Review

# Natural autoantibodies against G protein-coupled receptors as key for disease predisposition

R. Akbarzadeh[1], E.-B. Adjailia[1], J.Y. Humrich[1], H. Heidecke[2], G. Riemekasten[1]

[1]*Department of Rheumatology and Clinical Immunology, University of Lübeck;*
[2]*CellTrend GmbH, Luckenwalde, Germany.*

*Reza Akbarzadeh, PhD*
*El-Bara Adjailia, MD*
*Jens Y. Humrich, MD*
*Harald Heidecke, PhD*
*Gabriela Riemekasten, MD*

*Please address correspondence to:*
*Gabriela Riemekasten*
*Department of Rheumatology and Clinical Immunology,*
*University of Lübeck,*
*University Clinic of Schleswig-Holstein,*
*Ratzeburger Allee 160,*
*23538 Lübeck, Germany.*
*E-mail: gabriela.riemekasten@uksh.de*

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**ABSTRACT***Antibodies (Abs) targeting G protein-coupled receptors (GPCRs) are a natural component of the immune system. These antibodies reflect the unique GPCR expression profile of the individual, shaped by environmental and non-genetic factors. Due to their tightly regulated levels, GPCR antibodies have emerged as valuable biomarkers across a range of inflammatory diseases. In this review, we explore their crucial role in modulating immune responses, focusing on the mechanisms by which they influence the strength, composition, and localisation of inflammation. These properties position them as key players in determining host-specific susceptibility to various diseases. Importantly, GPCR antibodies can mimic the receptor-mediated signalling found in affected individuals, offering a potential pathway to identify disease-specific mechanisms. Their ability to modulate ligand-GPCR interactions and trigger ligand-independent GPCR activity makes them promising tools for both pharmacological development and precision medicine, particularly in the context of inflammation. This review aims to inspire further research on natural GPCR antibodies, with a special emphasis on mechanistic studies.*

## G protein-coupled receptors as key structures for variable cellular responses

G protein-coupled receptors (GPCRs) are a large and diverse family of membrane proteins that play a critical role in cellular communication and signal transduction. They are expressed in immune cells and, depending on the specific GPCR, in resident cells of selected tissues. GPCRs respond to a variety of extracellular signals, including hormones, infections, neurotransmitters, and cell micro-environmental stimuli, by activating intracellular signalling pathways through the binding and activation of distinct types of G proteins, each initiating specific downstream effects (1).

In addition, extracellular and transcellular interactions have emerged to critically impact GPCR function and pharmacology. GPCRs are increasingly found in complex with extracellular binding partners (2) and with secreted extracellular proteins such as with extracellular matrix (ECM) components, adhesion molecules, or multimeric complexes (3). In addition, GPCRs often cluster with other GPCRs, further enhancing the variability in activation and signal transduction (4). This versatility in structures and signalling mechanisms allows GPCRs to regulate numerous physiological processes in response to different environmental challenges and thus regulate sensory perception, immune responses, or cellular growth, making them crucial for maintaining cellular homeostasis and key targets for therapeutic interventions (1).

Taken together, the expression of GPCRs and their conformations is increasingly recognised to be affected by a high number of specific cellular micro-environmental factors. Accordingly, in specific conditions, the corresponding signalling restricted to a distinct GPCR is difficult to predict. Contrasting this variability in receptor expression and signalling, several pharmacological drugs targeting GPCRs have been successfully developed focusing on a single GPCR and its ligand interaction in a restricted number of cells and conditions. Current approaches target polypharmacologic ligands to address the complexity of GPCR expressions in specific diseases (5).

### Autoantibodies directed to GPCRs as a marker for acquired changes in the GPCR expression

So far, many endogenous and exogenous factors such as genetic, epigenetic, immunological stimuli, neurological factors, endocrine conditions (*e.g.* obesity and diet), comorbidities (*e.g.* diabetes and hypertension), and environmental influences (*e.g.* smoking, air pollution, solvents) were found to affect GPCR expression (Fig. 1) (6, 7). In addition, several viral agents recognise and target GPCRs. For instance, the chemokine receptor CXCR4 is required for the entry of human immunodeficiency virus type 1 (HIV-1) into target cells (8). In HIV infection, CXCR4 expression correlates with more profound pathogenicity, rapid progression to acquired immunodeficiency syndrome (AIDS), and greater AIDS-related mortality. Viral binding also has the potential to generate neoepitopes and autoantibodies directed at GPCRs as well as at other receptors (9, 10). Interestingly, several viral proteins, such as those of cytomegalovirus, encode GPCR homologs, *e.g.* to the chemokine receptor CXCR2 (11), which can also result in autoantibody generation. Recently, epigenetic modulation of GPCR expression has come into focus, including DNA methylation and multiple histone post-translational modifications such as histone methylation, acetylation, and crotonylation, as well as the generation of microRNAs (miRNAs) (12). For example, smoking upregulates angiotensin receptor type-1 (AT1R) expression through histone modification in peripheral blood cells (13). Some microRNAs, such as miR-155, miR-146a/b, miR-132/122, and miR-483-3p, modulate renin-angiotensin proteins, mediating cardiovascular remodelling and inflammation (14). In the context of autoimmunity, endogenous and exogenous factors change from the time of tolerance development after birth and the changes are highly individual. As a result, the acquired variability in GPCR expression levels, in conformational changes, or protein-protein interactions result in the generation of neoepitopes, a break in immune tolerance, class switching, and induction of an immune response leading to the generation of GPCR-specific IgG autoantibodies (abs).

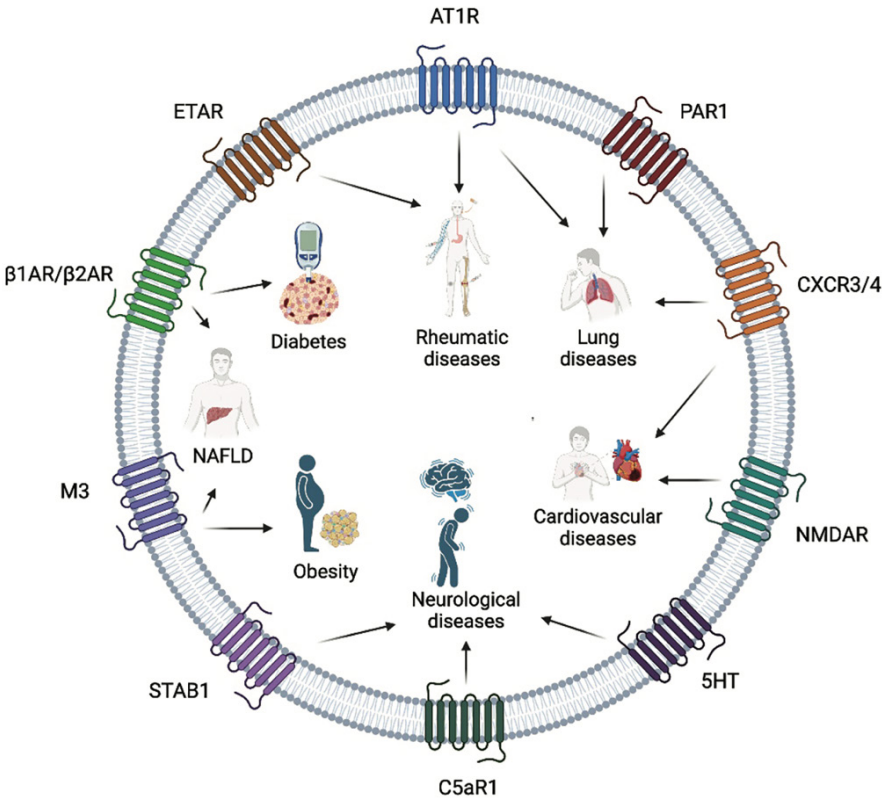


**Fig. 1.** Examples of diseases and clinical conditions associated with changes in the expression of GPCR. Created with BioRender.com.

In summary, based on their high plasticity, GPCRs are ideal targets for the development of autoimmunity, particularly "physiological" autoimmunity. Consequently, autoantibodies directed at GPCRs (GPCR abs) are present in all individuals with an efficient adaptive immune system (1). They reflect GPCR expression and, therefore, the numerous factors affecting GPCR conformation and its signalling (Fig. 2).

In addition, various GPCRs are still considered orphan because their natural or endogenous ligands have yet to be identified. Autoantibodies could provide ideal candidates as ligands and should be considered by researchers and the pharmacological industry (15).

### GPCR abs as biomarkers for multiple diseases

The generation of GPCR abs as markers for GPCR expression and for the numerous environmental factors is supported by studies analysing the contribution of these abs as biomarkers for diseases. Due to the high variability of environmental and external factors affecting GPCR expression and inducing antibody generation, these antibodies may differ across various ethnicities or geographic locations. This presents a challenge for biomarker studies, which often require age- and sex-matched controls from the same ethnic background and environment. Since not all factors influencing GPCR antibody generation are defined under specific conditions, even these controls remain to be a narrative. Despite these limitations, several GPCR antibodies have been identified as biomarkers in various conditions, including autoimmune diseases, infections, cardiovascular diseases, neurodegenerative diseases, and cancer (Fig. 2). Unlike disease-specific autoantibodies, both high and low GPCR ab levels are relevant as biomarkers.

In systemic sclerosis, high levels of autoantibodies directed at the AT1R and endothelin receptor type-A (ETAR) are associated with vascular complications. These autoantibodies predict pulmonary arterial hypertension (PAH) and SSc-related mortality (16). Au-

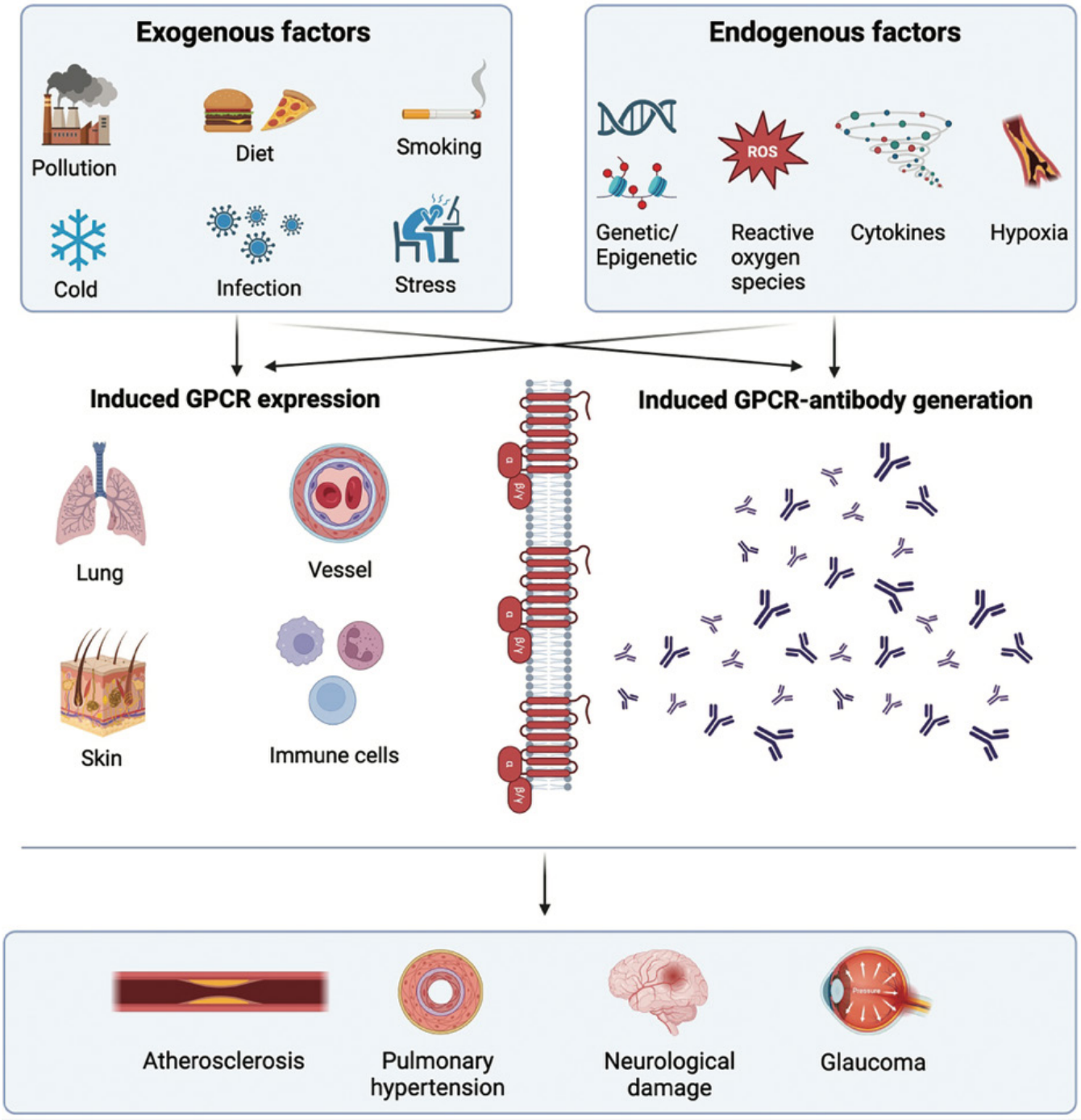


**Fig. 2.** Samples of environmental factors affecting GPCR expression, which is reflected by changes in the autoantibody generation compared to healthy person based on biomarker and experimental studies. Created with BioRender.com.

toantibodies against the chemokine receptors CXCR3 and CXCR4 predict the progression of interstitial lung disease (17). In patients with giant cell vasculitis, low levels of ETAR abs (18) forecast early ischemic events and disease flares. Conversely, low levels of abs directed at the complement receptor C5a are markers of disease activity and relapse in patients with polyangiitis with granulomatosis (19). In patients with coronavirus (COVID-19) infections, high levels of CXCR3 and AT1R abs were among the best predictors of admission to the intensive care unit (ICU), the need for ventilation, and mortality (20). Those directed at the thrombin receptor 1 (PAR-1) have been shown to be associated with both worse outcomes and thromboembolic events. They correlate with D-dimer levels (21). Abs directed at the β1 adrenergic receptor (β1AR) were associated with myocardial infarction and ST elevation (STEMI) in patients with acute coronary syndrome. In these patients, particularly those under 60 years of age, low β1AR autoantibodies identify individuals at high risk for re-infarction (22). In a population-based

study involving around 5000 people, CXCR3 abs predicted all-cause mortality and cardiovascular events (23). In Alzheimer's disease, dopaminergic and serotonergic abs were found to be associated with mortality, while those directed at cholinergic receptors were linked to mood symptoms (24). In patients with primary epithelial ovarian cancer, PAR1 ab levels were lower compared to healthy donors and negatively correlated with histological grading (25). As recently shown, ambrisentan, an ETAR-selective antagonist, inhibits cancer cell migration, invasion, and metastasis in a preclinical murine model of metastatic breast cancer (26). Notably, cancer cells also express GPCRs such as ETAR (26). Although the latter experiments did not study autoantibodies, these studies suggest the potential for naturally occurring abs to modulate cancer development and metastasis.

To summarise all biomarker studies across diseases (Fig. 2), GPCR abs may reflect tissue damage or continuous immune responses across diseases. They indicate specific pathways associated with the presence of distinct GPCR antibodies. Thus, autoantibodies directed at AT1R have been found in patients with vascular and tissue remodelling (27), those directed at the chemokine receptor CXCR3 in chronic inflammation and atherosclerosis, and abs directed at the thrombin receptor PAR1 in the activation of the coagulation system.

## GPCR abs determine and orchestrate effective immune responses to harm

Functionally, GPCR abs interact with their respective receptors. They have the potential to directly activate, block, or inhibit receptor functions, as demonstrated in Graves' disease with thyrotropin receptor antibodies, which makes these abs increasingly attractive candidates for pharmacological research (28). Additionally, they can modulate the response to natural GPCR ligands (*e.g.* angiotensin II for AT1R or thrombin for the thrombin receptor PAR-1). Thus, like GPCRs and their ligands, GPCR abs have the potential to regulate crucial physiological and pathophysiological processes.

Indeed, several GPCR abs wield significant systemic influence, directly stimulating their target receptors while also amplifying ligand-GPCR activation, as observed with AT1R and PAR-1 abs (29-33). For example, in the regulation of tissue-resident cells, AT1R abs sensitise vascular AT1R receptors in small resistance vessels of the lung and kidneys to angiotensin II, the natural ligand, increasing vasoconstriction. GPCR abs also have other specific features (30-34): In contrast to natural ligands, GPCR abs are highly variable in their function (28). For instance, AT1R abs from systemic sclerosis (SSc) patients induce the expression of the profibrotic chemokine CCL18 in monocytes, a response not triggered by angiotensin II or by AT1R abs from healthy donors (28, 30). In monocytes stimulated with AT1R abs derived from SSc patients, angiotensin II acts as an inhibitor of AT1R ab-induced CCL18 expression (30). These functional differences between AT1R abs from healthy donors and patients underscore that GPCR abs reflect receptor expression in their respective patients.

GPCR abs act systemically, unlike natural ligands, which are often locally expressed in specific tissues. Due to the high expression of GPCRs in immune cells (30, 35), GPCR abs function as specific micro-environmental modifiers, playing a crucial role in regulating immune cell homeostasis and tissue-specific inflammatory processes (1). They directly activate immune cells to produce cytokines and chemokines (30, 35), stimulate tissue-specific endothelial cells to produce adhesion molecules, and prompt tissue-specific stromal cells to produce proteins such as cytokines (26). Collectively, these processes drive the targeted migration of specific GPCR-positive immune cells or other cells into tissues expressing the respective receptors. For instance, AT1R abs induce the accumulation of lymphocytes in the skin and lungs, both of which express AT1R (36), while CXCR3 abs promote the migration of immune cells into the aorta and its branches (23), a key factor in atherosclerosis development. Thus, GPCR abs are sophisticated modulators of immune responses and immune cell homeostasis and act as pivotal checkpoints in tissue-specific immune responses.

As ligands, GPCR abs also function as chemoattractants for immune cells expressing their cognate receptors, often at varying levels (37). For example, abs directed at ETAR attract neutrophils (29), while AT1R abs induce the migration of T cells in a concentration-dependent manner (35). These findings suggest that GPCR ab levels play a critical role not only in determining the strength of the immune response but also in shaping its composition. Accordingly, they are a key to understand autoimmune diseases.

## GPCR abs as key in determining host-specific susceptibility to diseases

As shown by several studies, and reflecting individual external and internal environmental challenges, healthy donors (HD) exhibit variable levels of GPCR abs (1, 29). Given the functional role of GPCR abs and particular in the regulation of the immune response, their presence likely confers benefits to the organism.

When infections occur in interface tissues, pathogens such as bacteria or viruses invade cells or tissues, triggering an immune response. Conventionally, it is believed that the body's immune system detects these invaders through pattern recognition receptors (PRRs) on immune cells like macrophages and dendritic cells. Subsequently, these innate immune cells release cytokines and chemokines, which attract other immune cells, including lymphocytes, to the infection site, initiating inflammation and promoting pathogen destruction. This coordinated response helps to contain and eliminate the infection, thereby restoring tissue health. However, recent research, particularly on COVID-19-infected patients, indicates that GPCR abs are crucial modulators of host susceptibility and the response to harm. During COVID-19 infection, AT1R expression increases, shifting the renin-angiotensin system

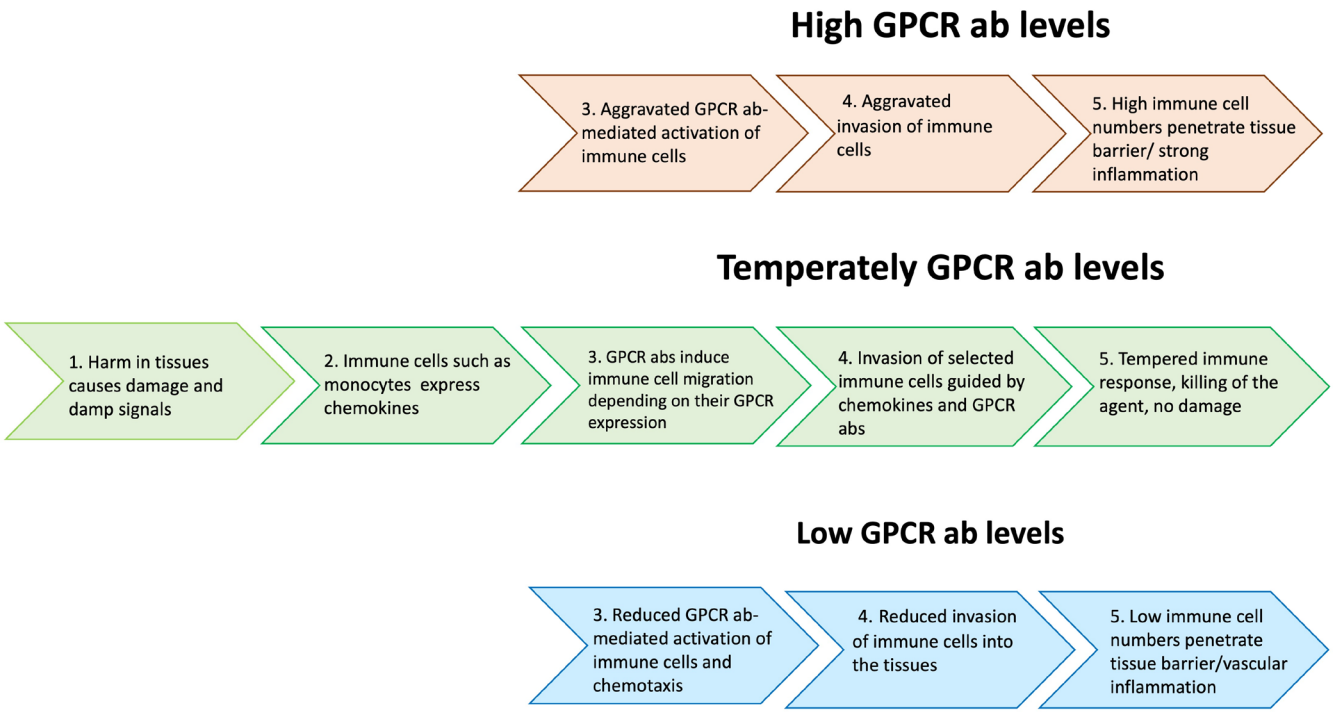


**Fig. 3.** Current concept how GPCR abs and their levels modulate the immune response and host susceptibility to harm.

(RAS) towards vasoconstriction, inflammation, apoptosis, and fibrosis (38). Additionally, upregulation of AT1R could also attract abs as soluble mediators and ligands, stimulating both tissue-resident and immune cells from tissues and peripheral blood to produce chemokines (35, 37).

Accordingly, individuals with high levels of GPCR abs show exacerbated inflammation, supporting biomarker studies, particularly those on CXCR3 and AT1R abs, which indicate heightened tissue inflammation (20). These data suggest that GPCR abs function as acquired micro-environmental mediators, contributing to tissue priming and increasing susceptibility to severe infections. Conversely, the presence of elevated GPCR abs, such as AT1R abs, in healthy individuals might offer an advantage in harmful conditions, such as exposure to multiple bacterial and viral agents or harmful factors (*e.g.* smoking), by providing an adaptive mechanism that strengthens the immune response to lung infections (Fig. 3).

Assuming that GPCR abs reflect individual GPCR expression, this concept may also explain how external environmental conditions prime immune responses. For example, air pollution has been shown to increase AT1R expression in the lung (39). Furthermore, pre-admission exposure to ambient air pollution and blood-soot particles predicts hospitalisation outcomes in COVID-19 patients (40). While AT1R abs have not yet been directly linked to air pollution, elevated AT1R expression could lead to increased AT1R ab production or heightened ab-mediated receptor activation, which is associated with more severe infection.

**Low GPCR ab levels may favour distinct vascular abnormalities**

Indeed, considering the significance of GPCR abs in immune cell homeostasis and immune response regulation, low GPCR antibody levels may prove detrimental**.** Several pathologies are associated with low levels of GPCR abs, particularly those affecting vascular integrity, as discussed previously (18, 19, 22). In these conditions, low GPCR ab levels predicted worse outcomes.

In such cases, insufficient activating GPCR ab levels are unable to adequately stimulate tissue-resident cells and immune cells as needed. Consequently, the response to harm is diminished. On the other hand, the harm-induced DAMP signal may lead to immune cell accumulation, but the immune response remains weak. Low ab levels fail to activate immune cells effectively, preventing them from passing through the vascular barrier and causing them to accumulate in the vessels of the affected tissue. This could result in vascular inflammation and increased cardiovascular risk, as indicated by our biomarker studies (Fig. 3). The link between chronic inflammation and cardiovascular risk is well-established.

This concept may explain the associations between low GPCR ab levels and vasculopathies. Additionally, it highlights the importance of precisely regulating GPCR ab levels to maintain tissue-specific immune cell homeostasis and endothelial barrier function. Supporting this, AT1R deletion specifically from T cells resulted in more severe ureteral obstruction-induced kidney injury in mice, characterised by increased TGF-β1 expression, fibrosis, and inflammation (41). This suggests that AT1R activation directly in T cells protects against kidney inflammation and fibrosis while somehow limiting the proinflammatory impact of local AT1R activation in kidney parenchymal cells that secrete chemokines (41).

High and low GPCR abs as regulators

of the immune response could explain the varying susceptibility to acute or chronic environmental challenges. Although not specifically studied, we did not observe any seasonality in the antibody levels. In contrast, GPCR antibody levels are often stable and are not affected by autologous stem cell transplantation, unlike disease-specific autoantibody levels. This indicates their generation by long-lived plasma cells in the tissues (42). Interestingly, the development of cancer has also been associated with low GPCR ab levels, fitting the concept of an inadequate immune response against malignant cells (25).

**GPCR abs often form groups of abs and cross-react with other abs**

Disease- and symptom-specific ab correlations between different GPCRs, as well as corresponding functional studies, implicate a contribution of GPCR interactions and the generation of dimers as another crucial event that switches naturally physiological abs into pathogenic abs.

Considering the importance of ab specificity, the significance of ab correlations has been recognised, particularly for their variability in different disease contexts (20, 29). As recently shown for AT1R abs, they reflect cross-reactive abs, cross-activation of different receptors, ab binding to a heterodimer of the respective receptors, and the induction of a specific signalling cascade (32, 34). In this context, ACE/AT1R/AT2R and ACE2/MasR are co-expressed in most tissues, though their relative expression may vary under disease conditions (12). AT1R, AT2R, and MasR are also present in nuclei and mitochondria, highlighting the role of intracellular signalling by the RAS (12, 43).

However, cross-reactive abs need to be considered carefully, as blocking one receptor does not necessarily block others and can even increase the activation of the receptor that remains unblocked. Additionally, cross-reactive abs may influence the immune response by attracting cells that express different receptors.

The detection of ab correlations and cross-reactivities could help identify specific pathways. For instance, cross-reactivity between AT1R and topoisomerase I, a specific SSc autoantigen, has been reported (44). Thus, AT1R abs could serve as a bridge to the formation of disease-specific abs in autoimmune diseases. Given the hypothesis that the generation of neoepitopes or molecular mimicry accounts for the loss of tolerance and GPCR ab generation, it is reasonable to assume that local tissue conditions act as triggers for GPCR expression and subsequent GPCR ab generation.

**GPCR abs, along with IgG fractions from patients, as key to identify disease-specific pathways**

GPCR abs translate disease-specific signalling into reporter cells, tissues, or murine models, as demonstrated by a high number of studies (*e.g.* 27, 29-37). F or example, antibodies from SSc patients with obliterative vasculopathy induce obliterative vasculopathy in mice (31). The transfer of individual pathways by IgG fractions into innate immune cells was first demonstrated by our group (45) and later confirmed by others in tissue-resident cells (46) using IgG fractions from SSc patients. Here, the antibody-induced transcriptome varied depending on the antibodies of their donors and the disease subtype. GPCR abs can be considered "classical" proteins that interact with other proteins, either through charge interactions or by inducing conformational changes. In cells expressing multiple GPCRs, they likely induce the same conformations and GPCR heterodimerisations present in their donors. Consequently, they activate cells in a similar manner, which can be exploited to identify disease-specific pathways and, hopefully, to pinpoint disease-specific targets. Thus, GPCR abs could serve as a measurable indicator of the pathways active in diseased patients. Interestingly, IgG fractions derived from healthy individuals using commercially available intravenous immunoglobulins (IVIGs) induce a high number of cytokines in immune cells, indicating that antibodies contribute to the physiological blood cytokine milieu of healthy donors. The IVIG-induced proteome differs significantly from those of patients' IgG (45). The IVIG-induced cytokine expression is mediated via the Fab fragment, suggesting antibody-receptor binding and activation. Although demonstrated only for a few cytokines, GPCRs are involved in this process (45). The large number of healthy donors required for the production of IVIGs, and their use as therapeutic agents, suggests that a balance of antibodies is necessary to treat autoimmune diseases. Nevertheless, our studies support the use of IVIGs in the treatment and interception of autoimmune diseases. Additionally, antibodies could act as ligands for orphan GPCRs that currently lack identified ligands. We are only beginning to understand the role of natural regulatory antibodies and their significance.

**Conclusions**

Natural autoantibodies against G-protein-coupled receptors are a key reflecting cellular micro-environmental challenge. These antibodies play a central role in determining the immune response and maintaining immune cell homeostasis. GPCR ab levels are tightly controlled and both elevated and diminished levels have been shown to be associated with tissue damage. High or low ab levels could be a risk for the development of autoimmune disorders in asymptomatic carriers. Moreover, GPCR abs have emerged as biomarkers for numerous diseases. Recent research suggests that GPCR abs, acting as acquired micro-environmental mediators, contribute to tissue priming and influence susceptibility to severe infections or other disease conditions. Given that GPCR abs reflect the individual GPCR expression of patients, they can serve as indicators of underlying disease-specific pathways. Looking forward, it is crucial to consider not only ligand-GPCR binding but also ligand-ab-GPCR interactions for the development of more precise therapies, particularly those using antibodies derived from specific disease conditions. The time has come for the pharmaceutical industry to bring GPCR antibodies into sharper focus.

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