Review

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Review

Bridging Periodontal Disease and Myeloproliferative Neoplasms: The Role of Immune Dysregulation and Inflammatory Mediators

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Abstract: Periodontal disease (PD) and myeloproliferative neoplasms (MPNs) are linked through common inflammatory mediators and immune dysregulation. Chronic inflammation plays a pivotal role in both conditions, with markers such as Chitinase-3-like protein 1, vascular endothelial growth factor, and interleukin-23 reflecting disease severity in PD and heightened inflammatory responses in MPNs. The NLRP3 and AIM2 inflammasomes are implicated in promoting excessive cytokine release, contributing to the pathogenesis of both diseases. This interplay underscores a bidirectional relationship between PD and MPNs, where pathogen-induced inflammation and immune dysregulation exacerbate disease progression. Understanding these mechanisms is crucial for developing targeted therapeutic strategies to manage inflammation and improve outcomes in affected individuals.

Keywords: periodontal disease; essential thrombocythemia; immune dysregulation; inflammation; myelofibrosis; myeloproliferative neoplasms; polycythemia vera; saliva pH

1. Introduction

Periodontal disease (PD) encompass a range of chronic inflammatory conditions affecting the gum, the supporting bone, and the connective tissue fibers that anchor the teeth to the alveolar bone. These diseases involve the soft tissue surrounding the teeth as well as the structures that provide support and stability [1]. Gingivitis is the most common and the incipient form of PD and is caused by the accumulation of bacteria and debris between the gumline and tooth (dental plaque) that consecutively leads to inflammation [2]. Progression of PD beyond the gingiva leads to Periodontitis a more destructive and permanent inflammatory state [3]. In the novel classification of Periodontal/Peri-implant Diseases and conditions, periodontitis can be subdivided in: Necrotizing periodontitis, Periodontitis and Periodontitis as a manifestation of systemic disease [4]. The same classification also includes systemic diseases associated with loss of dental supporting tissues like neoplastic conditions, and these can affect the periodontal apparatus non-related to biofilm induced periodontitis [5]. Tissue damage in PDs is mainly caused by the host's inflammatory response, with complement activation—via microbial components like LPS (lipopolysaccharide) playing a key role [6].

As PD progresses to periodontitis, anaerobic bacteria like *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* trigger a host inflammatory response, leading to the release of inflammatory markers such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), matrix metalloproteinases (MMPs) and interleukins. Elevated CRP levels suggest a potential link between periodontitis and cardiovascular disease, while smoking exacerbates the disease by promoting pathogen growth [7,8].

Philadelphia negative-Chronic Myeloproliferative Neoplasms (MPNs) characterized by clonal expansion of hematopoietic cells. Among them they are three most common MPNs: Polycythemia Vera (PV), Essential Thrombocythemia (ET) and Primary Myelofibrosis (PMF) [9]. Recent reports show that inflammasome NLPR3 genes and different cytokines are highly expressed in MPNs and

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they contribute to the progression of the disease, especially in patients who are positive for JAK2 V617F variant [10,11]. Moreover, allelic load of the JAK2 variant is correlated with plasma levels of inflammatory cytokines [12]. Inflammation in general is linked to atherosclerosis as study shows that LIGHT, a member of the TNF superfamily, decreases lipolytic gene expression and increases lipogenic gene expression in oxidized LDL-induced macrophages, promoting lipid accumulation through NF-κB activation and linking inflammation to hyperlipidemia. Additionally, the loss of Δ-5 fatty acid desaturase 1 has a proinflammatory effect in the liver, contributing to atherosclerosis and further reinforcing the connection between inflammation and atherogenesis [13–15]. These neoplasms are associated with higher cardiovascular risk and accelerated atherosclerosis mostly through dysregulated expression of cytokines like interleukin 1-β (IL1-β), Transforming growth factor -β (TGF-β), absent in melanoma 2 inflammasome (AIM2) and by disrupting the cholesterol efflux on foam cells [16,17].

In this review, we aim to comprehensively explore the potential relationships between chronic inflammation and the development of PD as a secondary condition in patients with MPNs. Our goal is to investigate both the direct and indirect mechanisms through which MPNs may contribute to periodontal pathology. Specifically, we will examine the role of biofilm-mediated pathways, where microbial colonization and dysbiosis may trigger inflammatory responses, as well as non-biofilm-mediated mechanisms, including systemic inflammatory mediators and immune dysregulation inherent to MPNs. By identifying the possible molecular and cellular pathways involved, we seek to provide a clearer understanding of how MPN-related inflammation influences PD progression and clinical implications.

2. Dysregulation of Inflammatory Cytokines in MPNs and Cytokine Pattern

In MPNs both healthy and mutated cells produce excessive amounts of inflammatory cytokines, with IL1-β, TNF-α, IL-6 and Colony stimulating factors (G-CSF) being the most important [18–20]. Chronic inflammation contributes to the initiation and expansion of leukocyte and platelet clones. These cells, in turn, release proinflammatory mediators, creating a self-sustaining cycle of inflammation [21]. While inflammation is a common feature across MPNs and more pronounced in JAK2-positive patients, each type of neoplasm exhibits a distinct cytokine profile, which influences clinical manifestations and prognosis in different ways [22]. Systemic consequences of the prolonged inflammation in MPNs have the most important impact on cardiovascular level with enhanced atherosclerosis, thrombotic events, myocardial fibrosis and pulmonary arterial hypertension (PAH) [23]. Additionally, these patients can present with constitutional symptoms osteoporotic features sharing similar traits with chronic inflammatory conditions like Lupus, rheumatoid arthritis and many more [22,24,25].

Major contributors to this inflammation are genetic driver mutations like the JAK2 46/1 haplotype which is associated with an abnormal myeloid response, promoting inflammation, myeloid neoplasms, and overexpression of genes like insulin-like 6 (INSL6) and insulin-like 4 (INSL4), which amplify pro-inflammatory cytokine production. Additionally, the telomerase reverse transcriptase (TERT) rs2736100 SNP, linked to increased enhancer activity and myeloproliferative neoplasm (MPN) susceptibility, may drive cytokine overproduction, particularly interleukin-6 (IL-6), contributing to MPN onset [26–28].

Overall, MPNs are characterized by the overexpression of a wide range of inflammatory mediators, including pro-inflammatory cytokines such as IL-1β, interferon alpha (IFN-α), interleukin-6 (IL-6), and interleukin-12 (IL-12), as well as anti-inflammatory cytokines like interleukin-4 (IL-4) and interleukin-10 (IL-10)(29–31). Additionally, MPNs elevate chemokines like macrophage inflammatory protein 1 alpha and beta (MIP-1α/β), and interferon-inducible protein 9 (IP-9), growth factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and platelet-derived growth factor (PDGF), and pro-fibrotic cytokines, including macrophage inflammatory protein (MIP), platelet-derived growth factor (PDGF), and interleukin-8 (IL-8) [30,32–35].

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Patients with ET are noted for elevated levels of circulating vascular endothelial growth factor (VEGF) and growth-related oncogene alpha (GRO-α) [12,36]. Although RANTES (regulated upon activation, normal T cell expressed and secreted) levels are also elevated in these patients, they do not exceed those observed in PMF [31]. Individuals with PV exhibit higher levels of interleukin-23 (IL-23) and, similar to ET patients, elevated levels of eotaxin [12,37]. PMF patients, however, display the highest cytokine burden, with increased levels of pro-inflammatory cytokines such as IL-2, IL-2R and TNF-α, along with chemokines like RANTES and MIP-1β. They also show elevated growth factors, including thrombopoietin (TPO), and pro-fibrotic molecules like fibroblast growth factor (FGF) and TGF-β [22,31,35,38].

3. Inflammatory Origin of the PD

There are three primary reasons why PD leads to chronic low-level systemic inflammation: oral inflammation, alterations in gut microbiota, and the activity of gingipains [39,40]. PD is caused by several hundred bacterial species known as periodontal pathogens. Among these, three key species—*Porphyromonas gingivalis, Tannerella forsythia*, and *Treponema denticola*—collectively referred to as the "*red complex*," have been strongly linked to the development of PD [41,42]. Studies suggest that oral bacteria can enter the bloodstream, particularly in individuals with gum inflammation or those undergoing multiple dental treatments. The inflammation driven by these bacterial infections is an independent risk factor for acute cardiovascular events. Improved oral hygiene, in turn, has been shown to reduce cardiovascular risk [43–46].

One key mechanism is oral inflammation from PD, which triggers the release of cytokines—crucial regulators of the immune response. In studies with mouse models and in vitro, cytokines have been shown to perform several functions, such as inducing neutrophil and lymphocyte activity and facilitating immune system communication. This cytokine release leads to chronic low-level systemic inflammation [47,48]. Furthermore, experiments on mice exposed to *P. gingivalis* have shown changes in gut microbiota composition, although *P. gingivalis* itself does not colonize the gut. Instead, it alters the microbial community, contributing to systemic inflammation [49].

Additionally, gingipains—proteases produced by periodontal pathogens—play a role in sustaining low-level systemic inflammation. These proteases include lysine-specific gingipain (Kgp) and arginine-specific gingipain (Rgp) [50]. Recent studies have indicated that periodontal pathogens also release outer membrane vesicles (OMVs), which prevent the resolution of inflammation caused by gingipains [51]. OMVs have been shown to elevate levels of cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8), and inhibiting gingipains can reduce TNF-α levels, despite an initial increase in response to OMV stimulation [52].

4. Pathogen-Induced Inflammation Through JAK/STAT Signaling in PD

Reactive oxygen species (ROS) are reactive molecules formed by the partial reduction of oxygen and play a key role in diseases like rheumatoid arthritis, atherosclerosis, and periodontitis [53–55]. Besides their tissue-damaging effects, ROS act as signaling molecules in cell proliferation, immune responses, and inflammation [56]. *P. gingivalis*, triggers ROS production while evading immune defenses through antioxidant enzymes like superoxide dismutase and thiol peroxidase, and protective mechanisms like a hemin layer [57,58]. *P. gingivalis* can survive within epithelial cells by enhancing the antioxidant glutathione (GSH) response and inducing ROS [59]. This ROS production, driven by extracellular adenosine triphosphate (ATP), activates the JAK2 signaling pathway in both epithelial and myeloid cells, which regulates inflammatory cytokine production via Toll-like receptors (TLRs) and downstream pathways like signal transducer and activator of transcription (STAT) and mitogen-activated protein kinase (MAPK), including c-Jun amino-terminal kinase (JNK) [60,61]. Neutralizing ROS with N-acetyl-L-cysteine (NAC) blocks JAK2 activation and reduces *P. gingivalis*-induced production of IL-6 and IL-1β. JAK2 activation triggers the JNK/c-Jun pathway, and inhibiting JAK2 or JNK/c-Jun reduces cytokine levels. This shows that ROS-driven JAK2 activation is crucial for the inflammatory response to *P. gingivalis* (Figure 1*)* [62].

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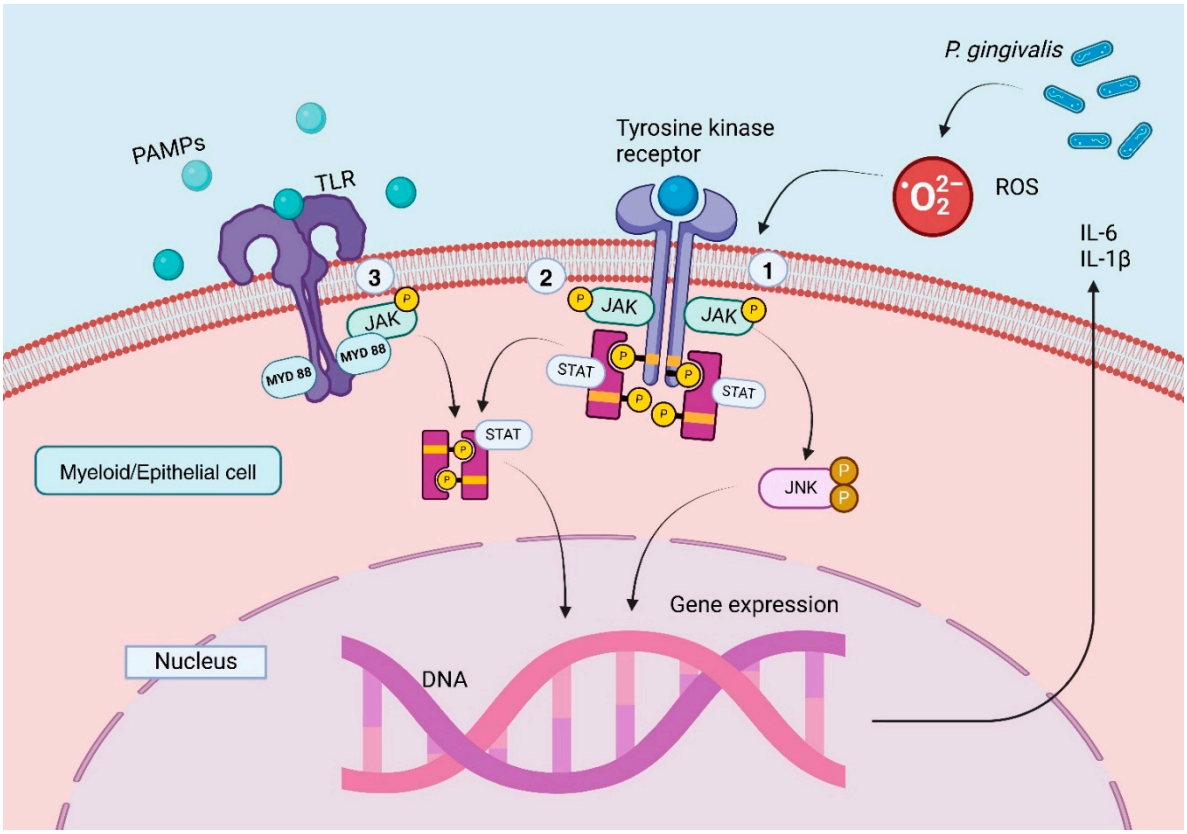

Figure 1. *Pathogen-induced inflammatory response in periodontal disease mediated through JAK2 signaling cascade; 1. ROS induced-JAk2 phosphorylation and activation as a result oxidative stress related to immune response to pathogens leading to JNK activation (60); 2. Classical JAK2 signaling cascade with subsequent STAT3 phosphorylation (64); 3. TLR-mediated JAK2 signaling through MYD88 association (62); In this scenario, one can assume that a mutation with gain of function in JAK2 gene (like JAK2 V617F) could lead to pathogen dependent inflammatory response enhancement in periodontal disease, since JAk2 signaling is common to both epithelial cells and myeloid cells (60). Abbreviations:IL-1β- Interleukin 1-beta; IL-6 -Interleukin 6; JAK2-Janus kinase 2; JNK- c-Jun N-terminal kinase; MYD88-Myeloid differentiation primary response 88; MAPK-mitogen activated protein kinase; PAMPs- pathogen associated molecular patterns; P. gingivalis- Porphyromonas gingivalis; ROS- Reactive oxygen species; STAT- signal transducer and activator of transcription; Created in BioRender.com.*

In a study, baricitinib treatment for rheumatoid arthritis (RA) showed significant improvement in both RA activity and periodontal inflammation, including reductions in gingival inflammation (GI), bleeding on probing (BOP), and probing depth (PD). However, changes in bacterial plaque were minor [63]. Another study indicates that baricitinib may help reverse periodontitis by reducing oxidative stress and inflammation while promoting the regeneration of periodontal tissues through enhanced osteogenic differentiation in a model of periodontal ligament stem cells (PDLSCs) by blocking the JAK/STAT signaling pathway, which helps restore cell viability, reduce pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6, and support tissue regeneration [64].

Blockade of the Janus kinase (JAK) signaling pathway, particularly through JAK1-3 inhibitors, has shown promise in reducing inflammation and preventing bone resorption in periodontitis, suggesting its potential as a therapeutic approach. Studies indicate that JAK inhibition can improve periodontal clinical parameters and modulate the inflammatory response, warranting further investigation into its clinical efficacy, proving [65]. Interestingly, a study showed that patients with MPNs receiving ruxolitinib had higher incidence of tooth cracks and dental abscess [66]. However, JAK/STAT signaling pathway is not only an inflammatory pathway it is also a key signaling cascade for differentiation of neural crest stem cells [67]. Moreover, not all JAK/STAT pathways lead to inflammation, JAK3 plays a protective anti-inflammatory role in innate immune cells by inhibiting the ubiquitination of Wnt3a through the phospho-inactivation of Nedd4-2, thereby reducing pro-

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inflammatory cytokine production and attenuating inflammation in response to the periodontal pathogen *P. gingivalis* [68].

Inappropriate activation of the renin-angiotensin system (RAS) exacerbates atherosclerosis, endothelial damage, and insulin resistance, while promoting coronary heart disease (CHD) progression, potentially due to heightened JAK/STAT signaling, and angiotensin-converting enzyme (ACE) inhibitors have shown therapeutic benefits in conditions like PV and MF by optimizing hematocrit (HCT) levels and reducing fibrosis by interfering with JAK/STAT signaling [23,69,70]. A research showed that telmisartan, an angiotensin II receptor blocker, blocks LPS-induced nitric oxide (NO) and IL-1β production in macrophages, promotes M2 macrophage polarization, and downregulates JAK-STAT signaling by attenuating STAT proteins phosphorylation. As a consequence this may lead to reduction in inflammatory response in PD, highlighting the role of JAK/STAT signaling in bacterial-induced inflammation [71]. Another study revealed that JAK inhibitor ruxolitinib was shown to partially reduce necroptotic effects of INF-β, suggesting that JAK-STAT signaling plays a crucial role in regulating INF-β-induced cell death during bone formation [72].

5. Circulating Cells and Periodontal Disease

We have arguments to believe that circulating cells might have an impact on PD since a report has shown that CD34+ cells are positively correlated with the degree of PD [73].

MDSCs (myeloid-derived suppressor cells) expand in MPNs due to chronic inflammation and oxidative stress, driven in part by the JAK2 V617F mutation. This mutation promotes ROS production, which helps MDSCs suppress immune responses, contributing to disease progression in MPNs [74,75]. However, MDSC levels don't directly correlate with JAK2 allele burden, highlighting complex interactions in these diseases [76]. MDSCs are elevated in both the peripheral blood and bone marrow of patients with MPNs, including PMF, where they correlate with disease progression and fibrosis. These cells, influenced by chronic inflammation, exhibit immunosuppressive functions and may contribute to creating a fibrotic microenvironment, making them potential targets for therapy in MPNs [77,78]. MDSCs contribute to PD by suppressing T cell activity and promoting chronic inflammation in the periodontium. Key periodontal pathogens like *P. gingivalis* and *Fusobacterium nucleatum* activate MDSCs, leading to tissue damage through amino acid depletion and the production of reactive oxygen and nitrogen species [79]. PD associated with other inflammatory conditions as obesity, rheumatoid arthritis (RA) or cancer can induce systemic expansion of MDSC subpopulations or recruitment to tissues [80].

In patients with MPNs, an elevated neutrophil-to-lymphocyte ratio (NLR) and increased release of neutrophil extracellular traps (NETs) have been observed, potentially linked to heightened JAK2 kinase activity [81,82]. While NETs, composed of nucleic acids, proteins, and enzymes, are critical for pathogen defense and innate immunity, their excessive release in MPNs contributes to sterile inflammation, suggesting a role in the chronic inflammatory state associated with these conditions [83,84]. In murine models with PD, NETs promote macrophage polarization toward the pro-inflammatory M1 phenotype by inhibiting the JAK2/STAT3 pathway, which worsens inflammation, but this is rather the result of hyperglycemia, in contrast to MPNs where JAK2 variant induces a background sterile inflammation [85].

While NETs are essential for capturing and neutralizing pathogens, their excessive formation in periodontal tissues leads to heightened inflammation and immune dysregulation. This overaccumulation of NETs triggers the release of pro-inflammatory cytokines, drives the polarization of macrophages toward a destructive M1 phenotype, and exacerbates tissue damage, including alveolar bone resorption. Furthermore, gingival fibroblasts have been found to enhance NET production via the MIF-CD74/CXCR4 signaling pathway, further amplifying the inflammatory environment [86,87]. CXCR4 plays a critical role in immune regulation by modulating neutrophil dynamics, promoting their infiltration in periodontal tissues, and influencing inflammation through mechanisms such as the recruitment of proinflammatory monocytes/macrophages and the signaling of CXCL12, which enhances cytokine expression and chemotaxis [88].

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A possible connection with platelets can be seen in the context of periodontitis, elevated levels of soluble P-selectin (sP-selectin), a marker of platelet activation, have been observed, and this activation is associated with the severity of the disease. The presence of higher numbers of platelets and activated platelets in periodontitis patients could explain the heightened risk of coronary heart disease and stroke seen in individuals with this condition, moreover mean platelet volume in these patients is also positively correlated with the degree of PD [89,90]. Interestingly, research on ET and PV show high levels of soluble P-selectin as a marker of thrombocyte activity when compared to healthy individuals [91].

6. Common Circulating Inflammatory Mediators in MPNs and Periodontal Disease

The new classification of periodontal diseases recognizes that neoplastic diseases can affect the periodontal tissues independently of plaque-induced periodontitis, and such cases should be classified based on the primary systemic disease, under the category of *"Systemic Diseases or Conditions Affecting the Periodontal Supporting Tissues"*[4]. Current evidence shows that conditions with systemic inflammation like auto-immune disease like LES and RA can manifest with PD [92,93].

Chitinase-3-like protein 1 (CHI3L1), also known as YKL-40, is an inflammatory protein elevated in chronic periodontitis (CP), showing a strong correlation with disease severity and periodontal pocket depth (PPD). This makes YKL-40 a promising biomarker for tracking PD progression [94]. Furthermore, YKL-40 levels increase progressively with the PD evolution, alongside other inflammatory cytokines like IL-6 [95]. YKL-40 is a promising biomarker for monitoring athero-protective therapy, as it is linked to inflammation and disease severity in cardio-metabolic disorders, potentially improving risk prediction for cardiovascular events [96]. Also, Anti-YKL-40 therapy has shown promising effects by inhibiting tumor migration and inducing apoptosis, proving YKL-40 pro-oncogenic effects [97]. Elevated circulating YKL-40 levels in Philadelphia-negative MPNs are associated with increased inflammation, higher C-reactive protein levels, poor performance status, and greater cardiovascular risk, with specific correlations showing that elevated YKL-40 predicts an increased risk of thrombosis in ET and PV patients and impaired survival in MF patients [98].

Inflammatory cytokines in gingival tissues around human gingival fibroblasts (HGFs) are vital for initiating inflammatory responses. Human gingival fibroblasts produce VEGF, which increases vascular permeability and contributes to the severity of periodontal disease [99,100]. Evidence so far indicate that VEGF production is generally upregulated in patients with periodontitis, suggesting it plays a crucial role in the etiology of gingivitis and its progression to periodontitis. VEGF enhances vascular permeability and angiogenesis, potentially linking it to periodontal disease [101]. In patients with ET, levels of VEGF are significantly elevated, particularly in untreated individuals [102]. This could explain partially the gums-bleeding tendency sometimes seen in these patients [103].

GRO-alpha is an important inflammatory mediator found in higher concentrations in gingival crevicular fluid from inflamed periodontal sites, where it stimulates neutrophil chemotaxis, and its secretion can be inhibited by compounds like A-type proanthocyanins AC-PACs, Epigallocatechin-3-gallate (EGCG) and LL-37, which prevent immune cell activation [104]. Even though in periodontal disease GRO-β is not a central element, in patients with ET, intracellular flow cytometry revealed that monocytes, particularly the proinflammatory CD56+/CD14+ subset, were the predominant producers of GRO-alpha, with significantly elevated levels correlating with an increased risk of disease transformation to MF, confirmed in an extended cohort [105–107].

IL-23 is crucial in the pathogenesis of periodontal disease, evidenced by its increase expression in gingival tissue samples from patients with chronic and aggressive periodontitis compared to healthy controls, correlating with inflammatory infiltrate intensity and clinical parameters such as probing depth and clinical attachment loss, highlighting its involvement in promoting Th17 cell responses that exacerbate tissue damage and inflammation during disease progression [108]. Moreover, IL-1β stimulates the production of IL-23 p19 in human periodontal ligament fibroblasts (hPDLFs) through NF-κB and MAPK-dependent pathways, suggesting that targeting this interaction could provide therapeutic benefits in managing Th17-driven inflammatory diseases such as periodontitis [109]. **Plasma levels of IL-23** were significantly higher in patients with MPN compared

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to controls. Specifically, there was a significant difference in IL-23 levels between patients affected by **PV** and the control group [37]. Furthermore, the importance of this cytokine in periodontal disease is indicated by the fact that IL-23 not only enhances cell proliferation in oral cancer cells but also plays a critical role in modulating NF-kB activity, leading to tumor growth and survival in oral squamous cell carcinoma. However, there is no evidence that this could lead to a higher incidence of oral cancers in PV or other MPN [110].

Eotaxin-1 is categorized as a pro-inflammatory cytokine, which can contribute to the inflammatory microenvironment that often accompanies cancer, including OSCC, being involved in the recruitment of inflammatory cells, such as eosinophils, may play a role in both promoting and regulating tumor progression [111]. Eotaxin-1 is associated with prolonged inflammation in periodontitis, with levels that can be influenced by the A variant of interferon gamma inducible protein 16 (IFI16) [112]. Also they are elevated in PV and TE [12].

TGF-β plays a dual role in periodontitis, acting both as a pro-inflammatory and anti-inflammatory mediator. It induces immune cells to secrete pro-inflammatory cytokines like IL-1β and IL-6, contributing to inflammation, while also acting as a chemoattractant for neutrophils, monocytes, and lymphocytes. However, in inflammatory environments, TGF-β can lose its immunosuppressive properties, promoting tissue destruction instead of repair, as seen in PD [113,114]. Elevated TGF-β levels in MPNs are linked to arterial plaque growth and coronary injury, though its role remains unclear, making it a promising research focus. Additionally, TGF-β contributes to cell phenotype switching, which may play a role in oncogenesis, atherogenesis, and bone marrow fibrosis [115–117].

RANTES (Regulated upon Activation, Normal T Cell Expressed and Secreted) is a chemokine that significantly attracts immune cells like monocytes and T cells to inflamed tissues. In periodontal disease, elevated RANTES levels are linked with disease activity, particularly in aggressive periodontitis, where its high concentration correlates with severe tissue destruction. After periodontal therapy, RANTES levels decrease, reflecting a reduction in inflammation, but this alone is not enough to determine the need for further treatment or surgery [118–121]. In ET, platelets show increased secretion of the chemokine RANTES, particularly via TLR2 and TLR4 signaling, contributing to thromboinflammatory processes like monocyte recruitment and atherogenesis. However, despite elevated platelet-derived RANTES, its plasma levels remain low, suggesting that RANTES primarily mediates localized rather than systemic inflammation in ET [122–125]. Other reports have shown similar levels between bone marrow aspirate and peripheral blood of RANTES [126].

Hepatocyte growth factor (HGF) is a key angiogenic and regenerative factor with cytoprotective effects, playing a significant role in cardioprotection during coronary ischemia and infarction, and is linked to various chronic diseases, including coronary artery disease (CAD) [127]. In periodontal disease, HGF levels increase proportionally with disease progression, and its synthesis is stimulated by *P. gingivalis*, highlighting the relationship between oral health and systemic inflammation [128]. In MPNs, particularly those associated with the JAK2 V617F mutation, HGF is overproduced by both malignant myeloid progenitors and bone marrow stromal cells (BMSCs), independent of JAK2 signaling [129]. This deregulation of HGF not only enhances the proliferation and survival of hematopoietic progenitors but also contributes to an inflammatory microenvironment by promoting the production of various cytokines such as interleukin (IL)-6 and IL-11 [130,131]. While the production of HGF in MPNs occurs independently of JAK2, the mutation enhances the responsiveness of progenitor cells to various growth factors, including HGF [132]. The heightened responsiveness of progenitor cells to HGF due to JAK2 mutations may exacerbate inflammation and tissue remodeling in periodontal disease, potentially worsening tissue destruction and impairing immune responses against periodontal pathogens.

The NLRP3 inflammasome is a critical component of the host immune defense, activated by a wide range of structurally diverse stimuli such as extracellular ATP, pore-forming toxins, and RNA viruses. In myeloproliferative neoplasm (MPN) patients, NLRP3 inflammasome genes are upregulated in hematopoietic cells, contributing to the inflammatory state. When dysregulated, NLRP3 also plays a role in various inflammatory disorders, including Alzheimer's disease, diabetes,

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gout, and atherosclerosis, by triggering caspase-1 activation and the release of pro-inflammatory cytokines like IL-1β and IL-18 [10,133]. The dysregulation of the NLRP3 inflammasome in MPN may contribute to the pathogenesis of periodontitis by promoting chronic inflammation and excessive cytokine production, as a report shows that COVID-19 induced NLPR3 activation leads to periodontitis, supporting the hypothesis that biofilm-unrelated inflammatory response could lead to tissue damage by underlying inflammatory cytokine dysregulation [134]. Another inflammasome [112] AIM2 is activated in response to double-stranded DNA (dsDNA) fragments from pathogens. Upon activation, it associates with caspase-1, leading to the formation of the AIM2 inflammasome, which is crucial for the maturation of pro-inflammatory cytokines such as IL-1β, IL-18, and IL-33. This cytokine release contributes to the inflammatory processes associated with periodontitis [112]. In MPN AIM2 inflammasome hyperactivity is caused by JAK2 mutation leading to increased IL-1β signaling [135].

IL-1β and IL-6 are produced in response to infections in the root canal system, driven by the host immune response and epigenetic changes like DNA hypomethylation and pro-inflammatory signaling. Their increased levels lead to enhanced osteoclastic activity, resulting in bone resorption and tissue damage associated with apical periodontitis. Ultimately, the dysregulation of these cytokines exacerbates inflammation and contributes to the severity of the disease [136]. In MPN Il-1β and Il-6 are elevated in all subgroups (ET/PV/PMF) compared to healthy controls [22,29,30]. One could speculate that elevated pro-inflammatory signaling associated with NLPR3 and AIM2 inflammasome hyperactivity could lead to both biofilm dependent/independent inflammatory response and IL-1β signaling and contributing to periodontal disease.

7. The Bidirectional Impact of Periodontal Disease and Myeloproliferative Neoplasms

Recent studies have increasingly elucidated the relationship between periodontal disease (PD) and various forms of cancer, including lung, breast, prostate, pancreas and colorectal cancers [141–145]. Research, indicates that indicators of PD, like probing pocket depth and clinical attachment loss, are positively associated with an increased risk of lung cancer, particularly in smokers. Meta-analyses further confirm a significant link between PD and heightened cancer risks, with findings showing that individuals with PD may have up to a 51% higher likelihood of developing lung cancer and an increased risk of other cancers, such as breast and colorectal cancer, which can escalate with tooth loss [141,142,146,147]. New evidence suggest that the impact of PD could have implication even in hematological malignancies like Non-Hodgkin Lymphoma (NHL) [148]. Even though there are few researches on the impact of PD on MPN there are few links between cytokine expression and MPN occurrence. IL2Rα (IL-2 receptor alpha) gene variants may contribute to periodontal disease susceptibility in individuals with type 1 diabetes mellitus by altering T cell activation and immune responses, leading to increased inflammation and tissue damage in the periodontal region [137]. High IP-10 (interferon gamma-induced protein 10) levels are indicative of an ongoing inflammatory response, as they attract immune cells to the inflamed periodontal tissue, thus contributing to the disease's progression and severity [140]. There are at least two reports in IL2Rα and one for IP-10 that mention the risk associated of MPNs and the high circulating levels of both cytokines [138,139]. The potential bidirectional influence between PD and MPNs underscores a sophisticated interplay between chronic inflammation and hematological disorders (Figure 2) (Table 1).

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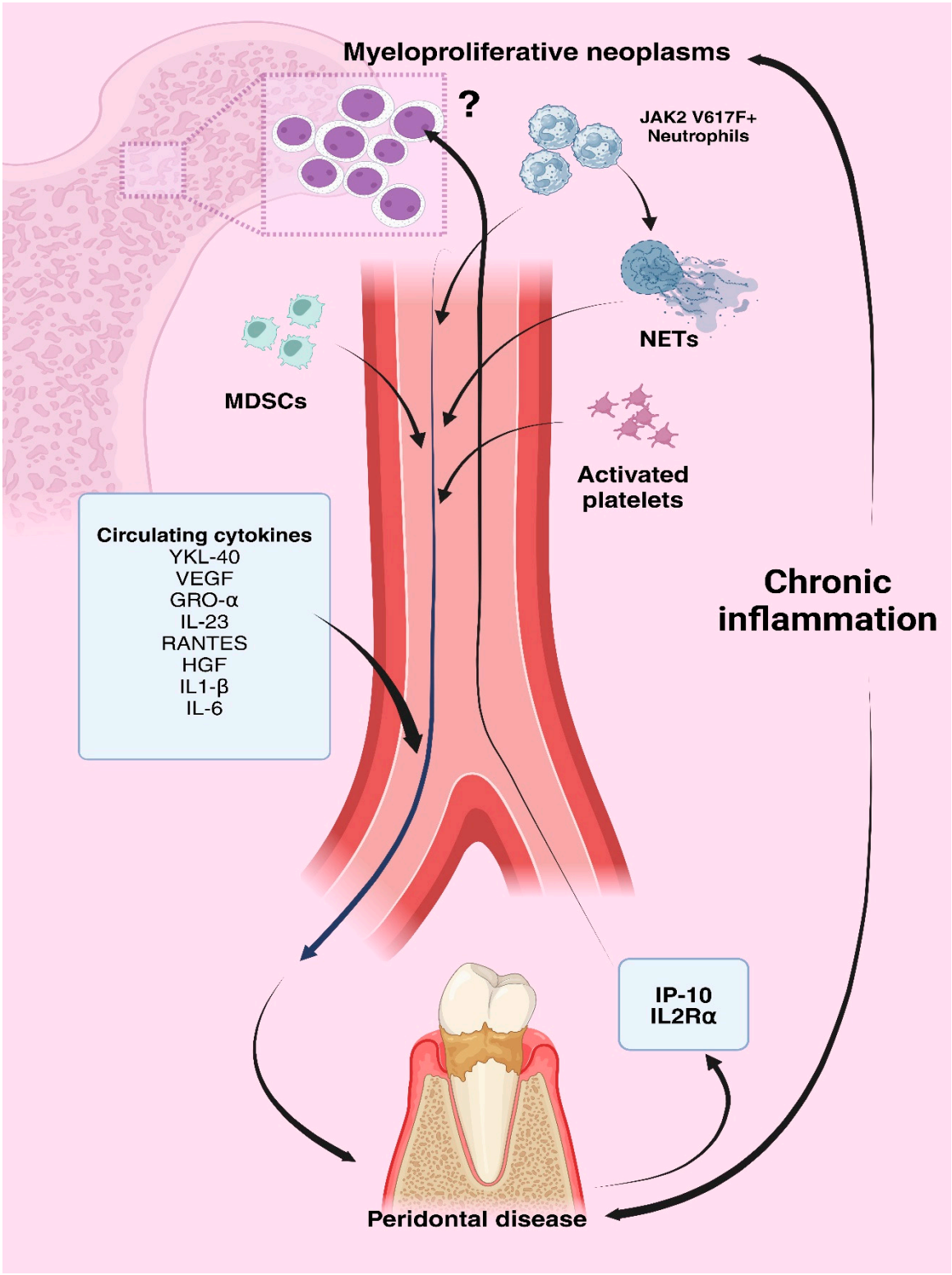

Figure 2. *Proposed Interrelationship Between Periodontal Disease Inflammation and Myeloproliferative Disorders; Created in BioRender.com.*

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Table 1. Key Circulating Inflammatory Mediators in PD and MPNs.

Mediator	Role in PD	Role in MPNs	References
YKL-40 (CHI3L1)	Correlates with disease severity, elevated with IL-6	Linked to increased inflammation, cardiovascular risk, thrombosis in ET/PV	[94,95,98]
VEGF	Increases vascular permeability, exacerbating inflammation	Elevated in ET, associated with bleeding tendencies	[99,100,102]
GRO-alpha	Promotes neutrophil chemotaxis in inflamed tissue	Elevated in ET, correlates with progression to MF	[104,105]
IL-23	Enhances Th17 response and tissue damage	Elevated in PV, promotes cell proliferation and tumor growth	[37,109,110]
Eotaxin-1	Recruits eosinophils, contributes to inflammation	Elevated in PV/ET, linked to chronic inflammation	[111,112]
TGF-β	Dual role in inflammation and tissue repair	Contributes to arterial plaque and coronary damage	[113–117]
RANTES	High levels in severe PD; attracts immune cells	Increased in ET, linked to localized thrombo-inflammatory processes	[118,119,124–126]
HGF	Increases with disease progression, stimulated by *P. gingivalis*	Overproduced in JAK2 V617F MPNs; promotes progenitor cell growth	[127,128,130,132]
NLRP3 inflammasome	Drives chronic inflammation, triggered by pathogens	Upregulated in MPNs, leading to excessive cytokine release	[10,133,134]
AIM2 inflammasome	Releases IL-1β, IL-18, and IL-33 in response to pathogens	Hyperactive in JAK2-mutant MPNs, driving IL-1β signaling	[112,135]
IL-1β and IL-6	Induces bone resorption and tissue damage	Elevated in MPNs (ET/PV/PMF), leading to systemic inflammation	[22,29,30,33,36,136]
IL2Rα	Genetic variant linked to PD susceptibility in Type 1 Diabetes	High levels associated with MPN risk	[137–139]
IP-10	Attracts immune cells to periodontal tissue, intensifying inflammation	High levels associated with MPN risk	[137,139,140]

Legend: AIM2 = Interferon-Inducible Protein AIM2; GRO-alpha = Growth Regulated Oncogene Alpha; HGF = Hepatocyte Growth Factor; IP-10 = Interferon Gamma-Induced Protein 10; NLRP3 = NLR Family Pyrin Domain Containing 3; RANTES = Regulated on Activation, Normal T-Cell Expressed and Secreted; TGF-β = Transforming Growth Factor Beta; VEGF = Vascular Endothelial Growth Factor.

This review highlights the intricate relationship between PD and MPNs, emphasizing the role of common inflammatory mediators. Elevated levels of cytokines such as YKL-40, VEGF, and IL-23 illustrate how chronic inflammation can impact both conditions. Genetic variants like IL2Rα and markers such as IP-10 further underscore the bidirectional influence of PD and MPNs, suggesting that managing systemic inflammation and oral health may be crucial for improving patient outcomes.

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