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KEY ROLE OF INFLAMMATION IN MYELOPROLIFERATIVE NEOPLASMS: INSTIGATOR OF DISEASE INITIATION, PROGRESSION. AND SYMPTOMS

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Abstract

Purpose of review: Chronic inflammation is a characteristic feature of myeloproliferative neoplasm (MPN) and impacts many aspects of the disease including initiation, progression, and symptomatology.

Recent findings: The chronic inflammatory state of MPN results from disruption of immune signaling pathways leading to overproduction of inflammatory cytokines by both the neoplastic clones and bystander immune cells. This chronic inflammation may allow for the neoplastic clone to gain a selective advantage. The symptomatic burden felt by MPN patients may be a result of the chronic inflammation associated with MPN, as several cytokines have been linked with different symptoms. Pharmacologic as well as nonpharmacologic treatments of the inflammatory component of this disease may lead to decreased symptomatic burden, prevention of disease progression and improvement in overall disease trajectory.

Summary: Inflammation plays a key role in the pathogenesis of MPN and represents an important therapeutic target.

Keywords

myeloproliferative neoplasm; JAK/STAT signaling; inflammation in cancer; diet in cancer; lifestyle in cancer; inflammatory cytokines; fatigue; quality of life; nonpharmacological approaches

INTRODUCTION

Inflammation plays a crucial role in the development and progression of myeloproliferative neoplasms (MPN). Myeloid malignancies are characterized by elevated levels of inflammatory cytokines, which correlate with disease initiation and progression,

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symptomatic burden, and prognosis. Increased inflammatory cytokines, including tumor necrosis factor alpha (TNFα) and interleukin 6 (IL-6), are typically observed in MPN patients(1, 2) as well as MPN mouse models(3). These findings suggest that inflammatory cytokines are involved in the natural course of the disease and are driving the clinical manifestations.

The clinical burden of MPN develops from a combination of unrestrained production of mature myeloid cells by the neoplastic clone, and a bone marrow microenvironment of inflammatory products from activated leukocytes and platelets, which leads to the accumulation of reactive oxygen species (ROS) in the hematopoietic stem cell (HSC) compartment(4).

ROLE OF INFLAMMATION IN MPN DISEASE INITIATION

Inflammation may create an environment which is highly favorable for growth of the $JAK2^{V617F}$ neoplastic hematopoietic stem cells. The $JAK2^{V617F}$ mutant hematopoietic progenitors are resistant to inflammation, while $JAK2^{WT}$ cells are suppressed by inflammation, possibly through the induction of apoptosis, quiescence, or reduced self-renewal/increased differentiation of HSC(5). Moreover, $JAK2^{V617F}$ mutant cells themselves produce inflammatory cytokines (most notably TNF-α) and also induce bystander normal cells to produce inflammatory cytokines(6, 7).

A chronic inflammatory state may increase one's risk of developing MPN. MPN patients are more likely to have a preceding diagnosis of autoimmune disease(8). Interestingly, the JAK2 46/1 haplotype identified as associated with JAK2-mutated MPN is also associated with Crohn's disease(9). Lai et al found that MPN patient monocytes produce TNF-α for prolonged periods of time after Toll-like Receptor (TLR) stimulation because they are less able to respond to the anti-inflammatory cytokine IL-10(7). This defective negative regulation of TLR signaling was observed in both the mutant and wild-type cells alike from MPN patients, suggesting this is not a cell intrinsic consequence of $JAK2^{V617F}$. Moreover, the unaffected identical twin of an MPN patient was found to have prolonged TNF-α production following stimulation similar to her twin with MPN, suggesting this abnormality may be a genetic feature rather than a consequence of MPN. This work also demonstrates that the chronic inflammatory state in MPN may be due to defects in quelling inflammation after stimulation.

Aging is considered a pro-inflammatory state due to the increased release of inflammatory cytokines and immunosenescence which may likely play a role throughout myeloid malignancies. MPN is generally a disease of the elderly with the average age of onset being 65 years old, further highlighting the association between inflammation and development of MPN.

SOURCE OF INFLAMMATION IN MPN AND PATHWAY TARGETS

The mechanisms driving inflammation in MPN are multifactorial and not fully understood (Figure 1). Production of inflammatory cytokines is not exclusive to the $JAK2^{V617F}$ mutant clone, demonstrating that the presence of the mutant clone creates an environment which

induces bystander normal cells to produce inflammatory cytokines. Using single-cell profiling, Kleppe et al showed that hematopoietic cells from MPN mouse models as well as primary MPN patient samples aberrantly secrete inflammatory cytokines(6). In addition, Stat3 was found to be critical for the production of inflammatory cytokines in MPN. Pan hematopoietic deletion of Stat3 reduced inflammatory cytokines and attenuated disease severity, however deleting Stat3 in the MPN cells while preserving Stat3 in non-mutant cells did not reduce cytokine production nor attenuate disease pathology further supporting the key role of bystander cells as producers of inflammatory cytokines in MPN.

The ability of the mutant clone to induce inflammation may create a self-perpetuating environment for its continued selection. An inflammatory environment may be critical to the maintenance and/or expansion of the mutant clone. If so, blocking this inflammation induced by the mutant clone could be a useful therapeutic approach to potentially blunt the expansion of mutant over wild-type cells. Blockade of mutant clone induced inflammation would also likely have an impact on the negative consequences of the mutant clone such as accelerated atherosclerosis or potentially even thrombosis.

Derangement of JAK/STAT signaling is not the sole contributor to inflammation in MPN. Although ruxolitinib reduces inflammatory cytokines in MPN patients, it may not be enough to fully return cytokines to normal. Fisher et al found a modest difference in pre versus post ruxolitinib plasma levels cytokines such as VEGF, TNF-α, IL-6, IL-10, and IL-16 in MF patients, demonstrating that JAK inhibition may not be sufficient to normalize inflammatory cytokines(10).

Hyperactivation of the NFκB signaling pathway is a key contributor to chronic inflammation in MPN. Using mass cytometry Fisher et al found that primary samples from myelofibrosis (MF) and secondary acute myeloid leukemia samples had constitutive NFκB signaling and many NFκB target genes were found to have increased expression in MF patient $CD34^+$ cells. Moreover, NFκB inhibition suppressed colony formation from MF $CD34^+$ cells implicating NFκB as a therapeutic target in MPN(11).

Yang et al found a significant enrichment of the NFκB signaling pathway in sorted hematopoietic stem cells from $JAK2^{V617F}$ mice as compared to wild-type mice(12). They found that the NFκB inhibitor dimethylaminoparthenolide (DMAPT) reduced proliferation of Ba/F3-EpoR-JAK2V617F cells, inhibited the growth of human $JAK2^{V617F}$-positive cell lines, and inhibited the hematopoietic progenitor colony outgrowth in $JAK2^{V617F}$ mice BM and MPN patient peripheral blood $CD34^+$ cells. Treatment of combination therapy with ruxolitinib and DMAPT reduced mutant myeloid precursors in the bone marrow and spleen of $JAK2^{V617F}$ mice and reduced bone marrow fibrosis.

Kleppe et al(13) also identified activation of NFκB in both malignant and non-malignant cells in MPN and found that inhibition of BET bromodomain proteins attenuated NFκB signaling and reduced cytokine production *in vivo*. They also found that combined treatment with ruxolitinib and the BET inhibitor JQ1 reduced inflammatory cytokines, reduced disease burden, and reversed bone marrow fibrosis in mouse MPN models.

There is abundant pre-clinical evidence to support evaluation of NFκB inhibition in MPN patients. A clinical trial is currently open at Washington University in St. Louis investigating the combination of the NFKB inhibitor pevonedistat in combination with ruxolitinib in patients with myelofibrosis (NCT03386214).

INFLAMMATION AND SYMPTOMS IN MPN

MPN patients can experience a variety of symptoms including fatigue, sleep disturbance, night sweats, weight loss, depression, anxiety, early satiety, pruritus, and bone pain. Fatigue is the predominant symptom, which affects 81–95% of MPN patients, and has been reported as an important distressing factor causing decreased quality of life (QoL) by cancer survivors(14–19). Fatigue in MPN not only stems from the disease itself which will be discussed below, but can also be caused by cytoreductive therapies used in MPN treatment, such as hydroxyurea, anagrelide, and interferon-alpha. In MPN, a patients QoL can also be affected by disease complications including thrombosis, hemorrhage, hepatosplenomegaly, anemia, cachexia, and weight loss(15).

Several studies have shown a correlation with inflammatory markers and perceived symptoms of disease. Elevated levels of IL-6, a highly expressed cytokine within MPNs, has been linked to cancer-related fatigue, and has shown a correlation with depression (32% in a cohort of 1788 MPN patients)(20–22). Similarly, fever and night sweats are well known to be influenced by pyrogenic cytokines (IL-1, IL-2, IL-6, TNF-α, and IFN)(23). Clinically, Bower et al reported a positive correlation among TNF- α levels and post-chemotherapy fatigue in women with breast cancer(24).

Abdominal symptoms are common among MPN patients and can be mostly attributed to splenomegaly, portal hypertension, mechanical obstruction, and splenic infarcts. Splenomegaly has been associated with the expansion of the malignant clone from the bone marrow microenvironment to extramedullary sites, and with specific cytokines including MIG, HGF, and IL-1RA(2).

Thrombosis, one of the principal targets of MPN therapy particularly in essential thrombocythemia (ET) and polycythemia vera (PV) patients, may result in a variety of abdominal complaints. An evaluation of 244 PV and ET patients demonstrated a positive association between the highest CRP protein tertile and the highest rate of major thrombotic events(25). Likewise, patients with the lowest pentraxin 3 levels were at higher risk for major thrombotic events.

Microvascular events also affect MPN patients, which can result in headaches, concentration problems, lightheadedness, dizziness, vertigo, numbness/tingling, and sexual dysfunction(26). Inflammation has been identified as a cause for cognitive impairment in both animal and human models. IL-6 deficient animals are protected from lipopolysaccharide (LPS) induced cognitive impairment, suggesting that IL-6 plays a key role in interrupting the process of memory and learning(27). In patients suffering from hematological disorders, the presence of high levels of IL-6 usually correlates with poor executive function(28).

Weight loss in MPN is complex and multifactorial. Cancer patients often suffer from cancer cachexia, a dysregulation of carbohydrate and fat metabolism in which TNF-α is responsible for the proteolysis of skeletal muscle and the enhancement of genes related to enzymes in the ubiquitin dependent proteolytic pathway(29–32).

Pruritus has also been linked to the inflammatory cascade, which affects over 50% of the MPN population. Pruritis is predominantly observed in PV patients (65%), who have been noted to have increased number of constitutively activated and hypersensitive circulating basophils(33). Interestingly, an increased number of mast cells was demonstrated in *Jak2*^{V617F} transgenic mice with the PV phenotype, which also may contribute to pruritis(34). These mast cells are a source of prostaglandin, leukotriene, histamine, and tryptase, mediators of the inflammatory response involved in pruritus. Recent studies evaluating the effects of infrared thermography have documented mast cell degranulation due to changes in temperature with the release of pyrogenic factors such as interleukins, histamine, and leukotrienes(35, 36), this may provide some explanation for pruritis after hot showers in MPN.

LIFESTYLE AND ENVIRONMENTAL INFLUENCE MPN DEVELOPMENT

Although there is a familial predisposition to acquire MPN most cases are sporadic which suggests that lifestyle choices and environment may play an important role in MPN disease initiation. Cigarette smoking leads to a chronic inflammatory state that is the pre-stimulus for several chronic illnesses including cardiovascular disease, chronic obstructive pulmonary disease (COPD) and cancer. The association of smoking with different hematologic malignancies has been investigated and sufficient evidence indicates a role in the development of acute myeloid leukemia(37, 38). Evidence for the role of cigarette smoking in MPN development has, until recently, been limited. Two studies of women only cohorts found a correlation between exposure to tobacco smoke and the incidence of myeloproliferative neoplasms. The UK Million Women Study was one of the largest studies to provide sufficient power to assess tobacco smoking as a risk for subtypes of hematological malignancies and they found that current smokers had a higher risk for developing myelodysplastic syndrome (MDS) and MPN compared to never-smokers(39). The Iowa Women's Health Study found that current cigarette smoking was associated with an increased risk of all MPNs and for the particular subtypes there was a stronger association for PV than ET(40). In addition, a case-control study carried out by Sørensen and Hasselbalch studied the relationship between smoking and MPN using chronic lymphoid leukemia (CLL) patients as controls and found that a history of smoking increased the odds of developing MPN compared to CLL(41). Very recently, a Danish population-based study found smoking to be a significant risk factor for developing MPN when comparing smokers to never-smokers(42). Also, a meta-analysis that combined several published studies reported an increased odds ratio for MPN when comparing ever-smokers to never-smokers(43). Interestingly, the most common somatic mutation in MPN, the *JAK2*^{V617F} mutation, is more common in smokers than non-smokers, further supporting the idea that the pro-inflammatory effects of tobacco smoke induce genetic changes in hematopoietic stem cells (HSCs)(44, 45). The positive association between a history of smoking and the risk of MPN has been postulated to occur via chronic inflammation and

oxidative stress leading to genomic instability, derivation of a malignant clone and clonal expansion in HSCs(46).

In addition to the risk for developing MPN due to smoking behavior, the effects of past or current tobacco use on MPN symptom burden is largely unknown. An internet-based survey developed by a team of MPN investigators for MPN patients has found significant differences in symptom burden between ever-smokers and never-smokers. Of the 435 patient participants, 58% reported no history of tobacco use while 42% of the population consisted of former or current users of some form of tobacco. In terms of severity of symptom burden, current and former smokers were more likely to experience significantly higher levels of fatigue, inactivity, concentration difficulties and decreased quality of life compared to never smokers (personal communication, R. Scherber). While smoking behavior is gaining attention in MPN, it is also important to evaluate the molecular effects of smoking on HSCs in the MPN setting.

The human intestinal gut microbiome is increasingly appreciated for its role in metabolism and interaction with host immune cell populations. The host microbiome can also influence MPN phenotype since dysbiosis is now well-recognized to play a role in autoimmune diseases such as inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis (UC)(47, 48), and graft-versus-host disease (GVHD)(49). There also exists described associations between microbiota and hematopoiesis such as size of the bone marrow myeloid pool(50) steady-state hematopoiesis(51). Now, it has been shown that microbiota induced differentiation of Th17 cells drives the appearance of multiple myeloma in transgenic mice and the presence of IL-17 in the bone marrow also predicted disease progression in multiple myeloma patients(52). Interestingly, we have preliminary data indicating that the Prevotellaceae family of bacterium, as also reported by Calcinotto et al (52), is increased in MPN patients compared to normal controls and found that the cytokines TNF-alpha and IL-17a explained the most variance in microbiome data (Fleischman lab unpublished data). Further studies with larger cohorts are required to address the causal role of microbiota in driving inflammation in MPN. Considering that the enteric microbiome plays an integral role in host immunity, there are various efforts targeting the intestinal microbial communities such as fecal microbial transplantation (FMT)(53), antibiotics and anti-fungals, and dietary interventions(54) to manage or prevent chronic inflammatory conditions.

Clonal hematopoiesis is the expansion of peripheral blood cells derived from a single HSC and has been recently reported to occur during aging(55, 56). Age-related clonal hematopoiesis has been associated with adverse clinical outcomes relating to hematologic cancer, coronary heart disease, ischemic stroke and overall mortality(55). Clonal hematopoiesis of indeterminate potential (CHIP) refers to mutations occurring in a candidate driver genes for hematological malignancy such as DNMT3A or TET2 at a variant allele frequency greater than 2%(57). CHIP is rare under the age of 40 but the frequency increases with age with 1 in 10 (10%) people over the age of 70 exhibiting detectable mutant peripheral blood cells and represents precursor cells for neoplasia(55). Clonal hematopoiesis (CH) is very common in the elderly and is significantly associated with smoking behavior and was also found to associate with the number of mutations detected in CH(58). Tobacco

use was also associated with a higher likelihood of clonal hematopoiesis in patients with non-hematologic cancers(59).

Ionizing radiation is a human carcinogen with an established casual role in leukemias, particularly acute myeloid leukemia in Japanese A-bomb survivors(60). Although no direct evidence exists for increased MPN incidence following radiation exposure, it is interesting to note that MPN patients in Ukraine, exposed to the radiation from the Chernobyl nuclear accident, exhibit a different genetic profile when compared to unexposed patients. Radiation exposed patients had a lower rate of $JAK2^{V617F}$ mutation, higher rate of the type I CALR mutation and increased number of triple negative cases in exposed subjects when compared to unexposed MPN patients(61). These findings indicate that MPNs acquired via exposure to ionizing radiation display distinct genomic characteristics that require further investigation.

A cluster of PV exists in Pennsylvania, which raises the question of local environmental exposure, where elevated levels of radon gas was found in indoor air and radium in the soil. In 2009 The Agency for Toxic Substances and Disease Registry (ATSDR) collected peripheral blood samples from 1170 full time residents of Luzerne, Schuylkill, or Carbon County who had lived in the tri-county area for 1-year or longer and tested them for $JAK2^{V617F}$ using a PCR-based method with a detection limit of 0.05% allele burden(62). They found 19 (1.6%) residents who tested positive for $JAK2^{V617F}$, 14 of whom did not have a diagnosis or symptoms of MPN. In the majority of JAK2 positive cases without an MPN diagnosis the JAK2 allele burden was 1.2% or less. It is difficult to compare the prevalence of JAK2 positivity in this area of Pennsylvania with published reports of JAK2 screening in other populations due to differences in analytical methodologies and participant selection.

NONPHARMACOLOGICAL APPROACHES TO REDUCE INFLAMMATION IN MPN

Our current pharmacologic treatment of MPN often inadequately control symptom burden and have significant side effect profiles. Traditional therapies like therapeutic phlebotomies in patients with PV (63) have been shown to be ineffective and in some cases worsen symptom burden. The JAK1/2 inhibitor ruxolitinib reduces inflammatory cytokines and improves symptoms, but not without significant side effects such as thrombocytopenia, anemia, increased risk of skin cancer, and immunosuppression(64). There is a crucial need to explore low-risk therapies to diminish inflammation in MPN, particularly in patients with early stage disease, as this may be an ideal way to reduce inflammation and empower MPN patients to change their disease trajectory (Figure 2). Besides the minority of patients who are on interferon-alpha, little attention is placed on preventing disease progression, instead we wait until the patient progresses to myelofibrosis and then attempt to intervene. This “watch and wait” approach can make both MPN patients and physicians alike feel powerless.

The use of exercise to combat fatigue in malignancy is an emerging field. Recently, a study found that MPN patients who were physically active reported less fatigue than those who were not(19). Yoga has been used effectively in various conditions related to stress and

inflammation, including cancer (breast, lung, pancreatic and most recently in MPN) since it has improved the QoL by relieving stress, anxiety, depression, fatigue, and emotional and social function(65–68). A randomized trial investigating yoga in a breast cancer cohort demonstrated a reduction in inflammatory cytokines(69).

Yoga can produce stimulating effects on physical and mental energy, and thereby could alleviate levels of fatigue in MPN patients(68, 70). A feasibility study consisting of 38 analyzable participants(71) followed by a qualitative study with a sample size of 39 participants(72) were conducted to explore the benefits of yoga in MPN. In both studies, MPN patients were required to complete an hour of weekly yoga for 12 weeks. Preliminary data demonstrated that online yoga was a more feasible option compared with in-person yoga because many patients travel significant distances to receive specialty MPN care. Seventy-one percent (20 of 28) of patients traveled out of town and 36% (10 of 28) traveled out of state for their MPN care, suggesting that many MPN patients may not have easy access to a facility to actively engage with for in-person interventions. Furthermore, participating in online yoga may help MPN patients overcome other limitations of in-person activities, such as fatigue, pain, transportation, and scheduling difficulties(72, 73).

At the end of both trials the research team conducted a 15- to 20-minute phone interview with participants consisting of 10 questions pertaining to patients' thoughts, feelings, and perceptions of their experiences practicing online yoga. Almost all patients reported a positive impact on their physical health as a result of yoga practice. The most common mentioned benefits were increases in physical activity, reductions in fatigue, and improved sleep. Some participants reported reduced pain, easier breathing, improved circulation, improved eating habits, improvement of their MPN symptoms, or just feeling better or more health conscious in general. It was noted, however, that the primary limitations in these studies were an overrepresentation of women (n = 34/39) and that several participants (n = 25/39) had prior yoga experience. This prevents the ability to generalize the findings of the present trials to all MPN patients, the majority of whom likely have no experience with yoga. Larger studies investigating the impact of yoga on MPN patient QoL, symptom burden, inflammatory cytokines are forthcoming.

Diet is another nonpharmacological approach to reduce inflammation. The Mediterranean diet which is rich in fruits, vegetables, legumes, whole grains, fish, nuts, and low-fat dairy products has proven to effectively reduce CRP ($p = 0.015$) and IL-6 levels ($p = 0.025$)(74). In addition, implementation of the Mediterranean diet has been associated with decreased incidence of various cancers such as breast, lung and colon(75–77), suggesting that it may have some preventative effects. Low-inflammation diets have been found to induce changes in thrombotic markers with decreases in homocysteine levels ($p = 0.031$), white blood cell counts ($p = 0.001$), and fibrinogen levels ($p = 0.025$)(78).

The PREDIMED (Prevención con Dieta Mediterránea) trial was a Mediterranean diet nutritional intervention among individuals with high cardiovascular risk, but who had not yet developed a cardiovascular disease(79). Participants were randomized into two different Mediterranean diet groups and one control group. One of the Mediterranean diet arm was given provisions of extra-virgin olive oil and the other one was given provisions of mixed

nuts. Participants in both Mediterranean arms had a significantly lower incidence of major cardiovascular events (hazard ratio 0.70 for group assigned to Mediterranean diet with extra virgin olive oil and 0.72 to the group assigned to Mediterranean diet with nuts).

Diet is an attractive tool to empower MPN patients to reduce inflammation, manage symptoms, and prevent disease progression. In February 2017, an online survey hosted by the Mayo Clinic Survey Research Center was advertised on multiple internet websites and communities that focused on MPN(80, 81). The purpose of this questionnaire was to collect data on demographics, MPN characteristics, nutritional habits, supplement use, and symptom burden using the MPN-10. 1,329 MPN patients from all over the world (37 countries) responded to the online survey, out of which 24% were diagnosed with MF, 37% with PV, and 38% with ET. Some of the respondents (34%) reported that they were already using diet as a measure to help control their symptoms. A wide variety of sources such as books (28.2%), websites (27.1%), health care providers such as physicians, naturopaths (28.2%), online forums (23.2%), friends (12.2%), nutritionists (9.5%), phone or tablet applications (9.1%), or videos (4.2%) were used for nutritional education. About 96% of MPN patients responded that they would be willing to restrict their diet by eating only certain foods if it helped control symptom burden and the great majority, 98% would do so if it could help stabilize or improve the course of their disease. A correlation was made between the intake of at least once per week of fast food (P=0.0007), fried foods (p=0.0198), pre-made snacks (P=0.03), soda (P<0.0001), refined sugar (P=0.01), and tacos (P=0.03) with worsened symptom score compared with no intake at all. Otherwise, patients who ingested at least once per week alcohol (p<0.0001) and rice (p=0.0452) noticed significant improvement in their symptom burden. With these last two being basic components of the Mediterranean diet, preliminary data suggests that diet may play a role in MPN symptoms and disease course.

This data provides rationale for looking at nutritional control of inflammation as a new alternative therapy to the limited interventions that have currently shown to alleviate the symptom burden of MPN patients. A feasibility trial investigating a Mediterranean Diet intervention in MPN is currently open and enrolling at University of California, Irvine. This study will determine whether MPN patients are able to adhere to a Mediterranean Diet if given in-person dietician counseling and weekly written curriculum. The exploratory endpoints of this study are improvement of MPN symptom burden and reduction of plasma inflammatory cytokines.

CONCLUSION

There is an emerging body of evidence to support the importance of inflammation in disease pathogenesis of MPN. A combination of over-production of inflammatory cytokines and the inability to regulate and reduce these cytokines can lead to a state of chronic inflammation which self-perpetuates the neoplastic clone. Interventions that can reduce inflammation overall or target specific cytokines may play a role in the prevention of and future treatments for MPN. Lifestyle modification, including diet and exercise has been associated with qualitative improvement of MPN disease burden. Future research may aim to develop measurable inflammatory markers of MPN that can help define the disease and may

correlate to prognosis, phenotype, progression and remission of disease. These markers may be used in conjunction with molecular studies, cell counts, age and co-morbidities to risk stratify patients' disease and therefore direct treatment.

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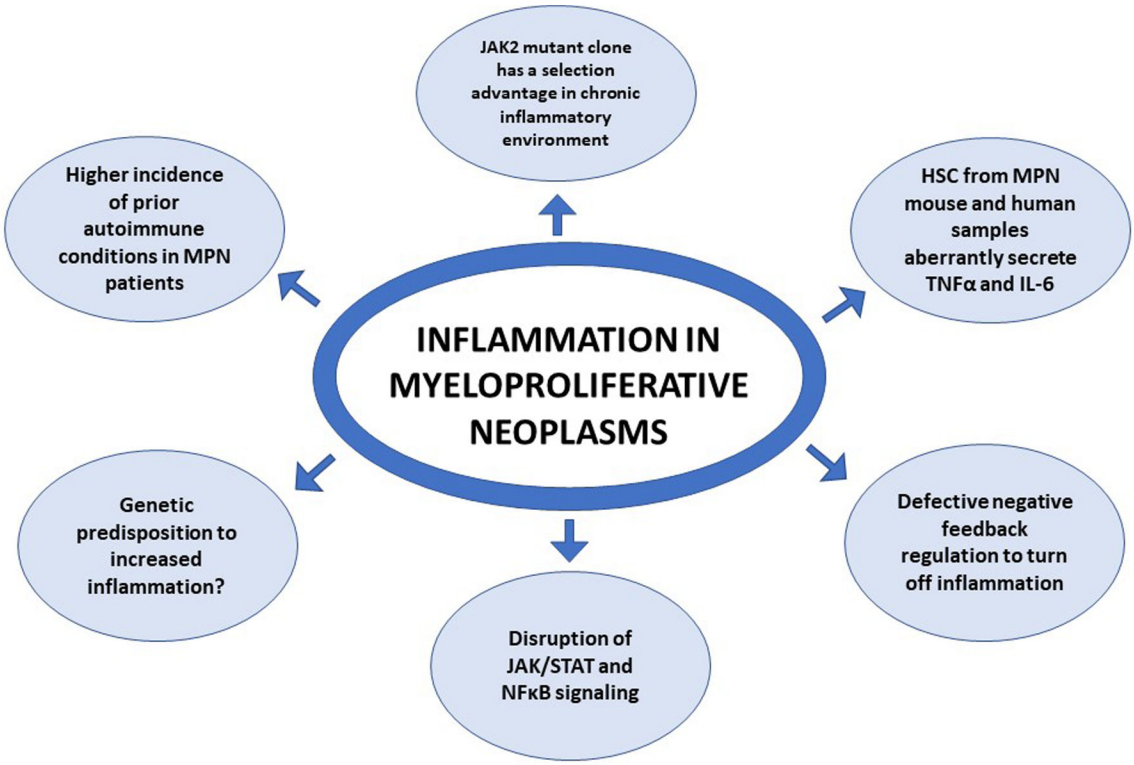

Figure 1. Factors Influencing Inflammation in Myeloproliferative Neoplasms.

Chronic inflammation is a multifactorial process in MPN. It is difficult to assess if it is the result from a preceding pro inflammatory environment or if the neoplastic clone itself predisposes to its development. Understanding the different drivers of inflammation in MPN may lead to targeted treatments in the future.

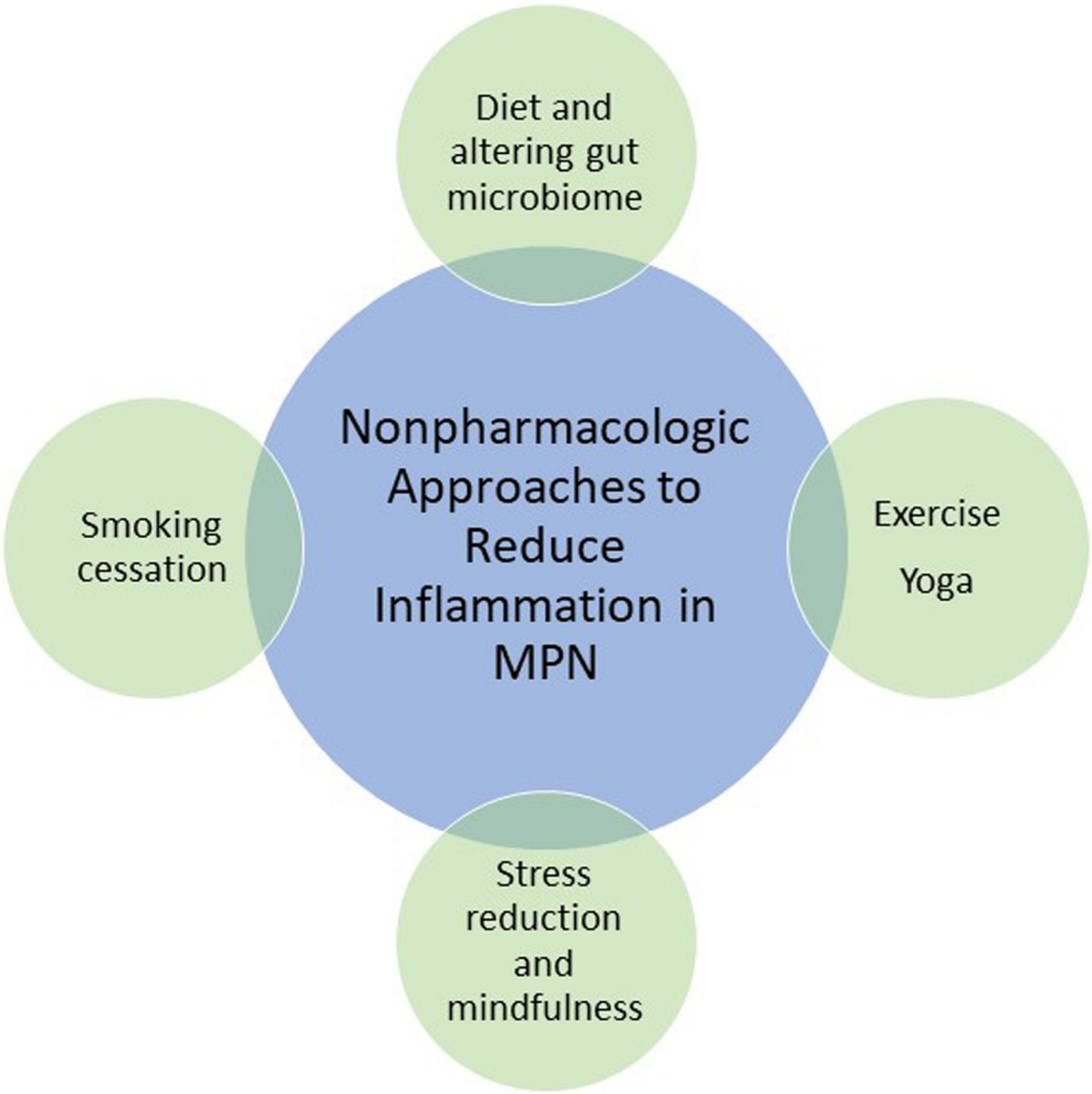

Figure 2. Nonpharmacologic Approaches to Reduce Inflammation in MPN.

Maintaining a healthy lifestyle may help prevent a chronic inflammatory environment in patients with strong family history of MPN and/or patients on early stages of the disease. These nonpharmacologic approaches may be able to reduce overall inflammation with the goal of reversing some of these factors or mitigating their effects.