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Advancing research on regulatory autoantibodies targeting GPCRs: Insights from the 5th international symposium

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ABSTRACT

The 5th International Symposium on Regulatory Autoantibodies Targeting GPCR (RAB-GPCRs) advanced the understanding of the significant role played by autoantibodies targeting G-protein-coupled receptors (GPCRs) in various human diseases. Once considered passive markers, RAB-GPCRs are now recognized as active modulators of cellular signaling, immune regulation, and inflammation. The symposium highlighted their involvement in multiple prominent pathologies, including autoimmune diseases, cardio- and cerebrovascular diseases, and neuroimmunologic disorders such as myalgic encephalomyelitis/chronic fatigue syndrome and post-COVID-19 syndrome (ME/CFS/PCS), as well as solid organ and hematopoietic stem cell transplantation (SOT/HSCT). Experts from rheumatology, immunology, and neurology presented interdisciplinary discussions on the potential of RAB-GPCRs as biomarkers and therapeutic targets. Advances in screening methods, biomarker identification, and therapeutic strategies were shared, emphasizing their diagnostic potential and application in novel therapeutic interventions. This report summarizes key insights from the symposium, particularly focusing on the modulatory properties of RAB-GPCRs and their relevance in both immune-mediated diseases and other pathologies (e.g., vascular, degenerative) that are traditionally not considered primarily immune-mediated. Ongoing research is expected to further establish these autoantibodies as crucial components in disease modulation and systems biology contexts, offering new opportunities for precision medicine and improved clinical outcomes in immune-related disorders.

1. Introduction

G protein-coupled receptors (GPCRs) represent one of the largest and most versatile superfamilies of membrane proteins [1–3], mediating diverse physiological processes and playing a central role in various pathophysiological conditions [4–6]. Over the past decade, an increasing body of evidence has demonstrated the presence of functional autoantibodies targeting GPCRs, which contribute to the development and progression of autoimmune diseases [7–9], transplant rejection [7,10–12], cardio- and cerebrovascular diseases [13], neuroimmune disorders [14,15], and post-viral syndromes [16–18]. These findings have fostered an ongoing international dialogue on the implications of anti-GPCR autoantibodies in human health and disease [9].

Over the past decade, studies on Regulatory Autoantibodies targeting GPCRs (RAB-GPCR) have played a pivotal role in shaping our understanding of functional autoantibodies targeting GPCRs and their role in human disease [9]. Remarkably, the 5th International Symposium on RAB-GPCRs, held in Lübeck, Germany, continued this tradition of scientific exchange and collaboration. Bringing together leading experts from the fields of rheumatology, immunology, neurology, and translational medicine, the symposium served as a platform to discuss the latest discoveries and therapeutic perspectives [19] regarding these autoantibodies. A key highlight of the event was the exploration of the role of anti-GPCR autoantibodies in chronic inflammatory contexts, underscoring their potential as both biomarkers and therapeutic targets.

As we celebrate the tenth anniversary of these dedicated meetings, the discussions at the 5th Symposium reinforced the necessity of interdisciplinary approaches to unveil the complex mechanisms underlying autoantibody-mediated diseases. The symposium's scientific program was structured around six thematic sessions and four keynote addresses, offering a comprehensive exploration of the evolving landscape of regulatory autoantibodies. The sessions spanned a broad spectrum of interconnected topics, including chronic inflammation, neuroimmunology, exosome biology, and therapeutic targeting strategies, highlighting the multidisciplinary nature of the field. RAB-GPCRs have emerged as key players in the pathogenesis of complex diseases, including systemic sclerosis, myalgic encephalomyelitis/chronic fatigue syndrome, post-COVID syndrome (ME/CFS/PCS), vasculitis, and transplant rejection. By integrating mechanistic insights with translational research, the scientific program underscored the growing relevance of RAB-GPCRs as both biomarkers and therapeutic targets across multiple immune-mediated conditions. Advances in high-throughput screening methods [20,21], biomarker identification [20,22], and targeted therapeutic strategies were extensively debated, providing novel insights into the impact of these autoantibodies on immune regulation and disease pathology [23,24].

This report summarizes the key scientific contributions presented at the 5th Symposium, emphasizing emerging research, innovative experimental approaches, and future directions in the field. Building on the foundation established in previous symposia, we continue to deepen our understanding of anti-GPCR autoantibodies and their broader implications, not only in homeostasis and autoimmune diseases but also in other physiological and pathological contexts, such as neuropsychiatric manifestations.

2. Anti-GPCR autoantibodies are endogenous modulators of GPCR signaling

In recent decades, RAB-GPCRs have emerged as crucial players in the modulation of immune responses and disease pathophysiology [9]. These autoantibodies, long considered passive biomarkers of disease, are now recognized for their active role in influencing cellular signaling, immune regulation, and inflammatory responses [12,23,25]. Understanding their function is essential for deciphering the mechanisms underlying various autoimmune and chronic inflammatory diseases, including systemic sclerosis (SSc) [8], ME/CFS [26], PCS [18,27,28], and a diverse spectrum of neuroinflammatory disorders [29,30].

Previously, it was widely assumed that antibodies targeting GPCRs were exclusively associated with autoimmune diseases. However, emerging evidence now indicates that these antibodies, particularly RABs, play a more nuanced role in immune regulation, contributing not only to autoimmunity but also exerting physiological and homeostatic effects by altering receptor activity, signaling pathways, and immune responses [31,32]. Thus, endogenous self-reactive GPCR-targeting autoantibodies, especially RAB-GPCRs, are increasingly recognized as active modulators of receptor signaling rather than mere biomarkers of disease [24] (Fig. 1).

RAB-GPCRs have been detected across multiple GPCR families, including adrenergic, muscarinic, and angiotensin receptors [23]. The roles of anti-GPCR autoantibodies as endogenous modulators of GPCR signaling have been recently reviewed elsewhere [24]. Unlike

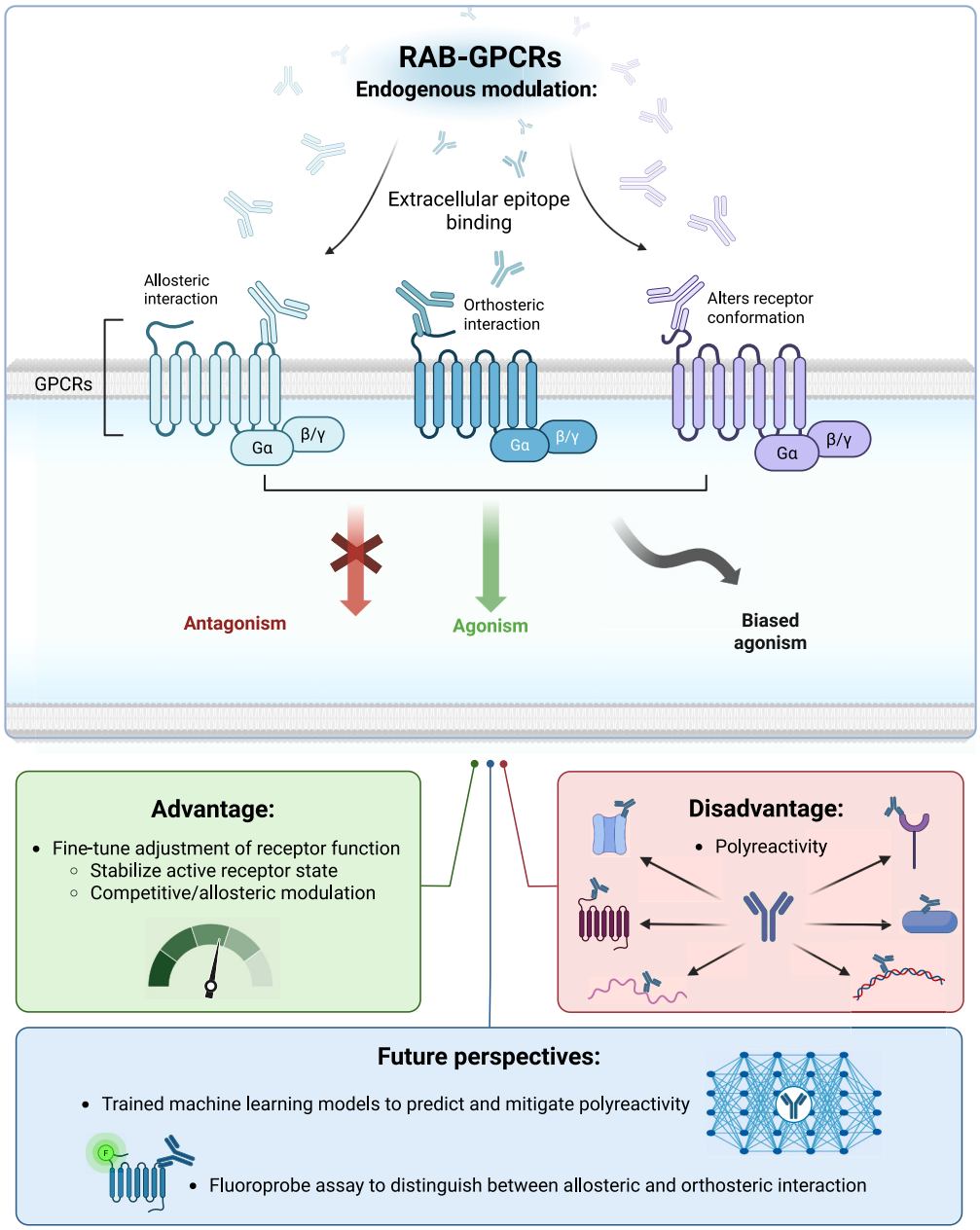

Fig. 1. – Endogenous Modulation of GPCRs by RAB-GPCRs through Extracellular Epitope Binding. Antibody interactions can occur through different mechanisms: allosteric interaction (left), orthosteric interaction (center), and receptor conformational alteration (right). Any of these mechanisms can result in antagonistic, agonistic, or biased agonistic effects. The advantages of this type of modulation include the ability to fine-tune receptor function by stabilizing the active state or through competitive and allosteric modulation. However, antibody polyreactivity represents a potential disadvantage. Future perspectives involve using machine learning models to predict and mitigate polyreactivity, as well as employing fluoroprobe assays to distinguish between allosteric and orthosteric interactions. Created in BioRender. Marques, O. (2025) https://BioRender.com/ek1uvez

traditional orthosteric binding, which refers to the direct binding of a molecule to the active site of a receptor or enzyme, where it typically exerts its biological effect, these autoantibodies can modulate receptor function by interacting with extracellular epitopes (allosteric binding), particularly its extracellular loop 1-3 (ECL1-3) domains [24]. For instance, autoantibodies can function as allosteric agonists, stabilizing active receptor states and potentially modulating interactions with endogenous ligands [23]. Additionally, anti-GPCR autoantibodies can alter receptor conformation, leading to biased signaling and selectively activating distinct intracellular pathways rather than uniformly triggering receptor activation [23] (Fig. 1).

However, a significant scientific challenge remains to elucidate the in vivo role of RAB-GPCRs under various homeostatic conditions, a topic that has largely been unexplored. Consequently, it is essential to differentiate between their regulatory and pathogenic functions to effectively leverage RAB-GPCRs as reliable diagnostic biomarkers and therapeutic targets.

3. Autoantibodies targeting GPCRs as modulators of endothelial integrity

Emerging evidence indicates that autoantibodies targeting the angiotensin II type 1 receptor (AT1R) contribute to endothelial glycocalyx (eGC) degradation [33], which compromises vascular barrier integrity and promotes systemic inflammation. In a recent systems biology investigation by our research group, AT1R-targeting autoantibodies were found to strongly associate with the persistence of core symptoms in COVID-19, partly through their disruptive action on the eGC [17], a protective, carbohydrate-rich layer covering both macro- and particularly microvascular endothelial cells (ECs) [34]. Notably, this pathological effect was reversed by losartan, an AT1R antagonist, suggesting a mechanistic link between receptor-specific autoantibodies, endothelial dysfunction, and clinical severity (Fig. 2). These findings underscore the role of antibody-mediated endothelial-immune crosstalk, which is central to the pathogenesis of both infectious and autoimmune diseases [35,36].

The convergence of anti-GPCR autoimmunity and endothelial glycocalyx (eGC) biology highlights a novel paradigm that we have explored in our previous RAB-GPCR meeting report [9]. Vascular homeostasis is regulated not only by inflammatory mediators but also by autoantibodies that act as functional modulators of key signaling hubs at the vascular-immune interface. Since anti-GPCR autoantibodies are not exclusively pathogenic and naturally occurring autoantibodies targeting GPCRs exist in healthy individuals [32], we hypothesize that they participate in fine-tuning physiological processes such as vascular tone, immune surveillance, and neuroimmune communication [23,32]. These antibodies may act as endogenous modulators, engaging receptors in a biased or partial agonistic manner to maintain balance in signaling pathways.

Their presence supports the concept of an "autoantibody network" that contributes to systemic equilibrium and tissue homeostasis, akin to the functions of hormones or cytokines. Disruptions in this regulatory network may shift these autoantibodies from being regulatory to pathogenic, triggering or perpetuating disease through: 1) altered concentrations (e.g., increased or decreased levels compared to the homeostatic levels found in healthy physiology), 2) altered affinity for their target epitopes (e.g., those found on the extracellular regulatory domains of GPCRs), or 3) altered epitope specificity (e.g., recognizing new epitopes with pathological downstream effects that are not typically found in the antibody repertoire of healthy individuals). Thus, understanding the dual nature of these molecules is essential for distinguishing physiological autoimmunity from autoimmune pathology and opens avenues for therapeutic modulation of autoantibody activity rather than mere suppression.

This concept is supported by the findings of Amendt et al. [37], who demonstrated that autoreactive antibodies contribute to the regulation of insulin homeostasis and blood glucose levels in healthy individuals. This highlights their role as active participants in metabolic regulation and reflects the growing recognition of autoantibodies as integral components of the immune-endocrine signaling network. Another

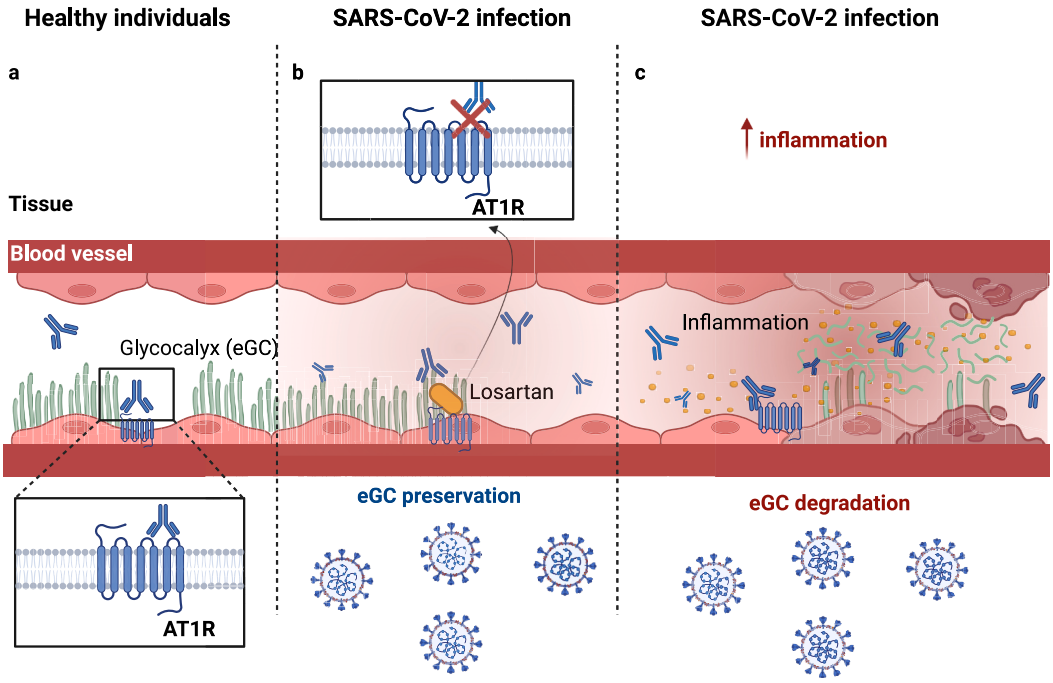

Fig. 2. – Anti-AT1R Autoantibodies and Endothelial Damage. a) In healthy endothelium, the endothelial glycocalyx (eGC) remains intact, allowing physiological interactions between anti-AT1R autoantibodies and angiotensin II type 1 receptors (AT1R) without causing damage. b) Losartan, an AT1R antagonist, blocks this interaction, protecting the endothelium and preserving the eGC from degradation during SARS-CoV-2 infection. c) In dysfunctional endothelium, SARS-CoV-2 infection leads to glycocalyx degradation and promotes inflammation, amplifying vascular damage through anti-AT1R-mediated pathogenic effects. Created in BioRender. Marques, O. (2025) https://BioRender.com/7wfjjhk

example supporting the physiological functions of RAB-GPCRs comes from a recent study by Klapa et al. [38] on eosinophilic granulomatosis with polyangiitis (EGPA), where decreased concentrations of autoantibodies against the C5a complement receptor (C5aR1) were associated with disease relapse. A decrease in anti-C5aR antibodies associated with relapse appears to be a disease-relevant immunological "signature" consistently observed across all three ANCA-associated vasculitis subgroups, as recently illustrated [39]. This inverse correlation challenges the conventional view of autoantibodies as mere markers or mediators of pathology and instead suggests that, in some contexts, their presence may exert protective or regulatory effects. For instance, similar to hormones or neurotransmitters, their balanced presence may be necessary for immune regulation, receptor desensitization, or maintaining vascular and tissue homeostasis. This nuanced perspective reinforces the idea that the immune system's repertoire includes RABs [18], whose dysregulation, whether through deficiency or excess, can contribute to disease [40].

4. Vasoregulatory autoantibodies and functional outcomes after ischemic stroke

Further supporting the view that autoantibodies targeting GPCRs and related receptors play a modulatory role in vascular diseases, a recent prospective study by Liman et al. [13] investigated the impact of vasoregulatory autoantibodies in a cohort of patients with ischemic stroke. Using data from the PROSpective Cohort with Incident Stroke-Berlin (PROSCIS-B) cohort, the authors measured autoantibody levels against a panel of vasoregulatory receptors (Fig. 3), including vascular endothelial growth factor (VEGF) receptors (VEGFR-1/2), VEGF-A/B, complement factor receptors (C3aR, C5aR), AT1R, and ETAR, in nearly 500 stroke patients. Remarkably, individuals with high levels of autoantibodies against VEGFR-2, VEGF-B, and C3aR had statistically significant worse functional outcomes at one year, independent of classical vascular risk factors. These antibodies were also associated with persistently lower Barthel Index scores over a 3-year follow-up, indicating long-lasting impacts on recovery and physical function.

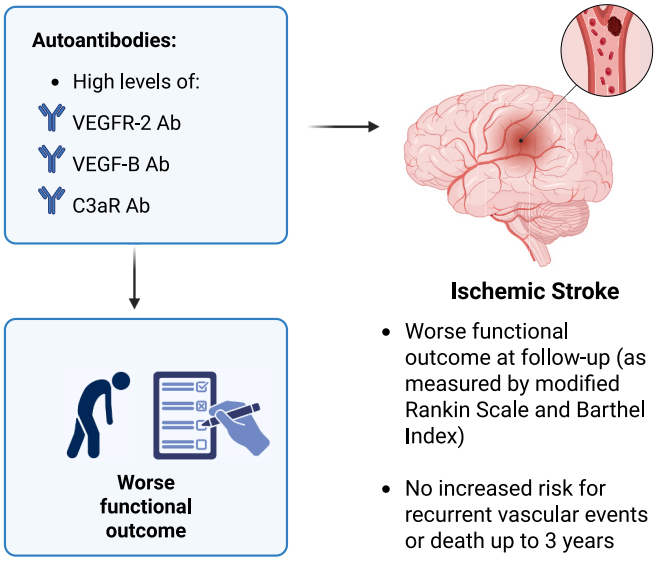

Fig. 3. – Association between High Levels of Vasoregulatory RAB-GPCRs and Functional Outcomes after Ischemic Stroke. Patients with elevated levels of functional autoantibodies against VEGFR-2, VEGF-B, and C3aR show worse functional recovery, as evidenced by higher modified Rankin Scale scores at one year and lower Barthel Index scores over three years of follow-up. However, the presence of these autoantibodies was not associated with an increased risk of recurrent vascular events or death. Created in BioRender. Marques, O. (2025) https://BioRender.com/e19hyu1

Interestingly, elevated antibody levels were not linked to an increased risk of recurrent vascular events or death. The association of certain vasoregulatory antibodies with poor outcomes and recovery, but not with the risk of recurrent events, may suggest that these antibodies modulate vascular repair, angiogenic signaling, or neurovascular remodeling rather than driving systemic thrombosis or atherosclerosis. These findings reinforce the idea that anti-GPCR, particularly vasoregulatory autoantibodies, occupy a functional space at the interface of damage and repair, capable of shaping disease trajectories based on their levels, targets, and biological context. In the post-stroke setting, they may act not as direct drivers of vascular events but rather as modifiers of recovery and vascular remodeling, emphasizing the importance of including these biomarkers in longitudinal neurovascular research.

5. Anti-GPCR autoantibodies in neuropsychiatric and Neuroimmunologic conditions

Neuropsychiatric disorders, including schizophrenia, bipolar disorder, major depressive disorder (MDD), and autoimmune encephalitis, are among the leading causes of disability worldwide, significantly affecting quality of life and public health systems [41,42]. The increasing number of patients diagnosed with these conditions has driven a growing interest in understanding the immune-mediated mechanisms that contribute to their pathophysiology [43,44], a topic also debated in the 5th International Symposium on RAB-GPCRs.

Among these mechanisms, RAB-GPCRs have gained attention as potential modulators of neuroimmune interactions, playing a role in neuropsychiatric disorders, particularly those targeting dopaminergic receptors [45]. These autoantibodies can modulate receptor function, alter neurotransmission, and drive persistent neuroimmune dysregulation [46]. For instance, studies have demonstrated the presence of anti-GPCR autoantibodies in patients with both primary neuropsychiatric conditions and post-infectious syndromes [45]. Autoantibodies targeting adrenergic, serotoninergic, and dopaminergic receptors have been implicated in mood disorders, psychosis, and cognitive impairment, suggesting a mechanistic link between altered GPCR function and neuropsychiatric manifestations [45]. Despite these insights, the pathogenic mechanisms underlying autoimmune neuropsychiatric and neuroimmunologic conditions remain complex, and definitive biomarkers for infection-related complications are still lacking. Understanding the role of anti-GPCR autoantibodies in these disorders could provide new diagnostic and therapeutic opportunities.

5.1. Neuropsychiatric manifestations, infectious and autoimmune diseases

Of note, neuropsychiatric disorders have been increasingly associated with microbial infections [45]. Growing evidence suggests that infections can trigger neuroinflammatory responses, potentially leading to autoimmune reactions that target the brain [47]. Additionally, infections have been implicated as environmental triggers that can drive both autoimmunity and psychotic disorders, possibly through mechanisms involving molecular mimicry and sustained immune activation [45]. Among patients with PCS [46], increasing evidence indicates that anti-GPCR autoantibodies may contribute to persistent neurological symptoms, including attention deficit, tremor, fatigue, and dysautonomia [18]. The SARS-CoV-2 infection has been shown to trigger long-lasting immune dysregulation, leading to the production of autoantibodies that may interfere with GPCR-mediated neurotransmission and immune homeostasis [18]. Related findings have also been reported in other autoimmune disorders affecting the nervous system, such as autoimmune encephalitis, where autoantibodies against $GABA_B$ receptors ($GABA_BR$) and dopamine D2 receptors (D2R) are associated with seizures, psychosis, and cognitive decline [48].

Given the expanding recognition of RAB-GPCRs as potential disease

modulators, there is an urgent need to further characterize their prevalence, functional effects, and clinical relevance in both primary neuropsychiatric disorders and post-viral syndromes. Notably, the involvement of immunological pathways in the pathophysiology of psychotic disorders has gained increasing attention in recent decades. A growing body of evidence suggests a link between autoimmune diseases and psychosis [43], supported by genetic studies associating immune-related markers with schizophrenia [49] and clinical findings showing elevated inflammatory markers in individuals with psychotic disorders [50].

Large-scale epidemiological studies have consistently reported positive associations between autoimmune diseases, such as multiple sclerosis and systemic lupus erythematosus (SLE), and a higher prevalence of neuropsychiatric symptoms, including psychosis [42]. Furthermore, both cross-sectional and longitudinal studies indicate a bidirectional relationship between autoimmune diseases and schizophrenia, with an increased risk of psychotic disorders observed in individuals with a family history of autoimmunity [51]. Given these associations, anti-GPCR autoantibodies have emerged as potential contributors to the immune dysregulation observed in neuropsychiatric disorders (Fig. 4). By targeting key receptors involved in neurotransmission and immune signaling, these autoantibodies may disrupt neuroimmune homeostasis, leading to altered neuronal communication and chronic inflammation.

Despite these insights, the precise role of autoantibodies, particularly those targeting GPCRs in psychiatric conditions such as depression [48], remains poorly understood. Further research is needed to elucidate their contribution to psychotic disorders and their potential as biomarkers or therapeutic targets. Understanding these immunological mechanisms could pave the way for novel diagnostic and treatment strategies that integrate immune modulation in managing neuropsychiatric disorders.

6. EBV-driven autoimmunity and GPCR autoantibodies in ME/CFS/PCS

While SARS-CoV-2 infection has been recognized as a well-established trigger of PCS and ME/CFS-like manifestations [46], emerging evidence now highlights Epstein-Barr Virus (EBV) as a central driver in the autoimmune cascade underlying these conditions. The recent study by Hoheisel et al. [52] sheds light on the upstream triggers of autoantibodies, specifically implicating EBV-derived poly-arginine

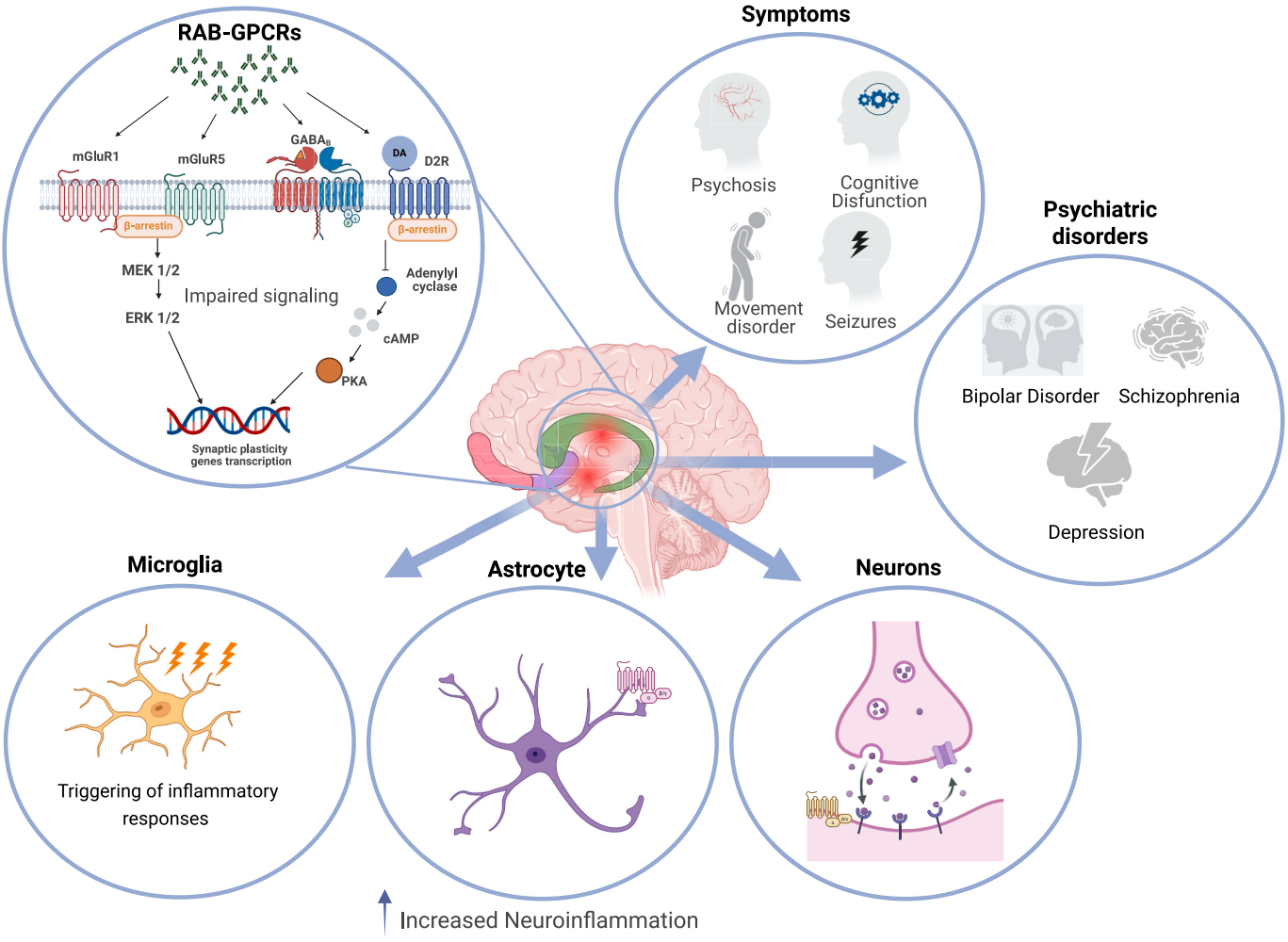

Fig. 4. – Conceptual Model of RAB-GPCR Involvement in Neuroimmune Dysregulation and Neuropsychiatric Disorders. Autoantibodies targeting GPCRs, including metabotropic glutamate receptors (mGluR1, mGluR5), GABAB_BB receptors, and dopamine D2 receptors (D2R), negatively modulate intracellular signal transduction via β-arrestin and cAMP-PKA, as well as ERK/MAPK-dependent signaling cascades. This impairment affects the transcription of genes associated with synaptic plasticity. The resulting alterations in neurotransmission and neuroimmune homeostasis can lead to microglial activation, promoting neuroinflammation and sustained immune dysfunction. Astrocytes and neurons are also impacted, exacerbating synaptic and inflammatory dysregulation. These changes are linked to neuropsychiatric symptoms such as psychosis, cognitive dysfunction, movement disorders, and seizures, which are clinical features of psychiatric disorders, including schizophrenia, bipolar disorder, and depression. Growing evidence suggests that infections may act as environmental triggers, inducing the production of anti-GPCR autoantibodies and contributing to persistent inflammation and neuroimmune dysregulation, thereby promoting the development of neuropsychiatric manifestations. Created in BioRender. Marques, O. (2025) https://BioRender.com/r54w51d

(poly-R) sequences in the EBV nuclear antigens EBNA4 and EBNA6. The authors demonstrated that immunoglobulin G (IgG) responses to these viral epitopes are elevated in both ME/CFS and PCS patients; critically, these sequences exhibit strong homology to several human proteins, including GPCRs such as adrenergic receptors (Fig. 5).

This molecular mimicry supports the hypothesis that EBV reactivation, frequently observed during or after SARS-CoV-2 infection [53], may initiate or perpetuate autoimmune processes through cross-reactivity. The resulting autoantibodies, particularly those targeting GPCRs, were significantly elevated in patients compared to controls and were positively associated with symptom severity, especially in PCS [52]. These antibodies may directly interfere with adrenergic receptor signaling, contributing to dysautonomia, fatigue, cognitive dysfunction, and pain.

Furthermore, the study proposes a mechanistic model in which B-cell activation by EBV antigens leads to somatic hypermutation and epitope spreading, enhancing autoreactivity to GPCRs and other self-proteins. These findings bridge the viral and autoimmune dimensions of ME/CFS/PCS and underscore the relevance of EBV as a priming factor in generating pathogenic GPCR autoantibodies. This new evidence indicates that EBV infections also contribute to a broader post-viral autoimmune landscape, where GPCR autoantibodies serve as critical mediators of symptomatology and potentially as biomarkers or therapeutic targets.

7. Role of RAB-GPCRs in POTS: Pathophysiology and emerging insights

The complex interplay between autoantibodies and autonomic dysfunction in Postural Orthostatic Tachycardia Syndrome (POTS) is gaining increasing attention within the scientific community. This topic was highlighted at the 5th International Symposium on RAB-GPCRs, where researchers discussed emerging insights into the role of functionally active autoantibodies in cardiovascular and neuroimmune regulation. POTS is a heterogeneous and multifactorial condition characterized by a postural worsening of symptoms with an excessive increase in heart rate upon standing, typically a rise of ≥30 beats per minute (bpm) (or ≥ 40 bpm in individuals aged 12–19), in the absence of orthostatic hypotension [54]. It affects approximately 0.1–1.0 % of the general population, disproportionately impacting young women of childbearing age. Patients with POTS commonly present with symptoms such as palpitations, lightheadedness, fatigue, exercise intolerance,

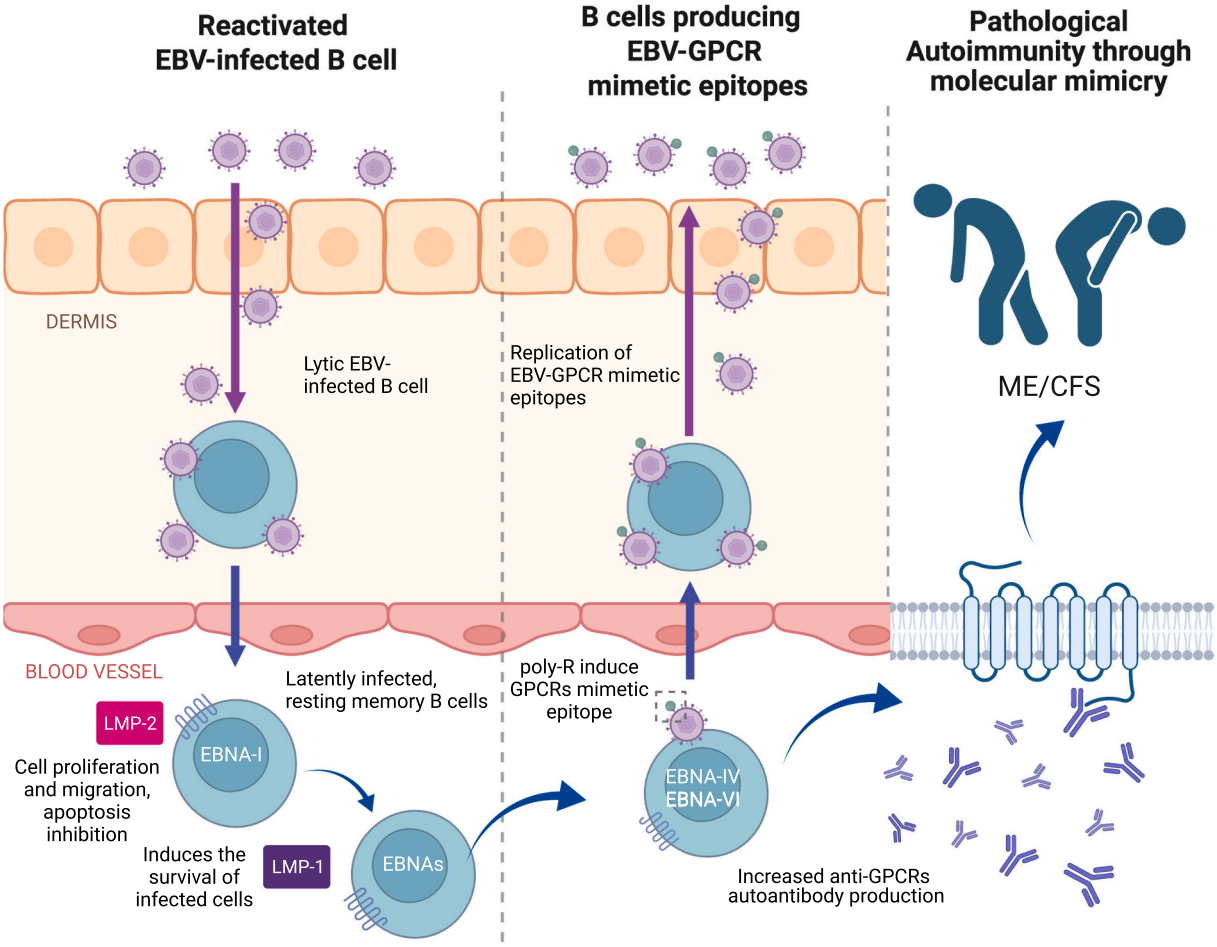

Fig. 5. – Molecular Mimicry and Autoimmune Activity Linked to Epstein-Barr Virus (EBV) Infection. Epstein-Barr virus (EBV)-infected B cells in a latent state can become reactivated. Viral proteins such as EBNA4 and EBNA6 contain poly-arginine (poly-R)-rich sequences that mimic regions of human proteins, including G protein-coupled receptors (GPCRs). This molecular mimicry can induce the production of autoantibodies that recognize both viral epitopes and human receptors, potentially promoting autonomic dysfunction, fatigue, and cognitive symptoms in patients with post-COVID syndrome (PCS) and ME/CFS. The ongoing immune response can lead to somatic hypermutation and epitope spreading, intensifying autoreactivity against GPCRs and expanding the autoimmune basis of these conditions. During primary EBV infection, latent membrane proteins LMP-1 and LMP-2 contribute to viral persistence and immune evasion. LMP-1 induces the survival of infected cells by activating pro-survival signaling pathways, while LMP-2 promotes cell proliferation and migration and inhibits apoptosis, mimicking tonic B cell receptor (BCR) signaling. Together, these proteins facilitate long-term B cell infection and may contribute to chronic immune dysregulation. Created in BioRender. Marques, O. (2025) https://BioRender.com/hefem4i

chest discomfort, cognitive impairment ("brain fog"), and sometimes syncope. These symptoms often lead to significant functional impairment and diminished quality of life [54].

The hallmark of POTS is autonomic dysregulation, particularly an exaggerated sympathetic nervous system response upon orthostatic stress [54]. This dysautonomia is often accompanied by a paradoxical decrease in effective circulating blood volume and altered baroreceptor sensitivity. Several subtypes of POTS have been proposed, including hyperadrenergic, neuropathic, hypovolemic, and autoimmune forms, reflecting the complex interplay of mechanisms involved [54]. A systematic review by Ruzieh et al. [55] further consolidated the autoimmune hypothesis by highlighting the association between POTS and other autoimmune disorders, such as Hashimoto's thyroiditis, Sjögren's syndrome, and SLE. The review also emphasized the potential benefit of immunomodulatory therapy in selected patients, although controlled clinical trials are lacking [55].

Further evidence has implicated autoimmunity in the pathogenesis of POTS, particularly through the presence of autoantibodies targeting GPCRs and components of the autonomic nervous system [56]. A seminal study by Fedorowski et al. [57] identified functionally active autoantibodies against α1-adrenergic (α1-AR) and β1/β2-adrenergic (β1-AR, β2-AR) receptors in a significant subset of POTS patients, implicating these autoantibodies in abnormal vasoconstriction and heart rate regulation. These findings were extended by Yu et al. [58], who reported the presence of AT1R autoantibodies in POTS patients, suggesting a role in modulating vascular tone and sodium-water balance. Moreover, Vernino and Stiles [59] provided a comprehensive overview of the autoimmune landscape in POTS, noting the increased frequency of neural receptor autoantibodies (e.g., ganglionic acetylcholine receptor antibodies) and the co-occurrence of small fiber neuropathy in many patients, which may result from immune-mediated injury to autonomic fibers [59].

In contrast, Hall et al. [60] conducted a study assessing the prevalence of GPCR autoantibodies against AT1R, endothelin receptor A (ETAR), alpha- and beta-adrenergic receptors 1 and 2 (e.g., α1-AdR, α2-AdR, β1-AdR, and β2-AdR), and muscarinic receptors 1 through 5 (M1R, M2R, M3R, M4R, M5R) in POTS patients and found no statistically significant difference compared to healthy controls, questioning the specificity and pathogenicity of these autoantibodies. Hence, additional research is required to clarify whether the functional activity of these autoantibodies, rather than their absolute concentrations, plays a more decisive role in their clinical significance for some patients. Identifying biomarkers, such as AdR autoantibodies, AT1R autoantibodies, or inflammatory mediators, may offer future diagnostic and prognostic value.

8. Anti-CXCR3 autoantibodies predict cardiovascular risk and promote atherosclerosis

Extending the relevance of GPCR-targeting autoantibodies to cardiovascular health, a recent large-scale population-based study investigated the clinical impact of autoantibodies against the chemokine receptor CXCR3, a GPCR critically involved in leukocyte recruitment and atherosclerotic plaque development. In the Gutenberg Health Study [61], which included over 4000 rigorously characterized individuals without autoimmune diseases, high levels of anti-CXCR3 autoantibodies were found to correlate with multiple markers of cardiovascular end-organ damage, such as increased intima-media thickness, left ventricular mass, and elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP), even after adjusting for traditional cardiovascular risk factors. Moreover, individuals with anti-CXCR3 autoantibody levels above the 75th percentile exhibited a significantly higher risk of all-cause mortality and cardiac death, as well as a trend toward increased major adverse cardiovascular events and incident heart failure.

Importantly, proteomic profiling linked these antibodies to Th1-skewed immune activation, suggesting a pro-inflammatory milieu as the underlying driver. Experimental validation in ApoE$^{-/-}$ mice confirmed the causal contribution of anti-CXCR3 autoantibodies to accelerated atherosclerosis, reinforcing their functional role in vascular disease pathogenesis [61]. These findings underscore a critical point: even in individuals free from overt autoimmune disease, functionally active anti-GPCR autoantibodies can emerge as independent modulators of vascular health, shaping both subclinical tissue remodeling and long-term clinical outcomes. They exemplify how the immune system, through a repertoire of natural autoantibodies, continuously interacts with cardiovascular signaling pathways, sometimes tipping the balance toward pathology in the absence of classic inflammatory triggers.

9. Anti-GPCR autoantibodies in transplantation: Biomarkers, functional mediators and modulators of allograft outcomes

At the 5th International Symposium on RAB-GPCRs, transplantation immunology emerged as a key focus, highlighting the growing diagnostic and mechanistic relevance of RAB-GPCRs in this field. Collaborative overview presentations by Dr. Guido Moll (Charité Universitätsmedizin Berlin, Germany) and Prof. Miroslaw Banasik (Wroclaw University, Poland) summarized recent advances from leading international transplant centers. These included large-scale, multicentric studies, such as those led by the Paris Transplant Group within the EUTRAIN consortium, which collectively reinforced the evolving understanding that anti-GPCR autoantibodies (anti-GPCR-AABs), once thought to play a marginal role, are now recognized as central mediators of allograft injury and emerging biomarkers of graft outcomes. These findings complement established markers of allograft function and rejection, including donor-specific anti-HLA class I and II antibodies (DSAs), and align with ongoing efforts to validate cell-free DNA (cfDNA) as a reliable, non-invasive biomarker for transplant monitoring [7,10–12,62].

A key insight highlighted during the symposium was the paradigm shift in understanding anti-GPCR autoantibodies, from being considered mere bystanders or indirect indicators of immune activation to being recognized as active contributors to graft pathophysiology. Emerging evidence supports their functional role in modulating both short- and long-term outcomes in kidney transplantation, particularly in the context of acute and chronic allograft rejection [7,10–12]. Specifically, autoantibodies against GPCRs such as AT1R, ETAR [63,64], and β-adrenergic receptors [65] were shown to directly contribute to transplant pathology by engaging in receptor agonism, triggering downstream pro-inflammatory and pro-fibrotic signaling cascades (Fig. 6) [12,64,66]. For example, anti-AT1R autoantibodies have been reported to activate extracellular signal-regulated kinase 1/2 (ERK1/2) signaling and enhance the nuclear activity of key transcription factors such as AP-1 and nuclear factor kappa B (NF-κB) [12].

The potential pathogenicity of these antibodies is further supported by evidence of synergistic interactions with donor-specific anti-HLA antibodies, which amplify or even cause antibody-mediated rejection (ABMR), thereby accelerating graft deterioration [67]. Notably, anti-ETAR autoantibodies can potentiate AT1R signaling when co-present, contributing to more aggressive forms of rejection (e.g., heart and renal transplantation) [68,69]. This synergy underscores the need for a broader immunological risk assessment in transplant patients that includes non-HLA autoantibodies. Future research must now move toward systems-level integration in transplant monitoring to better harness the diagnostic and therapeutic potential of anti-GPCR autoantibodies in transplantation [9]. Combining autoantibody profiles with transcriptomic, proteomic, and metabolomic data will provide a more nuanced understanding of how these molecules interact with broader immune and vascular networks.

Ultimately, the integration of anti-GPCR autoantibody assessment into transplant immune-monitoring protocols may improve personalized immunosuppression, enable earlier interventions, and enhance long-term graft survival. The growing convergence of basic,

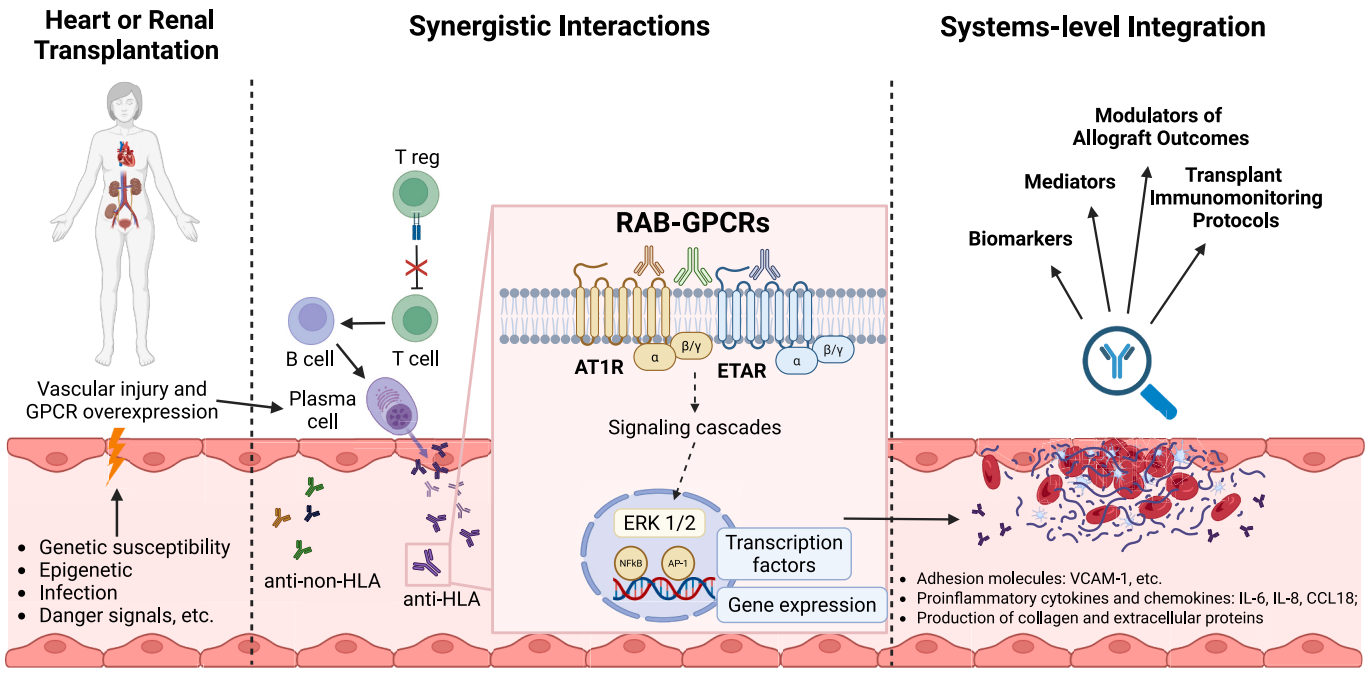

Fig. 6. – The Involvement of RAB-GPCRs in Transplant Rejection. Heart or kidney transplantation can lead to vascular injury and the overexpression of G protein-coupled receptors (GPCRs), influenced by genetic, epigenetic, infectious, and danger signals. The interaction between B cells, regulatory T cells, and plasma cells results in the production of antibodies against both HLA and non-HLA antigens, including anti-GPCR autoantibodies such as anti-AT1R and anti-ETAR. These autoantibodies activate intracellular signaling cascades, including ERK 1/2, NF-κB, and AP-1, modulating gene expression and promoting inflammation. A systems-level integration highlights the role of biomarkers and inflammatory mediators, such as adhesion molecules (VCAM-1), pro-inflammatory cytokines and chemokines (IL-6, IL-8, CCL18), and extracellular matrix proteins, which influence allograft outcomes and immune monitoring protocols in transplantation. Created in BioRender. Marques, O. (2025) https://BioRender.com/tn1mpi7

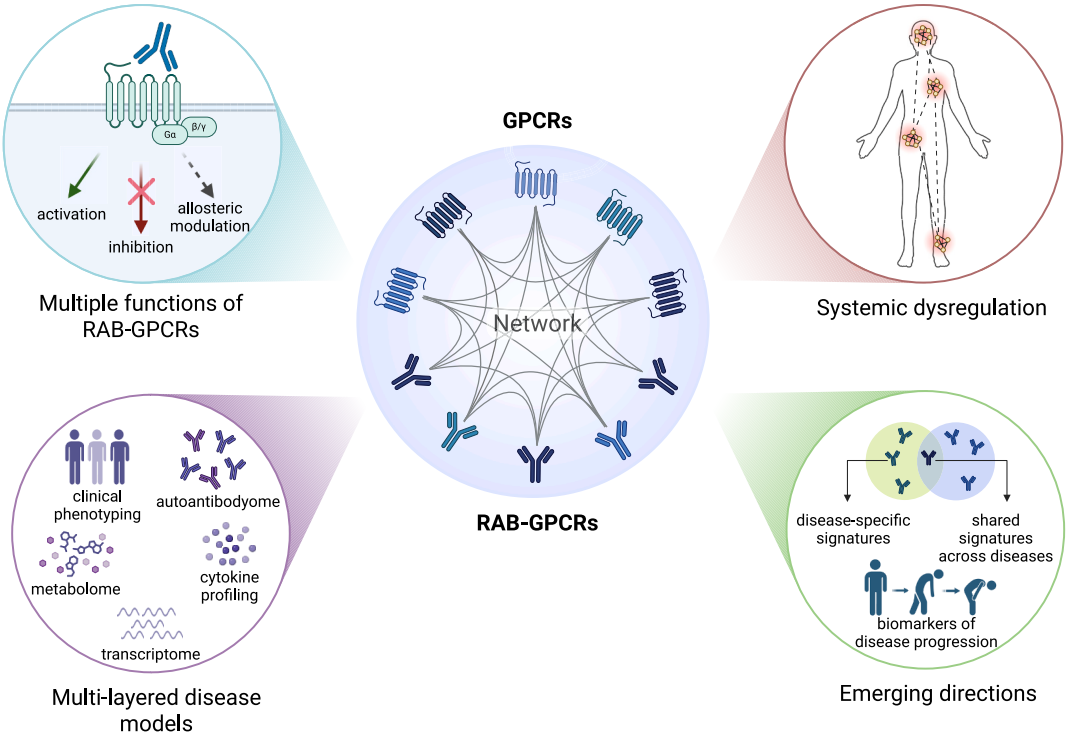

Fig. 7. – Highlighting the Need for Systems-Level Investigation of RAB-GPCRs. The immunological network formed through the interconnection and intraconnection of RAB-GPCRs and their receptors holds significant potential for systems biology investigations, particularly through high-throughput approaches. Such studies could explore the functional roles of RAB-GPCRs across different tissues and systems within the organism. These investigations may include the development of multi-layered disease models that integrate the autoantibodyome with multi-omics and clinical data. This approach could lead to the identification of disease-specific autoantibody signatures and shared alterations across diseases, paving the way for targeted therapies and the identification of potential RAB-GPCR biomarkers. Created in BioRender. Marques, O. (2025) https://BioRender.com/htsvy1h

translational, and computational science showcased at the past two RAB-GPCR Symposia marks a turning point in how these antibodies are perceived, not merely as bystanders, but as key orchestrators of immune-mediated transplant outcomes [7,9–12]. This new perception of RAB-GPCRs is significant for the entire transplant field, not only solid organ transplantation (SOT) but also hematopoietic stem cell transplantation (HSCT) and the clinical immunology underlying transplant matching and the monitoring of functional/clinical outcomes.

10. Emerging directions in GPCR-directed functional autoantibody studies

10.1. Systems biology analysis of RAB-GPCRs

The immune system's interaction with the nervous and vascular systems forms a highly dynamic and complex network that is central to the pathogenesis of many chronic diseases [70]. Within this network, RAB-GPCRs have gained increasing attention due to their ability to modulate receptor activity rather than merely blocking or tagging antigens for destruction. These functional RABs can behave as agonists, antagonists, or allosteric modulators, influencing multiple physiological systems simultaneously (Fig. 1) [71]. In addition to their dysregulation in autoimmune diseases and disorders such as ME/CFS/PCS [46], POTS [60], and psychiatric syndromes [48], as discussed in the 5th International Symposium on RAB-GPCRs, suggests systemic autoantibody dysregulation with potential feedback loops involving neuroimmune and vascular signaling (Fig. 7).

10.2. Autoantibodyome datasets and the opportunity for anti-GPCR systems-level profiling

Traditional immunological approaches often fall short of capturing the multifaceted and interconnected actions of these antibodies. This is where systems biology (SysBio) and the adjunct use of artificial intelligence (AI) provide a powerful framework for a better understanding of the data [72]. By integrating multi-omics data, network analysis, and computational modeling, SysBio allows for a holistic investigation [73] into how anti-GPCR-AABs contribute to disease mechanisms. Recent studies have highlighted that these autoantibodies may function within interdependent immunological networks rather than in isolation, modulating broader molecular pathways such as inflammation and endothelial signaling [16,32]. The integrated use of AI may further enhance data analysis and interpretation in holistic fashion [74].

The concept of the autoantibodyome, the complete repertoire of autoantibodies present in an individual [75], represents a valuable dimension of immune profiling in various diseases such as psychotic disorders [43], neuropsychiatric lupus [76], Parkinson's disease [77], multiple sclerosis [78], and Alzheimer's disease [79]. These studies of high-throughput autoantibodyome datasets have already been used to distinguish disease-specific autoantibody signatures, identify shared immune alterations across disorders, and uncover potential biomarkers of disease progression. Hence, these data suggest that autoantibody profiles could reflect deeper systemic immune dysfunction.

However, within these emerging autoantibodyomes, anti-GPCR autoantibodies still remain underexplored at the systems level, despite their known pathophysiological relevance. Given the central roles of GPCRs in intercellular signaling and homeostatic regulation, studying these AABs in the broader context of "autoantibody networks" could yield profound insights. Specifically, integrating anti-GPCR data with transcriptomics, cytokine profiles, metabolomics, and clinical phenotyping would enable the construction of multi-layered disease models that capture not only correlation but also potential causality within immune-mediated signaling circuits (Fig. 7).

This represents a unique and timely opportunity for the field. By leveraging existing autoantibodyome datasets and applying systems biology approaches, researchers can begin to decode the systemic effects of anti-GPCR autoantibodies across diseases. Such integrative work could facilitate the identification of shared immunological endophenotypes, highlight mechanistic convergence between seemingly unrelated conditions, and ultimately support the development of targeted interventions aimed at modulating dysfunctional GPCR signaling pathways.

Hence, systems biology provides not only a comprehensive lens through which to study anti-GPCR autoantibodies but also a strategic opportunity to situate them within the broader landscape of immune dysregulation. Embracing this integrative perspective may catalyze significant advances in our understanding and therapeutic targeting of complex, chronic diseases.

10.3. Harnessing anti-GPCR autoantibody's modulatory properties for therapeutic innovation

One key example of anti-GPCR autoantibodies with modulatory properties is those targeting the AT1R, which have been implicated in SSc [25], hypertension [25,80], COVID-19 [81,82], and cardiovascular diseases [83]. These antibodies can act as receptor agonists, leading to vascular dysfunction and fibrosis, hallmarks of progressive autoimmune and inflammatory conditions [25].

Recent research [84,85] has explored the potential of autoantibody-like functions to modulate GPCR activity, paving the way for their application in therapeutic monoclonal antibody development. For instance, traditional small-molecule inhibitors, such as AT1R blockers, are effective but unsuitable for treating pregnancy-related hypertensive disorders like preeclampsia due to their teratogenic effects [86]. Recent studies [85] have successfully engineered nanobody antagonists targeting AT1R with high specificity, ensuring their effects remain restricted to maternal circulation. Structural analyses have revealed that these nanobodies interact with AT1R extracellular domains, influencing receptor signaling through allosteric mechanisms. Interestingly, even closely related nanobody sequences can exhibit different pharmacological properties, demonstrating the versatility of antibody-based GPCR modulation [85].

Another pathway to understanding anti-GPCR autoantibody biology has emerged from the recent study by Carreira et al. [87], which introduces a novel fluoroprobe-based method to distinguish between allosteric and orthosteric modulators of the cannabinoid receptor CB1R. This innovative approach enables real-time, quantitative monitoring of ligand-receptor interactions, providing a powerful platform to dissect the subtle pharmacological profiles of GPCR modulators. By facilitating the classification of ligands based on their binding dynamics and functional outcomes, this strategy significantly enhances our ability to refine drug development targeting not only CB1R but potentially a wide range of GPCRs.

Although the study focuses specifically on CB1R, the underlying methodology is broadly applicable to GPCR research and potentially relevant for investigating the functional effects of anti-GPCR autoantibodies. The ability to precisely characterize allosteric modulation opens new avenues for exploring the functionality of autoantibodies. In the context of autoimmunity and neuroimmune disorders, this approach may prove instrumental in identifying previously unrecognized allosteric interactions between endogenous antibodies and GPCRs, shedding light on complex immunopathological processes.

Notably, we discussed during the 5th International Symposium on RAB-GPCR, as well as in our previous meeting on RAB-GPCRs [9], the evidence supporting the role of these antibodies as potential predictors of disease severity and therapeutic development. However, several challenges remain regarding their efficacy. For instance, one major limitation is their potential for unintended binding to off-target proteins and biomolecules, leading to polyreactivity [84]. This phenomenon can compromise experimental reproducibility and hinder the clinical translation of antibody-based therapies. To address this challenge, recent efforts have focused on leveraging machine learning models to

predict and mitigate polyreactivity in antibody engineering [84].

Altogether, this growing body of evidence highlights the therapeutic promise of RAB-GPCRs, which could serve as both competitive and allosteric modulators. Their ability to fine-tune receptor function without the risks associated with small-molecule drugs positions them as potential next-generation therapeutics for diverse pathological conditions requiring GPCR modulation.

11. Conclusions

Over the past decade, functional autoantibodies targeting GPCRs have transitioned from peripheral curiosities to central players in understanding immune-mediated disease mechanisms. The 5th International Symposium on RAB-GPCRs underscored this paradigm shift, offering a platform for multidisciplinary exchange that illuminated both the pathogenic and regulatory roles of these molecules. It is now evident that anti-GPCR autoantibodies function as more than static biomarkers; they are dynamic, functionally active agents capable of modulating receptor signaling, altering immune homeostasis, and influencing clinical outcomes across a wide spectrum of diseases.

From systemic autoimmune disorders and cardiovascular diseases to neuropsychiatric syndromes and post-viral sequelae, these antibodies have demonstrated the capacity to serve as predictors, mediators, and even potential therapeutic targets. Notably, their dual nature, where they may either contribute to homeostatic balance or trigger pathology depending on concentration, epitope specificity, and receptor context, challenges traditional immunological frameworks. This evolving understanding demands new conceptual models that accommodate the continuum between physiological autoimmunity and overt autoimmune disease.

The symposium also highlighted innovative tools for the functional profiling of these antibodies, including high-throughput screening, systems immunology, and machine learning-guided nanobody design, which are accelerating the translation of basic findings into clinical applications. In transplantation, stroke recovery, cardiovascular risk assessment, and post-infectious syndromes such as long COVID and ME/CFS, anti-GPCR autoantibodies are emerging as crucial indicators of disease course and response to treatment.

Looking ahead, we advocate for the adoption of integrative, systems-level approaches to decode the full impact of these autoantibodies within the broader immunological landscape. By situating anti-GPCR autoantibodies within autoantibodyomes and multi-omic disease networks, we can uncover shared endophenotypes and therapeutic targets that transcend organ-specific paradigms. Ultimately, embracing the complexity of anti-GPCR autoantibodies as both regulators and disruptors of GPCR signaling will be key to unlocking novel strategies for diagnosis, prognosis, and precision immunomodulation in chronic, multifactorial diseases.

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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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2025.103855.

Data availability

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

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