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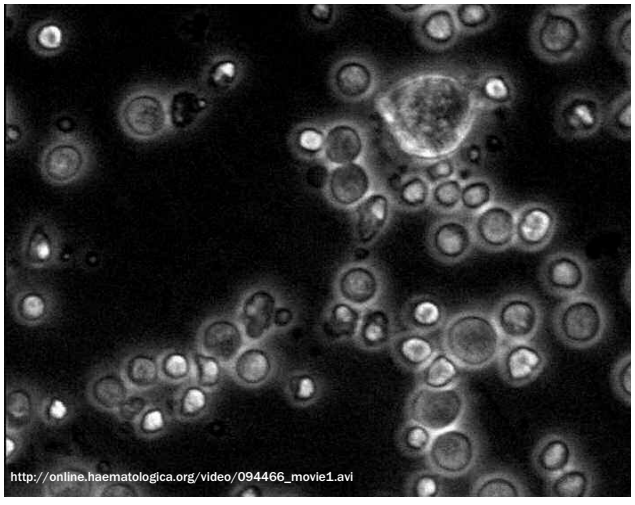

Movie 1. Interaction between macrophages and human erythroblasts in vitro. Time lapse videomicroscopy of cells obtained after 14 days of culture under Human Erythroid Massive Amplification (HEMA) conditions from peripheral blood of one healthy donor. Samples were observed by an Olympus phase-contrast microscope equipped with incubator chamber and high speed, high-resolution camera (Hamamatsu), objective lens x20. Two hours of video recording are shown. Frames were collected every 30 seconds and movie was accelerated at 10 frames per second. The movie presents erythroblasts at various stages of maturation surrounding a macrophage (top right) recognizable for being larger than the other cells, for its motility, and for its ability to protrude its cytoplasm. During the movie, the macrophage appears to explore the space in its surroundings protruding filaments of different sizes. These filaments establish contacts with numerous erythroblasts. Some of the contacts are temporary while others persist in time. The variegation of these interactions suggests that the macrophage is engaging in multiple types of biological conversations possibly in response to specific signals emitted by each erythroblast. Kindly provided by Mario Falchi PhD, National Aids Center, Istituto Superiore di Sanità, Rome, Italy.

Autonomic regulation of hematopoiesis and cancer

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The functions of the autonomic nervous system have expanded in the last years from 'fight-or-flight' responses to fine-tuned control of multiple homeostatic and pathological processes. Recent evidence has demonstrated that hematopoiesis, cancer progression and metastasis do not escape the control of this rheostat.

The autonomic nervous system comprises two branches that frequently exert opposite biological actions: the sympathetic and the parasympathetic nervous systems. Some of the first evidence of sympathetic regulation of hematopoiesis came from studies on circadian rhythms, the daily oscillations that govern most biological processes. It has been shown that the postsynaptic neurotransmitter of the sympathetic nervous system (SNS) noradrenaline exhibits a circadian rhythm in the murine bone marrow (BM), peaking at night. This peak coincides with an increase in the number of cells in the G2/M and S phases of the cell cycle.[1] Also, administration of noradrenaline stimulated BM cell proliferation and rescued mice from chemotherapy,[2] and this has recently been confirmed.[3,4] Similarly, noradrenaline was shown to directly stimulate the proliferation and migration of human hematopoietic stem cells (HSC).[5] The role of the SNS in regulating HSC traffic and enforced mobilization was only recently uncovered by serendipitous observations. Different groups found that the selectin inhibitor fucoidan increased circulating hematopoietic progenitors (HSPCs) independently of selectin function.[6,7] The hypothesis was advanced that sulfated glycans expressed in the BM microenvironment, like sulfatide, might regulate HSC trafficking. Sulfatide, a major component of myelin, is synthetized by the UDP-galactose:ceramide galactosyltransferase (Cgt) enzyme. $Cgt^{-/-}$ mice did not only show reduced myelin and activity of myelinated nerve fibers,[8] but also compromised G-CSF-induced HSC mobilization.[9] Although these mice exhibited a

defect in stromal cells that support lymphopoiesis,[10] impaired HSC mobilization was not found to be caused by the lymphopenia or by the absence of sulfatide. Instead, it was proposed to be the result of impaired sympathetic regulation of osteoblasts.[9] These short-lived bone-forming cells had been previously described by other groups as HSC niche cells[11-13] negatively regulated by the SNS.[14] It has been shown that β2-adrenergic receptor activation of osteoblastic cells increases the expression of vitamin D receptor, which is required for G-CSF-induced HSC mobilization.[15,16] Other bone-forming cells have been shown to receive sympathetic input and also contribute to HSC mobilization. Osteocytes embedded in the bone matrix have been shown to transmit β_2-adrenergic signals to the BM microenvironment in a critical manner for proper HSC mobilization, adding a new bone cell type to the neural-blood-bone triad.[17] Our data suggested that G-CSF-induced HSC mobilization requires the participation of both β_2- and β_3-adrenergic receptors.[18] However, osteoblasts and osteocytes do not express the β_3-adrenergic receptor, which we found to regulate physiological HSC release to circulation.[19]

In multiple tissues, circadian oscillations are maintained by a peripheral clock that is periodically reset by the central pacemaker in the brain, the suprachiasmatic nucleus. The retinal-hypothalamic tract connects the retina with the central clock, allowing for synchronization of different organs to day/night cycles.[20] The central pacemaker resets the peripheral clock in different tissues through the SNS. In humans, the major post-synaptic neurotransmitters of the SNS also show circadian levels in plasma and urine.[21-23] Since the SNS relays circadian signals to peripheral organs and participates in G-CSF-induced HSC mobilization, we studied the role of the SNS in circadian HSC traffic. A model was proposed where light-entrained circadian information is transmitted from the central pacemaker to the BM through the SNS, that releases noradrenaline rhythmically in the BM microenvironment, activating β_3-adrenergic receptors expressed in stromal cells different from the osteoblast and triggering cyclic *Cxcl12* downregulation and rhythmic HSC release to the bloodstream.[19] The neural signal locally delivered could be propagated to the BM microenvironment via electromechanical coupling. Indeed, the gap junction protein connexin-43 has been shown to regulate HSPC homing and engraftment. While one study has shown that BM stromal CXCL12 secretion requires electromechanical coupling by connexin-43 and -45,[24] another study has shown that connexin-43 deficiency increases BM stromal CXCL12 secretion but it compromises HSC homing and hematopoietic recovery upon myeloablation.[25] This is at least partly due to connexin-43-mediated transfer of high, damaging amounts of reactive oxygen species to the BM stroma, which would protect HSCs during stress hematopoiesis.[26] However, we noted that systemic activation of β-adrenergic receptors, e.g. by isoprenaline injections, did not increase circulating HSPCs unless the homing process of these cells was additionally blocked.[19] This suggested that systemic adrenergic stimulation might enhance not only mobilization, but also homing of HSPCs in the BM and/or in peripheral tissues. This hypothesis has been recently confirmed in a study that has shown the participation of the SNS in circadian homing of leukocytes and HSPCs to the BM, which occurs preferentially during the night phase in mice.[3] However, it remains unclear how local sympathetic activity in the BM can induce both HSPC egress and homing seemingly through very similar mechanisms.

Based on our previous studies,[19] we hypothesized that the BM stromal cells regulating HSC traffic might be mesenchymal stem cells (MSCs) which were known to express the intermediate filament protein nestin. Indeed, nestin expression allowed us to identify cells in the BM that fulfilled all the criteria of *bona fide* MSCs and were physically and functionally associated with HSCs and sympathetic nerve fibers.[27] We have shown that sympathetic fibers inhibited the proliferation of nestin positive MSCs,[27] as recently confirmed.[4] Given the association of *bona fide* MSCs and HSCs in the BM, we

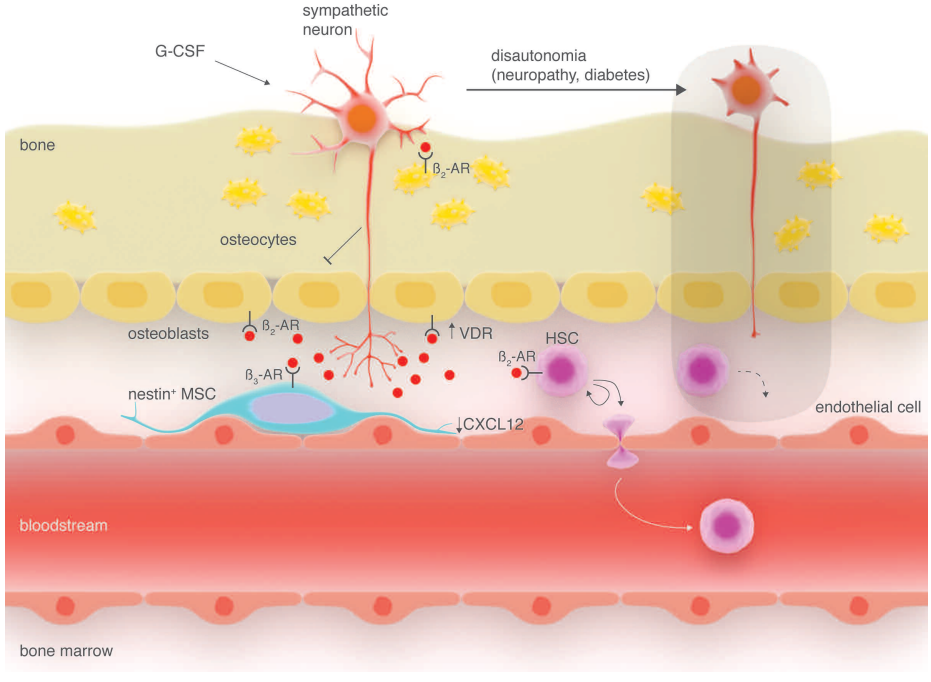

Figure 1. Sympathetic regulation of BM HSC egress and mobilization. G-CSF elicits HSC mobilization in part through stimulation of sympathetic activity which is propagated along osteocytes and leads to increased VDR expression and suppression of osteoblasts, CXCL12 downregulation in osteoblasts and nestin+ MSCs, and HSC proliferation and migration to bloodstream. Neuropathy/disautonomia caused by chemotherapy or diabetes impairs HSC mobilization. G-CSF, granulocyte colony-stimulating factor; HSC: haematopoietic stem cell; MSC: mesenchymal stem cell; VDR: vitamin D receptor; AR: adrenergic receptor.

devised novel culture conditions to better preserve MSC self-renewal, a stem cell property that has rarely been proven for MSCs due to the lack of proper assays. Unlike other BM stromal cells, nestin-positive cells formed clonal multipotent and self-renewing mesenchymal spheres.[27] We have first reported that similar human BM mesenspheres can indeed expand human umbilical cord blood HSPCs (S Mendez-Ferrer, personal communication, 2012),[28] and this was later confirmed.[29]

Recently, there has been increasing evidence involving the disautonomia (or malfunction of the autonomic nervous system) in abnormal hematopoiesis and also in cancer progression. The disautonomia associated to diabetes has been shown to affect also the BM, disrupt the peripheral clock and compromise the mobilization of endothelial and hematopoietic progenitors from the BM.[30,31] In addition, the BM neuropathy caused by chemotherapy has been shown to compromise hematopoietic recovery[4] (Figure 1).

Psychological and behavioral factors, including stress, depression and social isolation, are considered to contribute to the progression of certain types of cancer in humans. Activation of the hypothalamic-pituitary-adrenal axis plays an important role in this response. Stress-induced release of catecholamines has been shown to activate the β_2-adrenergic receptor on ovarian carcinoma cells and trigger increased expression of vascular endothelial growth factor (VEGF), resulting in enhanced tumor vascularization and more aggressive growth and spread of malignant cells.[32] Similarly, increased noradrenaline, adrenaline, cortisol, VEGF and cAMP in a social stress mouse model promoted the progression of pancreatic cancer xenografts, whereas reduction of cAMP by the inhibitory neurotransmitter g-aminobutiric acid (GABA) prevented tumor progression.[33] Poor prognosis in some epithelial cancers also has been correlated to perineural invasion, a process by which tumor cells migrate and proliferate along the nerves. A retrospective blinded analysis of prostate adenocarcinoma specimens has correlated the density of sympathetic and parasympathetic nerve fibers with a poor clinical outcome. In addition, this provocative study has shown in mouse models that peripheral nerves, both sympathetic and parasympathetic fibers, regulate the progression and dissemination of prostate cancer, although the mechanisms that drive the growth of these nerves into the prostatic tumor and their specific effects on the tumor and stromal cells remain to be determined.[34]

A population-based study has shown less advanced breast cancer and reduced associated mortality in patients that had been taking β-blockers.[35] This promotion of breast cancer progression by β-adrenergic signaling seems to be mostly due to increased tumor infiltration by macrophages and enhanced metastasis, rather than to changes in primary tumor growth.[36] Along this line, a very elegant work has recently shown that the breast tumor stroma can skew heterogeneous cancer cells towards clones that have constitutively higher Src activity and are, therefore, hypersensitive to CXCL12 and IGF-1; the blockade of CXCL12/IGF-1 receptors did not change tumor growth but reduced their metastasis to bone. Since CXCL12 and IGF-1 are highly enriched in the BM, the breast tumor stroma would prime these cancer cells for bone metastasis[37] (Figure 2). In the BM, macrophages have been shown to induce CXCL12 expression by resident MSCs[38] which in turn can regulate the migration of pro-inflammatory monocytes.[39] It remains unknown whether the sympathetic regulation of MSCs and/or monocytes underlies some of the observed changes in the primary tumor stroma and the metastatic BM environment. In addition, sympathetic-dependent but CXCL12-independent pathways have been shown to increase the bone metastasis of breast cancer cells; the β_2-adrenergic-induced expression of receptor activator of nuclear factor κ B (RANKL), a known activator of bone degradation, has been shown to increase bone metastasis of breast cancer cells independently of CXCL12 signaling.[40]

In summary, emerging evidence underscores the importance of the autonomic nervous system in the regulation of hematopoiesis and cancer. Malfunction of this master regula-

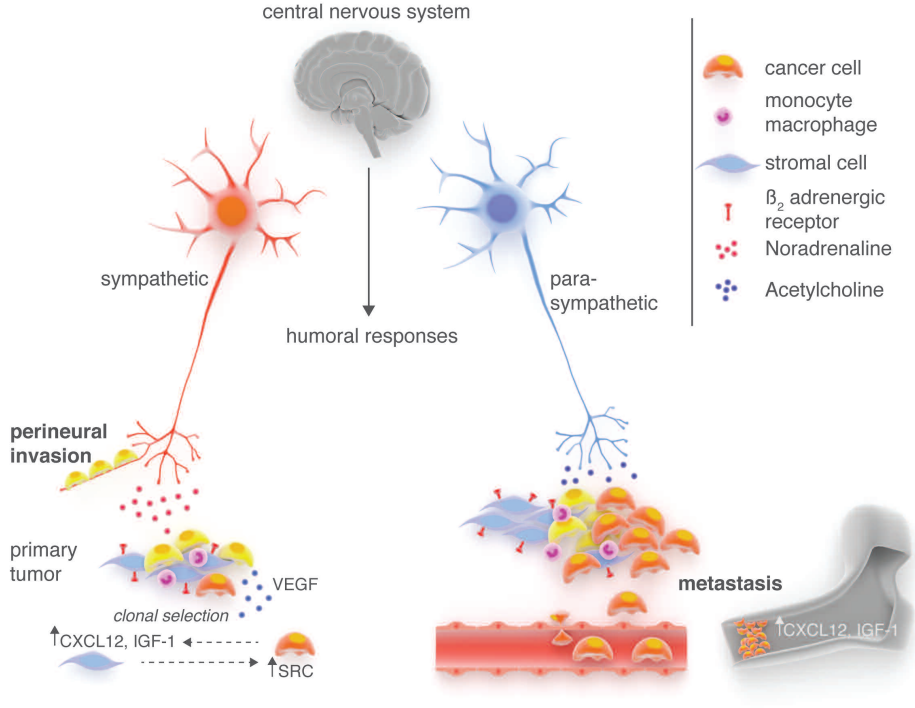

Figure 2. Autonomic regulation of cancer progression and dissemination. Model containing recent findings on the role of the autonomic nervous system and stromal cells in tumor growth and metastasis. Sympathetic nerves have been shown to contribute to perineural invasion of cancer cells, stimulate the tumor growth and the infiltration of monocytes. Cancer cells induce the expression of CXCL12 and IGF-1 by stromal cells, which in turn select for the growth of clones that are hypersensitive to these factors and are primed for metastasis in CXCL12- and IGF-1- enriched bone marrow. Parasympathetic nerves contribute to cancer cell expansion and dissemination.

tor is gaining relevance as a contributor to impaired hematopoiesis, cancer progression and dissemination. The ground is paved for creative multisystem physiology research on pathways whose participation in human disease was previously underappreciated.

The authors truly apologize for the omission of relevant literature only due to space constrictions.

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