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Autonomic nervous system control of multiple myeloma

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Abstract

The autonomic nervous system (ANS), which consists of antagonistic sympathetic (adrenergic) and parasympathetic (cholinergic) arms, has emerged as an important regulator of neoplastic development, yet little is known about its role in multiple myeloma (MM). Clinical findings that anti-adrenergic β-blocker intake reduces risk of disease-specific death and overall mortality in patients with MM have indicated that adrenergic input may worsen myeloma outcome. However, preclinical studies using β-adrenergic receptor agonists or antagonists produced controversial results as to whether sympathetic pathways promote or inhibit myeloma. Retrospective outcome data demonstrating that high message levels of cholinergic receptor genes predict inferior survival in the Multiple Myeloma Research Foundation CoMMpass trial suggest that parasympathetic input may drive myeloma progression in a subset of patients. Here we review the ill-defined role of the ANS in MM, put myeloma in the context of other cancers, and discuss knowledge gaps that may afford exciting research opportunities going forward.

Keywords

Plasma cell malignancy; Sympathetic and parasympathetic tone; Adrenergic and cholinergic signaling

1. Introduction

Multiple myeloma (MM) is a neoplasm of terminally differentiated, immunoglobulin-producing B-lymphocytes, called plasma cells, that depend on the bone marrow microenvironment (BMM) for growth and survival. Quintessential disease manifestations include serum paraprotein, focal bone loss, hypercalcemia and kidney damage. With an estimated 30 thousand cases annually, MM is the second most common blood cancer in the United States. Frank myeloma is preceded by the premalignant condition, monoclonal gammopathy of undetermined significance (MGUS) [1]. Owing to both newly developed myeloma drugs and the refinement of therapeutic regimens that combine high-dose chemotherapy (melphalan) with hematopoietic stem cell (HSC) transplantation, the outcome of MM has significantly improved in recent years [2]. Nonetheless, after a period of successful therapy, the great majority of patients relapse with drug-resistant aggressive

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Author contributions

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disease that leaves few if any therapeutic options. Recent progress in our understanding of the mechanism with which the BMM supports myeloma has been expertly reviewed [3]. Strategies for targeting the BMM to block the MGUS-to-MM transition and thus prevent frank myeloma from manifesting itself are also emerging [4]. In contrast, little attention has been paid to an integral yet understudied player in the BMM: 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, infiltrate the BMM and interact with resident cells presumably including myeloma cells (Fig. 1). In the past the ANS has been perceived as a passive bystander in myeloma, yet recent research reviewed in the following has implicated autonomic nervous input in the pathophysiology and outcome of myeloma. Here, we summarize the new findings, put myeloma in the context of other blood and solid cancers, and discuss knowledge gaps that may afford exciting research opportunities going forward.

2. Pharmacological inhibition of sympathetic input improves myeloma outcome

A recent retrospective outcome analysis of multiple myeloma 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 [5] (Table 1). The result, which indicated that dampening adrenergic signaling benefits patients with myeloma (Fig. 2A), agreed with preclinical studies using laboratory mice (Fig. 2B) and findings from a recent clinical trial on the broad-spectrum β-blocker, propranolol, [6] demonstrating that adrenergic inhibition down regulates the conserved transcriptional response to adversity (CTRA) in myeloma [7]. The result was also consistent with population-based studies associating β-blocker intake with reduces mortality in other cancers [8–10] and a large body of evidence that sympathetic activation due to psychological distress including anxiety and depression results in heightened mortality in cancer [11]. In a meta-analysis of myeloma survival, psychological distress was associated with significantly inferior death outcome at a hazard ratio of 2.36 [12]. A prospective study, which arrived at the same conclusion, demonstrated that myeloma and lymphoma patients with depressive symptoms have an approximately twofold risk elevation for all-cause mortality [13]. Due in part to intense treatment regimens requiring long periods of hospitalization [14], chronic stress and depression are prevalent in patients with myeloma and other hematological cancers [15]. In a study on myeloid neoplasia, for example, 40% and 31% of patients met National Comprehensive Cancer Network (NCCN) and Hospital Anxiety and Depression Scale (HADS) criteria for distress and anxiety, respectively; and one of eight patients (12.5%) was diagnosed with outright depression [16]. Clinical trials are warranted to determine whether myeloma patients may benefit from interventions to enhance positive psychological resources using psychotherapy [17,18] and antidepressants [19]. Simple yet efficient tools for assessing mental health and psychological burden are available to support trials of this sort [20], and to develop viable strategies for enhanced quality of life (QOL) and improved outcome of patients with myeloma.

3. Divergent impact of sympathetic input modulation on myeloma growth and survival

Consistent with the clinical and epidemiologic evidence described above, preclinical studies have demonstrated that the β-blocker propranolol hampers proliferation and survival of the myeloma cell line U266 [21]. Conversely, adrenergic receptor stimulation with epinephrine (adrenaline) promoted growth and chemoresistance of these cells [22], and norepinephrine (noradrenaline) stimulated the growth of IL-6 dependent FLAM-76 myeloma cells [23] (Table 1, rows 6, 8 and 10). Although these findings support the notion that blocking β-adrenergic signaling may provide a new myeloma treatment approach, other preclinical studies suggest the opposite. Increased rather than decreased β-adrenergic signaling killed myeloma in a drug interaction assay that demonstrated synergism of the β2 adrenergic receptor (β2AR) agonist, salmeterol, with backbone myeloma drugs [24]. Similarly, another β2AR agonist, dobutamine, killed myeloma in cell culture via down regulation of MAPK signaling [25] (Table 1, rows 7 and 9). Taken together, the in vitro results are inconsistent and suggest that the beneficial effect of adrenergic inhibition on myeloma outcome in patients can perhaps better be explained by invoking an indirect mechanism, such as the impact of sympathetic signaling on the immune system or BMM. Current views on adrenergic control of adaptive immune responses [26] and the role of autonomic BM innervation in normal immune function [27] are compatible with the hypothesis that pharmacological inhibition of sympathetic input bolsters anti-myeloma immune responses. In support of that possibility, β-blocker usage improved the survival of patients with metastatic melanoma undergoing immunotherapy [28] and chronic stress in patients with breast and colon cancer was found to dampen anti-tumor immunity by virtue of a pathway that included M2 macrophage polarization [29] and a shift from the Th1 to the Th2 response [30]. Preclinical results on enhanced tumor-suppressive cytotoxic T-cell responses in both β2AR-deficient mice [31] and normal mice treated with β-blockers [28] are also in line with the possibility that adrenergic inhibition boosts the immune response to cancer. Dedicated clinical trials on immune regulatory effects of β-blockers in patients with myeloma and the potential utility of these drugs to enhance immune therapies of myeloma are warranted.

4. Autonomic control of skeletal homeostasis may impact myeloma bone disease

Because bone remodeling is modulated by ANS activity under normal and pathological conditions, it seems reasonable to postulate that the general and focal bone loss seen in patients with 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 [32]. In sync with that, anti-adrenergic β-blockers have beneficial effects on rebuilding bone mineral density and reducing fracture risk [33]. The full impact of autonomic signals on myeloma bone disease (MBD) has not yet been determined, but circumstantial evidence reviewed by Olechnowicz and Edwards [34] suggests that the sympathetic nervous system (SNS) plays a significant role. Accordingly, psychological stress and anxiety experienced by patients with myeloma may cause SNS-dependent bone loss, using a mechanism that relies

on the β-adrenergic pathway in osteoblasts to increase the effect of signals that inhibit osteoblast but activate osteoclast function (Fig. 3A) [34]. An important treatment-related connection of MBD with autonomic nerve damage and adrenergic signal strength is bortezomib (proteasome inhibitor) induced peripheral neuropathy [35,36]. The underlying pathophysiology is poorly understood but appears to involve NFκB-dependent downregulation of brain-derived neurotrophic factor (BDNF) [36–38], a newly emerged serum marker for risk assessment of peripheral neuropathy in patients with myeloma [39]. 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 [40]. In sum, elucidating the impact and mechanism with which the ANS modulates MBD is an interesting area for future research.

5. Autonomic control of hematopoietic stem cell activity may extend to myeloma stem cells

Biological pathways that govern ANS control of normal hematopoietic stem cell (HSC) activity [41] are of interest to myeloma because they may also govern dormancy and activation of multiple myeloma stem cells (MMSCs), enigmatic cancer stem cell-like cells that are of great relevance for tumor relapse and acquisition of drug resistance in myeloma [42]. Similar to the regulation of skeletal homeostasis discussed above, the sympathetic input to hematopoietic sternness is better defined than its parasympathetic counterpart. Sympathetic nerves are an intrinsic constituent of the HSC niche and participate in both niche-driven blood cancers and niche remodeling by cancer cells [43]. Sympathetic signaling is also involved in early niche development [44] and, conversely, age-dependent niche deterioration brought about by adrenergic nerve degeneration [45]. The latter has been modeled in mice, in which surgical denervation or genetic ablation of β3AR led to premature HSC aging [46]. It is unclear whether these results can be extrapolated to MMSCs, but recent findings on adrenergic support of breast cancer stem cells [47] and sympathetic signal-dependent re-activation of quiescent, BM-resident prostate cancer cells [48] point to a broader relevance across the cancer spectrum. Of note, hyperactivation of adrenergic signaling may be as detrimental for stem cell function as loss of signaling. This has been recently shown for chronic stress-induced greying of black laboratory mice that could be attributed to the SNS hyperactivation-dependent depletion of melanocyte stem cells in hair follicles [49]. Whether cancer stem cell-like cells exhibit similar susceptibilities is not known. A schematic overview of ANS control of HSC function, with a MMSC and a mesenchymal stem cell (MSC) shown in a neighboring niche, is presented in Fig. 3B. Defining what role, if any, sympathetic nerves may play in creating and maintaining MMSC survival and proliferation niches is an important task for future research.

6. Autonomic control of stem cell mobilization in myeloma treatment

Sympathetic signaling is also involved in induced mobilization of HSCs [43], an important aspect of myeloma treatment protocols that involve autologous or allogeneic bone marrow transplantation (BMT). Sympathetic input governs, in part, egress of stem cells from bone marrow niches into the peripheral blood stream [50]. This relies on a molecular pathway that

includes adrenergic activation of the β3 receptor on BM stromal cells and reduced expression of chemokine receptor ligand CXCL12 (C-X-C motif chemokine ligand 12) [51]. The ligand binds to CXCR4 (C-X-C motif chemokine receptor 4) on HSCs and malignant plasma cells, providing not only a crucial mechanism for the retention of these cells in the bone marrow but also a promising opportunity for therapeutic targeting [52,53]. Stimulation of SNS neurons with granulocyte-colony stimulating factor (G-CSF) potentiates the sympathetic tone by increasing norepinephrine availability due to reuptake inhibition [54]. Desipramine, a FDA-approved tricyclic antidepressant, takes advantage of this mechanism to increase sympathetic activity and, thereby, synergize with G-CSF in HSC mobilization in mice [54] and patients with myeloma [55]. Indeed, an open-label single-arm pilot study on autologous stem cell transplantation in myeloma showed that the combination of desipramine and G-CSF is safe and, importantly, results in improved HSC mobilization versus G-CSF alone [55]. This backdrop demonstrates that elucidating ANS pathways of hematopoietic stem and progenitor mobilization may refine established BMT protocols and render them more effective. What is more, research along this line may lead to new strategies for flushing out quiescent myeloma cells, including stem cell-like cells, from their survival-protecting BM niche to the peripheral circulation. This may force them to re-enter the active cell cycle and thus become vulnerable to killing using conventional cytostatic agents.

7. Widespread sympathetic control of cancer progression suggests complicity in myeloma

The involvement of the ANS in the natural history of solid and hematologic cancers is increasingly recognized [56,57]; however, dedicated studies on myeloma are lacking. While both arms of autonomic tissue control have been firmly implicated in solid cancer development (see the next section for a brief discussion of cholinergic pathways), the bulk of evidence for blood cancers points to the sympathetic arm. Thus, in an orthotropic mouse model of acute lymphoblastic leukemia (ALL), two weeks of daily restraint stress (accompanied by elevated sympathetic tone) enhanced tumor progression, whereas treatment of mice using the β-blocker propranolol slowed it down [58]. This model of ALL provides an example of SNS-promoted oncogenesis by virtue of BMM remodeling [59]. The elucidation of the mechanism with which sympathetic input drives cancer began with pioneering studies on mouse models of human cancer [29,60,61]. For example Magnon et al. analyzed sympathetic innervation of prostate cancer in mice, demonstrating that sympathetic denervation – either by means of surgical cutting or injection of neurotoxic drugs – suppresses tumor progression and metastasis [61]. The most well-understood input is the β2-adrenergic signal delivered by sympathetic nerves to cancer and bystander cells equipped with β2AR. Binding of (nor)epinephrine to the receptor activates the c-AMP/PKA pathway that regulates many aspects of cancer biology [62,63]. Additional mechanisms of β2AR-dependent tumor promotion include AKT-dependent metabolic reprogramming and inhibition of autophagy, as seen in hepatocellular carcinoma [64]; neoangiogenesis and remodeling of the tumor microenvironment, observed in ovarian [60] and prostate cancer [65]; and neurotrophin-induced outgrowth of nerve ends (axogenesis) found in pancreatic

ductal adenocarcinoma [66]. Elevated axogenesis resulting in increased overall tumor innervation may also be accomplished by tumor cell-released exosomes [67].

In contrast to the results summarized above, two landmark studies on myeloid malignancy progression in mice have demonstrated that sympathetic input can also inhibit neoplastic growth. In this case, sympathetic neuropathy (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 [68,69]. The neuropathy seen in this model system resulted from proinflammatory factors secreted by tumor cells in the BMM. This is the stark opposite of the neuroprotective and axon-nurturing effect of pancreatic cancer cells mentioned above. Taken together, the 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. This raises an urgent need for clarifying how SNS control plays out in the natural history of plasma cell neoplasia including MM. Mechanistic studies of this kind are difficult to pursue in humans but can be readily carried out with the assistance of a genetically engineered mouse model (GEMM) of human myeloma available in our laboratory (Fig. 4). This model takes advantage of adoptive transfer of oncogene-activated premalignant B cells genetically “hard wired” to undergo neoplastic plasma cell development in a preconditioned host. Among the many strengths of the model is the opportunity to compare the impact of a potential driver of oncogenesis, such as adrenergic signaling, in tumor precursors vs bystander cells in the tumor microenvironment (TME).

8. Possible role of cholinergic signaling in myeloma progression and outcome

Clear-cut experimental evidence of parasympathetic input contributions to tumor progression is currently limited to solid cancers, in which acetylcholine may be produced by two principal sources: the parasympathetic nerve in the TME and the tumor cell itself. Prostate cancer cells, for example, co-express the key enzyme for acetylcholine synthesis, ChAT (choline acetyltransferase), and one of the receptors acetylcholine is binding to, CHRM3 (cholinergic muscarinic receptor 3). The ability of the tumor cells to secrete acetylcholine 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 [70], whereas treatment of mice with the selective CHRM3 antagonist, darfenacin, inhibited these phenotypes [70]. In a gastric cancer study, cholinergic signaling was found to facilitate neuron expansion and tumor development by virtue of upregulating NGF production and activating YAP (yes-associated protein 1) signaling, respectively [71]. Conversely, inhibition of parasympathetic input downregulated Wnt signaling and suppressed tumor stem cell expansion in a CHRM3-dependent fashion [72]. On the other hand, 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 sternness [73]. These results underline the complexity of parasympathetic control of tumor progression and direct attention to CHRM3, which is involved in the prostate and gastric cancer models mentioned above. We found in ongoing, unpublished work that upregulation of the receptor-encoding gene, *CHRM3*, is associated with inferior survival in a large, publicly available database of patients with myeloma (Fig. 5). Similar associations were observed for three additional cholinergic receptor genes (*CHRM2, CHRNA5, CHRNB4*) but not for any of the βAR-encoding genes (results not shown). Intriguingly, a large body of epidemiologic evidence links occupational exposure to cholinergic compounds (pesticides) with increased incidence of MM [74,75]. This lends support to the possibility that parasympathetic signals are involved in myeloma development. GEMMs of human myeloma, including the one shown i: Fig. 4, may lend themselves to testing this hypothesis in a definitive manner, under genetically and environmentally controlled conditions not feasible for clinical trials.

9. Summary and future directions

A growing body of evidence demonstrates the involvement of sympathetic (adrenergic) and parasympathetic (cholinergic) pathways of autonomic tissue control in the development and progression of solid tumors including breast, prostate, pancreatic, colon and stomach cancer [76]. In contrast, little is known about the significance of autonomic signaling in multiple myeloma (MM) and related plasma cell neoplasms. To remedy this shortcoming and enhance our understanding of ANS control of myeloma, a joint interdisciplinary collaborative research effort of expert oncologists and laboratory-based investigators from diverse fields of neuro- and cancer biology, genetics and immunology will be required. The clinical and epidemiologic results that are available at this juncture suggest that adrenergic input plays a role in the pathophysiology and outcome of myeloma. Chronic stress including anxiety and depression, going hand in hand with smoldering sympathetic (hyper)activation, have been repeatedly linked to elevated death rates in myeloma. In sync with that, a recent retrospective outcome analysis showed that anti-adrenergic β-blocker intake is associated with reduced risk of disease-specific mortality in patients with myeloma [5]. The beneficial effect of β- adrenergic receptor blockade is not unique to myeloma but has also been demonstrated in other cancers. For example, use of β1/β2 inhibitor, atenolol, for at least 3 years has been recently shown to lead to a significant reduction in odds of detecting clinically-significant intermediate and high-risk prostate cancer on initial prostate biopsy [77].

To develop a more complete understanding of the impact of the ANS on myeloma, it will be important in future studies to distinguish the direct crosstalk of autonomic nerves with tumor cells (using a synapse-like makeup?) from interactions with non-malignant bystander cells in the bone marrow microenvironment (BMM) such as immune, endothelial and bone cells. Indirect effects of ANS signaling may be highly relevant for MM, a prototype of a malignancy that exhibits exquisite dependence on a supportive tumor microenvironment (TME). Indirect ANS effects are important for normal plasma cell formation in mice, which requires B lymphocytes to express cholinergic nicotinic receptors that bind ACh supplied by NE-stimulated $CD4^+$ T cells [78]. A challenging research task going forward concerns the possibility that ANS neurotransmitter (NE, ACh)-stimulated pathways regulate distinct

stages of tumor development; e.g., the MGUS-to-MM transition early on as opposed to drug-resistant relapse at the terminal stage of disease progression. Another outstanding problem is to elucidate the role, if any, of parasympathetic signaling in myeloma. The somewhat surprising finding reported here that high message levels of cholinergic receptor genes in myeloma cells predict poor survival in the MMRF CoMMpass study suggests that cholinergic pathways promote myeloma progression. However, the reality that experimental data in support of this theory is lacking; the possibility that the elevation of receptor message is a simple compensatory change driven by some other autonomic dynamic (e.g., low cholinergic pathway activity due to low ACh ligand levels); and the preclinical result described in the previous section that cholinergic input inhibits pancreatic carcinoma in laboratory mice [73] all put us on guard to keep an open mind.

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Declaration of Competing Interest

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Abbreviations:

ACh	acetylcholine
AChR	cholinergic receptor
ANS	autonomic nervous system
AR	adrenergic receptor
BM	bone marrow
BMM	bone marrow microenvironment
ChAT	choline acetyltransferase
CHRM	cholinergic muscarinic receptor
HSC	hematopoietic stem cell
HSPC	hematopoietic stem and progenitor cell
MBD	myeloma bone disease
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma

NE	norepinephrine
PSN	parasympathetic nervous system
SNS	sympathetic nervous system
TME	tumor microenvironment

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Practice points

- Chronic stress and depression, along with heightened sympathetic input, are prevalent in myeloma and associated with twofold risk elevation for all-cause mortality.
- Myeloma patients may benefit from β-blockers, competitive small-compound inhibitors of β-adrenergic signaling.
- Myeloma patients may benefit from stress relief, psychotherapy and interventions aimed at enhancing positive psychological resources.
- Evidence that environmental and occupational exposure to cholinergic compounds promotes myelomagenesis suggests that conclusions that sympathetic activation and adrenergic signaling are the sole drivers of adverse ANS-dependent outcomes in myeloma are premature and oversimplified.
- Enhanced understanding of the ANS-myeloma crosstalk is important because it may lead to the design and testing of new approaches to treat and prevent myeloma.
- Cancer neuroscience, a burgeoning field that studies both the role of the nervous system in the natural history of cancer and the effect of cancer and cancer therapy on nervous system function [79], is relevant for myeloma.

Research agenda

- Assembling integrated bench-to-bedside-and-back research teams to assess the impact of autonomic tissue control on myeloma development, progression, and outcome.
- Taking advantage of GEMMs of human myeloma to attack fundamental knowledge gaps on biological pathways and molecular mechanisms of ANS regulation of myeloma.
- Determining mRNA and protein expression levels of adrenergic and cholinergic receptors in new and relapses myeloma and conducting biochemical studies on NE- and ACh-producing pathways in myeloma.
- Translating insights into ANS control of normal HSC activity to new strategies for therapeutic targeting of multiple myeloma stem cells (MMSCs).
- Assessing impact of peripheral neuropathy on myeloma bone disease (MBD).
- Evaluating whether sensory nerves – which, just like their autonomic counterparts, belong to the peripheral nervous system (PNS) – act as more than conduits for MBD-related pain transmission in myeloma [80].
- Designing clinical trials that target ANS-dependent pathways of myeloma treatment and progression to improve the outcome of myeloma.

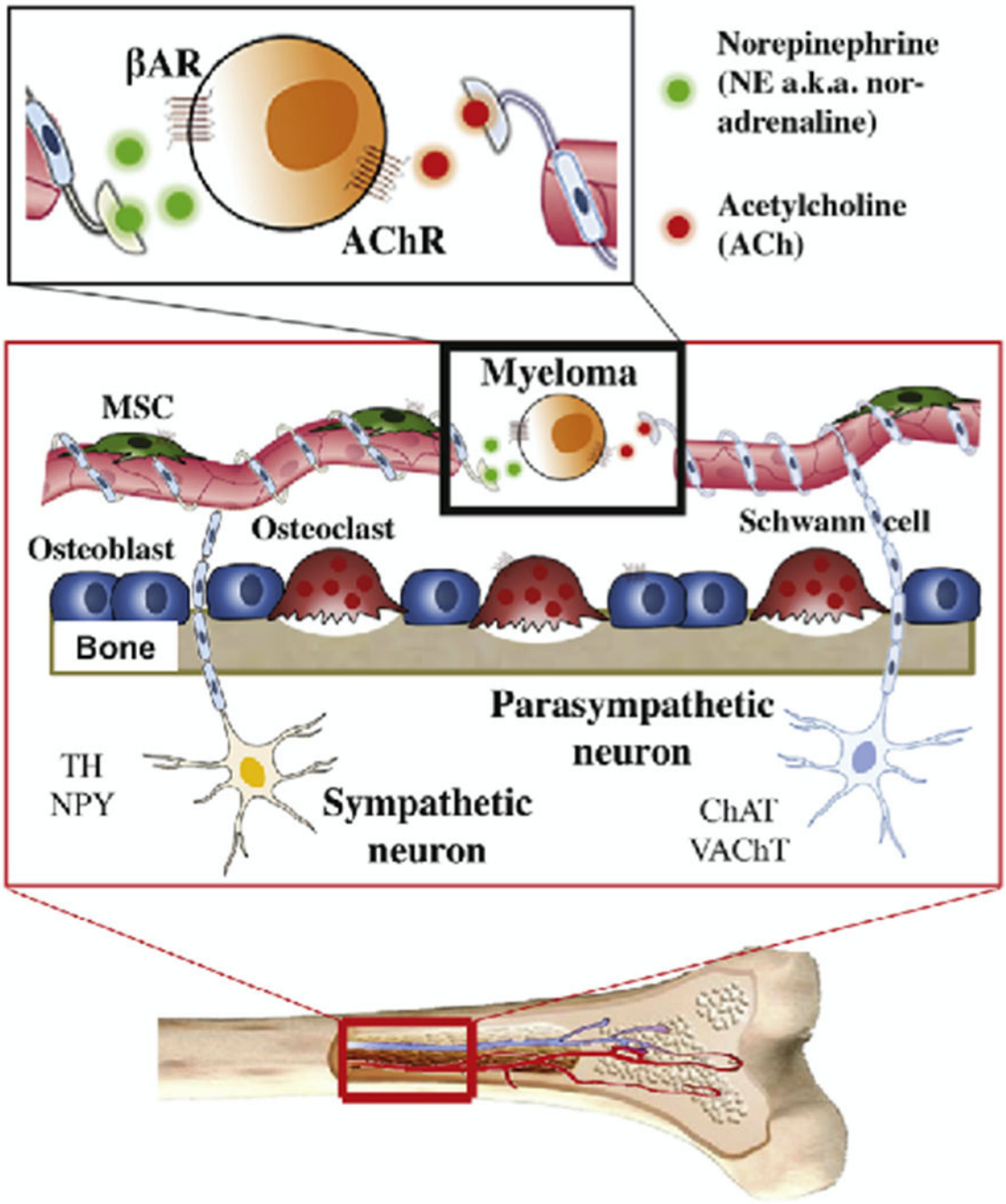

Fig. 1.

Hypothetical scheme of ANS control of myeloma in the BMM. BM in highly innervated by sympathetic and parasympathetic nerve fibers, the topographical distribution of which can be visualized with the help of immunostaining for neuronal markers. Tyrosine hydroxylase (TH), the rate-limiting enzyme of catecholamine synthesis, identifies sympathetic nerves, which are typically warped in a spiral pattern around blood vessels in the BM parenchyma and periosteum [81,82]. Neuropeptide Y (NPY), a neurotransmitter stored at sympathetic nerve endings, reveals a distribution pattern similar to that of TH fibers, yet NPY fibers are

often smaller and less abundant [82]. Choline acetyltransferase, ChAT, the key enzyme for acetylcholine production by cholinergic neurons, detects parasympathetic nerves, which are observed in proximity to hematopoietic islets under normal conditions [83]. Vesicular acetylcholine transporter (VAChT), a member of the vesicular amine transporter family, visualizes parasympathetic fibers in intertrabecular spaces [84]. Just like bone cells and mesenchymal stem (MSC) and other cells residing in the hematopoietic BM, myeloma cells are exposed to and regulated by adrenergic (sympathetic) and cholinergic (parasympathetic) signals. The former are transmitted by norepinephrine (NE), which binds to β-adrenergic receptors (β-AR). The latter are transmitted by acetylcholine, which binds to cholinergic receptors (AChR). The role of adrenergic/cholinergic signaling in myeloma development and progression is ill understood.

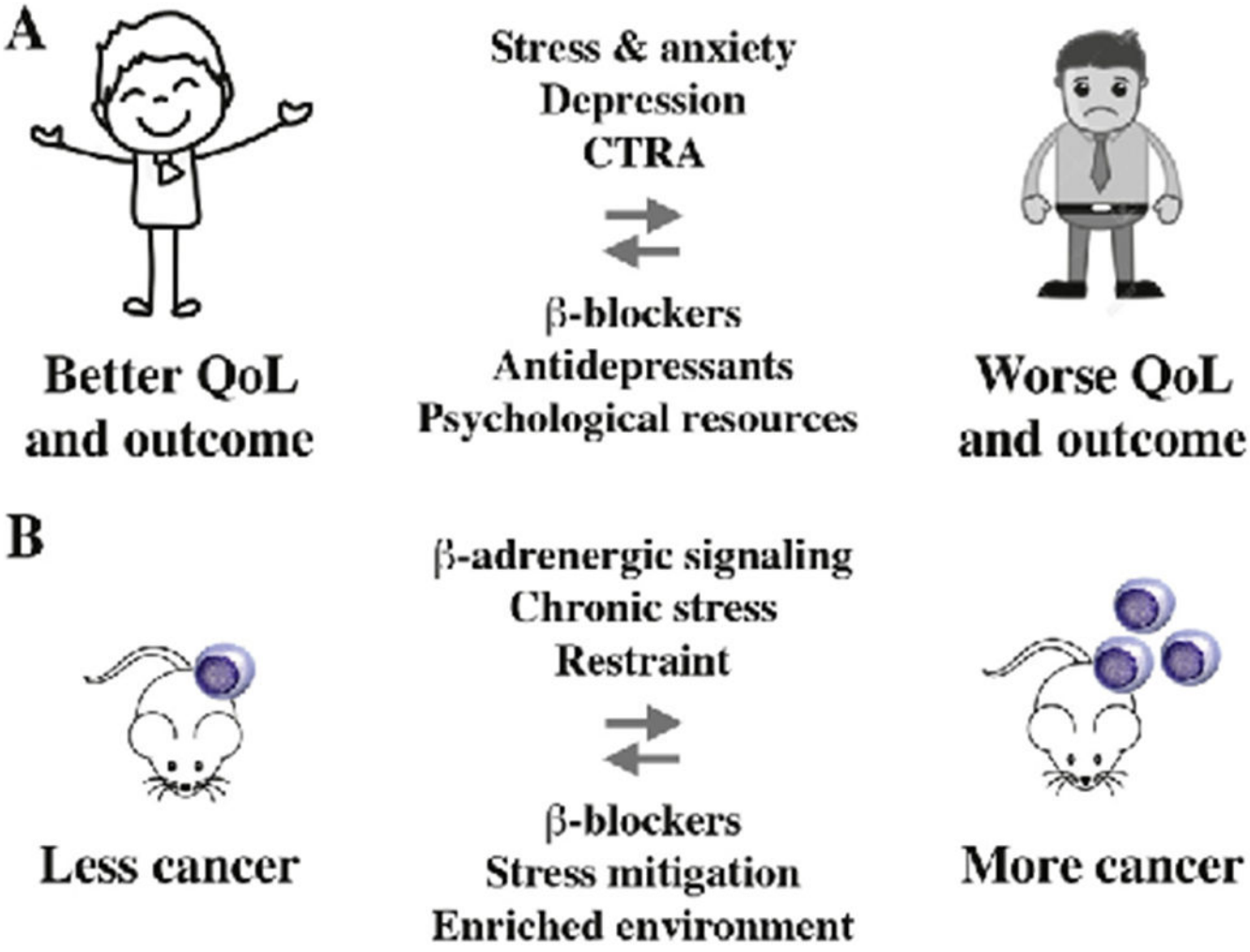

Fig. 2.

Dampening adrenergic signaling benefits patients with myeloma. Panel A shows that β-blocker intake, which dampens adrenergic signaling, reduces disease-specific mortality in patients with myeloma (arrow pointing left). Conversely, psychological distress (anxiety, depression), which leads to increased adrenergic signaling, is associated with inferior survival and reduced quality of life (QoL; arrow pointing right). Stress and anxiety relief using antidepressants and/or psychotherapy may improve outcome of myeloma by virtue of a mechanism that involves adrenergic regulation of immune cells in the BMM [85]. Dysregulation of adrenergic and other stress-related signaling pathways is evident at the transcriptomic level, as recently shown in a study on lethal prostate cancer [86] and, more broadly, in the context of a newly developed psycho-oncological framework [87] termed conserved transcriptional response to adversity (CTRA) [88]. In accordance with that, the broad-spectrum β-blocker propranolol [6] inhibited the CTRA in a recent clinical trial in myeloma [7]. Panel B depicts the principal outcome of preclinical studies using laboratory mice that linked chronic stress (elevated adrenergic signaling) and cancer (right-pointing arrow) [29,60,89–92]. In contrast, mice housed in a stress-mitigated, enriched environment or treated with anti-adrenergic β-blocker exhibited reduced rates of malignant growth, such

as melanoma and colon cancer (left-pointing arrow). Tumor inhibition relied on a pathway that involved downregulation of leptin production in adipocytes in response to β-adrenergic input [93].

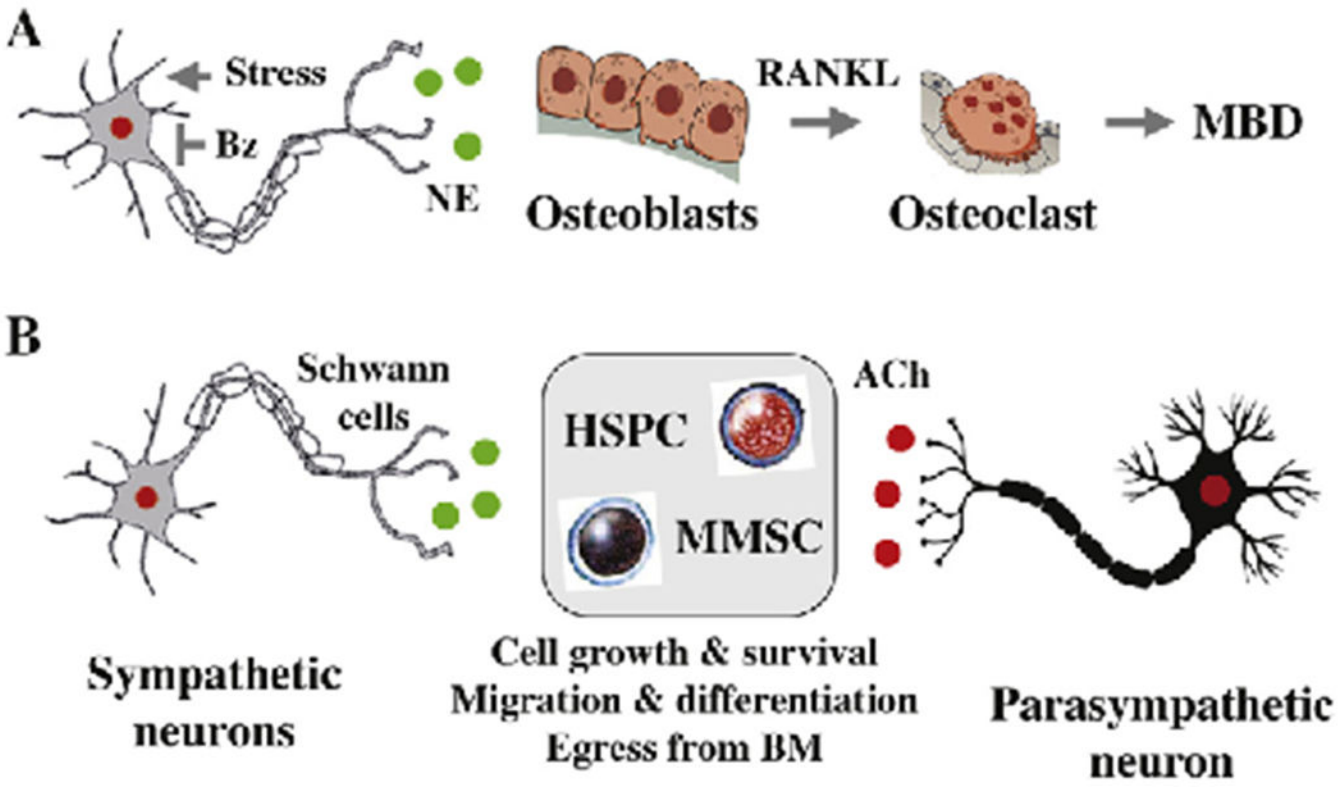

Fig. 3.

Proposed mechanism of ANS control of myeloma bone disease and sternness. Evidence that autonomic innervation of bone and bone marrow is crucial for skeletal [32] and hematopoietic homeostasis [94,95] suggests that the ANS is also involved in myeloma bone disease (MBD) and myeloma sternness. Autonomic nerve fibers form synapse-like structures with bone cells such as osteoblasts and osteoclasts (panel A) as well as hematopoietic stem and progenitor cells (HSPC, panel B). Neurotransmitter NE and ACh release at the synapse stimulates autonomic receptors on target cells, initiating downstream signal transduction. It is possible that high sympathetic tone caused by chronic stress promotes MBD through increased osteoblast secretion of RANKL, leading to enhanced osteoclast-dependent bone resorption (panel A) [95–97]. It is also possible but has not been shown that the well-established anabolic effect of bortezomib (Bz) on bone relies, in part, on Bz-induced sympathetic neuropathy that curbs adrenergic signaling (panel A). Whether multiple myeloma stem cell (MMSC) function is governed by autonomic signals, similar to HSC and MSC function, is a task for future research (panel B). Encouragement for taking on this challenge is provided by reports that other types of stem cell-like cancer cells (breast, prostate) are regulated by autonomic signals. See main text for details.

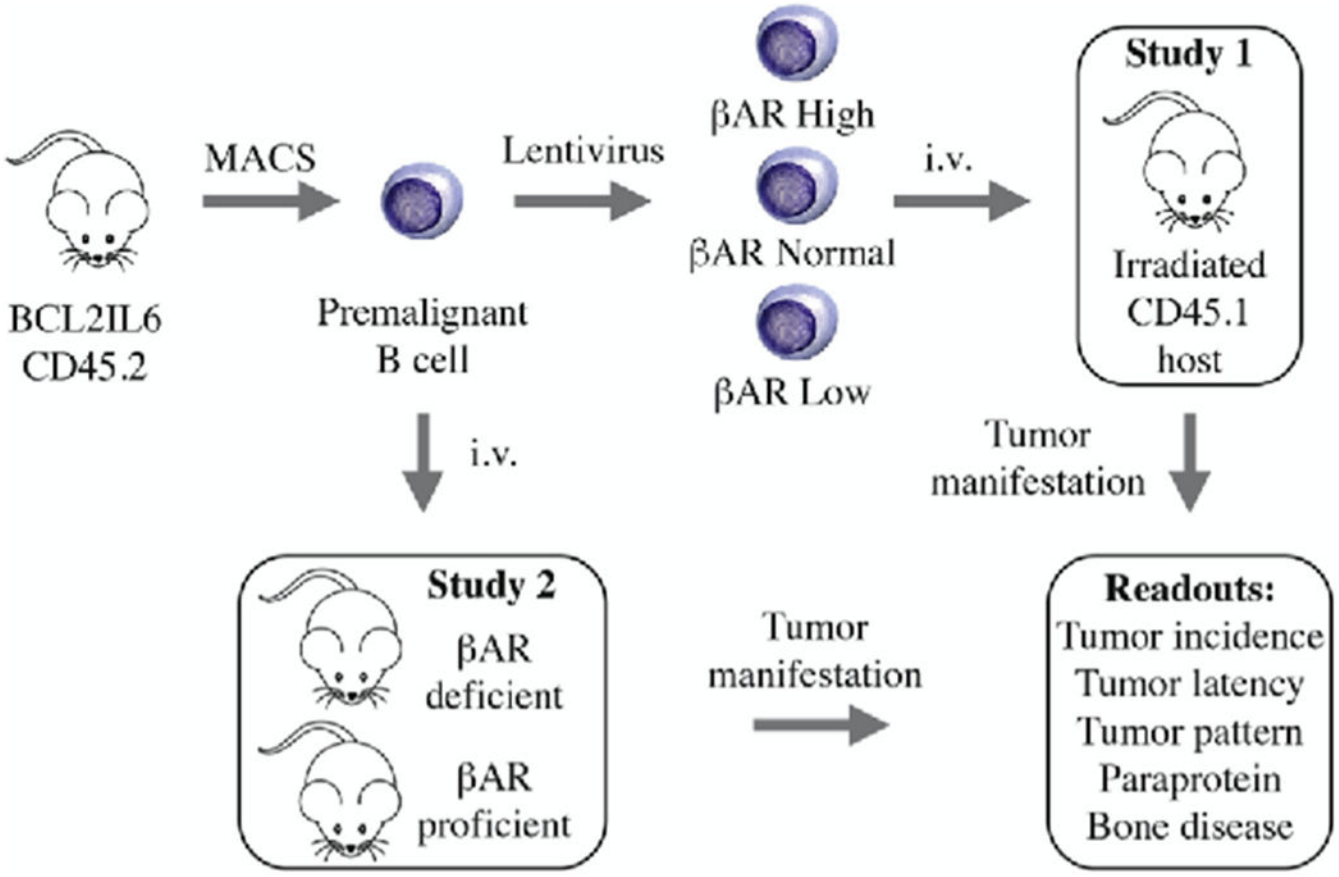

Fig. 4.

Experimental strategy to evaluate the role of adrenergic signaling in plasma cell tumor (PCT) development in mice. Adoptive B-cell transfer provides a flexible platform for assessing role and significance of adrenergic input in the natural history of myeloma-like PCTs. Effects on tumor precursors (Study 1) can be distinguished from those on the TME (Study 2), as recently shown in a study on the impact of IL-6 (interleukin 6) on PCT development [98]. Briefly, donor B cells are isolated from double-transgenic BCL2IL6 mice on the genetic background of BALB/c, using MACS® magnetic bead columns (cartoon to the upper left). Next, B cells are genetically modified in short-term cell culture using lentiviral gene transduction, which results in enforced expression of a βAR gene of interest (βAR High) or RNAi-mediated downregulation of βAR expression (βAR Low). Transfection with non-coding "empty" virus that leaves endogenous βAR expression unchanged is used as control (βAR Normal). Adoptive transfer of transfected B cells to sub-lethally irradiated hosts congenic for CD45.1 generates 3 cohorts of mice distinguished only by the level of βAR message in tumor precursors (upper right). Tumor incidence, latency and pattern will serve as endpoints of the study. Specific antibodies for the two CD45 allotypes involved provide a convenient tool for monitoring engraftment and neoplastic expansion of donor cells in host tissues, using flow cytometry and immunohistochemistry as measurement tools. Transfer tumor precursors to host mice that are either deficient or proficient in βAR signaling (Study 2) may show whether βAR signaling in the TME is critical for PCT development.

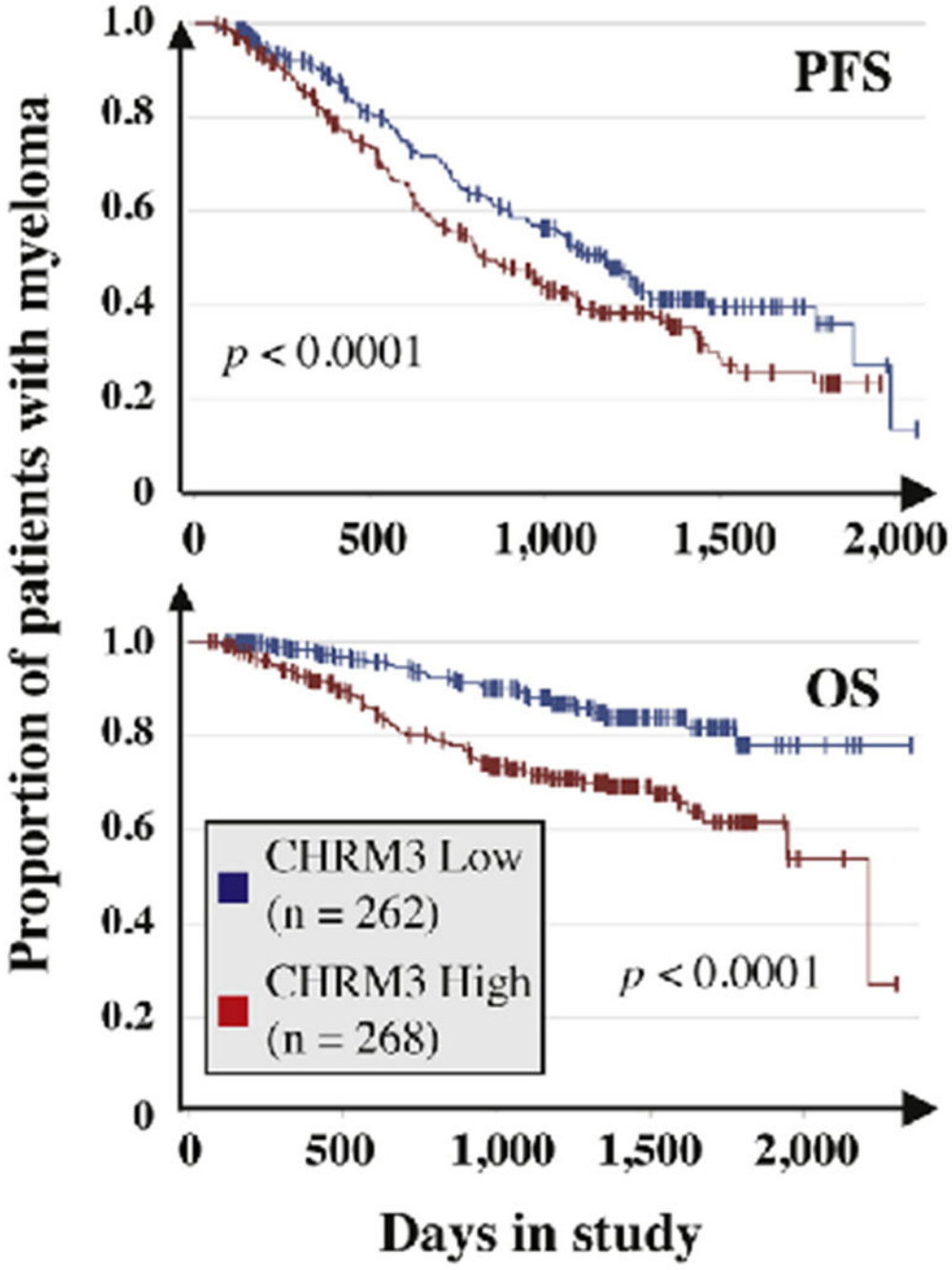

Fig. 5.

Elevated cholinergic receptor muscarinic 3 (CHRM3) mRNA level in myeloma cells predicts 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 also

included. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

Evidence for impact of β-adrenergic signaling in patients with myeloma (rows 1–5) or continuous human myeloma cell lines (rows 6–10).

Type of investigation	Main finding or clinical question	Year published	Ref.
Retrospective outcome analysis	In patients with multiple myeloma, β-blocker intake is associated with reduced disease-specific death and overall mortality	2017	5
Meta-analysis of prospective cohort studies	Psychological distress (depression, anxiety) results in 2-fold increase in disease-specific mortality	2017	12
Clinical pilot study (NCT01899326)	Stimulation of adrenergic activity by tricyclic antidepressant desipramine enhances HSC [a] mobilization induced by G-CSF[b]	2017	54
Clinical pilot study (NCT02420223)	Do patients with myeloma that undergo HSC transplantation benefit from anti-adrenergic treatment with propranolol?	2018	6
Phase 2 biomarker trial (NCT02420223)	In patients with myeloma undergoing HSC transplantation, treatment using unspecific β-blocker propranolol inhibits conserved transcriptional response to adversity (CTRA)	2020	7
Preclinical in vitro study using one HMCL[c]	Norepinephrine (noradrenaline) stimulates interleukin 6 (IL-6) dependent FLAM-76 myeloma cells	2008	23
High-throughput drug interaction study in vitro	β2AR[d] agonists synergize with backbone myeloma drugs in myeloma cell killing	2012	24
Preclinical in vitro study using one HMCL	Propanol inhibits growth and promotes apoptosis of U266 myeloma cells	2013	21
Preclinical in vitro study using three HMCLs	β1AR[e] agonist dobutamine inhibits myeloma in a MAPK [f] dependent manner	2016	25
Preclinical in vitro study using one HMCL	Epinephrine (adrenaline) enhances growth, proliferation and chemoresistance of U266 myeloma cells	2017	22

[a] Hematopoietic stem cell.

[b] Granulocyte-colony stimulating factor.

[c] Human myeloma cell line.

[d] β2 adrenergic receptor.

[e] β1 adrenergic receptor.

[f] Mitogen-activated protein kinase.