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Antibodies against GPCR

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1. ABSTRACT

G-protein-coupled receptors (GPCRs) are the largest family of receptors in humans. GPCRs are seven-transmembrane receptors that are activated by the binding of a ligand to the extracellular domain. In addition to the endogenous ligands, auto-antibodies (aab) can also bind to the GPCRs. They can activate different and specific cellular pathways which contribute to various diseases. In this review, the authors summarize the knowledge about antibodies targeting GPCRs and their effects and relevance in the pathogenesis of various diseases and their use in clinical diagnostics. We highlight the role of different activating anti-GPCR aab in solid organ transplantations, stem cell transplantations, systemic sclerosis, preeclampsia, chronic fatigue syndrome, cardiovascular diseases, Alzheimer's disease, and cancer.

2. INTRODUCTION

G protein coupled receptors compose a family of receptors which are located in cell membranes and in endosome membranes. GPCRs are the biggest protein superfamily with more than 1000 members. Of the approximately 21,000 genes in humans, approximawwtely 1000 are GPCR genes (1). The main structural element of a GPCR is the seven trans-membrane receptor domain which is able to use GTP-binding proteins for signal transduction. The research considering the function and clarifying the structure of GPCRs was awarded by the Nobel Prizes for Medicine in 1971 to E. W. Sutherland, in 1974 to A. G. Gilman and M. Rodell, and in 2012 by the Nobel Prize for Chemistry to B. Kobilka and R. Lefkowitz. Pharmaceuticals created to target GPCR structures made up to more than 30% of all prescribed

drugs in 2017 (2). The most well-known drugs are antihistamines, angiotensin receptor inhibitors, beta receptor blockers, dopamine agonists, neuroleptics, opioids, and triptanes.

Pathophysiologic antibodies against GPCRs were initially described in 1956 in Graves disease. In this context, the antibodies are directed against the TSH (thyroidea stimulating hormone) receptor and stimulate the proliferation of the thyroid gland and the absorption of iodine. In Hashimoto's thyroiditis the antibodies against the TSH receptor lead to the destruction the thyroid gland which is associated with a loss of function (3). The main target of autoimmunity in Hashimoto is thyreoglobuline. Moreover, Hashimoto is a mostly t-cell mediated disease whereas Graves is a mainly B-cell mediated disease (4, 5).

In a groundbreaking work Sterin-Borda et al. described for the first time anti-beta adrenergic aab associated with Chagas disease (6). Wallukat et al. discovered anti-beta-1 adrenergic receptor aab in patients with idiopathic dilated cardiomyopathy (7). These findings were confirmed by Magnusson et al in their landmark research work. The authors described anti-beta-1 adrenergic receptor aab in sera samples of dilated cardiomyopathy patients (8). Venter et al. identified anti-beta-2 adrenergic receptor aab in sera samples of allergic asthma patients (9, 10).

In the last couple of years, very intensive research work was performed on antibodies against GPCRs mainly by German research groups. V. Homuth et al. initially described the AT1R-Ab in 1999 (11). Based on this first description, D. Dragun et al. examined the anti-AT1R aab in transplantation medicine (12). Based on Dragun's work, detection of AT1R-Abs is now almost worldwide used in routine diagnosis and has been interpolated into transplantation medicine. Alongside D. Dragun, G. Riemekasten, D. N. Muller, R. Dechend et al. have carried out groundbreaking research in the area of antibodies against the angiotensin receptor and endothelin receptor. Antibodies against the beta adrenergic receptor were examined very intensively by F. Boege, R. Jahns, V. Jahns, M. J. Lohse, G. Wallukat, I. Schimke, R. Hetzer, M. Ungerer, and by H. P. Holthoff et al. C. Scheibenbogen et al. described anti-beta-adrenergic receptor aab and anti-muscarinic cholinergic receptor aab in chronic fatigue syndrome (CFS/ME) for the first time indicating their important role in various diseases. L. Gill et al. and M. Bimmler et al. described for the first time antibodies against GPCRs in the case of Alzheimer's disease.

In the following review the author will give an overview of antibodies against GPCRs and their current relevance in clinical diagnostics of (i) vascular transplant rejection, (ii) cardiovascular diseases, (iii) neurological disorders, (iv) bona-fide autoimmune diseases, and (v) cancer-associated syndromes.

3. GPCR-AUTOANTIBODIES IN TRANSPLANTATION

3.1. Rejection of kidney transplantation

D. Dragun, D. N. Müller, and R. Dechend *et al* described AT1R-Ab as a risk factor for a rejection after kidney transplantations for the first time in 2005 (12). In a translational approach, they identified the role of anti-AT1R aab as drivers for non-HLA-dependent transplant rejections.

N. L. Reinsmoen *et al.* showed for the first time a correlation between anti-AT1R-aab levels and antibody-mediated rejection (AMR) in patients without antibodies against human leukocyte antigen (HLA) or major histocompatibility class I chain-related gene A (MICA) (13). Sera from 63 recipients were determined to have no HLA- donor-specific HLA antibodies (DSA) and no donor-specific MICA antibodies pre-transplant and at the time of acute rejection AR 16 of these recipients were diagnosed with AR including seven with AMR and nine with cellular AR (cell-mediated rejection). High-binding AT1R antibodies were identified in six of seven in the AMR+ group, but in none of nine patients with the cell-mediated rejection (P=0.0009).

Anti-AT1R aab are an independent risk factor for the loss of function of kidneys after a *Transplantation.* P. I. Terasaki *et al*. tested anti-AT1R aab and DSA in pre and post-transplant sera from 351 consecutive kidney recipients (14). 134 patients have biopsy-proven rejection and/or lesions and 217 remain free of rejections (control group patients). The rate with rejection or lesions of anti-AT1R was significantly higher compared to the control group (18% vs. 6%, $p < 0.001$). Moreover, 79% of patients with rejection or lesions with anti-AT1R aab lost their grafts (vs. 0% in the control group). Anti-AT1R aab levels increased post-transplant in 58% of the patients with graft failure. Patients with both anti-AT1R aab and DSA had lower graft survival than those with DSA alone (log-rank $p = 0.007$). Multivariate analysis showed that anti-AT1R aab levels above the cut-off were an independent predictor of graft failure in the abnormal biopsy group (ABG), alone (HR: 6.6.) and in the entire population (HR: 5.4.).

In addition, J.P. Soulillou *et al.* showed that the presence of pre-transplant anti-AT1R aab are an independent risk factor for long-term graft loss in association with a higher risk of early acute rejection (AR) episodes (15). The study included 599 kidney recipients between 1998 and 2007 from Nantes, France. Patients with anti-AT1R aab levels >10 U had a 2.6.-fold higher risk of graft failure from 3 years post-transplantation onwards ($p = 0.0005$) and a 1.9.-fold higher risk of experiencing an AR episode within the first 4 months of transplantation ($p = 0.0393$).

In the following years a higher risk of a rejection after kidney transplantation related to the presence of anti-AT1R aab was confirmed by more groups (16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30). Furthermore anti-AT1R aab are a marker for the deterioration of organ function after transplantation independent of or together with donor-specific antibodies (31, 32, 33, 34, 35, 36, 37). Moreover, recurrence of focal segmental glomerulosclerosis (FSGS) in the kidneys post transplantation is a major problem. The detection of anti-AT1R aab levels before transplantation appears to be a helpful biomarker in identifying patients at high risk of post-transplant FSGS recurrence (34, 38, 39).

Due to the overwhelming evidence NL Reinsmoen, Cedar Sinai Los Angeles, stated in a review (40) the absolute necessity to stratify the immunological risk of patients before kidney transplantation (and probably heart transplantation) by examining HLA as well as non-HLA antibodies. Hence, she voted for the implementation of tests determining anti-AT1R aab in the profile of routine clinical antibody analyses Profile (41). In addition, the XIII Banff meeting, associated with the Canadian Society of Transplantation in Vancouver, reviewed the clinical impact of the relationship of donor-specific antibody tests (anti-HLA and non-HLA) with transplant histopathology for the first time (42). It was highlighted that anti-AT1R aab can produce allograft injury alone or together with anti-HLA DSAs. Because rising healthcare costs dictate judicious use of laboratory testing, the department of Medicine, Johns Hopkins University School of Medicine, Baltimore sought to define characteristics of kidney transplant recipients who may benefit from screening for anti-AT1R aab (39). Philogene MC, Montgomery RA, Leffell MS, Zachary AA *et al.* investigated Kidney recipients transplanted between 2011 and 2016 at Johns Hopkins, for anti-AT1R aab. Pre-transplant antibody levels were compared to clinical and biopsy indications of graft dysfunction. Biopsies were graded using the Banff' 2009-2013 criteria. Patients with focal segmental glomerulosclerosis (FSGS) showed higher titers of anti-AT1R aab at time of transplantation (p=0.04). In addition, recipients who were positive for anti-AT1R aab prior to transplantation had increases in serum creatinine within 3 months post-transplantation (p<0.0001) and developed abnormal biopsies earlier than did anti-AT1R aab negative patients (126 days versus 368 days respectively; p=0.02).

3.2. Heart transplantation

Anti-AT1R aab are strongly associated with antibodies against the endothelin receptor type-A (ETAR) and the ab levels correlate with each other (43). In heart transplant recipients, cardiac allograft vasculopathy (CAV) is a major factor of morbidity and mortality in the long-term graft outcome. R. Hetzer *et al.* discovered an association between elevated levels of anti-AT1R and anti-ETAR aab with early onset of microvasculopathy as well as with antibody mediated rejection (AMR) and with cellular-mediated rejection (CMR) (44). In a study of 30 cardiac transplant recipients, patients with high pre-transplant levels of anti-AT1R and anti-ETAR aab presented CMR, AMR, and microvasculopathy more often than patients without these antibodies at one year post-transplant (p=0.041, p=0.0002, and p=0.048, respectively).

J. Kobashigawa established that the presence of both DSA and non-HLA specific antibodies appeared to increase the risk of heart allograft rejection (45). In 200 heart recipients, freedom from AMR and/or CMR was significantly decreased at two years' post-transplant when both de novo DSA and increased AT1R antibodies levels were identified; the hazard ratio was 7.1 for patients with de novo DSA (P=<0.0002), 2.0 for patients with anti-AT1R aab levels >12 U (P=0.2), and 10.5 when both de novo DSA and AT1R antibody levels >12 were considered (P=<0.0001).

These two studies (44, 45) in heart transplantation indicate that antibodies to the non-HLA antigens AT1R and ETAR have a negative impact on heart allograft outcome. Therefore anti-AT1R and anti-ETAR aab were described in the Banff 2015 Heart Meeting Report (46). In detail, P. Bruneval *et al.* indicate that newly ELISAs allow a reliable detection of anti-AT1R and anti-ETAR aab (CellTrend GmbH, Luckenwalde, Germany). These reagents together with the availability of proficiency testing programs have allowed their implementation in testing for clinical *Transplantation.*

A few weeks ago N. Reinsmoen *et al.* published the development of anti-AT1R aab after mechanical circulatory support device implantation (47). The implantation of mechanical circulatory support devices significantly increases anti-AT1R aab levels. The saturated level of anti-AT1R-aab is associated with lower patient survival post implantation.

3.3. Hand transplantation

Banasik *et al.* investigated the presence of anti-AT1R and anti-ETAR aab in five patients with hand transplantations (48). Both anti-AT1R and anti-ETAR aab were found strongly positive in one patient who repeatedly developed acute rejection episodes. Therefore, further investigations are necessary to confirm a possible association between the rejection and high levels of anti-AT1R and anti-ETAR aab.

3.4. Liver-transplantation

O'Leary *et al.* identified the role of anti-AT1R and anti-ETAR aab and the interaction between HLA

DSA and non-HLA autoantibodies also in liver transplant patients (49). They analyzed 1269 recipients of primary liver transplantation from January of 2000 to April of 2009 with known HLA DSA status for anti-AT1R and anti-ETAR aab pre and one year post liver *Transplantation.* The combination of anti-AT1R or anti-ETAR aab and HLA DSA was associated with an increased mortality risk. Isolated de novo anti-AT1R and anti-ETAR aab were associated with an increased risk of rejection and progression of fibrosis. Ohe *et al.* investigated 81 pediatric patients who stopped immunosuppression (IS) after living-donor liver transplants at Kyoto University Hospital in a cross-sectional study (50). After withdrawal of immunosuppression high incidence of long-term progressive graft fibrosis is a major challenge for these patients. In this study, the authors showed that all patients with a high-level of both HLA DSA and anti-AT1R aab were found to have advanced fibrosis ($p<0.001$).

3.5. Lung transplantation

Reinsmoen *et al.* determined the impact of anti-AT1R and of anti-ETAR aab on graft outcomes in lung transplantation (51). Pre-transplant and post-transplant sera from 162 lung recipients transplanted between 2011 and 2013 at Cedars-Sinai Medical Center, Los Angeles, Thomas E. Starzl Transplantation Institute, University of Pittsburgh Medical Center, Pittsburgh, and University of Texas Health Science Center, San Antonio, were tested for the anti-AT1R and anti-ETAR aab levels using the enzyme-linked immunosorbent assay (CellTrend GmbH). There was a negative impact on antibody mediated rejection (AMR)-free survival for those recipients with increased pre-transplant levels of anti-AT1R ($p = 0.014$) and anti-ETAR aab ($p = 0.005$). These findings suggest the importance to stratify the patient's immunologic risk by assessing both the HLA and non-HLA-specific antibodies.

3.6. Stem cell transplantation

Riemekasten *et al.* reported the association between anti-AT1R and anti-ETAR aab and an autoimmune disorder with clinical fibrotic symptoms developed by patients with systemic sclerosis (43). The chronic graft-versus-host disease (cGVHD) after hematopoietic stem cell transplantation may have similar clinical fibrotic features and its pathogenesis could be similar to systemic sclerosis. In addition, Riemenkasten *et al* described the presence of anti-CXCR3 and anti-CXCR4 aab in systemic sclerosis associated with fibrosis (52, 110).

Based on these findings, Chiron *et al* investigated the association of anti-AT1R aab and cGVHD in patients after stem cell transplantation (53). Sera from 87 patients including 45 hematopoietic stem cell transplantation patients with extensive cGVHD and 42 without cGVHD were retrospectively analyzed for the presence of anti-AT1R aab using an enzymatic immunoassay (CellTrend GmbH). In the cGVHD group, anti-AT1R aab levels were significantly higher compared to the non-cGvHD group ($p=0.04$, 24.4% vs 7.1%).

By analyzing sera from 205 patients, Taniguchi *et al.* showed that patients with increasing levels of anti-AT1R aab during engraftment had significantly higher chance of developing acute GVHD ($p=0.03$) as those lacking this complication (54).

Luft *et al.* identified antibodies against CXCR3 in acute GVHD (55). The authors measured the anti-CXCR3 aab levels in 98 patients with high grade (grade 3 and 4) acute intestinal GVHD (CellTrend GmbH). The group showed significantly decreased anti-CXCR3 aab concentrations compared to the levels obtained before conditioning ($p<0.001$). In multivariable analyses decreased concentrations of anti-CXCR3 aab at disease onset were strong predictors of survival after acute GVHD. High anti-CXCR3 aab levels were protective in patients with low endothelial activation and stress index (EASIX), an endothelial risk score.

4. GPCR-AUTOANTIBODIES IN CARDIOVASCULAR DISEASE

4.1. Chronic heart failure

Aab targeting a variety of GPCRs are described in chronic heart failure and are comprehensively summarized by Boivin-Jahns *et al.* in this issue of Frontiers in Bioscience (56, 57, 58, 59). Antibodies against adrenergic and muscarinic cholinergic receptors are associated with idiopathic dilated cardiomyopathy, Chagas disease and ischaemic heart disease. Sterin-Borda *et al.* described for the first time antibodies associated with Chagas disease, those targeting beta adrenergic receptors expressed on the heart (6). Wallukat *et al.* discovered antibodies against the beta-1 adrenergic receptor in patients with idiopathic dilated cardiomyopathy (7). The ETICS (Etiology, Titre-Course and Survival) study is investigating the role of beta-1 adrenergic receptors in heart diseases (60). Boege and Jahns are working on a validated, good laboratory practice (GLP)-conform measurement of beta-1 adrenergic receptor antibodies for routine use in clinical laboratories (61, 62, 63, 64). This assay is necessary and should be used as a companion diagnostic, this means as a predictor for the response of a therapy with new developed drugs, neutralizing anti-beta-1 adrenergic antibodies or for immunoadsorption therapy (65, 66, 67, 68). ELISAs using peptide coated microtiter plates are not reliable, the plates should be coated with the whole beta-1 adrenergic receptor. The first results with this new ELISA (CellTrend GmbH) are now available. Lund *et al.* measured beta-1 adrenergic receptor antibodies and antibodies against 24 more new targets in ischemic

(n=155) or non-ischemic (n=36) heart failure patients using a full-receptor sandwich ELISA (69). Anti-beta-1 adrenergic receptor antibodies showed correlations with biomarkers of inflammation and myocardial damage, which further modifies their association with disease severity in heart failure. Düngen *et al.* determined anti-beta-1 adrenergic receptor aab in patients of the Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD) trial (n=569) at baseline and 12 week follow up after titration of bisoprolol vs. carvedilol (70). Healthy volunteers (n=198) served as controls. The authors summarized that this novel ELISA (CellTrend GmbH), utilizing the full beta1-adrenoceptor, offers the possibility to measure anti-beta1-adrenoceptor aab in the clinical routine. In addition, higher levels of anti-beta1-adrenoceptor aab were found in patients with a lower ejection fraction and higher heart rates indicating a role of anti-beta-1 adrenergic receptor aab in heart failure. At follow up investigations, anti-beta-1 adrenergic receptor aab were higher in patients treated with bisoprolol. The interactions between anti-beta-1 adrenergic receptor aab and beta receptor blockers should be investigated in larger studies. The findings from the CIBIS study could be a first indication that anti-beta-1 adrenergic receptor aab have an impact on the clinical efficacy of beta blockers.

4.2. Preeclampsia

In 1999, V. Homuth *et al.* discovered anti-AT1R aab in general (11). Preeclampsia (PE), a syndrome affecting 5% of pregnancies, which is characterized by hypertension and proteinuria, is a leading cause of maternal and fetal morbidity and mortality. The authors investigated 25 patients with preeclampsia and compared them to 10 pregnant women with essential hypertension and 10 normotensive pregnant women. Using a bioassay based on neonatal rat cardiomyoctes, it was found in immunoglobulin stimulating the AT1R from all 25 patients suffering from preeclampsia whereas all controls showed no effect.

These findings were confirmed and substantiated by Dechend *et al.* in independent studies (71) and in basic research work (72, 73). In addition, Szpera-Gozdziewicz *et al.* showed increased levels of anti-AT1R aab in 16 patients with preeclampsia compared to 17 healthy pregnant women (74). Kellems *et al.* showed clinical evidence that anti-AT1R aab are elevated in preeclampsia (75, 76).

Staff *et al.* found that levels of anti-PAR-1 (Thrombin-Receptor, CellTrend GmbH) and anti-PAR-2 (Thrombin-like-Receptor-1, CellTrend GmbH) aab were lower ($p<0.05$) in preeclamptic pregnancies (n=42) compared to normotensive pregnancies (n=46). They have speculated that these antibodies may play a protective role in the development of preeclampsia (77).

4.3. Malignant and pulmonary hypertension

Wallukat *et al.* described anti-alpha adrenergic receptor aab in essential and in malignant hypertension (78, 79). Pulmonary hypertension (PAH) is associated with different diseases. Guo *et al.* described that anti-ETAR aab occurred more frequently in systemic Lupus Erythematosus (SLE) associated PAH than in controls (80). In addition, anti-ETAR aab are identified in systemic sclerosis and correlate with the occurrence of pulmonary hypertension (43, 107).

4.4. Thromboangiitis obliterans (Buerger's disease)

Buerger's disease (thromboangiitis obliterans) is a rare disease of the arteries and veins in the arms and legs (81). Klein-Weigl *et al.* observed the occurence of various anti-GPCR aab in Buerger'disease.

5. GPCR-AUTOANTIBODIES IN NEUROLOGICAL DISORDERS

5.1. Chronic Fatigue Syndrome (CFS/ME)

Chronic Fatigue Syndrome has an estimated prevalence of 0.2–0.3% (82); it is a frequent and severe chronic disease. Scheibenbogen *et al.* determined antibodies against alpha and beta adrenergic receptors, muscarinic cholinergic receptors 1-5, dopamine receptors, serotonin receptors, AT1R, and ETAR by ELISA (CellTrend GmbH) in sera from chronic fatigue syndrome patients (n=268) and healthy controls (n=108). Anti-beta-2 adrenergic receptors, anti-muscarinic cholinergic receptors 3 and anti-muscarinic cholinergic receptors 4 aab were significantly elevated in CFS patients compared to controls (83). In addition, pre and post-treatment samples from 25 patients treated during the KTS-2 rituximab trial were analyzed for aab against GPCR (84, 85). In patients receiving rituximab and responded to therapy, anti-beta-2 adrenergic receptor and anti-muscarinic cholinergic receptor 4 aab significantly decreased. In contrast, the aab levels in non-responders did not reduce. This is the first sign that anti-beta-2 adrenergic receptor and the anti-muscarinic cholinergic receptor 4 aab could be used as a companion diagnostic for rituximab treatment in chronic fatigue syndrome.

In addition, Scheibenbogen *et al.* showed that immunoadsorption (IA) was effective to remove anti-beta-2 adrenergic receptors aab in chronic fatigue syndrome patients and improve their outcome (86). In detail, elevated anti-beta-2 adrenergic receptor aab rapidly decreased during IA in 9 of 10 patients. Furthermore 6 months later anti-beta-2 adrenergic receptors aab were significantly lower compared to pretreatment. A rapid improvement of symptoms was reported by 7 patients during the IA. 3 of these patients

had long lasting and ongoing moderate to marked improvement for 6 - 12 months, 2 patients had short improvement only and 2 patients improved for several months following initial worsening.

Kämpf *et al.* described for the first time an association between anti-muscarinic cholinergic receptors 3 and anti-muscarinic cholinergic receptors 4 aab and cancer related fatigue syndrome (87).

5.2. Alzheimer 's disease

Giil *et al.* investigated aab against 33 targets (CellTrend GmbH) in sera from patients with mild Alzheimer's disease (n=91) and healthy controls (n=102) (88). Aab against the serotonin receptors 5-HT2AR (p=0.004), 5-HT2CR (p=0.0005) and 5-HT7R (p=0.003), Stabilin-1 (p=0.001) and complement receptor C5aR (p=0.004) were increased in patients with Alzheimer's disease. Psychomotor speed was associated with anti-dopamine receptor aab (p<0.001), depression with anti-ETAR aab (p<0.001), and visuospatial function with increased levels of serotonin receptor 5-HT1AR aab (p=0.004). This is the first description that the antibodies against GPCRs are dysregulated also in Alzheimer's disease. Bimmler *et al.* described anti-alpha-1 adrenergic anti-beta-2 adrenergic receptor aab (89, 90).

5.3. Complex regional pain syndrome

Complex regional pain syndrome (CRPS, Morbus Sudeck) is a debilitating disease associated with vasomotor, sudomotor, and sensory disturbances in an affected limb or region of the body (91). The pathophysiological mechanisms of CRPS are not fully understood, and anti-beta-2 adrenergic receptors, anti-alpha-1 adrenergic receptors, and anti-muscarinic cholinergic receptors 2 aab have recently been associated with this condition (92, 93). Due to the suspected auto-immune nature of the disease (in at least a subset of patients), steroids, intravenous immunoglobulin (IVIG), and rituximab have been tried and shown to have variable responses (94, 95, 96). There are a few studies that have reported the efficacy of therapeutic plasma exchange (TPE) on this condition (97, 98). 37 out of 44 (84%) of CRPS patients who underwent TPE (5–7 TPEs over 2–3 weeks) had reported positive response in terms of pain and improvement of other systemic symptoms. The majority required ongoing maintenance TPEs and/or immunosuppressive medications and adjunctive therapies, to maintain symptomatic improvement.

5.4. Orthostatic hypotension and postural tachycardia syndrome

Orthostatic hypotension (OH) is frequently associated with autonomic dysfunction caused by a variety of primary or secondary autonomic disorders (99). OH of varying severity afflicts up to 2% of the adult population (100). Li *et al.* demonstrated in a mechanistic study the association of aab directed toward the anti-beta-2 adrenergic receptors and anti-muscarinic cholinergic receptors 3 aab in patients with demonstrable orthostasis (101). In addition, Yu *et al.* detect anti-beta-1 adrenergic receptors, anti-beta-2 adrenergic receptors, anti-muscarinic cholinergic receptors 2, and anti-muscarinic cholinergic receptors 3 aab in sera samples from OH patients (102).

Postural tachycardia syndrome (POTS) occurs most commonly in young women of child-bearing age, less frequently in males or at older ages (103). Li *et al.* described elevated levels of anti-alpha-1 adrenergic receptors, anti-beta-1 adrenergic receptors, and anti-beta-2 adrenergic receptors aab (104). These findings have been confirmed by us (own unpublished data).

5.5. NMDA encephalitis

Anti-N-methyl-d-aspartate receptor (anti-NMDAR) encephalitis is a disease of the central nervous system (CNS) with prominent neurologic and psychiatric features (105). The disease is associated autoantibodies to NMDAR, a protein involved in memory function and synaptic plasticity. Affected patients develop symptoms ranging from memory deficits, seizures and psychosis, to potentially lethal catatonia, and autonomic instability. The outcome can be much improved by immunosuppressive therapy. However, the clinical phenoptype can be nonspecific and Identification of NMDAR autoantibodies is crucial for diagnosis, timely treatment selection, and monitoring.

6. GPCR-AUTOANTIBODIES IN BONA-FIDE AUTOIMMUNE-DISEASES

6.1. Systemic Sclerosis

Aab targeting GPCRs have been characterized in several rheumatic diseases. In particular, anti-GPCR aab have been deeply investigated in patients with Systemic sclerosis (SSc), which is an autoimmune disease mainly characterized features by the development of autoimmunity, vasculopathy and tissue fibrosis. The renin-angiotensin and endothelin systems have been implicated in vasculopathy and fibrosis. Riemenkasten *et al.* identified the association of anti-AT1R and anti-ETAR aab with clinical symptoms of SSc (43). They investigated serum samples from SSc patients from three independent cohorts (n=478) and compared them with healthy controls (n=372) and control diseases (n=311). Antibodies against

AT1R and ETAR were elevated in patients suffering from SSc. Higher levels of anti-AT1R and anti-ETAR aab were associated with different severe disease manifestations and predicted SSc-related mortality. Anti-AT1R and anti-ETAR aab contribute to disease pathogenesis and therefore they should be used as biomarkers for the risk assessment of disease progression.

Avouac *et al.* showed that in patients with SSc (n=90) anti-ETAR aab are strong predictors for digital ulcers in a five year follow-up (106).

In addition, Becker *et al.* investigated patients with SSc related pulmonary arterial hypertension (PAH, n=81) and connective tissue disease-associated PAH (n=110) compared with other forms of pulmonary hypertension (n=106), (107). The predicted outcomes for PAH, associated with SSc, was worse than for the other forms of PAH. Anti-AT1R and anti-ETAR aab are more frequent in SSc related PAH and in connective tissue disease related PAH compared to other forms of pulmonary hypertension. Anti-AT1R and anti-ETAR aab serve as predictors and prognostic biomarkers in SSc related PAH.

Kill postulates that Angiotensin and endothelin-receptor activation via anti-AT1R and anti-ETARaab mediate pathogenic effects, indicating their contribution to pathogenesis of SSc (108, 109).

Weigold *et al.* investigated the role of anti-CXCR3 and CXCR4 aab in systemic sclerosis (110). Chemokine receptors CXCR3 and CXCR4 are involved in fibrosis, a key feature of systemic sclerosis. Anti-CXCR3 and anti-CXCR4 aab were measured in 327 SSc patients and in 234 sera from healthy donors by ELISA (CellTrend GmbH). Patients with SSc-related interstitial lung disease (SSc-ILD) exhibited higher anti-CXCR3 and CXCR4 aab titers, which negatively correlated with lung function parameters. However, patients with deterioration of lung function showed lower anti-CXCR3/4 ab levels compared to those with stable disease.

6.2. Sjögren's syndrome

Sjögren's syndrome (SjS) is a systemic autoimmune disorder characterized by lymphocytic infiltration in the salivary and lacrimal glands, resulting in severe dry mouth or eyes (111). There is strong evidence of anti-muscarinic cholinergic receptors 3 aab to have pathogenetic relevance in SjS and current belief holds that these aab should be used as a biomarker for SjS (112, 113, 114, 115). To evaluate the diagnostic value of anti-muscarinic cholinergic receptors 3 aab in SjS a meta-analysis was performed (116). Eleven studies were included. The anti-muscarinic cholinergic receptors 3 aab had high specificity but relatively low sensitivity for the diagnosis of SjS, which may be due to the fact that it occurs only in a subgroup of these patients.

7. GPCR-AUTOANTIBODIES IN CANCER

Catar *et al.* described for the first time a decrease of naturally occurring antibodies against PAR1 (Thrombin receptor) in patients with metastatic cancer after kidney transplantation compared to patients with kidney transplantation without cancer (117).

Furthermore, Kreienbring *et al* showes in this issue of Frontiers in Bioscience that anti-PAR-1 aab correlated significantly with histological grading ($p=0.007$) and was significantly lower in the patient's group compared to healthy controls ($p<0.001$) (118).

8. CONCLUSIONS

Antibodies against GPCR are present in autoimmune and non-autoimmune diseases. Both elevated as well as decreased anti-GPCR ab are present in diseases (119). There are a growing number of antibodies against different GPCR. Current researches indicate the role of anti-GPCR aab patterns as markers of diseases. The role of anti-GPCR aab in disease pathogenesis is an emerging field in different diseases. In addition, studies determining quantity and quality biological spectrum of aab targeting GPCRs in healthy subjects according to sex, age and geographic areas will bring valuable parameters for future investigations.

A major challenge in the field of anti-GPCR aab is the determination of the aab with reliable assays. There are two methods in general, functional assays (so called bioassays) and IgG-binding assays using a variety of antigenic target molecules (ELISAs or similar methods). Many ELISAs employ peptid homologues of the presumed target epitope as capture antigen. Current belief holds that these may not be useful in many cases (63). ELISAs using the full GPCR protein are reliable and have high-through-put ability. A few of these (e.g. anti-AT1R-Ab and anti-ETAR-Ab, CellTrend GmbH) are registered as *in vitro* diagnostics (IvD). Table 1 gives an overview of, which type of assay has been used in the characterisation of GPCR-aab in the various diseases discussed here.

Anti-GPCR aab are another ligand of the receptor with specific effects on the receptor. They are a target for the development of a new class of drugs as well as for new diagnostic tools for the personalized medicine.

Table 1. Methods used for determining GPCR-autoantibodies in human diseases

Disease	Method	Target	Approval[1]
Kidney Transplantation			
	GPCR-membran-ELISA	AT1R	IvD
	GPCR-membran-ELISA	ETAR	IvD
Heart Transplantation			
	GPCR-membran-ELISA	AT1R	IvD
	GPCR-membran-ELISA	ETAR	IvD
Hand Transplantation			
	GPCR-membran-ELISA	AT1R	IvD
	GPCR-membran-ELISA	ETAR	IvD
Liver Transplantation			
	GPCR-membran-ELISA	AT1R	IvD
	GPCR-membran-ELISA	ETAR	IvD
Lung Transplantation			
	GPCR-membran-ELISA	AT1R	IvD
	GPCR-membran-ELISA	ETAR	IvD
Stem Cell Transplantation			
	Protein-ELISA	CXCR3	RUO
Dilated Cardiomyopathy			
	Bioassay	β1-adrenergic receptor	RUO
	GPCR-membran-ELISA	β1-adrenergic receptor	IvD
	FACS	β1-adrenergic receptor	RUO
Chagas Disease			
	Bioassay	β1-adrenergic receptor	RUO
	Bioassay	β2-adrenergic receptor	RUO
Ischaemic Heart Disease			
	FACS	β1-adrenergic receptor	RUO
	Bioassay	β1-adrenergic receptor	RUO
	GPCR-membran-ELISA	β1-adrenergic receptor	IvD
Preeclampsia			
	Bioassay	AT1R	RUO
	GPCR-membran-ELISA	AT1R	IvD
	Peptid-ELISA	AT1R	RUO
	Protein-ELISA	PAR1	RUO
Essential Hypertension			
	Bioassay	α-adrenergic receptor	RUO
Malignant Hypertension			
	Bioassay	α-adrenergic receptor	RUO
Pulmonary Hypertension			
	GPCR-membran-ELISA	ETAR	IvD
	Peptid-ELISA	ETAR	RUO
Chronic Fatigue Syndrome			

	GPCR-membran-ELISA	β2-adrenergic receptor	IvD
	GPCR-membran-ELISA	muscarinic cholinergic receptors-3	IvD
	GPCR-membran-ELISA	muscarinic cholinergic receptors-4	IvD
Cancer Related Fatigue			
	GPCR-membran-ELISA	muscarinic cholinergic receptors-3	IvD
	GPCR-membran-ELISA	muscarinic cholinergic receptors-4	IvD
Alzheimer's Disease			
	GPCR-membran-ELISA	Serotonin Receptor 5-HT1AR	RUO
	GPCR-membran-ELISA	Serotonin Receptor 5-HT2AR	RUO
	GPCR-membran-ELISA	Serotonin Receptor 5-HT2CR	RUO
	GPCR-membran-ELISA	Serotonin Receptor 5-HT7R	RUO
	GPCR-membran-ELISA	Dopamine Receptor	RUO
	GPCR-membran-ELISA	ETAR	IvD
	GPCR-membran-ELISA	Complement Receptor 5a	RUO
	Protein-ELISA	Stabilin-1	RUO
	Bioassay	α1-adrenergic receptor	RUO
	Bioassay	β2-adrenergic receptor	RUO
Complex Regional Pain Syndrome			
	Peptid-ELISA	α1-adrenergic receptor	RUO
	Peptid-ELISA	β2-adrenergic receptor	RUO
	Peptid-ELISA	muscarinic cholinergic receptors-2	RUO
Orthostatic Hypotension			
	Peptid-ELISA	β1-adrenergic receptor	RUO
	Peptid-ELISA	β2-adrenergic receptor	RUO
	Peptid-ELISA	muscarinic cholinergic receptors-2	RUO
	Peptid-ELISA	muscarinic cholinergic receptors-3	RUO
Postural Tachycardia Syndrome			
	Peptid-ELISA	α1-adrenergic receptor	RUO
	Peptid-ELISA	β1-adrenergic receptor	RUO
	Peptid-ELISA	β2-adrenergic receptor	RUO
Systemic Sclerosis			
	GPCR-membran-ELISA	AT1R	IvD
	GPCR-membran-ELISA	ETAR	IvD
	Protein-ELISA	CXCR3	RUO
	Protein-ELISA	CXCR4	RUO
Sjögren's Syndrome			
	Peptid-ELISA	muscarinic cholinergic receptors-3	RUO
	GPCR-membran-ELISA	muscarinic cholinergic receptors-3	IvD
Cancer			
	Protein-ELISA	PAR1	RUO

[1]IvD = *In vitro* Diagnostic. RUO = Research use only.

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