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Review

Aging-related autonomic nervous system imbalance and adrenergic regulation of immunity: Implications for inflammaging, autoimmunity, and long COVID

Sergio Giunta [a], Jacopo Sabbatinelli [b,c,*], Fabiola Olivieri [b,d,1], Angelica Giuliani [b,c,1]

[a] Casa di Cura Prof. Nobili (Gruppo Garofalo GHC), Castiglione dei Pepoli, Bologna, Italy.
[b] Department of Clinical and Molecular Sciences, Università Politecnica delle Marche, Ancona, Italy.
[c] Clinic of Laboratory and Precision Medicine, IRCCS INRCA, Ancona, Italy.
[d] Advanced Technology Center for Aging Research, IRCCS INRCA, Ancona, Italy.

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ABSTRACT

The autonomic nervous system (ANS) plays a central role in immune homeostasis by integrating sympathetic and parasympathetic signals that regulate inflammation, immune cell trafficking, and tolerance. Aging is associated with a progressive autonomic imbalance characterized by sympathetic overactivation, reduced parasympathetic tone, and impaired β-adrenergic signaling in immune cells, which together contribute to inflammaging and immune dysregulation. In this review, we discuss how aging-related alterations in adrenergic pathways affect immune cell differentiation and cytokine networks, with particular emphasis on β_2-adrenergic control of the Th17/regulatory T cell balance through cAMP-dependent mechanisms interacting with cytokine-driven STAT signaling. Chronic sympathetic stimulation and β-adrenergic desensitization weaken these regulatory constraints, favoring pro-inflammatory immune trajectories and loss of immune tolerance. Finally, we propose Long COVID as a paradigmatic condition in which pre-existing inflammaging and autonomic vulnerability are amplified by viral infection, leading to persistent inflammation, impaired immune regulation, and increased susceptibility to autoimmune manifestations.

1. Introduction

The autonomic nervous system (ANS) plays a central role in maintaining immune homeostasis by continuously modulating the activity of innate and adaptive immune cells. Bidirectional neuroimmune communication is essential for controlling inflammation, coordinating host defense, and restoring physiological equilibrium after stress or infection (Bellinger and Lorton, 2014; Chavan et al., 2017; Sharma and Farrar, 2020). Within this framework, the two main branches of the ANS perform complementary functions. Sympathetic nervous system (SNS) activation triggers rapid adaptive responses by releasing catecholamines, which affect immune activation and trafficking. Meanwhile, the parasympathetic nervous system (PNS) helps resolve inflammation through cholinergic pathways that limit excessive cytokine production (Zhu et al., 2022). Catecholamines (i.e., epinephrine and norepinephrine (NE)) released by the SNS activate adrenergic receptors (ARs) expressed on immune cells, whereas acetylcholine (ACh) released by the PNS acts on muscarinic and nicotinic receptors (Wachsmuth et al., 2025). While α-adrenergic receptors predominantly support rapid, pro-inflammatory modulation of innate immunity in response to acute sympathetic activation, β-adrenergic receptors (β_{1-3}ARs) mediate more specialized and long-range regulatory functions in a cell-type and context-dependent manner, including modulation of hematopoiesis, cytokine programming, lymphocyte differentiation, and immune tolerance (Nayak et al., 2024; Pongratz and Straub, 2014). The dynamic balance between sympathetic and parasympathetic activity acts as an essential regulatory mechanism that prevents inflammatory responses from exceeding normal limits (Padro and Sanders, 2014).

The consequences of ANS dysfunction on immunity have been primarily characterized within the tumor microenvironment (Wachsmuth et al., 2025). Chronic sympathetic activation and catecholamine-driven α- and β-adrenergic signaling have been shown to promote

* Corresponding author at: Università Politecnica delle Marche, Department of Clinical and Molecular Sciences, Via Tronto 10/A, 60126 Ancona, Italy.
E-mail address: j.sabbatinelli@staff.univpm.it (J. Sabbatinelli).
[1] Contributed equally

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tumor growth, angiogenesis, metastatic programs (Zhang et al., 2017), and the development of an immunosuppressive niche enriched in myeloid-derived suppressor cells and alternatively activated M2 macrophages, impairing immunosurveillance and contributing to therapy resistance (Huan et al., 2017; Yu et al., 2025). Moreover, β-adrenergic signaling suppresses $CD4^+$ T cell-mediated anti-tumor immunity, revealing a previously underappreciated neuroimmune checkpoint that tumors may exploit to evade immune control (Fjaestad et al., 2025). These findings underscore the therapeutic potential of repurposing β-blockers as adjuncts to cancer immunotherapy, where inhibition of β-adrenergic pathways could enhance T cell effector functions, improve responses to immune checkpoint inhibitors, and potentially overcome tumor-induced immunosuppression (Li et al., 2025b).

A parallel dysregulation of autonomic signaling also becomes evident with aging. Older individuals experience an increased load of stress-related stimuli, which trigger physiological responses to both interoceptive and exteroceptive changes, that is, to any biological, psychological, or environmental shift occurring in daily life (Barthelemy et al., 2022). Under normal conditions, stress responses are adaptive and beneficial; however, when activated too intensely or for prolonged periods, they become detrimental. Chronic or excessive stress drives a persistent activation of the SNS accompanied by a reciprocal reduction in PNS. Sustained sympathetic overactivity coupled with reduced parasympathetic tone has been associated with a pro-inflammatory milieu and may contribute to enhanced systemic inflammatory signaling and impaired resolution of inflammation (Jiang et al., 2022). We recently focused on how ANS imbalance contributes to the maintenance and amplification of the chronic, low-grade inflammatory state known as inflammaging (Giunta et al., 2025; Giunta et al., 2024b). This shift may weaken host defenses and lower the threshold for autoreactive immune activation, potentially increasing susceptibility to degenerative and autoimmune conditions. This link is particularly relevant because it supports the hypothesis that inflammaging may represent an important contributing factor not only for age-related chronic degenerative diseases (Fulop et al., 2018), but also for the development of autoimmune conditions (Santos-Moreno et al., 2021).

Here, we discuss how aging-associated ANS imbalance and sympathetic overactivation may contribute to a sterile, low-grade, chronic and systemic pro-inflammatory-state and potentially impair endogenous anti-inflammaging strategies, integrating this mechanism with the others previously delineated in the framework of inflammaging (Giunta et al., 2024b). In this context, an integrated understanding of how age-related neuro-immune-endocrine remodeling shapes the balance between protective and pathological immunity is needed. This review examines the mechanistic role of adrenergic signaling in immune regulation across the lifespan, with particular attention to evidence suggesting that autonomic imbalance may contribute to inflammaging, impaired immune tolerance, and increased vulnerability to autoimmunity, especially in the setting of post-viral syndromes.

2. Neuroimmune regulation under physiological conditions: autonomic innervation and adrenergic control of immune cells

The anatomical organization of sympathetic innervation across lymphoid organs provides the structural basis for rapid neuroimmune communication. The bone marrow receives dense noradrenergic input that influences hematopoietic stem and progenitor cell activity, leukocyte retention, and circadian egress into the bloodstream (Maestroni, 2025). The thymus is similarly innervated, particularly during early postnatal life, where catecholaminergic signals modulate thymocyte maturation and selection (Tsunokuma et al., 2023). Sympathetic fibers also reach gut-associated lymphoid tissues, including Peyer's patches, integrating luminal antigenic stimuli with systemic immune tone (Al-Shalan et al., 2020; Boahen et al., 2023).

Among secondary lymphoid organs, the spleen displays the most functionally relevant sympathetic innervation (Kirkland et al., 2022; Mota and Madden, 2022). The splenic nerve releases NE directly into the parenchyma, regulating macrophage activation, cytokine production, NK cell cytotoxicity, and lymphocyte trafficking. This organization supports the role of the spleen as a major effector organ of the inflammatory reflex. In preclinical models, vagal afferent signaling initiated by peripheral inflammation is relayed to brainstem autonomic centers and translated into splenic NE release. NE can stimulate β_2AR-expressing $CD4^+$ cholinergic T cells to produce ACh, which in turn activates α7 nicotinic acetylcholine receptors (α7nAChRs) on monocytes and macrophages, thereby suppressing NF-κB-dependent pro-inflammatory cytokine release and contributing to an anti-inflammatory reflex response (de Jonge et al., 2005; Kelly et al., 2022; Pavlov and Tracey, 2012; Tracey, 2002). Thus, the β_2AR–α7nAChR-dependent pathway is best viewed as a well-characterized preclinical effector arm of the inflammatory reflex, with translational support from human neuromodulation studies showing reduced TNF production and attenuation of disease activity after vagus nerve stimulation in rheumatoid arthritis, rather than definitive cell-by-cell validation in humans (Koopman et al., 2016).

Adrenergic receptors are expressed not only on immune cells but also on endothelial and stromal vascular populations, and modulation of adrenergic tone has been shown to influence endothelial function and lymphocyte trafficking, suggesting that sympathetic activity can shape leukocyte entry and organization through effects on vasculature / high endothelial venules (HEV) (Chen et al., 2021; Sorriento et al., 2011). At the cellular level, AR expression is heterogeneous across immune subsets. Recent findings on human peripheral blood mononuclear cells (PBMCs) revealed β_1AR expression in monocytes and NK cells and the highest β_2AR levels in NK cells, followed by monocytes and T cells (Peklo et al., 2025). β_1-ARs, recently identified as immune checkpoints in T cells, influence differentiation and exhaustion programs (Globig et al., 2023; Li et al., 2025a). β_3ARs, although less extensively studied, are expressed in several immune populations, including $CD4^+$ and $CD8^+$ T cells, macrophages and cells residing in adipose-associated lymphoid clusters, where they participate in metabolic-immune integration and help maintain inflammatory tone within metabolic tissues (Bruno et al., 2023).

Among adrenergic receptors, however, β_2ARs constitute the principal immunoregulatory axis. β_2-AR signaling functions as a key anti-inflammatory and regulatory pathway in both innate and adaptive immunity, although, as new knowledge accumulates, an increasingly complex, cell- and context-dependent regulatory mechanism is emerging. In innate immune cells, particularly macrophages, β_2AR signaling has been shown to limit inflammatory activation through downregulation of TLR4 expression (Wang et al., 2024). However, recent evidence indicates that although β_2AR activation suppresses several key inflammatory genes in TLR-stimulated macrophages, it paradoxically enhances IL-1β gene transcription, highlighting the complex and context-dependent nature of β-adrenergic regulation in innate immunity (de Melo et al., 2026). A similar complexity emerges for NK cells. Acute adrenaline exposure suppresses early activation signaling, disrupts LFA-1 function, and reduces NK-cell adhesion to ICAM-1. As a consequence, degranulation, serial killing, and cytokine release are markedly impaired (Jurgens et al., 2024). This inhibitory effect, however, is not stable over time. Repeated β_2AR stimulation induces receptor desensitization through a PKA-dependent G-protein switching mechanism. Once desensitized, human NK cells become refractory to the suppressive action of acute epinephrine, indicating that prolonged exposure to β_2-agonists both disrupts cytotoxic function and reshapes adrenergic responsiveness (Jurgens et al., 2024).

In the framework of adaptive immunity, β_2AR signaling promotes Th2 over Th1 differentiation (Goleva et al., 2004; Padro and Sanders, 2014), enhances anti-inflammatory cytokines such as IL-10 at the expense of pro-inflammatory cytokines (Ağaç et al., 2018; Hinkle et al., 2021), attenuates $CD8^+$ T-cell effector functions (Estrada et al., 2016; Qiao et al., 2019) and limits inflammatory leukocyte recruitment (Silva

et al., 2016; Silvestri et al., 1999). In CD8$^+$ T cells, β₂AR signaling also contributes to circadian regulation, as β₂AR deletion disrupts clock gene oscillations and alters time-of-day–dependent antiviral responses and effector–memory differentiation (Sharma et al., 2025). β₂AR expression has also been identified on specific subsets of human CD4$^+$ T cells, particularly Th17 and regulatory T (Treg) cells (Carvajal Gonczi et al., 2017). These two lineages originate from a common naïve CD4$^+$ precursor under TGF-dependent differentiation signals (Zhou et al., 2008), yet they exert opposing functions: Th17 cells promote inflammation and autoimmunity, whereas Treg cells preserve tolerance and immune homeostasis (Brescia et al., 2024; Lauten et al., 2025a; Lauten et al., 2025; Lee, 2018; Sun et al., 2017). Th17 differentiation, driven by IL-6 and IL-1β, and stabilized by IL-23, exists in dynamic opposition to inhibitory cytokines such as IL-2 and IFN-γ (Melnikov et al., 2020; Romagnani, 2008).

At the mechanistic level, the Th17/Treg balance is shaped by opposing cytokine-driven transcriptional programs. Experimental studies in murine CD4$^+$ T-cell systems have shown that STAT3 promotes RORγt expression and IL-17 production under Th17-polarizing conditions, whereas IL-2–dependent STAT5 signaling constrains Th17 differentiation and supports FoxP3-associated regulatory programs (Laurence et al., 2007; Wei et al., 2008; Mahmud et al., 2013; Lamprianidou et al., 2021). Notably, STAT5 was shown to bind the Il17a promoter, suggesting that STAT5 may directly antagonize IL-17 transcription in addition to supporting Treg biology (Laurence et al., 2007). Regulatory T-cell fate is also influenced by intracellular metabolic signaling: in murine CD4$^+$ T cells, sustained PI3K–Akt–mTOR activity antagonizes FoxP3 induction, whereas inhibition of this pathway promotes FoxP3 expression and Treg-like transcriptional profiles (Sauer et al., 2008). In parallel, β₂AR signaling has been shown in murine CD4$^+$FoxP3$^+$ Treg cells to increase cAMP levels, activate PKA–CREB signaling, enhance CTLA-4 expression, and improve suppressive function (Guereschi et al., 2013). Moreover, cAMP-dependent signaling has been implicated more broadly in the transcriptional regulation of CD4$^+$ T-cell fate and β₂AR-mediated immunomodulation (Li et al., 2012; Thapa and Cao, 2023; Wei et al., 2008). Thus, β₂AR signaling may contribute to immune regulation by reinforcing cAMP–PKA-dependent regulatory functions and by interacting with cytokine-driven STAT3/STAT5 networks in a context-dependent manner.

Notably, autocrine catecholamines produced by murine T cells can maintain IL-17 A production even in the absence of exogenous adrenergic agonists, an effect that can be recapitulated by cAMP-enhancing stimuli (Lauten et al., 2025a). This observation further supports the view that cAMP-linked adrenergic pathways may exert divergent effects depending on the activation state and differentiation stage of the responding T cell. Overall, available evidence suggests that β₂AR signaling contributes to immune tolerance under selected physiological conditions and may help limit excessive effector responses during acute inflammatory challenges, including through rapid IL-10 induction, while its functional consequences remain dependent on cell type, activation state, timing, and ligand context (Ağaç et al., 2018) (Fig. 1).

Notably, β-adrenergic signaling can exert divergent effects depending on activation state, timing, ligand and disease context. In a murine experimental setting, acute β₁/₂-AR activation in differentiated Th17 cells engages the cAMP–PKA–CREB pathway and can promote IL-17 A transcription, indicating that cAMP-linked adrenergic signals are not

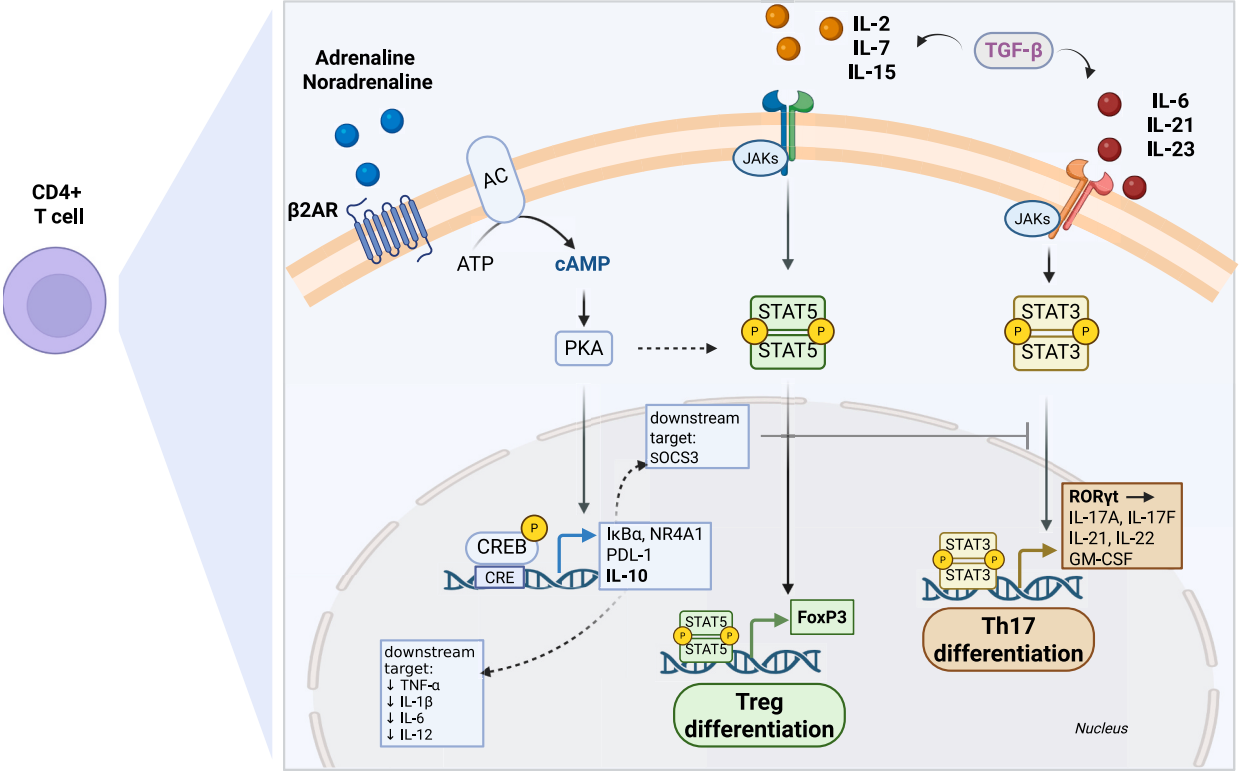


Fig. 1. β₂-adrenergic regulation of Th17–Treg balance in CD4$^+$ T cells. Adrenaline and noradrenaline engage the β₂-adrenergic receptor (β₂AR) on CD4$^+$ T cells, activating the Gs–adenylyl cyclase pathway and increasing intracellular cAMP. Elevated cAMP activates protein kinase A (PKA), which phosphorylates CREB (cAMP response element–binding protein). Activated CREB binds CRE elements in target genes and induces a regulatory transcriptional program, including IL-10, IκBα, NR4A1, and PD-L1. These factors suppress pro-inflammatory signaling cascades (↓ TNF-α, ↓ IL-1β, ↓ IL-6, ↓ IL-12) and contribute to the induction of SOCS3, which inhibits JAK1/JAK2 activity and functionally restrains IL-6/IL-23–mediated STAT3 activation. By limiting STAT3-driven RORγt expression, β₂AR signaling attenuates Th17 differentiation and the downstream production of IL-17 A, IL-17F, IL-21, IL-22, and GM-CSF. In parallel, cytokines such as IL-2, IL-7, and IL-15 activate STAT5 through JAK-dependent tyrosine phosphorylation. STAT5 promotes FoxP3 expression and supports Treg differentiation. Although β₂AR signaling does not directly activate STAT5, the cAMP–PKA–CREB regulatory environment facilitates STAT5/FoxP3 stability by antagonizing the competing STAT3–RORγt axis. Through these convergent mechanisms, β₂AR signaling shifts CD4$^+$ T-cell fate toward immunoregulation and away from pathogenic Th17 polarization.

uniformly anti-inflammatory (Wang et al., 2017). Conversely, β₁/₂ blockade has been reported to reduce IL-17 A$^+$ Th17 cells and increase FoxP3$^+$ Tregs in experimental models of autoimmune inflammation (Kanamori et al., 2016; Lauten et al., 2025a; Lee, 2018; Lu et al., 2023; Zhu and Paul, 2010). Thus, the reduction of β-adrenergic signaling shifts the Th17/Treg equilibrium toward a more regulatory phenotype, lowering IL-17 A and increasing IL-10 levels both ex vivo and in vivo (Lauten et al., 2025a; Lauten et al., 2025b). These apparently divergent findings suggest that β-adrenergic pathways should be interpreted as context-dependent modulators of Th17/Treg balance.

Finally, the temporal pattern of sympathetic activity critically shapes immune outcomes. Under physiological conditions, acute sympathetic activation during short-term stress responses transiently mobilizes leukocytes into the circulation, enhances NK-cell cytotoxicity and accelerates early innate defenses, as shown in human stress studies (Bigler et al., 2015; Schedlowski et al., 1993; Segerstrom and Miller, 2004).

These rapid and self-limited adjustments are generally considered part of an adaptive acute stress response, but they do not necessarily imply a uniformly anti-inflammatory profile. Indeed, acute psychological stress in humans can increase circulating inflammatory mediators such as IL-6, and pharmacological β-adrenergic blockade attenuated this response in men in a randomized placebo-controlled study (Steptoe et al., 2018). Thus, the immunological consequences of acute sympathetic activation should be viewed as mixed and context-dependent, involving leukocyte redistribution, transient inflammatory signaling, and regulatory feedback mechanisms rather than a purely protective or anti-inflammatory program (Dhabhar et al., 2012; Walsh et al., 2021). These considerations highlight the importance of distinguishing acute, self-limited sympathetic activation from more sustained patterns of adrenergic exposure, whose immunological consequences are discussed in the next section in the context of aging-related autonomic remodeling.

3. Aging-related modulation of β-adrenergic receptors in immune cells: Implications for inflammaging and autoimmune disease susceptibility

Persistent catecholaminergic stimulation, which may occur in several conditions characterized by sustained sympathetic activation, including chronic stress, chronic disease, and aging-related autonomic remodeling, has been associated with functional desensitization of β-ARs, a phenomenon extensively characterized in cardiovascular tissues and increasingly recognized in immune cells (Feldman et al., 1984; Ferrara et al., 2014; Mahmood et al., 2022; Noushad et al., 2021; Schocken and Roth, 1977). In human lymphocytes, early studies demonstrated an age-associated decline in β-AR density on membranes, whereas subsequent work clarified that reduced receptor affinity, impaired post-receptor signaling, and altered G-protein coupling, rather than receptor number alone, are the primary drivers of diminished β-adrenergic responsiveness in older individuals (Feldman et al., 1984; Noushad et al., 2021; Schocken and Roth, 1977). These changes are further compounded by aging-related alterations in membrane fluidity, receptor capping, and adenylate cyclase activity, leading to a progressive attenuation of cAMP-dependent signaling in immune cells (Krall et al., 1981; Rymkiewicz et al., 2012). A potential immunological consequence of impaired β-AR responsiveness is the weakening of β₂-AR–mediated regulatory constraints on immune activation. Because β₂AR signaling can modulate cytokine-driven inflammatory programs and supporting tolerance-associated pathways under defined conditions, loss or attenuation of this signaling provides a plausible mechanistic link between aging-related sympathetic predominance and the low-grade, chronic inflammation that characterizes inflammaging (Ferrara et al., 2014; Giunta et al., 2024a).

As discussed above, β₂AR-mediated regulation of the Th17/Treg axis has emerged as a relevant, but context-dependent, component of adrenergic immune modulation (Fig. 1). The chronic low-grade inflammatory environment associated with inflammaging is enriched in cytokine signals that converge on STAT3-dependent transcriptional programs involved in Th17 polarization. This concept is supported by mechanistic studies in murine CD4$^+$ T-cell systems showing that STAT3 promotes RORγt expression and IL-17 production, although direct validation of this pathway in human aging remains limited (Laurence et al., 2007; Park and Ciofani, 2025; Xia et al., 2024). Consistent with the clinical relevance of this pathway in human autoimmunity, preliminary longitudinal data in rheumatoid arthritis showed that pSTAT3$^+$ naïve CD4$^+$ T cells were enriched at baseline in patients who subsequently developed disease flare after csDMARD withdrawal, while pSTAT3 expression in Tregs increased during flare and correlated with IL-6-related inflammatory mediators (Anderson et al., 2024). Within this framework, chronic SNS predominance and impaired β-AR responsiveness should be regarded as factors that may lower the threshold for Th17-skewed responses by attenuating β₂AR/cAMP-dependent regulatory constraints and by acting in concert with cytokine-driven STAT3 activation.

Experimental autoimmune encephalomyelitis (EAE) and multiple sclerosis (MS) provide useful, although distinct, levels of evidence for this concept. In the murine EAE model, experimental studies directly support a role for adrenergic pathways in modulating encephalitogenic CD4$^+$ T-cell responses: β-adrenergic antagonism reduces Th17 frequency and IL-17 A production while expanding Tregs, whereas β₂AR signaling has been shown to suppress the generation of encephalitogenic CD4$^+$ T cells by restraining IL-2, IFN-γ, and GM-CSF production through ICER-dependent transcriptional repression (Araujo et al., 2019; Lauten et al., 2025b). In human MS, evidence is more translational and clinical: IL-17 A has been implicated in blood–brain barrier disruption and neuroinflammation, and therapeutic targeting of the IL-17 pathway has shown clinical relevance in selected neuroinflammatory contexts (Hiltensperger and Korn, 2018; Kolbinger et al., 2016; Omidian et al., 2019; Yamout and Alroughani, 2018).

Notably, the immunological outcome of adrenergic modulation remains highly context- and ligand-dependent. In human CD4$^+$ T-cell cultures, the β₂-adrenergic agonist terbutaline has been reported to increase Th17 cell frequency and IL-17 A production, indicating that β₂AR activation can amplify IL-17-associated responses under specific experimental conditions (Carvajal Gonczi et al., 2023). However, this effect does not generalize to all adrenergic compounds. For example, nebivolol, a β₂-biased ligand with β₁ agonist activity, was shown to potently inhibit IL-17 A production in human PBMCs, (Hajiaghayi et al., 2024), underscoring how differential receptor engagement and ligand bias can generate divergent immunological outcomes. These observations strengthen the view that adrenergic signaling functions as a regulatory checkpoint for IL-17–driven immune responses, with the direction and magnitude of its effects shaped by ligand properties, receptor subtype engagement, and cellular context. This point is particularly important for diseases in which IL-17 contributes to pathology, including MS, psoriasis, and rheumatoid arthritis (Maddur et al., 2012; Mills, 2023; Nash et al., 2018).

Tregs, defined by their CD4$^+$CD25$^+$FoxP3$^+$ phenotype, represent another relevant target of adrenergic immunomodulation.

β₂-AR signaling has been shown in murine CD4$^+$FoxP3$^+$ Treg cells to enhance suppressive function through cAMP–PKA-dependent mechanisms, including increased CTLA-4 expression and improved conversion of naïve CD4$^+$FoxP3$^-$ cells into induced Tregs (Guereschi et al., 2013). Additional preclinical evidence from inflammatory ocular disease models indicates that adrenergic modulation can also enhance Treg immunoregulatory function through α2B/2C receptor signaling, increasing IL-10 production and ameliorating ocular surface inflammation (Fan et al., 2025). These findings support the hypothesis that impaired adrenergic responsiveness during aging could weaken Treg-mediated control of autoreactive or inflammatory effector responses, although direct evidence in human aging remains limited.

Beyond CD4$^+$ T cells, chronic β-adrenergic signaling shapes CD8$^+$ T-

cell responses, particularly during viral infections and antiviral memory. In mice, β_2AR activation modulates $CD8^+$ effector differentiation, antiviral responses, and memory formation through cAMP-dependent transcriptional programs (Sharma et al., 2025).

In aging, reduced β-adrenergic responsiveness may interact with well-described features of $CD8^+$ T-cell immunosenescence, including impaired effector function, altered memory differentiation, and accumulation of dysfunctional late-differentiated subsets. Rather than acting as a sole driver of these changes, aging-related sympathetic predominance may contribute to a less coordinated antiviral response by reshaping adrenergic regulation of $CD8^+$ T-cell activation and memory. Experimental arthritis models further suggest that the balance between α- and β_2-adrenergic signaling can influence inflammatory outcomes, as combined α-adrenergic blockade and β_2AR stimulation attenuated early arthritis progression and preserved joint structure in adjuvant-induced arthritis (Bellinger et al., 2021).

Multiple aging-associated factors further shape β-adrenergic dysfunction. Oxidative stress, a major component of aging-related cellular remodeling, alters membrane microdomains, receptor–G protein coupling, and downstream cAMP generation, thereby contributing to functional impairment of β_2AR signaling (Elkhatib and Case, 2019; Santulli and Iaccarino, 2013; Singh et al., 2023). Neuroendocrine crosstalk also adds another layer of regulation: glucocorticoids can upregulate β_2AR expression through promoter-responsive elements, linking stress hormone exposure to adrenergic signaling plasticity (Mak et al., 1995). Consistent with this broader concept of post-receptor regulation, adipose tissue studies have shown that PI3K p110α inactivation potentiates β-adrenergic/cAMP signaling in aged mice and in human adipocyte-derived systems, highlighting how intracellular signaling nodes can tune β-adrenergic responsiveness independently of receptor expression (Araiz et al., 2019).

β-adrenergic signaling also intersects with interferon regulation, providing another mechanism through which altered adrenergic responsiveness may influence inflammatory tone. In innate antiviral signaling, β-adrenoreceptor-triggered cAMP–PKA activation negatively regulates antiviral type I interferon responses by acting upstream of IRF3 on adaptor proteins such as MITA/STING and MAVS, thereby limiting virus-induced IFN-β production (Guo et al., 2023).

In parallel, β-adrenergic tone suppresses IFN-γ production in activated rat lymphoid cells through a PKA- and AKAP-dependent inhibition of the calcineurin/NFAT pathway (Riether et al., 2011). The compartmentalized organization of cAMP–PKA signaling by A-kinase anchoring proteins provides the molecular basis for this selective immunomodulatory control (Wehbi and Tasken, 2016). This regulatory layer is relevant to aging because antiviral immunity is remodeled rather than uniformly suppressed: older individuals and aged immune-cell models often show impaired early type I IFN induction in response to viral or nucleic-acid sensing, particularly in dendritic cell and macrophage compartments (Connors, 2022; Sridharan, 2011). How age-related changes in β-adrenergic responsiveness affect the timing, magnitude, or persistence of interferon responses remains to be established.

Beyond β-adrenergic desensitization, aging-associated autonomic remodeling also involves reduced parasympathetic activity, which may weaken the cholinergic anti-inflammatory pathway. In a murine model, a progressive decline in vagal tone reduces the activity of the cholinergic anti-inflammatory pathway, impairing α7nAChR-mediated suppression of NF-κB–dependent cytokine release and removing a major inhibitory brake on TNF-α, IL-1β and IL-6 production (Fernandez et al., 2014). Experimental evidence across multiple inflammatory models has demonstrated that activating the cholinergic anti-inflammatory pathway exerts potent immunoregulatory effects. In sepsis, α7-nAChR stimulation reduces macrophage-derived TNF-α release (Borovikova et al., 2000). In arthritis, α7-nAChR agonists and vagus nerve stimulation reduce cytokine production and attenuate disease severity, with translational support from rheumatoid arthritis studies using vagus nerve stimulation (Koopman et al., 2016; van Maanen et al., 2009). In inflammatory bowel disease murine models, activation of α7-nAChR or vagal signaling ameliorates experimental colitis and suppresses mucosal inflammation (Ghia et al., 2006; Pu et al., 2022). Thus, reduced vagal regulation in aging may remove an important anti-inflammatory counterbalance to sympathetic predominance, although direct causal links between age-related vagal decline and autoimmune onset in humans remain incompletely defined.

At the organ level, murine experimental evidence indicates that aging disrupts splenic neuroimmune circuits. Aging alters the rhythmic noradrenergic activity of the splenic nerve, impairing the $NE\text{-}ChAT^+$ T cell-ACh axis that normally constrains macrophage-derived IL-1β, IL-6 and IL-23, and facilitating Th17-promoting microenvironments (Shang et al., 2025). Circadian regulation represents another layer of adrenergic immune control. In murine models of viral infection, loss of circadian oscillations in β_2AR signaling additionally disrupts time-of-day–dependent gating of immune activation and alters antiviral responses and effector–memory differentiation (Sharma et al., 2025).

Collectively, reduced vagal regulation, sympathetic predominance, impaired β_2AR signaling, and disruption of splenic neuroimmune circuits define an integrated model in which aging-related autonomic remodeling can amplify basal inflammatory tone, destabilize the Th17/Treg equilibrium, and weaken peripheral tolerance. Within this inflammatory background, age-associated B cells (ABCs) – a $T\text{-}bet^+$, $CD11c^+$, $CD21^-$ B-cell subset enriched in chronic inflammatory states – can progressively expand in response to persistent inflammatory stimuli, including IFN-γ–dominated environments and sustained TLR7/TLR9 signaling, particularly in the context of viral RNA exposure (Mouat et al., 2022; Nickerson et al., 2023). ABCs display enhanced antigen-presenting capacity, efficiently activate $CD4^+$ T cells, and favor Th17 polarization, while simultaneously producing class-switched antibodies with increased autoreactivity (Hao et al., 2011). Although a direct causal link between autonomic dysfunction and ABC expansion has not been formally established, the chronic inflammaging milieu provides a plausible permissive environment that supports ABC accumulation and lowers the threshold for loss of immune tolerance.

Consistent with this framework, reduced heart rate variability (HRV), an indirect physiological proxy of diminished parasympathetic activity and autonomic imbalance, has been associated with systemic inflammatory burden and increased disease activity across autoimmune disorders (Goda et al., 2025; Olivieri et al., 2024). In rheumatoid arthritis, low HRV correlates with higher DAS-28 disease activity scores, greater pain and functional disability, and elevated IL-6 and TNF-α levels (Saramet et al., 2023). In systemic lupus erythematosus (SLE), reduced HRV has been linked to greater disease flare frequency, elevated circulating cytokines, and vascular stiffness, consistent with impaired parasympathetic modulation of inflammation (Thanou et al., 2016). Across broader chronically inflamed and elderly populations, HRV reduction also predicts poorer cardiovascular outcomes, higher infection risk, and increased all-cause mortality (Jarczok et al., 2022). Although these studies do not establish causality, they support the clinical relevance of autonomic imbalance as a measurable correlate of inflammatory burden and provide a rationale for integrating autonomic markers into longitudinal studies of inflammaging and immune-mediated disease.

Epidemiological and clinical observations further suggest that chronic sympathetic predominance and reduced parasympathetic activity are associated with systemic autoimmune and inflammatory diseases, such as rheumatoid arthritis, lupus, and psoriasis, supporting autonomic imbalance as a measurable contributor to inflammaging-associated autoimmunity (Goda et al., 2025). Autoimmune diseases, particularly those with early onset, such as SLE, juvenile idiopathic arthritis, and type 1 diabetes, are paradoxically characterized by molecular and cellular features typically associated with advanced age, supporting the concept of premature immune aging in autoimmunity (Mittal et al., 2025). Notably, inflammatory biomarkers can remain elevated even during periods of clinical remission, indicating that

immune regulation may be constitutively rewired toward a pro-inflammatory set point (Abdel Galil et al., 2015). Although inflammaging was initially conceptualized within the domain of geriatric biology, growing evidence shows that many of its immunological, molecular, and metabolic hallmarks are already evident in young individuals with autoimmune diseases (Franceschi et al., 2025).

The integrated impact of aging-associated autonomic imbalance and β₂-adrenergic dysfunction on immune regulation is summarized in Fig. 2, while key experimental evidence and translational correlates are presented in Table 1.

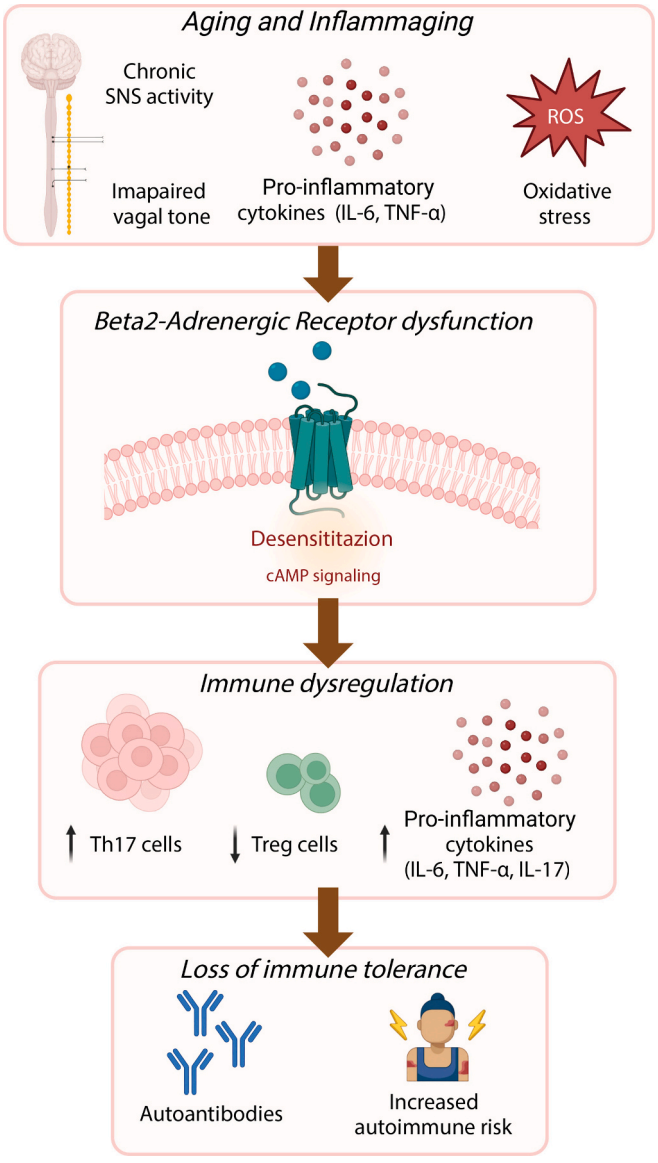


Fig. 2. Aging-associated β₂-adrenergic dysfunction as a permissive driver of immune dysregulation and loss of tolerance. Aging and inflammaging are characterized by chronic sympathetic nervous system (SNS) activation, reduced vagal tone, persistent exposure to pro-inflammatory cytokines (e.g., IL-6, TNF-α), and increased oxidative stress. Together, these factors impair β₂-adrenergic receptor (β₂AR) responsiveness, leading to functional attenuation of cAMP-dependent regulatory signaling. The resulting loss of β₂AR-mediated immune restraint weakens anti-inflammatory and tolerogenic pathways, thereby creating a permissive environment for immune dysregulation. Within this context, cytokine-driven effector programs are favored, resulting in a skewed Th17/Treg balance, sustained production of pro-inflammatory cytokines, and progressive erosion of immune tolerance. Over time, this neuro–immune imbalance contributes to autoantibody formation and increased susceptibility to autoimmune and autoinflammatory diseases.

4. Long COVID as a neuro-immune-endocrine breakdown within the Inflammaging "fertile field"

The "fertile field hypothesis" (von Herrath et al., 2003) posits that viral infections may facilitate autoimmune manifestations not through a single causal insult, but by acting upon a pre-existing biological terrain of vulnerability shaped by genetic, metabolic, neuroendocrine, and inflammatory factors (Chen et al., 2025). Aging represents a prototypical fertile field because autonomic imbalance, inflammaging, mitochondrial dysfunction, oxidative stress, and impaired adrenergic and cholinergic immune regulation collectively lower the threshold for persistent immune activation and loss of tolerance (Franceschi et al., 2025; Giunta et al., 2024b). Thus, the model should be interpreted as a vulnerability framework in which viral infection can act as a second hit that amplifies pre-existing neuroimmune instability. SARS-CoV-2 infection may therefore superimpose an intense inflammatory response and neuroimmune stressor on this vulnerable background. The acute phase of COVID-19 is characterized by IL-6, IL-1β, IL-23, TNF-α, and type I IFN responses (Costela-Ruiz et al., 2020; Ghaffarpour et al., 2025), all of which directly intersect with pathways involved in aging-related SNS predominance and Th17/Treg disequilibrium (Brescia et al., 2024; Lee, 2018; Sun et al., 2017). In individuals with reduced vagal tone and impaired cholinergic anti-inflammatory signaling, SARS-CoV-2–induced inflammation could contribute to a more prolonged disturbance of immune tolerance, although the relative contribution of autonomic, antigenic, and tissue-derived inflammatory signals remains to be clarified (Lauren et al., 2022).

The integrated mechanisms linking aging-related autonomic imbalance, persistent inflammatory signaling, impaired immune tolerance, and increased susceptibility to autoimmune manifestations in Long COVID are summarized in Fig. 3.

Several studies report prolonged elevation of pro-inflammatory cytokines, including IFN-α, TNF-α, IL-6, IL-17 A, and IL-1β, for up to 9–12 months after SARS-CoV-2 infection (Acosta-Ampudia et al., 2022; Phetsouphanh et al., 2022), as well as persistent autoantibody production (Son et al., 2023). ANS dysfunction is also frequently described in Long COVID and includes reduced HRV, sympathetic predominance, and impaired vagal activity (Del Rio et al., 2020; Goldstein, 2021).

In some cohorts, this dysautonomic profile coexists with autoantibodies targeting GPCRs, including β-adrenergic and muscarinic receptors, suggesting an autoimmune contribution to autonomic symptoms (Acosta-Ampudia et al., 2022; Wallukat et al., 2021). Recent analyses further document marked autonomic imbalance in post-COVID individuals, characterized by reduced HRV and increased physiological stress indices, consistent with persistent sympathetic overdrive and vagal impairment even after mild infection (Qin et al., 2025). Similarly, a controlled study of 82 participants showed that COVID-19 survivors exhibit persistent reductions in multiple HRV domains, including acceleration and deceleration capacity, SD2, DFA2, HF peak frequency, and LF/VLF power, approximately eight months after infection, despite being young to middle-aged adults without hospitalization (Haischer et al., 2024). These findings support a close association between Long COVID, persistent autonomic remodeling, and inflammatory immune activation; however, the directionality of this relationship remains unresolved and may involve bidirectional reinforcement between dysautonomia, inflammation, autoantibodies, and tissue-level injury.

In this framework, SNS overdrive and impaired β-adrenergic responsiveness may favor macrophage and dendritic cell activation, promote Th17 differentiation, and weaken Treg-mediated tolerance (Lauten et al., 2025a), while chronic IFN-I/IFN-γ signaling can interfere with β-AR–mediated immunomodulation and further sustain inflammatory circuits (Bruera et al., 2022; Hu and Ivashkiv, 2009). In this sense, Long COVID shares selected features with interferon-driven interferonopathy-like inflammatory states, in which persistent IFN

Table 1
Aging-related alterations in autonomic and β-adrenergic signaling and their immunological consequences.

Aging-related alteration	Main immunological consequence	Evidence context	Potential relevance	Key references
Reduced β-AR density and affinity on immune cells	↓ cAMP-dependent signaling, β-AR desensitization	Human lymphocyte studies	Impaired adrenergic immune regulation with aging	(Feldman et al., 1984; Schocken and Roth, 1977)
Oxidative stress → altered β_2AR G-protein coupling and cAMP generation	Functional impairment of β_2AR signaling	Cellular and tissue models (in vitro/ex vivo)	Links oxidative stress to β-AR dysfunction in aging	(Elkhatib and Case, 2019; Santulli and Iaccarino, 2013; Singh et al., 2023)
Chronic sympathetic predominance	Persistent low-grade inflammatory activation and inflammatory skewing	Human aging studies; experimental neuroimmune models	Contribution to inflammaging	(Barthelemy et al., 2022; Ferrara et al., 2014; Jiang et al., 2022)
Altered β_2AR regulation of Th17/Treg balance	Th17 polarization, impaired immune tolerance	Murine $CD4^+$ T-cell systems; human PBMC/$CD4^+$ studies	Increased susceptibility to autoimmune responses	(Carvajal Gonczi et al., 2023; Guereschi et al., 2013; Laurence et al., 2007)
Chronic β_2AR stimulation → NK cell desensitization	Impaired cytotoxicity, altered adrenergic responsiveness	Human NK-cell experimental studies	Dysregulated innate immune surveillance	(Jurgens et al., 2024)
Reduced vagal tone and impaired cholinergic anti-inflammatory pathway	Reduced suppression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6)	Murine models; translational VNS studies in RA	Maintenance of chronic inflammation	(Borovikova et al., 2000; Fernandez et al., 2014; Koopman et al., 2016)
Disrupted splenic neuroimmune circuits (NE-$ChAT^+$ T cell-ACh axis)	↑ IL-1β, IL-6, IL-23; Th17-promoting microenvironment	Murine aging models	Amplification of inflammaging and loss of local neuroimmune control	(Shang et al., 2025)
Loss of circadian oscillations in β_2AR signaling	Disrupted time-of-day-dependent immune activation; altered $CD8^+$ effector-memory differentiation	Murine viral infection models	Impaired antiviral responses and immune memory	(Sharma et al., 2025)
Expansion of age-associated B cells (ABCs) in chronic inflammatory environments	Enhanced $CD4^+$ T cell activation, Th17 polarization, autoantibody production	Murine models and human post-viral infection	Loss of peripheral tolerance, increased autoimmunity risk	(Hao et al., 2011; Mouat et al., 2022; Nickerson et al., 2023; Yam-Puc et al., 2023)
STAT3-driven Th17 differentiation favored by inflammaging	↑ RORγt, ↑ IL-17 A production	Murine $CD4^+$ T cell systems (in vitro/in vivo)	Th17/Treg imbalance favoring inflammation	(Laurence et al., 2007; Park and Ciofani, 2025; Xia et al., 2024)
Glucocorticoid-mediated β_2AR upregulation	Increased β_2AR transcription	Human lung cell studies (in vitro)	Neuroendocrine crosstalk modulating adrenergic signaling plasticity	(Mak et al., 1995)
PI3K p110α inactivation potentiates β-adrenergic/cAMP signaling	Enhanced β-adrenergic responsiveness independent of receptor expression	Aged mouse and human adipocyte-derived systems (ex vivo)	Intracellular signaling nodes as modulators of β-AR function	(Araiz et al., 2019)
Reduced heart rate variability (HRV) as proxy of autonomic imbalance	Association with higher inflammatory burden (IL-6, TNF-α), disease activity, and mortality	Human cohort studies (RA, SLE, elderly)	HRV as a non-invasive correlate of inflammaging and immune dysregulation	(Goda et al., 2025; Jarczok et al., 2022; Saramet et al., 2023; Thanou et al., 2016)

HRV, heart rate variability; VNS, vagus nerve stimulation; ABCs, age-associated B cells; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

signaling is associated with aberrant B-cell activation, autoantibody production, and a lower threshold for autoimmune manifestations.

Importantly, the interferon-rich inflammatory environment described in Long COVID may also promote the expansion of T-bet^+ ABCs. In post-COVID individuals, ABC frequencies are significantly elevated, and their abundance has been associated with impaired formation of RBD-specific memory B cells and reduced neutralizing antibody titers following SARS-CoV-2 vaccination (Yam-Puc et al., 2023). ABCs are of particular interest in this context because they can produce IgG with increased autoreactivity and efficiently bind nucleic acid–containing immune complexes via TLR7/9. These immune complexes are well-known activators of the classical complement pathway through C1q binding and complement studies in Long COVID have demonstrated persistent activation of the classical, alternative, and terminal pathways, including elevated Ba, iC3b, C5a, and TCC and evidence of increased C1 complex consumption (Bayarri-Olmos et al., 2025; Cervia-Hasler et al., 2024). Thus, ABC-associated autoreactive antibody programs could contribute to immune-complex formation and complement activation, potentially linking B-cell dysregulation to endothelial dysfunction, monocyte-platelet aggregation, and persistent inflammation in Long COVID, although this pathway remains to be directly demonstrated.

The clinical consequences of Long COVID are increasingly recognized. New-onset or exacerbated autoimmune diseases, including SLE, inflammatory arthritis, myositis, and vasculitis, have been reported following SARS-CoV-2 infection (El Aoud et al., 2021; Kioi et al., 2023; Sumichika et al., 2025). In post-COVID SLE cases, serositis, lymphopenia, and high IFN signatures are common (Chang et al., 2021; Gracia-Ramos and Saavedra-Salinas, 2021; Ramachandran et al., 2022). Herpes zoster reactivation, linked to impaired interferon signaling and immunosenescence, has emerged as another marker of systemic immune dysregulation post-COVID and is associated with increased long-term risks of renal, infectious, and autoimmune complications (Chien et al., 2025). These observations are consistent with a model in which SARS-CoV-2 may act, at least in a subset of individuals, as an accelerator of pre-existing inflammaging and autonomic fragility rather than as a uniform de novo cause of autoimmunity. In older adults, where SNS overactivation, impaired β_2-AR signaling, and reduced vagal anti-inflammatory activity are already pronounced (Giunta et al., 2024b; Hernandez-Vicente et al., 2020), the acute viral insult may facilitate the transition from subclinical immune dysregulation to clinically apparent autoimmune or autoinflammatory manifestations.

In this framework, Long COVID can be viewed as a paradigmatic condition in which autonomic imbalance, persistent interferon signaling, inflammatory remodeling, and autoantibody responses coexist and may reinforce one another beyond viral clearance. Long COVID provides a clinically relevant model for examining how inflammaging and autonomic dysregulation may intersect with impaired maintenance of immune tolerance. Alternative, non-mutually exclusive explanations should also be considered, including persistent viral antigen or viral reservoirs, reactivation of latent viruses, endothelial and microvascular injury, tissue damage with release of self-antigens, immune imprinting after acute infection, comorbidities, sex-related susceptibility, and deconditioning-related autonomic changes (Kuchler et al., 2023; Opsteen et al., 2023; Saheb Sharif-Askari et al., 2021). However, key gaps remain. Current studies rarely include pre-infection autonomic or immunological baselines, often differ in Long COVID definitions and sampling time points, and generally cannot determine whether dysautonomia precedes immune dysregulation, follows

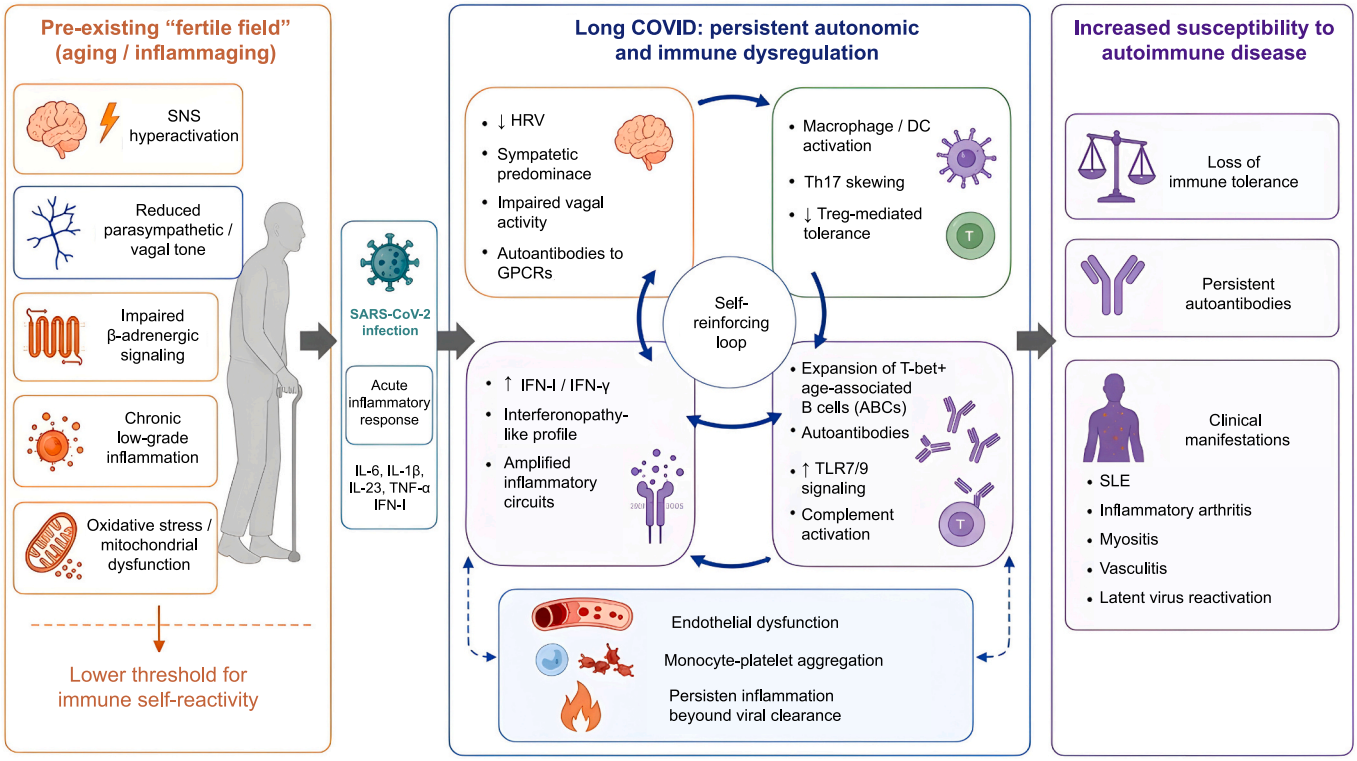


Fig. 3. Conceptual model linking aging-related autonomic imbalance, neuroimmune dysregulation, and increased susceptibility to autoimmune manifestations in Long COVID. Aging-associated sympathetic predominance, reduced vagal tone, impaired β-adrenergic responsiveness, and chronic low-grade inflammation (inflammaging) create a permissive neuroimmune environment characterized by altered cytokine signaling, Th17/Treg disequilibrium, impaired immune tolerance, and persistent activation of innate and adaptive immune pathways. SARS-CoV-2 infection may act as a secondary inflammatory and neuroimmune stressor superimposed on this vulnerable background, amplifying interferon signaling, autonomic dysfunction, autoreactive B-cell responses, complement activation, and inflammatory remodeling. Reciprocal interactions between dysautonomia and immune activation may contribute to the persistence of inflammatory and autoimmune-like manifestations after viral clearance.

persistent inflammation, or participates in a bidirectional feedback loop. Long-term monitoring of post-COVID individuals integrating autonomic markers, inflammatory profiles, autoantibody dynamics, viral persistence markers, and tissue-injury signatures will therefore be critical for identifying trajectories toward autoimmune and autoinflammatory disease, particularly in populations with pre-existing ANS dysregulation or accelerated biological aging.

5. Conclusions

This review highlights the autonomic nervous system as a critical, yet still underexplored, regulator of immune homeostasis across aging, chronic inflammation, and post-viral conditions. We summarize evidence showing that sympathetic and parasympathetic pathways shape immune cell differentiation, cytokine production, and tolerance mechanisms, and that age-associated autonomic imbalance contributes to the low-grade inflammatory state of inflammaging, progressively paving the way for increased susceptibility to autoimmunity. In this framework, β-adrenergic signaling emerges as a key modulatory axis rather than a deterministic driver of immune polarization, acting primarily by constraining cytokine-driven effector programs and supporting regulatory pathways.

Despite growing interest in this field, major gaps remain. Our understanding of how aging remodels adrenergic signaling in immune cells is still fragmentary, and most available studies focus on isolated molecular pathways or single immune subsets, without providing an integrated view of neuroimmune regulation at the organism level. Importantly, tools to assess autonomic function in clinical practice remain limited. Heart rate variability, although a valuable proxy of autonomic balance, is not routinely measured and requires specific technical expertise for both acquisition and interpretation (Ishaque et al., 2021). Similarly, circulating or urinary catecholamines and their metabolites primarily reflect systemic spillover, metabolic clearance, and circadian influences, and do not reliably capture regional or chronic sympathetic neural activity (Bisogni et al., 2016). Moreover, their relationship with other autonomic indices, such as HRV, is weak and context-dependent, limiting their utility as standalone measures of sympathetic tone (Chong et al., 2025).

These limitations indicate that autonomic markers should be interpreted within a broader phenotypic assessment. In patients with persistent post-viral symptoms, palpitations, fatigue, or exercise intolerance, feasible approaches include standardized resting HRV recordings, orthostatic vital signs, active standing or tilt-table testing when indicated, ambulatory ECG/Holter monitoring, and exclusion of secondary causes of sinus tachycardia or overlapping syndromes such as POTS, inappropriate sinus tachycardia, orthostatic hypotension, and supraventricular arrhythmias (Ahmed et al., 2022; Ishaque et al., 2021). This is particularly relevant in Long COVID, where tachycardia and autonomic symptoms may reflect heterogeneous mechanisms, including reduced vagal modulation, compensatory sympathetic activation, deconditioning, persistent inflammation, or cardiovascular involvement (Ahmed et al., 2022). From a translational perspective, autonomic imbalance may also represent a modifiable axis, provided that interventions are guided by the dominant clinical phenotype. β-blockade or other rate-controlling approaches may be considered in selected patients with sympathetic overactivity or tachycardic phenotypes, whereas ivabradine may be relevant when inappropriate sinus tachycardia-like features predominate (Ahmed et al., 2022). Strategies aimed at enhancing parasympathetic tone, including structured rehabilitation, breathing-based interventions, HRV biofeedback, and vagal modulation,

represent feasible adjunctive approaches with potential autonomic and anti-inflammatory effects (He et al., 2015; Mensinger et al., 2024; van Weperen et al., 2021). However, their impact on inflammatory biomarkers, autoantibody dynamics, and autoimmune outcomes in Long COVID or aging-related immune dysregulation remains to be tested in longitudinal and interventional studies.

A comprehensive assessment of sympathetic influence at the individual level would ideally require detailed immune phenotyping across multiple leukocyte subsets, a strategy that is technically demanding and rarely feasible outside established disease contexts. Long COVID has accelerated research at the intersection of autonomic dysfunction and immune dysregulation, but it remains an evolving clinical entity. Overall, current evidence underscores the need for integrative, longitudinal approaches that bridge neurophysiology and immunology to better define how autonomic imbalance contributes to chronic inflammation and immune-mediated disease, particularly in aging populations.

Author contribution

All authors contributed to information gathering, compiling, writing, editing and reviewing the manuscript.

CRediT authorship contribution statement

Sergio Giunta: Writing – review & editing, Writing – original draft, Conceptualization. **Jacopo Sabbatinelli:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Fabiola Olivieri:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Angelica Giuliani:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data were used for the research described in the article.

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