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Blood and Genomics

2021, 5(1): 68−72

B & G

Letter to the Editor

Impact of the sympathetic nervous system on multiple myeloma

Dear Editor,

Multiple myeloma (MM), the second most common blood cancer in the United States, is a neoplasm of immunoglobulin-producing plasma cells that depend on the bone marrow (BM) for growth and survival. Quintessential disease manifestations include a serum M-spike (paraprotein), osteolytic lesions, hypercalcemia, anemia and kidney damage. Owing to targeted myeloma drugs, newly developed immunotherapies and the refinement of therapeutic regimens that combine high-dose chemotherapy with autologous hematopoietic stem cell (HSC) transplants, the outcome of MM has significantly improved in recent years. Nonetheless, after a period of successful therapy, the great majority of patients relapse with drug-resistant disease that leaves few therapeutic options. Despite significant advances in our understanding of the mechanism with which the BM microenvironment (BMM) supports myeloma, little attention has been paid to an integral yet understudied player in the tumor microenvironment (TME): the autonomic nervous system (ANS). Autonomic nerves, which can be divided into an adrenergic "fight-or-flight" sympathetic branch and a cholinergic "rest-and-digest" parasympathetic branch, interact with the BMM. In the past the ANS has been perceived as a passive bystander in myeloma and related blood cancers, yet increasing evidence reviewed in greater depth elsewhere implicates autonomic nervous input – particularly from the sympathetic nervous system (SNS) – in the natural history and outcome of myeloma[1]. Here, we summarize findings on the role of the SNS in MM and point to knowledge gaps that may afford exciting opportunities for international research collaboration with myeloma and blood cancer centers in China.

Sympathetic input inhibition improves myeloma outcome

A recent retrospective outcome analysis of MM demonstrated that anti-adrenergic β-blocker intake led to reduced risk of disease-specific death and overall mortality compared to non-β-blocker cardiac drug use or no use of cardiac drugs[2]. The study, which indicated that dampening adrenergic signaling benefits patients with myeloma (***Fig. 1A***), was in agreement with a recent clinical trial on the broad-spectrum β-blocker propranolol[3] demonstrating that adrenergic inhibition in myeloma down regulates a gene expression signature of heightened risk called conserved transcriptional response to adversity (CTRA)[4]. The study also agreed with population-based findings that associated β-blocker intake with reduced mortality in other cancers and a large body of evidence that sympathetic activation due to psychological distress including anxiety and depression results in heightened mortality in cancer. In a meta-analysis of myeloma survival, psychological distress was associated with significantly inferior death outcome at a hazard ratio of 2.36. A prospective study that arrived at the same conclusion showed that myeloma and lymphoma patients with depressive symptoms have an approximately twofold risk elevation for all-cause mortality. This backdrop provides a strong rationale for future clinical trials on the potential benefits that patients with myeloma may gain from antidepressants and/or non-pharmacological interventions such as psychotherapy to enhance positive psychological resources. Traditional Chinese Medicine (TCM) approaches in trials of this sort may hold great promise.

Myeloma bone disease

Because bone remodeling is modulated by ANS activity under normal and pathological conditions, it stands to reason that the general and focal bone loss seen in myeloma is also impacted by autonomic signals. ANS regulates skeletal homeostasis by means of an "autonomic tone" i.e., the net result of the sympathetic and parasympathetic input that promotes bone resorption and bone formation, respectively. In sync with that, anti-adrenergic β-blockers have

https://doi.org/10.46701/BG.2021012021107

beneficial effects on rebuilding bone mineral density and reducing fracture risk. Conversely, psychological stress and anxiety increase SNS-dependent bone loss by virtue of a β-adrenergic RANKL (receptor activator of nuclear factor kappa-B ligand)-dependent pathway that activates osteoclast function (***Fig. 1B***). An important treatment-related connection between myeloma bone disease with autonomic nerve damage and adrenergic signal strength is bortezomib (proteasome inhibitor) induced peripheral neuropathy. The underlying pathophysiology is poorly understood but appears to involve NFκB (nuclear factor kappa-B)-dependent downregulation of brain-derived neurotrophic factor (BDNF), a newly emerged serum marker for risk assessment of peripheral neuropathy in patients with myeloma[5]. Because bortezomib exerts welcome anabolic effects on bone, research is under way to deliver the drug to target sites in bone without increasing the risk of neuropathy.

Putative multiple myeloma stem cell (MMSC)

Biological pathways that govern ANS control of normal hematopoietic stem cell (HSC) activity are of interest to myeloma because they may also regulate the reactivation of MMSCs – enigmatic, dormant cancer stem cell-like cells that are of great relevance for tumor relapse and acquisition of drug resistance. The sympathetic input to hematopoietic stemness is better defined than its parasympathetic counterpart (***Fig. 1C***). Sympathetic nerves are an intrinsic constituent of the HSC niche and participate in both niche-driven blood cancers and niche remodeling by cancer cells. Sympathetic signaling is also involved in early niche development and, conversely, age-dependent niche deterioration brought about by adrenergic nerve degeneration. It is unclear to which extent if any workings of SNS-dependent HSC regulation can be extrapolated to MMSCs. However, recent reports on adrenergic support of breast cancer stem cells and sympathetic signal-dependent re-activation of quiescent BM-resident prostate cancer cells suggest a broader relevance across the cancer spectrum. Thus, dedicated research projects are warranted to define the role sympathetic nerves may play in creating and maintaining MMSC survival niches in the hematopoietic BM and other tissue sites.

HSC mobilization

Sympathetic signaling is also involved in induced mobilization of HSCs, an important aspect of myeloma treatment protocols that involve bone marrow transplantation. Sympathetic input governs, in part, egress of HSCs from bone marrow niches into the peripheral blood stream. This relies on a molecular pathway that includes adrenergic activation of the β3 receptor on BM stromal cells, leading to reduced expression of the chemokine receptor ligand, CXCL12 (C-X-C motif chemokine ligand 12). Because binding of this ligand to CXCR4 (C-X-C motif chemokine receptor 4) on HSCs and malignant plasma cells provides a crucial BM retention signal for these cells, SNS-dependent downregulation of CXCL12 facilitates their exit from the BM. Stimulation of SNS neurons with granulocyte-colony stimulating factor (G-CSF) potentiates the sympathetic tone by increasing norepinephrine (NE) availability due to reuptake inhibition. Desipramine, an FDA-approved tricyclic antidepressant, which further increases sympathetic activity, synergizes with G-CSF in HSC mobilization in patients with myeloma[6]. Future research in this field may yield pharmacological interventions to flush out quiescent myeloma cells, including stem cell-like myeloma cells, from their survival-protecting BM niche, and force these cells into peripheral circulation where they could be readily killed with conventional cytostatic agents. If successful, this could be an important step towards finding a cure for myeloma.

Impact of SNS on myeloma development

Dedicated studies on the involvement of the ANS in the natural history of MM (myelomagenesis) are lacking. However, other types of blood cancer have been investigated at the preclinical level using mouse models. In an orthotropic model of acute lymphoblastic leukemia (ALL), two weeks of daily restraint stress (associated with elevated sympathetic tone) enhanced tumor progression, whereas treatment of mice using the β-blocker propranolol slowed it down[7]. This result, attributed in part to BMM remodeling, can be added to numerous additional findings on SNS-dependent promotion of solid and liquid tumors in laboratory mice (***Fig. 1D***). In contrast, studies on myeloid malignancy progression in mice demonstrated that sympathetic input can also inhibit neoplastic growth. In this case, sympathetic neuropathy (accompanied by diminished adrenergic signaling) promoted myeloid tumor development, whereas increased adrenergic signaling (upon treatment of mice using β2 or β3 agonists) protected sympathetic nerves and suppressed malignant growth[8]. Taken together, these findings indicate that – depending on type of malignancy and specific features of the model system employed – sympathetic pathways may promote or inhibit blood cancer development. Additional research is warranted to

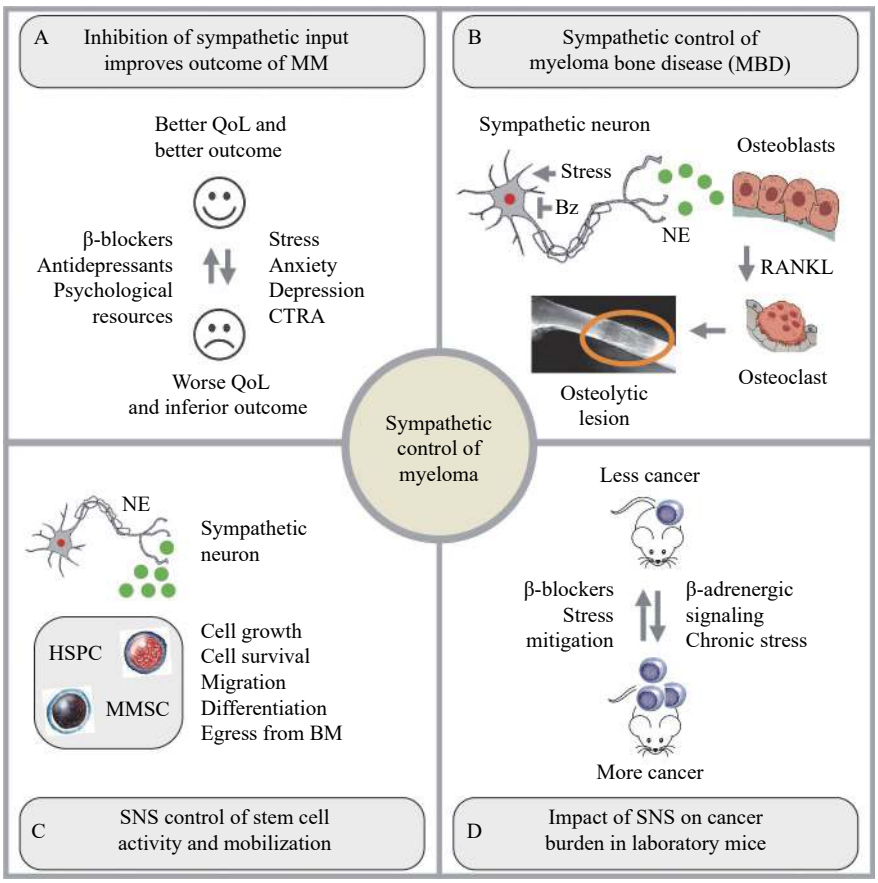

Fig. 1 **SNS impact on MM.** A: Dampening adrenergic signaling benefits patients with myeloma. β-blocker intake, which dampens adrenergic signaling, reduces disease-specific mortality in patients with myeloma (arrow pointing down). Conversely, psychological distress (anxiety, depression), which leads to increased adrenergic signaling, is associated with reduced quality of life (QoL) and inferior survival (arrow pointing up). Dysregulation of adrenergic and other stress-related signaling pathways can be evaluated with the help of the conserved transcriptional response to adversity (CTRA). B: Sympathetic nerve fibers form synapse-like structures with bone cells such as osteoblasts. Neurotransmitter NE release at the synapse stimulates β-adrenergic signal transduction leading to increased osteoblast secretion of RANKL. This in turn leads to enhanced osteoclast-dependent bone resorption and focal bone loss (beige ellipse). C: NE release by sympathetic nerves initiates signal transduction in hematopoietic stem and progenitor cells (HSPC) and, possibly, myeloma stem cells (MMSC). D: Chronic stress and elevated adrenergic input are strongly linked to malignant growth in laboratory mice (downward arrow). Conversely, mice housed in a stress-mitigated, enriched environment or treated with anti-adrenergic β-blocker exhibit reduced rates of neoplastic growth (upward arrow). In most model systems investigated thus far, enhanced adrenergic signaling promotes cancer. However, whether SNS input facilitates neoplastic plasma cell development (oncogenesis) has not been demonstrated. Reports on SNS-dependent inhibition of myeloid neoplasms in mice put the preclinical myeloma research community on guard to keep an open mind.

clarify how SNS control plays out in the natural history of plasma cell neoplasms in human beings. Genetically engineered mouse models (GEMMs) of human myeloma may provide valuable assistance to that end.

Uncertainty about parasympathetic input in myelomagenesis

Clear-cut experimental evidence of parasympathetic input contributions to tumor progression is currently limited to solid cancers, in which acetylcholine (ACh) may be produced by two principal sources: the parasympathetic nerve in the tumor microenvironment and the tumor cell itself. Prostate cancer cells, for example, co-express the key enzyme for ACh synthesis, choline acetyltransferase, and one of the receptors ACh binds to CHRM3 (cholinergic muscarinic receptor 3). The ability of the tumor cells to secrete ACh may result in high local concentrations of the neurotransmitter and, thereby, enable an autocrine cholinergic loop that drives tumor progression. Consistent with that, overexpression of CHRM3, or receptor activation using carbachol, promoted prostate cancer growth and castration resistance in mice, whereas treatment of mice with the

selective CHRM3 antagonist, darfenacin, inhibited these phenotypes. In a gastric cancer study, cholinergic signaling was found to facilitate neuron expansion and tumor development by virtue of upregulating NGF (nerve growth factor) production and activation of YAP (yes-associated protein 1) signaling, respectively. Conversely, inhibition of parasympathetic input downregulated Wnt signaling and suppressed tumor stem cell expansion in a CHRM3-dependent fashion.

Upregulation of cholinergic receptor genes prognosticates inferior survival of patients with myeloma

In sync with the possibility that cholinergic input may promote tumor progression, as suggested by the preclinical findings described above, a recent analysis of a large, publicly available database of patients with myeloma demonstrated that upregulation of cholinergic receptor-encoding genes is associated with inferior survival. The prognostic impact of two genes, *CHRM3* and *CHRNB4*, is depicted in ***Fig. 2***. Similar associations were observed for two additional cholinergic receptor genes, *CHRM2* and *CHRNA5*, but not for any of the β adrenergic receptor genes (results not shown). Intriguingly, epidemiologic evidence links occupational exposure to cholinergic compounds (pesticides) with increased incidence of MM. But these findings should be interpreted with caution because cholinergic input may also inhibit tumor progression. This was recently shown for pancreatic carcinoma in mice, in which subdiaphragmatic vagotomy or genetic knockout of CHRM1 accelerated oncogenesis, whereas cholinergic pathway activation following systemic administration of muscarinic agonist, bethanechol, suppressed tumor stemness. Thus, in analogy to the dual role of the SNS in oncogenesis, parasympathetic input may operate as a double-edged sword that either promotes or inhibits neoplastic growth depending on circumstances.

A growing body of evidence demonstrates the involvement of sympathetic (adrenergic) pathways of autonomic tissue control in the natural history and outcome of MM. Comparatively little is known about the role of parasympathetic (cholinergic) inputs. To enhance our understanding of ANS control of myeloma and make further progress in the field of neuro-oncology, a joint interdisciplinary research effort of clinical oncologists and laboratory-based investigators from diverse fields of neuro and cancer biology, genetics and immunology will be required.

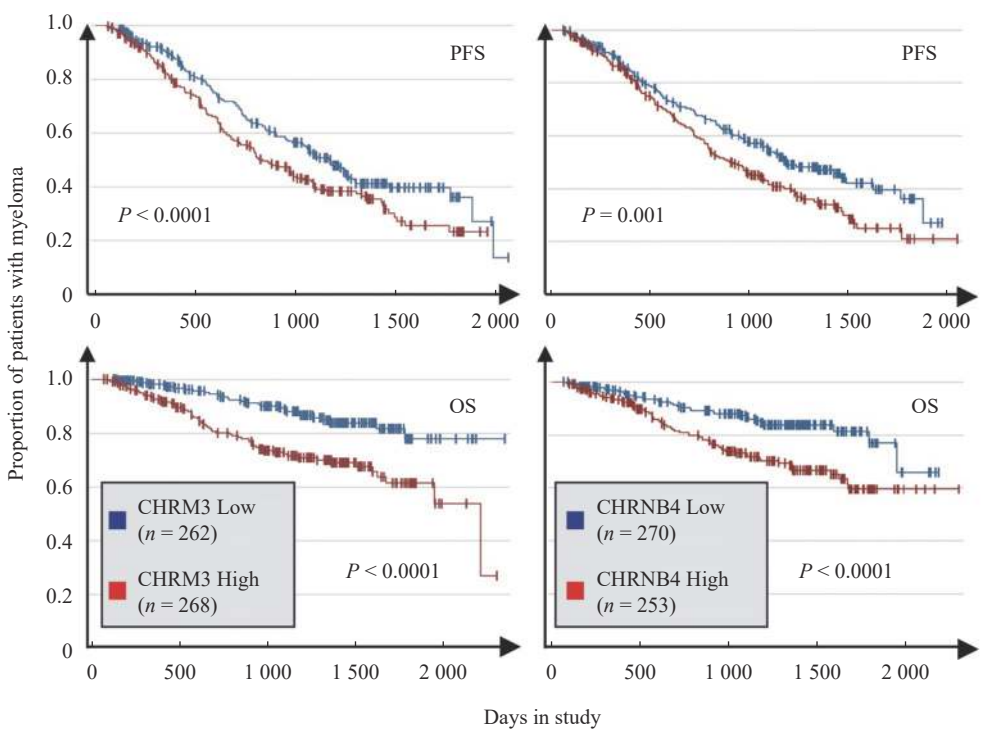

Fig. 2 **Elevated cholinergic receptor mRNA levels in myeloma cells predict poor survival in the MMRF CoMMpass study.** Kaplan-Meier curves of progression free survival (PFS) and overall survival (OS) are plotted. Censored patients are indicated by short vertical lines. Median gene expression was used as cutoff to allocate patients to the high expressor (red curve) or low expressor (blue curve) group. The number of patients in each group is shown. The results of log-rank analyses for differences in survival are included.

Dedicated clinical trials that target SNS-dependent pathways of myeloma treatment and progression in order to improve disease outcome should be designed to that end. Trials of this sort should be accompanied by biochemical measurements of mRNA and protein expression levels of adrenergic and cholinergic receptors in myeloma and by studies on NE- and ACh-producing pathways in tumor cells and the TME. GEMMs of myeloma may make an important contribution to this research field, particularly with regard to molecular mechanisms that are difficult to elucidate in clinical studies on myeloma. Because the number of references is limited in this letter to eight, the reader is referred elsewhere for an in-depth discussion of the subject matter[1].

This work was supported by the William G. Schuett, Jr., Multiple Myeloma Research Endowment. Additional support was provided by NCI R01 CA151354 (to SJ).

Yours Sincerely,

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Received 14 March 2021, Revised 20 April 2021, Accepted 18 May 2021