The New and Evolving Science of Polymyalgia Rheumatica

Unraveling PMR Pathophysiology: The Central Role of IL-6

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Dear Colleagues,

This is a very exciting time in the field of polymyalgia rheumatica (PMR). With an increased focus on basic and clinical research regarding the pathogenesis of PMR, we now understand more about this disease than ever before. We know that cytokines play many key roles in the inflammation that drives PMR. One such example is interleukin-6 (IL-6), a multifunctional cytokine that contributes to local and systemic inflammation in patients with PMR.

Sanofi and Regeneron Pharmaceuticals are excited to bring you additional educational materials describing some of the fundamental aspects of PMR through a series of scientific monographs entitled *The New and Evolving Science of Polymyalgia Rheumatica*. In this first installment, we will discuss the pathophysiology of PMR and the role IL-6 plays as a key factor in the disease.

We hope you find this installment informative and engaging.

Sincerely,

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I. Introduction to PMR

Polymyalgia rheumatica (PMR) is an inflammatory disease that generally affects individuals older than 50 years of age.[1] PMR is characterized by pain and stiffness, which manifest in the shoulders, neck, and hips, often leading to significant disability and impaired quality of life. PMR in its classic form often presents dramatically, with severe and symmetric pain emanating from the periarticular structures of the shoulders and hips. PMR can also present atypically, with features such as neck pain, unilateral shoulder pain, lower leg pain, carpal tunnel syndrome, tenosynovitis in hands and/or wrists, and abdominal pain, among other manifestations, making it diagnostically challenging.[2]

PMR is the second most common rheumatic disease in adults older than 50, second only to rheumatoid arthritis (RA). The overall annual incidence of PMR in the United States is 64 per 100,000 people aged ≥50 years and the estimated prevalence of PMR in the United States is approximately 800,000.[3-6] With an aging population, the prevalence of PMR is likely to increase in coming years.

Many research studies have traditionally tended to prioritize conditions that affect younger populations, such as RA or systemic lupus erythematosus (SLE); this has led to a relative lack of attention to PMR. With the increasing prevalence of PMR have come notable advancements in our understanding of its pathophysiology. An area of significant progress includes understanding the role of interleukin-6 (IL-6) in its pathophysiology.[7]

Risk factors

PMR is a complex inflammatory disorder with multifactorial origins, and while its exact cause remains elusive, certain risk factors have been identified that may contribute to its onset.

1. **Age and sex:** Advanced age is the most prominent risk factor for PMR. PMR is extremely rare among individuals under the age of 50, and its occurrence becomes progressively more prevalent with each passing decade, with its highest incidence at approximately 75 years of age. While the precise causes are still not fully understood, it is widely believed that immunosenescence, the process of the immune system aging, plays a crucial role in the development of PMR.[8,9]

2. **Genetics:** It is suspected that genetic predisposition may play a role in the development of PMR, as evidenced by its unequal geographical distribution. The incidence of PMR in northern Europe and other areas with Scandinavian populations is substantial, while in African and Native American populations, it is almost nonexistent.[10] Interestingly, within Europe, the incidence of PMR is higher in the northern regions compared to the southern countries for people aged 50 years and older. For example, the annual incidence of PMR per 100,000 people in Denmark (1982-1985) was 68.3 cases, and in Sweden (1985-1987) was 50 cases. In contrast, in Spain, the annual incidence per 100,000 people aged 50 years and older over the period 1987-1996 was 13.5 cases and in Italy, incidence ranged from 0.0012 to 0.023 cases per 100,000 people.[11,12]

   Additionally, certain genetic variations in immune-related genes have been associated with an increased susceptibility to PMR. Greater disease severity and relapse rate of PMR may also be associated with populations carrying the HLA-DRB1*04 allele.[10,13] A variation in NOS3 has been linked to vascular dysfunction, even in cases of PMR where vascular symptoms are absent. Additionally, certain HLA-DRB1 subtypes have been identified as predisposing factors for vascular complications in PMR patients. These observations may indicate a potential connection or continuum between PMR and large vessel vasculitis.[13] A polymorphism located in

the promoter region of the interleukin-6 (IL-6) gene at position -174 has been linked to the presence of PMR symptoms in individuals with GCA who lack the HLA-DRB1*04 allele. Additionally, variations in other genes that play roles in initiating and regulating the inflammatory response may contribute to the susceptibility for PMR. These genes include tumor necrosis factor (TNFα2, TNFβ3), intercellular adhesion molecule-1, chemokine (C-C motif) ligand 5 (CCL5, also known as RANTES), and interleukin-1 receptor antagonist (IL-1RN).[13,14] Studies of the immunogenetics of PMR have included somewhat limited numbers and need validation in larger patient cohorts.

3. **History of PMR or GCA:** Other risk factors for PMR include a family history of PMR or GCA, suggesting a shared genetic susceptibility in these conditions.[15] PMR and GCA are closely connected diseases; 15% to 20% of PMR cases present with obvious signs of GCA, whereas 40% to 60% of patients with GCA present with PMR.[7] These conditions show significant similarity in musculoskeletal and arterial inflammation along with strong inflammatory responses, a dominant IL-6 profile, a highly positive response to glucocorticoid treatment, a tendency towards chronic and relapsing patterns, (with flares and uncontrolled disease) and a higher prevalence among older individuals. Because of this correlation of incidence, similarity in epidemiologic features, and overlapping pathophysiology, it has been proposed that PMR and GCA may be manifestations of the same inflammatory disease that exists on a spectrum.[7]

   The precise interplay of genetic and immune factors in PMR remains an area of active research in order to gain deeper insights into the disease's etiology and potentially identify preventive strategies.

4. **PMR as a side effect of cancer treatments:** Immune check point inhibitors (ICI) have become increasingly used as cancer therapy, causing a paradigm shift and producing significant survival benefits for cancer patients. Their use, however, has been associated with a five-fold elevated risk of developing a "PMR-like illness" that has not been observed in cancer patients treated with other immunotherapies.[9,16] In a study analyzing case reports from 3 centers across the US and Europe, 49 patients that presented with PMR-like syndrome in the setting of ICI were assessed to determine whether they fulfilled the 2012 EULAR/ACR provisional criteria for PMR: 75% of the patients fulfilled the criteria for PMR classification. However, many of them exhibited atypical characteristics, leading to the possibility that these cases might represent a distinct condition. In the absence of a gold standard for the diagnosis of PMR, the relationship of checkpoint inhibitor-related PMR to the idiopathic form remains unclear and requires additional research.[16]

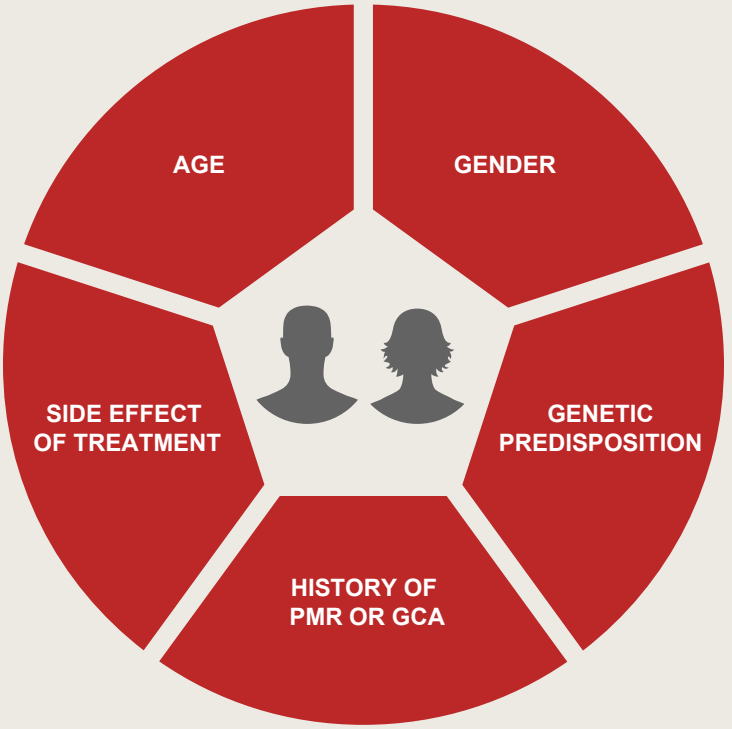


Figure 1: Risk factors for PMR include age, gender, side effect of treatment, genetic predisposition and history of PMR or GCA.

II. PMR Pathophysiology

Broadly speaking, the disease manifestation of PMR occurs due to the activation of specific types of immune cells of the innate and adaptive immunity arms, which secrete several pro-inflammatory cytokines, such as IL-6, TNFα, IL-1, IL-10, IL-17, and IFNγ[17] (Figures 2, 4). These cytokines, especially IL-6, contribute to the systemic inflammation observed in PMR and are responsible for inducing acute-phase reactants like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), commonly used as markers of disease activity.[17]

The primary pathology in PMR involves the periarticular structures surrounding the shoulders and hips, such as in the extrasynovial bursae as well as interspinous bursae and, less commonly, the joint itself.[18] Thus, there may be immunological changes occurring locally in the synovium that are different from immune modifications in the peripheral blood.[13] To this end, while most studies have focused on measuring immune alterations in peripheral blood, a few studies have examined changes in the synovium itself, via testing synovial fluid or tissue.[13] The signature of immune activation was found to be different in these two compartments, both in terms of immune cell activation and the cytokines that are secreted (Figure 3). The reason for these differences in immune signatures between the peripheral blood and the synovium is not entirely clear, but it could be due to the localized nature of the inflammation within the synovium, which may lead to unique cellular and molecular responses compared to the more systemic inflammation seen in peripheral blood.[13]

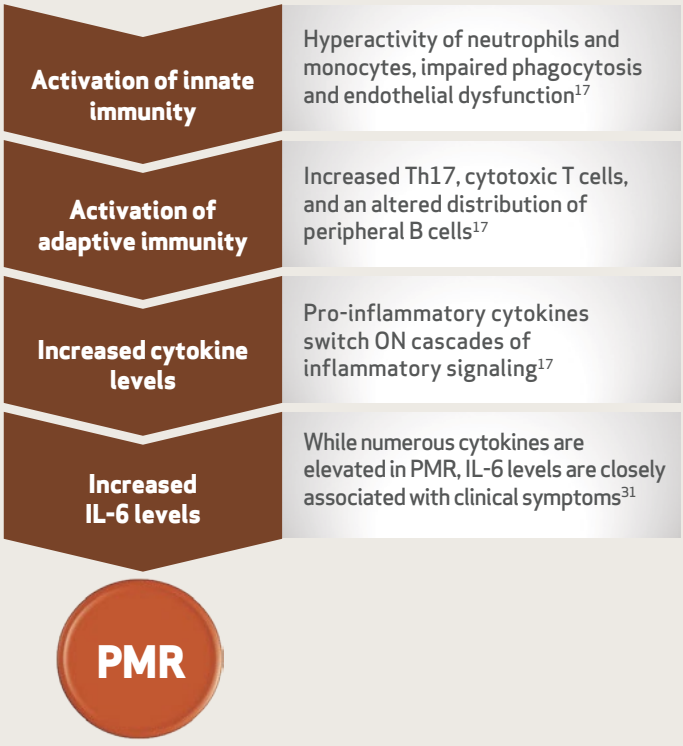


Figure 2: While PMR pathophysiology remains incompletely understood, it is clear that it involves the activation of specific cells mediating innate and adaptive immunity. This leads to an increase in the levels of pro-inflammatory cytokines, especially IL-6, which drive PMR pathophysiology.

Peripheral blood

In the peripheral blood, there are detectable changes in the immune system, including an increase in certain innate and adaptive immune cells, circulating cytokines, and elevated levels of acute-phase reactants like CRP and ESR; these indicate ongoing systemic inflammation (Figure 3). This systemic inflammation likely contributes to symptoms such as fatigue, malaise, anorexia, weight loss, or low-grade fever, which are experienced by approximately half of patients with PMR.[19]

Taking a closer look at cellular changes in the peripheral blood of patients with PMR, there was a significant expansion of myeloid cells (monocytes and neutrophils) and IL-17–producing T-helper 17 (Th17) cells and CD8+ cytotoxic T cells[17,20] (Figure 3). On the other hand, the prevalence of circulating Th1 cells has not been consistently reported across studies.[7] Patients with PMR in remission have a higher frequency of blood peripheral mucosal associated invariant T cells (MAIT) and γδ T cells (ie, innate T cells) compared to healthy controls, along with higher serum

concentration of cytokines that derive from these innate T cells, such as TNFα, IFNγ, and IL-17.[17]

In addition, the distribution of B cells was highly altered in patients newly diagnosed with PMR. Effector B cells—rather than regulatory B cells—were redistributed during active disease but returned during remission of PMR. These effector B cells demonstrated an enhanced potential to produce the pro-inflammatory cytokine IL-6. Interestingly, serum B-cell activating factor (BAFF) levels were initially increased in patients newly diagnosed with PMR, but readily dropped upon the return of B cells during remission. Overall, serum BAFF levels showed a strong inverse correlation with circulating B-cell numbers in patients with PMR. Levels of B cells expressing specific chemokine receptors (CXCR3, CXCR4, and CXCR5) are lower in peripheral blood; it is possible that these B cells enter inflamed synovia or the lymphatic system in PMR patients.[21,22]

Alteration of T-cell homeostasis to a pro-inflammatory state has been detected in patients with PMR.[23] Compared with control subjects, patients with PMR had a significantly higher percentage of pro-inflammatory Th17 cells, and a decreased frequency of Th1 cells and immunosuppressive Treg cells. While the frequency of Th17 precursors (CD161+CD4+ T cells) was similar in patients and control subjects, the ability to produce IL-17 in vitro was significantly enhanced in patients with PMR.[23]

One of the ways by which innate and adaptive immune cells drive PMR disease progression is by releasing pro-inflammatory cytokines: serum levels of IL-1, IL-6, IL-17, IFNγ, and TNFα were higher in patients with PMR compared to healthy controls or patients with PMR with inactive disease[24] (Figures 3, 4). Further, plasma IL-6 levels correlated with PMR disease activity and elevated levels of IL-6 and soluble IL-6 receptor were associated with the risk of relapse (Figure 5).

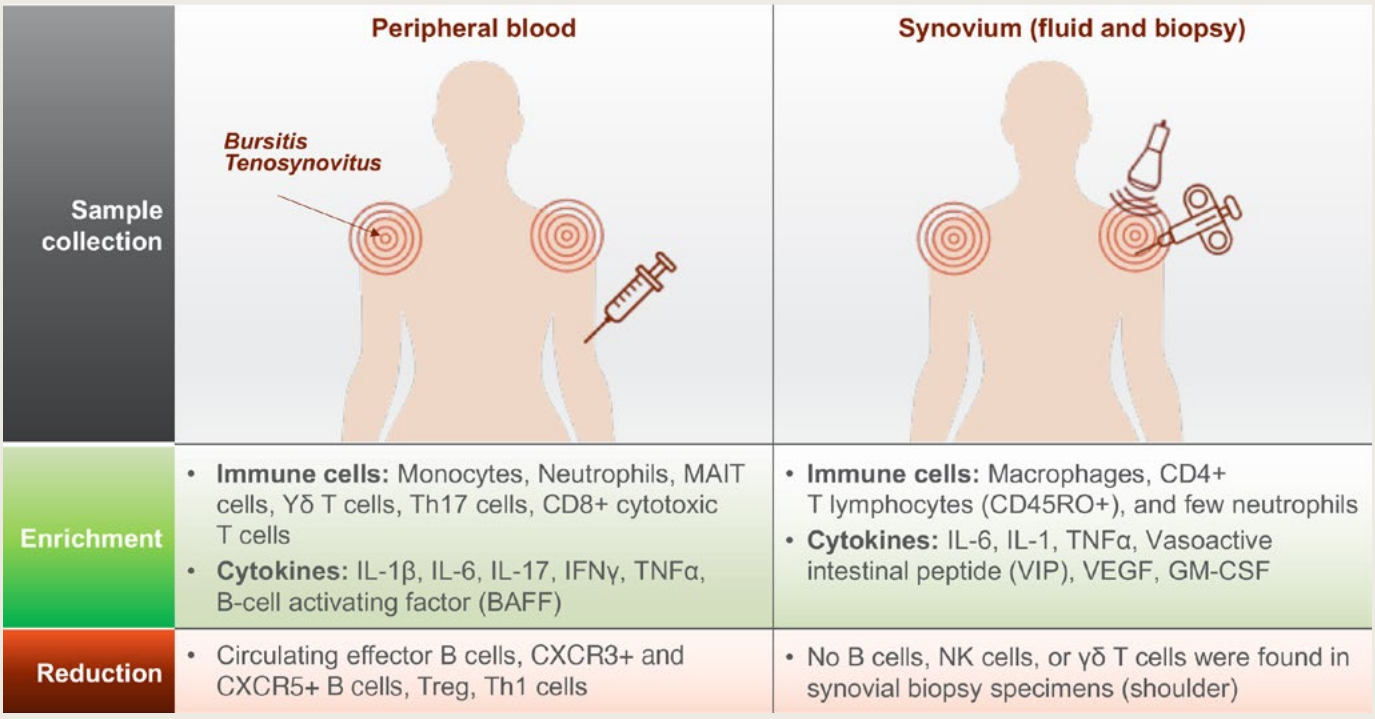


Figure 3: The pathophysiology of PMR has been studied by surveilling immune activity in the peripheral blood, as well as the synovium (via examining synovial fluid or tissue). The signature of immune activation is different in these two compartments with respect to immune cell activation and secretion of different cytokines.

In a study comparing patients with PMR of varying disease severity, elevated serum levels of IL-10 were associated with a milder form of PMR, suggesting that IL-10 may play a protective role in PMR pathogenesis.[17]

Synovium

Macrophages, along with T cells, infiltrate synovial tissues and temporal arteries of patients with PMR, leading to localized inflammation and contributing to the hallmark symptoms of pain and stiffness in affected areas. The inflammatory infiltrate found in shoulder synovial biopsy specimens from 12 PMR patients was composed mainly of macrophages, CD4+ T lymphocytes (virtually all T cells were CD45RO+ memory cells), intensely expressing HLA class II antigens, and few neutrophils. Notably absent from these specimens were B cells, NK, or γδ T cells.[17] In other studies, granulocyte–macrophage colony-stimulating factor (GM-CSF)–producing macrophages were found to be abundant in the PMR synovium.[7] The presence of cells from both the innate and adaptive arms of the immune system in the synovium suggests that both types of immunity contribute to PMR pathogenesis.[17,25,26]

PMR is characterized by an important chronic subclinical inflammatory component; treatment-naïve patients show endothelial dysfunction as assessed by flow-mediated dilation, a technique that measures endothelium-dependent vasodilation.[27] Activated endothelial cells, platelets, macrophages, and synovial fibroblasts are linked to increased concentrations of neoangiogenesis markers such as vascular endothelial growth factor (VEGF) and angiopoietin-2 in patients with PMR.[17] Endothelial cell dysfunction was identified in another study in patients with PMR, since they had an increased number of circulating endothelial microparticles (EMPs) and a reduced number of endothelial progenitor cells (EPCs) compared to healthy controls. This altered balance between EMP release and EPC generation has been demonstrated in patients with systemic autoimmune diseases and recognized as a potential surrogate marker of endothelial injury.[17,26]

IL-6 levels were increased in the synovial fluid of patients with PMR, and IL-6 is expressed in noninflamed arteries as well as synovial tissue obtained from patients with new-onset, treatment-naïve PMR.[13,29] Vascular infiltration of T cells producing inflammatory cytokines IL-1, IL-6 and TNFα was observed in patients with PMR.[13] Vasoactive intestinal peptide (VIP) expression was significantly increased in shoulder synovial tissues of PMR, and is thought to contribute to the typical musculoskeletal discomfort and may have a role in the immunomodulation of synovial inflammation.[30] While the levels of a variety of cytokines were found to increase in patients with PMR, IL-6 has been extensively studied, and found to play a central role in PMR pathophysiology (Figure 4).

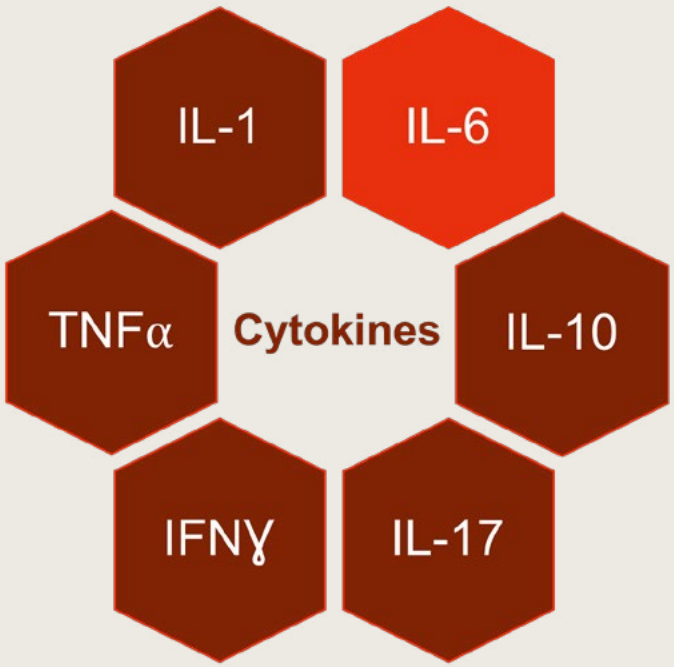


Figure 4: The levels of several cytokines are higher in the serum of patients with active PMR, yet IL-6 is the only cytokine whose levels correlate with disease activity and risk of relapses.

III. The Central Role of IL-6 in PMR Pathophysiology

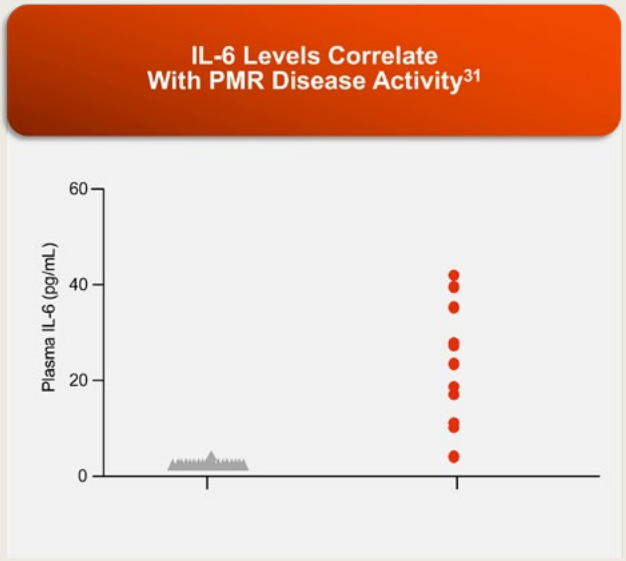
IL-6 correlates with disease activity in PMR

IL-6 is believed to be a major driver of PMR pathogenesis, since IL-6 levels correlate with disease activity (Figure 5). In one study, while healthy controls had no detectable plasma levels of IL-6, patients with PMR were characterized by significantly increased concentrations of plasma IL-6 before treatment was initiated[31] (Figure 5). Every single patient in the cohort had at least a four-fold increase in IL-6 levels compared to healthy controls. In a different study, serum IL-6 accurately distinguished patients with PMR from healthy controls, and its presence correlated strongly with the ESR and CRP in both patient groups.[21] Studies have shown IL-6 levels are rapidly suppressed by corticosteroids, which are commonly used to manage PMR symptoms. However, plasma IL-6 levels immediately increase upon short-term withdrawal of corticosteroids, despite several months of treatment, suggesting that corticosteroids do not correct the underlying mechanism that causes elevated IL-6 levels in PMR.[28,31]

Together, these findings confirm that in addition to its role in driving PMR pathophysiology, IL-6 may be a valuable marker for diagnosing active PMR and could be used as a proxy for monitoring disease activity.[21] Objective markers that reflect active inflammation in patients with PMR are important not only for daily clinical practice, but also for therapeutic trials in these patients. Other markers of inflammation such as ESR and CRP remain normal in a subgroup of patients with PMR with active disease, highlighting the need for additional markers of disease activity.[21]

Additionally, levels of sIL-6R correlate with the number of relapses and therefore have been suggested to serve as prognostic markers of PMR outcomes[32] (Figure 5). Upon dividing the patients according to outcome (no relapses, 1 relapse, or at least 2 relapses), significant differences in sIL-6R levels were observed, with the highest sIL-6R concentration corresponding to the group of patients with PMR who experienced at least 2 relapses. Thus, circulating levels of sIL-6R may predict future relapses in patients with PMR.[32]

A



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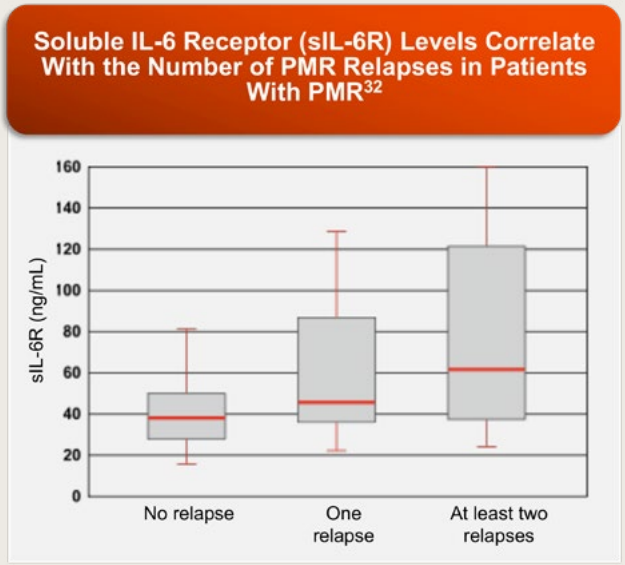


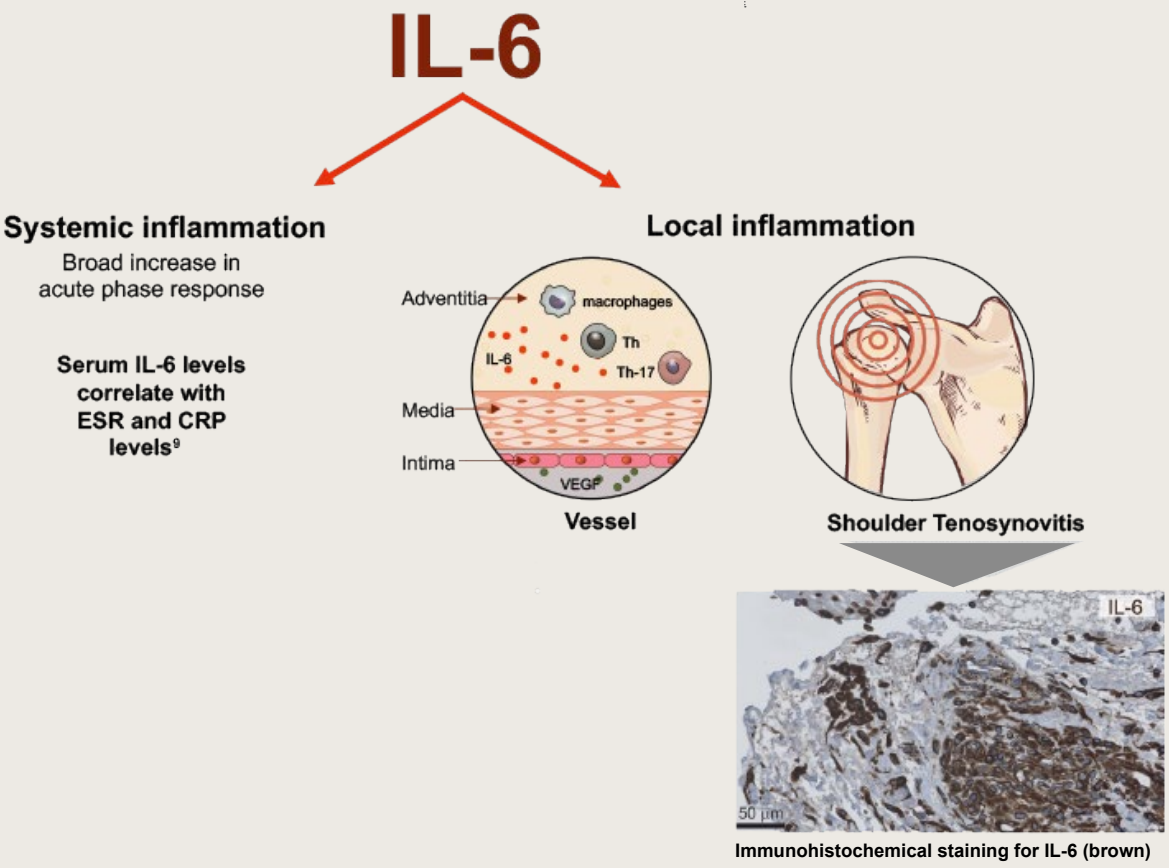
Figure 5: A. The levels of IL-6 are higher in patients with newly diagnosed PMR compared to healthy controls. **B.** Levels of sIL-6R are higher in patients with PMR with one, or at least two, relapses compared to those without any relapses.
Arthritis & Rheumatism Volume 36, Number 9, September 1993, pp 1286-1294. ©1993, American College of Rheumatology.

Arthritis & Rheumatism (Arthritis Care & Research). Vol. 59, No. 8, August 15, 2008, pp 1147-1154. DOI 10.1002/art.23924. © 2008, American College of Rheumatology.

In another study, patients with PMR with a CC genotype had higher levels of circulating IL-6 and had a higher risk of developing relapse or recurrence. The presence of persistently elevated IL-6 levels—but not the CC genotype per se—was associated with an increased frequency of relapse or recurrence.[32] Thus, IL-6 plays a central role in the pathogenesis of PMR because high IL-6/sIL-6R levels are associated with disease activity, increased risk of relapse, and recurrence of PMR symptoms.[31-33]

IL-6 acts both locally and systemically to drive PMR pathophysiology

IL-6 can exert its effects in multiple tissues to affect both *local* and *systemic* inflammation,[9,29,34] (Figure 6). Serum levels of IL-6 are increased in PMR, and IL-6 drives systemic inflammation, as measured by elevated CRP and ESR levels in the plasma.[9] IL-6 is expressed in the synovial tissue of patients with new-onset, treatment-naïve PMR, where it is thought to drive local inflammation.[13,29] Within the synovial tissue, IL-6 was widely expressed by various cell populations in the subacromial-subdeltoid (SASD) bursa of patients with PMR, such as CD34+ endothelial cells, CD34+ fibroblasts/stromal cells, CD90+ fibroblasts, and CD68+ macrophages.[29] Moreover, IL-6 was expressed in the temporal artery wall of patients with isolated PMR.[35]



IL-6 is expressed in synovial tissue obtained from patients with new-onset, treatment-naïve PMR[29]

Figure 6: IL-6 drives systemic inflammation by turning ON pro-inflammatory cascades (measured by higher ESR and CRP levels). IL-6 is also expressed within noninflamed arteries and in the synovium, where it drives local inflammation.

IL-6 plays a role in systemic manifestations of PMR

In addition to driving local and systemic inflammation that is characteristic of PMR, IL-6 contributes to other biological functions such as pain, morning stiffness, anemia, weight loss, fatigue, and depression, which are often coincident in patients with PMR.[1,19,36] IL-6 is able to affect a vast array of biological processes because unlike typical cytokines, IL-6 employs a unique dual-signaling mechanism comprising both cis-signaling and trans-signaling pathways.

Cis-signaling, also known as classical signaling, utilizes membrane-bound receptors present in a restricted array of cells, notably hepatocytes and specific leukocytes, including neutrophils, monocytes, macrophages, and certain lymphocytes.[41,42] Cis-signaling is believed to play a pivotal role in executing anti-inflammatory, homeostatic, and protective functions.[42]

In contrast, trans-signaling employs a soluble IL-6 receptor to engage a broader spectrum of cells lacking membrane-bound receptors.[41] This encompasses osteoclasts, fibroblast-like synoviocytes, endothelial cells, adipocytes, and neural cells. This is the predominant IL-6 signaling mechanism observed in inflammatory disease states. An essential player in both cis and trans IL-6 signaling is the widely expressed signal-transducing glycoprotein 130 (gp130). Effective IL-6 signaling, whether cis or trans, requires interaction with gp130, since binding of IL-6 to its receptors is insufficient to initiate signaling. Once the membrane-bound or soluble IL-6 receptor/IL-6 complex docks onto gp130, it prompts homodimerization.[42] This structural alteration triggers the autophosphorylation of JAK1, JAK2, and TYK2, subsequently phosphorylating the cytoplasmic tail of the gp130 receptor and setting in motion downstream signaling events.[42] In addition to the JAK/STAT pathway, IL-6 also activates the MAP-kinase and PI3-kinase pathways.[42]

The ability of IL-6 to signal via cis and trans receptors allows the cytokine to influence a myriad of cell types, organs, and tissues (Figure 7). In the liver, IL-6 acts on hepatocytes to drive acute-phase response and hepcidin production.[36] The action of IL-6 on osteoclasts and fibroblast-like synoviocytes contributes to bone resorption.[41] IL-6 also affects body physiology as a whole, due to its effects on fatigue, mood, sleep,

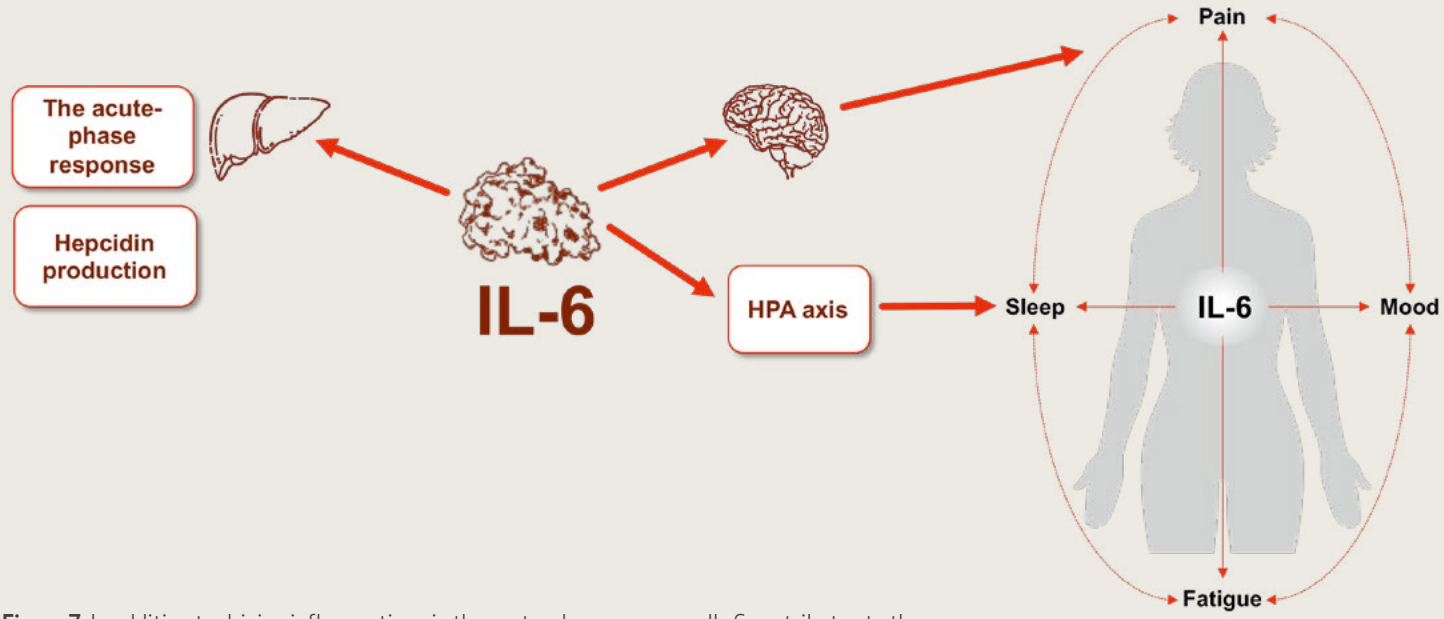


Figure 7: In addition to driving inflammation via the acute-phase response, IL-6 contributes to the development of chronic pain and fatigue, as well as sleep and mood disorders.

morning stiffness, and pain. Administration of low-dose IL-6 to healthy volunteers caused a prolonged increase in plasma concentrations of ACTH and cortisol, and subjects reported fatigue and mood changes, including feeling inactive and less capable of concentrating than after placebo.[43] IL-6 also affected sleep architecture; slow-wave sleep was decreased during the first half of a sleep interval and increased during the second half, while rapid eye movement (REM) sleep time was significantly decreased. The effect of IL-6 on fatigue, mood, and sleep was a result of its ability to stimulate the hypothalamic-pituitary-adrenal (HPA) axis.[43] In a study of patients with PMR, IL-6 levels demonstrated a circadian rhythm that peaked in the early hours of the morning and correlated with the duration of morning stiffness. Treatment with modified- (delayed-)release prednisone caused a marked reduction in both IL-6 and duration of morning stiffness.[40]

A growing body of evidence suggests that IL-6 is the most consistently increased cytokine in blood samples of patients with major depressive disorder (MDD) and several lines of evidence indicate that it plays a crucial role in the pathogenesis of depression.[44] IL-6 levels were elevated in the cerebrospinal fluid (CSF) of older women with depression, in patients with either depression or schizophrenia, in those who have attempted suicide, and in women experiencing postpartum depression.[45] Depressive-like behaviors were observed in rodents directly injected with IL-6 as well as in those who had stress-induced increase of IL-6 levels.[46] Further, IL-6–deficient mice were resistant to the development of depressive-like behaviors following exposure to stress, highlighting the importance of IL-6 in mediating depression.[46]

From a mechanistic perspective, increased IL-6 activity may cause depression through activation of the hypothalamic-pituitary-adrenal axis or via its ability to alter neurotransmitter metabolism.[46] For example, IL-6 alters levels of serotonin transporter (SERT) and therefore influences serotonin reuptake. IL-6–induced modulation of serotonergic neurotransmission through the signal transducer and activator of transcription 3 (STAT3) signaling pathway contributes to the role of IL-6 in depression. IL-6 can also increase dopaminergic and serotonergic turnover in the hippocampus and frontal cortex.[44] The interaction between IL-6 and NFkB may contribute to depression-associated behavior by modulating on synaptic plasticity.[45] Additionally, it is suggested that IL-6 alters brain morphology of patients with MDD. High serum levels of IL-6 were correlated with reduced left subiculum and right CA1, CA3, CA4, GC-DG, subiculum, and whole hippocampus volumes in patients with MDD. Additionally, serum IL-6 levels were inversely correlated with prefrontal cortex (PFC) thickness in patients with MDD.[44] In another study, patients with MDD showed increased IL-6 levels and smaller hippocampal volumes compared to healthy controls.[44]

IL-6 also plays an important role in the induction or amplification of pain in the central nervous system as well as in the periphery. Administration of IL-6 can lead to hyperalgesia and IL-6 levels are higher in the periphery and spinal cord of animal pain models.[47] Within the nervous system, IL-6 influences pain perception locally as well as systemically[38] (Figure 8). Electrophysiologic experiments have shown that IL-6 can sensitize C fibers (a type of unmyelinated nerve fiber within the joint) to mechanical stimulation, which is an important neuronal mechanism of inflammatory joint pain.[48] Persistent signaling from within inflamed joints can lower nociceptor thresholds, leading to hypersensitivity to nociceptive stimulation and pain sensitization.[38] IL-6 can also mediate mechanical allodynia (a painful sensation caused by innocuous stimuli like light touch) in a model of spinal nerve injury via an increased local growth of nerve fibers.[38]

Circulating IL-6 may also cross the blood-brain barrier to access the CNS, especially during chronic inflammation.[38] In addition to its role in modulating peripheral nerve activity, IL-6 plays a role in modulating

pain processing in the central nervous system[38] (Figure 8). Persistent signaling from sensitized peripheral neurons can induce prolonged hyperexcitability of CNS neurons (central sensitization), resulting in tactile allodynia and hyperalgesia.[38]

Thus, increased local and circulating levels of IL-6 in patients with PMR may contribute to the pain experienced by these patients.[9,29,38] Chronic pain is associated with a greater risk of developing mood disorders such as depression.[49]

It has been suggested that pain and mood have a common neurological basis due to the overlap in neuroanatomic substrates (eg, bilateral activation of the amygdala) and neurobiologic mechanisms (eg, dysregulation of noradrenergic and serotonergic pathways) for these conditions.[49] Similarly, pain can disrupt sleep, and shortened or disturbed sleep, in turn, lowers pain thresholds and increases spontaneous pain, resulting in a vicious cycle of chronic pain, fatigue, and sleep/mood disturbances, which are common clinical symptoms in PMR.[47]

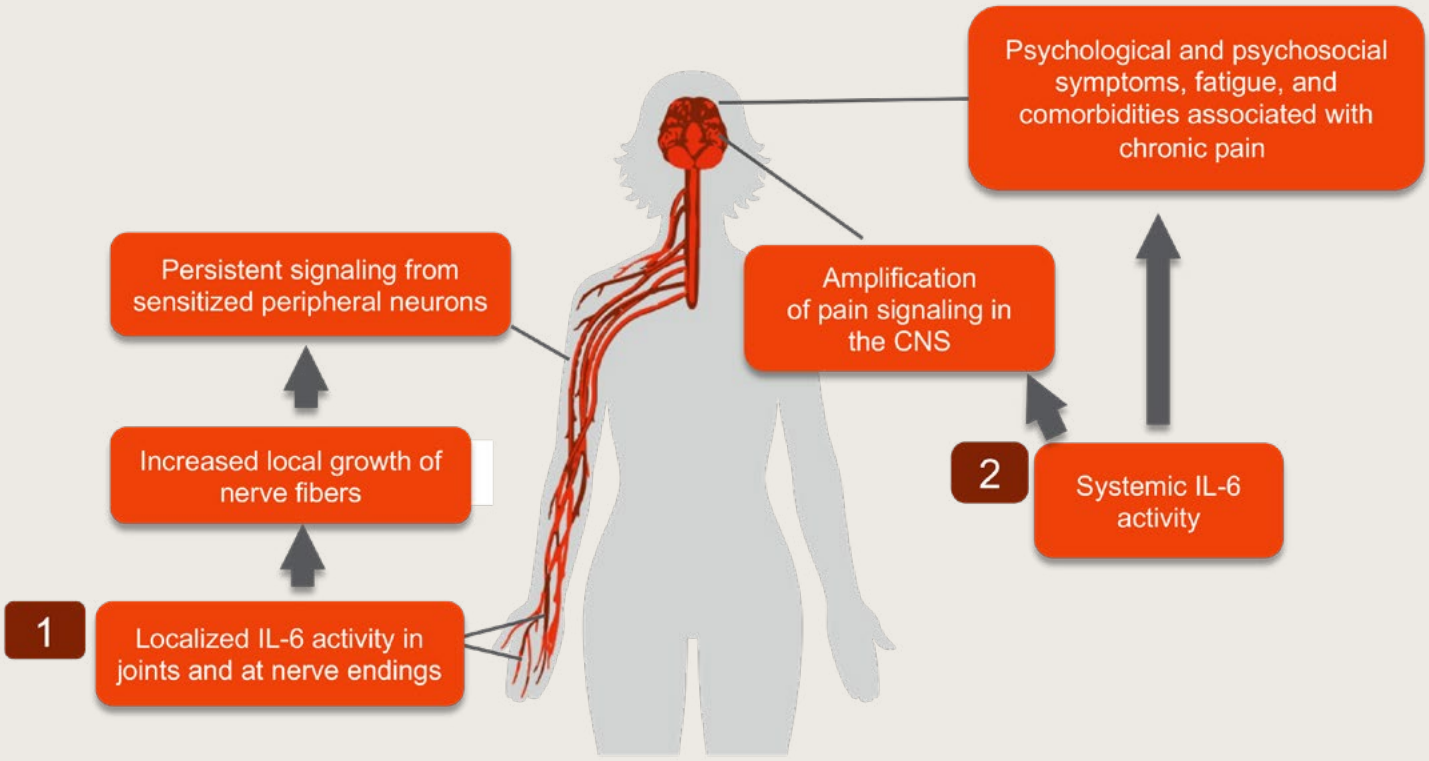


Figure 8: In the nervous system, IL-6 influences pain perception locally as well as systemically. Localized IL-6 activity in joints and at nerve endings causes increased local growth of nerve fibers, resulting in persistent signaling from sensitized peripheral neurons and enhanced pain conduction. At the systemic level, IL-6 can amplify pain signaling in the CNS, leading to increased psychological and psychosocial symptoms, fatigue, and comorbidities associated with chronic pain.

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IV. Proposed Relationships Between Aging and PMR Pathogenesis

Vascular and musculoskeletal tissue in younger people is elastic and distensible. Aging results in gradual loss of elasticity of connective tissues supporting both arterial and musculoskeletal structures (Figure 9). This likely predisposes these structures to microdamage, releasing danger signals that activate the innate immune system. Furthermore, innate and adaptive cell populations are modulated by immune aging.[50] Senescent T cells expressing NKG2D, a marker of immunosenescence, were increased in patients with PMR. In PMR patients, NKG2D receptor-expressing T-cells produce pro-inflammatory cytokines and may contribute to the pathogenesis of PMR.[51] Another aspect of aging that may influence the likelihood of developing inflammatory conditions such as PMR is that IL-6 levels increase with age, and in individuals who have aging-related diseases or disability.[52] Moreover, changes in the composition of the CD8 T-cell receptor repertoire associated with aging, including the appearance of particular clonal types, could potentially increase the likelihood of individuals developing PMR.[53] Additionally, homocysteine, as a reflection of vascular aging and inflammation, is higher in patients with PMR than in healthy controls.[13]

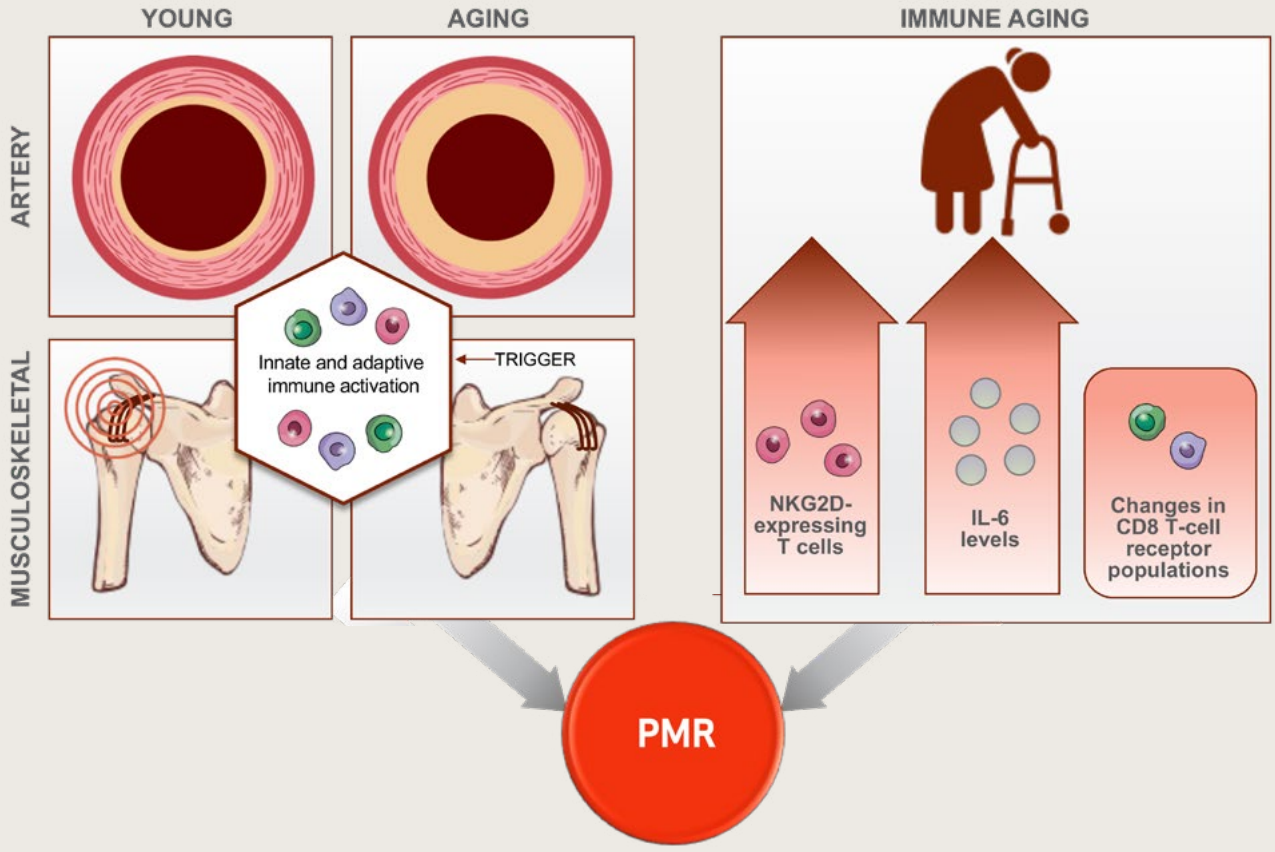

Figure 9: Aging results in reduced integrity and elasticity of arterial and musculoskeletal tissue, which leaves the tissue more vulnerable to microdamage and releasing danger signals, resulting in activation of the innate and adaptive immune system. At the same time, an aging immune system has altered T-cell populations and higher levels of IL-6. All these factors likely contribute to the risk of developing PMR.

Patients with PMR have a higher prevalence of a geriatric syndrome known as frailty, which is characterized by weakness, weight loss, and low activity associated with adverse health outcomes.[54,55] Frailty is believed to develop due to age-related changes to multiple physiological systems, particularly the neuromuscular, neuroendocrine, and immunological systems, leading to increased biological vulnerability to stressors and reduced ability to maintain physiological homeostasis.[56] Elderly people with frailty have increased inflammatory markers, such as IL-6, TNFα, and CRP, underscoring a physiological link between frailty and PMR.[57]

Several autoantibodies associated with PMR have been described, yet none have been correlated with disease activity.[17] Autoantibodies could be generated in PMR patients as a result of heightened inflammation, or due to cross-reactivity triggered by external factors (eg, infections) and the release of antigens from damaged tissues or cells.[17] Recently, there has been a re-evaluation of how autoreactivity is generated across the broad spectrum of inflammatory disease states, suggesting that in addition to a supportive genetic background, a cooperative microenvironment may be critical in certain conditions such as Type 2 diabetes and atherosclerosis.[58] Similarly, a host of physiological stressors associated with aging could contribute to the pathogenesis of PMR. Understanding how the biology of aging contributes to PMR pathophysiology is a promising avenue for ongoing and future research.

V. Concluding Thoughts

Even though PMR has been described as a clinical syndrome since the 1940s and 1950s, there is still much to learn about this condition.[59] PMR is a heterogeneous disease, with a high relapse rate, even after successful initial treatment with corticosteroids. Not all patients are able to take corticosteroids, and some patients with PMR do not respond well to treatment or may experience intolerable side effects. Additionally, although PMR disease activity is currently monitored by assessing symptoms and clinical activity, it would be beneficial to have biological markers to monitor disease activity or to predict the course of PMR. Identifying factors that correlate with disease activity, such as IL-6, could help with early diagnosis, assessing treatment response, and predicting disease relapse. Further characterizing the molecular and cellular pathophysiology of PMR will deepen our clinical understanding of this disease and pave the way to support PMR patients more effectively.

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