervous system dysfunction resulting from Diabetes Mellitus, is an independent risk factor for lower bone mineral density (35)**.**

A possible link between the nervous system and hematopoiesis is already suggested by the intimate innervation of cortical bone, cancellous bone and BM, and by the layers of periarterial adventitial cells that concentrically surround both nerves and arterioles (36) (Figure 2).

During the lifetime of the organism the bone undergoes continuous cycles of bone formation by the bone synthesizing osteoblasts as well as of bone resorption by osteoclasts. This ongoing bone remodeling enables bone competence, repairing bone breaks, and adapting to various mechanical demands essential for bone integrity. The intimate association between the immune and skeletal systems is well illustrated in patients suffering from defects in the adenosine deaminase gene (ADA) causing severe combined immunodeficiency (SCID), which is associated with skeletal pathology characterized by reduced numbers of osteoclasts and osteoblasts. A recent study demonstrated that ADA deficiency in a murine model causes a decrease in the osteoclast differentiation factor receptor activator of nuclear factor-kB ligand (RANKL), and consequently a reduction in osteoclast activity resulting in impaired capacity to support hematopoiesis (37).

The essential role of osteoblasts in supporting hematopoiesis was established by studies showing that either increasing murine osteoblast number or activity results in increased HSPC number (38, 4) or conversely depletion of OB is accompanied by decreased HSPC count (39). A recently published *in vitro* study also showed that osteoblasts increased murine HSPC expansion and marrow repopulating potential (40). Studies from others and our group have shown that HSPC-osteoblast interaction is by means of osteoblasts' secretion of the chemokine SDF-1 which binds to the CXCR4 receptor on HSPC. This interaction is fundamental for both human and murine HSPC migration, survival, anchorage and quiescence (41-45).

A putative role for nervous system interactions with osteoblasts was suggested more than a decade ago when catecholamines were shown to stimulate proliferation and specific enzymatic activity in murine osteoblast-like cells (46). Subsequent research identified beta 2 adrenergic receptors on mouse osteoblasts and demonstrated that administration of beta agonists resulted in reduced bone mass with the opposite effects seen with beta-blockers (47). Using mice knocked out for the adrenergic beta 2 receptor the same group demonstrated that the mechanism for neurally induced bone resorption was via osteoblast secretion of RANKL. Interestingly, their results suggested that the osteoblasts were regulated upstream by secretion of cocaine amphetamine regulated transcript (CART), a neuropeptide whose expression is controlled by Leptin, a hormone involved in nervous system regulation of food intake, energy balance, and fat storage, (48) and which regulates bone mass through modulation of osteoclast number (49). Further insight into the physiology of the niches was gained by the landmark study of Katayama et. al in mice (42), showing that sympathetic nervous system output, namely, norepinephrine, is an essential component of G-CSF induced HSPC mobilization via downregulation of SDF-1 secretion from osteoblasts. Taken together the aforementioned data seemed to indicate a direct involvement of the nervous system in bone metabolism and HSPC function and egress mediated by catecholamines, specifically via beta 2 adrenergic receptors. Ensuing investigations revealed that in fact daily circadian rhythms of reduced SDF-1 expression in the murine BM (and subsequently increased HSPC bone marrow egress) are mediated by beta 3 adrenergic receptors located on a murine stromal cell distinct from the osteoblast (50). This not along ago incognito cell was recently identified as a mesenchymal stem cell (MSC) expressing the protein nestin and in close contact with HSPC in the bone marrow. Furthermore, this cell was found to be highly innervated by adrenergic nerve fibers and to express high levels of SDF-1. Importantly, depletion of these nestin positive MSC significantly impaired bone marrow homing of HSPC and reduced their number in the bone marrow, thus sustaining the

concept of the "brain-bone-blood triad"(51).

In accord with the foregoing studies establishing neural modulation of osteoblasts in the HSPC niches, Matsui's group has recently uncovered an additional aspect of neuroendocrine-bone reciprocity (52). They demonstrated that G-CSF induced mobilization of HSPC, already noted above to be mediated via adrenergic signaling, is dependent on upregulation of Vitamin D receptor and its downstream gene RANKL on osteoblasts. These results indirectly support our hypothesis that RANKL activated osteoclasts are involved in G-CSF induced mobilization of hematopoietic progenitor cells (53).Interestingly, their results also seem to indicate that SDF-1 downregulation is essential for mobilization though not sufficient as mice knocked out for vitamin D receptor had reduced SDF-1 levels but nonetheless could not mobilize HSPC.

The functional counterparts of osteoblasts, the osteoclasts, are also regulated by sympathetic neural input as demonstrated in sympathectomy models (54) and in a study showing that beta-blocker therapy decreased osteoclast numbers (55).

Additional central nervous system control on bone formation is mediated via the Endocannabinoid system through the CB1 and CB2 cannabinoid receptors, expressed in the brain and peripheral nerves (CB1) and peripheral tissue (CB2). It was previously shown that CB2 is expressed in osteoblasts and osteoclasts where its signaling directly stimulates osteoblasts and reduces RANKL expression (56). Others suggest that CB1 receptor signaling regulates bone formation by modulating adrenergic signaling (57). Conversely, HSPC themselves express CB1 receptors and indeed endocannabinoids positively regulate hematopoiesis (58). Importantly, bone marrow stromal cells secrete endocannabinoids which were shown to be essential for G-CSF-induced HSPC mobilization, thus establishing the endocannabinoid system as an additional player in the hematopoiesis arena (59, also reviewed in 60).

In recent years attention has focused on the role of adipocytes in bone marrow physiology. In an elegant study Daley and colleagues found that different regions of the mouse skeleton have different levels of adipocytes and furthermore have different hematopoietic activity as manifested by colony forming activity and competitive repopulation assays. They found decreased hematopoiesis in regions with high adipocyte content (61). Interestingly, irradiated mice without adipocytes due to genetic deletion of gene x, or given PPAR gama inhibitors (blocking adipogenesis) had accelerated marrow recovery compared to WT mice. This is consistent with a recent publication showing that mice fed a high cholesterol diet have increased peripheral blood SDF-1 and subsequent increased HSPC egress from bone marrow (62). The aforementioned studies supplement the known role of the nervous system in adipocyte metabolism, via catecholamine receptors and the endocannabinoid system (reviewed in 63-64). Considering previous associations mentioned before regarding SDF-1 secretion and catecholamines, it could be possible that this is partly mediated by adipocytes.

Notwithstanding the data presented above indicating a pivotal hematopoieitic role for neurotransmitters of the sympathetic nervous system, some investigators propose a regulatory function for additional neuropeptides, among them: acetylcholinesterase, Glutamate, Substance P, and opioid receptors which are functionally expressed by immature human cord blood CD34+ cells and at higher levels on the more primitive CD34+/CD38- cells (65-69).
Taken together the emerging picture suggests that the nervous system stands atop a hierarchy exerting its influence via neurotransmitter secretion on the skeleton and thus on HSPC.

5. CIRCADIAN RHYTHMS OF BONE TURNOVER, BONE MARROW AND STEM CELL RECRUITMENT TO THE CIRCULATION

The complexity of the regulatory mechanisms governing the bone marrow niches and leukocyte reservoir is further emphasized considering an additional basic aspect of homeostasis- time. Indeed, circadian light and darkness cycles have emerged as major factors in homeostasis in many species. One noted example is the unicellular cyanobacteria, which uses two antagonistic energy producing strategies- photosynthesis and nitrogen fixation. The potential metabolic conflict is resolved by temporal separation of the two processes, that is photosynthesis during the day and nitrogen fixation at night (70). Climbing up the evolutionary ladder, circadian rhythms in mammals are integrated in increasingly complex physiological and behavioral processes including sleep, body temperature, and hormone secretion (reviewed in (71)).

In mammals this hierarchical system is controlled by a central pacemaker located at the hypothalamic suprachiasmatic nucleus. This master integrator receives external input from the environment, i.e. light, and in turn regulates downstream peripheral clocks present in lung, liver, skeletal muscle and in fact in almost all mammalian tissues. The peripheral clocks will in turn modulate the release of tissue specific transcription factors suited to the circadian context. For example, aberrant clock machinery of the liver, the major regulator of glucose homeostasis, results in loss of rhythmic expression of hepatic glucose regulatory genes and consequently in defective glucose metabolism (72). At the molecular level both the central and peripheral clocks consist of autoregulatory feedback loops which control transcription and translation of the clock genes (review in (73)).

Research of hematopoietic stem cells in the circadian context underscores the importance of light as a major regulator of immune response to stress. This was already suggested back in the 1960's with Halberg's study showing dramatic diurnal variations in the survival rate of mice subjected to an endotoxic shock challenge (74). A basic tenet of murine physiology is a nocturnal active phase

coupled with a repose phase during light time. These events are closely tied to marked differences in hematopoietic progenitor proliferation and peripheral blood levels. Specifically, peaks of murine progenitor peripheral blood levels and proliferation are observed soon after the commencement of light (coinciding with the murine repose phase) and 12 hours later towards the end of the murine active period (75). In humans, on the other hand, the situation is different with peak progenitor levels and proliferative activity occurring in a single peak during light time peaking around noon (76-80). Of note, murine HSPC engraftment also has a diurnal pattern (81). Mechanistic insight was provided only in recent years with the pioneering work of Frenette *et. Al* (50) demonstrating a pivotal role for neurally mediated circadian control over the egress of murine HSPC from the bone marrow. The investigators showed that the core genes of the molecular clock regulated the production of BM SDF-1. The connection between the clock genes and SDF-1 was mediated via adrenergic beta-3 receptors located on the stromal component of the bone marrow, probably on osteoblast precursors. Subsequent work from the same group focused on CXCR4, the cognate receptor of SDF-1. Complementing their previous study they demonstrated CXCR4's expression on HSPC (both murine and human) is also clock genes' dependent coinciding with SDF-1 levels and HSPC egress (82). In fact their results suggest that the optimal time for clinical mobilization of HSPC is later in the day, at early afternoon.

Granted the data above link hematopoietic stem cell motility and location indirectly to neural modulation with the participation of the circadian system, how does this apply to the bone marrow niches? Are the niches and the stem cells directly modulated by the nervous and circadian systems?

Indeed, during the last years a fascinating interplay involving the "brain-bone-blood triad" (12) is being revealed. The bone, being the host organ of the bone marrow niche is subjected to neural influence as discussed elsewhere in this review. Bone turnover is also carried out in a circadian rhythm in humans and other day-active animals, in which bone resorption and to a lesser extent, bone formation, increase during the night. In mice, which are nocturnal animals, the timing is reversed. The biochemical correlate of this circadian pattern is illustrated with the diurnal variation in the blood of the two main biosynthetic products of degraded osteoblasts, type I collagen and osteocalcin. (83,84)**.** Leptin was added as an additional player in the bone-circadian arena in a publication (85) demonstrating that Leptin also regulates the expression of the circadian genes Per and Cry via beta 2 adrenergic receptors, affecting immature bone lining osteoblast proliferation and ultimately bone formation. Of note, serotonin, a neurotransmitter active in the nervous and gastrointestinal tract systems, was also shown lately (86) to decrease murine osteoblast proliferation, and subsequently reduce bone mass, via the transcription factor CREB which is also known to regulate several clock genes (87). Intriguingly the paths of serotonin and Leptin are crossed as was demonstrated recently in an elegant study showing that brain derived serotonin and gut derived serotonin have opposite effects on bone dynamics with the former acting as an inducer of bone formation and moreover Leptin acts upstream as an inhibitor of serotonin release (88).

A preclinical investigation by Grant and colleagues (89) gives a clinical perspective to the data presented above. The investigators aimed to characterize the relation between two major pathologies associated with Diabetes mellitus, namely nervous system dysfunction and diabetic retinopathy. Using a model of diabetic mice it was shown that these mice have impaired sympathetic innervation of the bone marrow resulting in a reduced ability to release endothelial progenitor cells to the circulation, culminating in impaired reparative capacity of retinal vasculature. Intriguingly they also noted a reduced expression of clock genes in the bone marrow while central clock machinery was intact, thus indicating central sympathetic control of peripheral clock genes in the murine bone marrow.

In aggregate, the rapidly accumulating data strongly support the notion that integration of environmental cues at the organism level involves neuro-modulation of the bone marrow stem cell niches and constitutes an integral part of the organism's adaptive immunity.

6. PERSPECTIVES

Appreciating the true nature of HSPC niches physiology requires going a step further beyond examining discrete systems. Research from the last decade reveals that the immune system, the nervous system and the skeleton share common mediators, molecular signaling pathways, anatomical structures and pathologies providing impetus for considering them as integrated systems. This paradigm setting the CNS at the top of the hierarchy is not unique to the immune and skeletal systems and has been suggested also in regard to a gut-brain-liver axis where nutrient sensing in the gut sends signals to the brain which regulates glucose production in the gut via a neuronal network (90). In this review we considered recent data demonstrating the involvement of the nervous system in direct control of HSPC and indirectly, via control of their bone marrow microenvironment**.** Amounting evidence for the overlap of these systems is further supported as we consider the growth factor pleiotrophin, known for its proliferative effect on neurons, role in nervous system development and angiogenic activity (91-93). Recent work proposes that pleiotrophin is also a powerful inducer of HSPC expansion, with the investigators suggesting it might contribute indirectly to bone marrow recovery through promoting angiogenesis of the bone marrow vascular niche (94). This overlap is corroborated in an additional study investigating bone pain in pancreatic cancer patients. The authors were surprised to discover that sensory nerves expressed the receptors for G-CSF and GM-CSF and what was more interesting was that stimulation of these receptors caused the release of the neuropeptides CGRP and upon blocking this signaling cascade, both cancer pain and pancreatic

tumor growth were attenuated (95).

Is niche damage a key event in HSPC associated disease genesis and progression? And if so could pharmacologic manipulation of the nervous system be a potential therapeutic avenue? Two recent studies may provide preliminary answers to these questions. In the first one investigating graft-versus-host disease (GVHD) in a murine model it was suggested that the bone marrow is a target of immune rejection (GVHD) by transplanted donor T lymphocytes and furthermore host osteoblasts were identified as the affronted cells mediating subsequent bone marrow suppression (96). In the second study, Scadden and colleagues establish that dysregulation of murine osteoblasts can result in a state similar to myelodysplasia, a precancerous condition, and eventually lead to leukemia. The novel concept introduced by the investigators proposes that the afflicted stromal cells may be the initial step in a multi step process of leukocyte carcinogenesis (97). As neurotransmitters of the sympathetic nervous system have been shown to affect the bone marrow milieu through bone turnover and HSPC proliferation, differentiation and egress it would be interesting to evaluate their effects in the clinical context, perhaps in bone marrow mobilization protocols.

Moving the field forward will require using genetic markers and advanced *in vivo* imaging to elucidate the mechanisms by which neurons modulate HSPC and surrounding stroma. We might still be a long way from using directed therapy to modulate the neural component of the BM niches but future studies will help clarify the role of the nervous system in regulation of stem cells and their bone marrow niches at both steady state and disease conditions.

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Abbreviations: HSPC: hematopoietic stem and progenitor cells; BM: bone marrow; PTH: parathyroid hormone; AGM: aorta-gonad-mesonephros; ACE: angiotensin converting enzyme; RANKL: receptor activator of nuclear factor kappa B ligand; CART: cocaine amphetamine regulated transcript; G-CSF: granulocyte-colony stimulating factor; SDF-1: serum derived factor-1; GVHD: graft versus host disease; MSC: mesenchymal stem cell

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Send correspondence to: Tsvee lapidot, The Weizmann Institute of Science, Dept. of Immunology, Rehovot 76100, Israel, Tel: 972-8-9342481, Fax: 972-8-9344141, E-mail: Tsvee.Lapidot@weizmann.ac.il

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