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GPCR-autoantibodies in chronic heart failure

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1. ABSTRACT

Chronic heart failure (CHF) is a syndrome characterized by shortness of breath, fluid retention, and a progressive reduction in cardiac function. More than 60% of the cases are ischemic in origin (i.e., due to myocardial infarction) and about 30% are caused by non-ischemic myocardial damage (i.e., due to genetic or non-genetic causes like myocardial inflammation). Because of alterations in both cellular and humoral immunity patients with non-ischemic CHF often develop abnormal or misled immune responses, including cross-reacting antibodies and/or autoantibodies to various cardiac antigens. Non-ischemic myocardial damage was found to progress to CHF particularly, when associated (a) with the generation of autoantibodies directed against distinct myocyte membrane proteins critically involved in cardiac function – like G-protein coupled membrane receptors (GPCRs), or (b) with virus persistence in the myocardium. This article will review current knowledge on the pathophysiological relevance of GPCR-autoreactivity in CHF by giving an overview on the so far available evidence from pre-clinical, clinical and epidemiological studies on the CHF-inducing potential of GPCR-autoantibodies and thereon based novel therapeutic approaches in GPCR autoantibody-associated CHF.

2. INTRODUCTION

Heart failure is a life-threatening syndrome clinically characterized by shortness of breath, fluid retention, and a progressive decline in cardiac contractility and performance (1). Despite recent advances in pharmaco-therapy, high prevalence, morbidity, and mortality render chronic heart failure (CHF) an important health problem in Western countries, with about 50% of the patients deceasing within four years after primary diagnosis (2). In Germany, cardiovascular disorders are the main cause of hospitalization and death (43,3% of women and 35,7% of men with a prevalence that dramatically increases with age, i.e., in the elderly > 65a (3)). Still, the pathogenesis of various cardiac disorders leading to this final "common path" is not fully understood. About two thirds of cases are ischemic in origin (i.e., due to coronary artery disease and subsequent myocardial infarction); the remainder are due to non-ischemic myocardial damage (1). In about 30% of the latter cases, clear concepts for the genesis and perpetuation of progressive CHF are lacking despite recent efforts to re-classify these "*cardiomyopathies of unknown origin*" into genetic, non-genetic, acquired, and mixed forms (4). Particularly the non-genetic and acquired forms of dilated cardiomyopathy (DCM), which predominantly affect

younger patients, are thought to arise from an initial (mostly viral) infection leading to acute myocarditis which - dependent on the overall reactivity of the immune system - may progress to chronic autoimmune myocarditis together with a gradual decline in cardiac contractility and performance (5, 6). Recent research indicates that progression to CHF occurs particularly, when associated (a) with the generation of autoantibodies directed against distinct myocyte sarcolemmal or membrane proteins which are essential for cardiac function (7, 8), or (b) with virus persistence (active replication) in the myocardium (9). These findings are further strengthened by the fact, that CHF-patients with non-genetic DCM often have alterations in both cellular and humoral immunity (8, 10-12). These alterations facilitate progression of the initial acute inflammatory reaction into a kind of low-grade inflammation (13) triggering the development of abnormal or misled immune responses (7, 9, 13, 14). This might explain, why a substantial number of CHF-patients in the context of their humoral response develop cross-reacting antibodies (15) and/or autoantibodies to various cardiac antigens (5, 16, 17), including mitochondrial proteins (i.e., adenine nucleotide translocator, lipoamide and pyruvate dehydrogenase (18-21)), sarcolemmal proteins (e.g., actin, laminin, myosin, troponin (22-26)), and – most important – myocyte membrane GPCRs (e.g., β_1-, β_2-, β_3-, α_1-adrenergic receptors (27-31), M2-muscarinergic receptors (32), angiotensin II AT1-receptors (33), and the endothelin 1 receptor type A (34)). From these, only some selected (auto-) antibodies appear capable of inducing myocardial tissue injury and subsequent CHF by themselves, however. In addition, the individual genetic predisposition (including the respective human leukocyte antigen (HLA)- and the major histo-compatibility complex (MHC)-phenotype (35)) may also significantly contribute to the susceptibility to self-directed immune reactions as well as the phenotypic expression and severity of CHF (13, 36). The following paragraphs will review current knowledge and recent clinical and experimental evidence focussing on the possible role of GPCR-autoantibodies (GPCR-aabs) in the pathophysiology of CHF including current novel attempts to specifically and therapeutically target those of them, which have been shown to be involved in the development and/or progression of CHF.

3. THE PATHOPYSIOLOGICAL RELEVANCE OF GPCR-AUTOREACTIVITY IN HEART FAILURE

3.1. Formation and potential target-domains of GPCR-autoantibodies

In general, autoantibodies are also observed in the healthy population as “immunologic bystanders” without any relevance for the manifestation of an autoimmune disease. Whereas overall, more than 2.5 % of the population is thought to be affected by autoantibody-associated autoimmune diseases (37), the autoantibody-mediated pathologies may largely differ among different diseases, and - dependent on the targeted epitope(s) - also the functional effects of a particular autoantibody may largely differ, e.g. from an activation to an inhibition of distinct cellular paths or signalling cascades (16). With respect to autoantibodies directed against GPCRs that might involved in the development and/or progression of CHF, the prevalence in the general (healthy) population appears very low (< 5% (30)), whereas in certain cardiac disorders (most notably in non-ischemic CHF due to chronic autoimmune-myocarditis and/or DCM) it may amount up to 30-70%, depending on the detection method employed (see paragraph 3.2.).

In the last two decades, much knowledge has been accumulated regarding the potential pathophysiological and clinical implications of cardiac autoantibodies in CHF; of particular interest for researchers and clinicians have been such autoantibodies that target members of the rather large super-family of GPCRs which are (a) specifically expressed in the heart and/or major adjacent vessels (7, 8, 38), and (b) involved in the regulation of cardiac contractility and function. In this regard the adrenergic beta1-receptor subtype (β_1AR) represents one of the most important regulators of cardiac performance (contraction force as well as beating rate), and in the normal heart clearly dominates the β_2AR, β_3AR, and assumed atypical β_4AR subtypes (myocardial tissue expression 80% β_1AR vs. 20% β_2AR vs. <1% β_3AR/β_4AR (39-42), as well as other known cardiac GCPRs (i.e., α_1-adrenergic receptors, muscarinic M2-receptors, and angiotensin II AT1-receptors ((31, 33, 43)). Upon physical or psychical stress catecholamines are released and predominantly cardiac membrane β_1-ARs transmit the catecholamine-effects directly to the heart. Whereas short-term adrenergic stimulation serves to temporarily improve cardiac performance on demand, chronic activation of the sympathetic nervous system has the opposite effect, and over time leads to progressive deterioration of cardiac structure and function (44).

In chronic heart failure, potentially pathogenic GPCR-aabs were first described in Chagas’ heart disease (45), a slowly evolving inflammatory cardiomyopathy. Interestingly, IgG isolated from the sera of patients suffering from Chagas’ cardiomyopathy and CHF exhibited sympathomimetic activity *in vitro* (46). More than a decade after this landmark observation, it could be shown that – at least in Chagas’ heart disease – homologies between myocyte membrane GPCRs and viral or bacterial proteins might induce the formation of “endogenous” cross-reacting (auto-) antibodies by antigen mimicry (47, 48): Chagas’ disease originates from an infection with the protozoon *Trypanosoma cruzi*; molecular mimicry between the

ribosomal P2β-protein of *T. cruzi* and the N-terminal half of the second extracellular loop (EC_{II}) of the cardiac β_1AR resulted in the generation of cross-reacting (auto-)antibodies in about 30% of the patients with Chagas' cardiomyopathy (49). Because β_1AR-autoantibodies from CHF-patients with DCM preferentially recognize the C-terminal half of the same loop (50), it was speculated that in these patients the autoantibodies might be induced in a similar fashion by molecular mimicry between the β_1AR and a hitherto unidentified viral pathogen (51).

However, to date the central question whether structural damage to the heart muscle is a mandatory pre-requisite for the formation of GPCR-aabs (in the absence of molecular mimicry) is still not answered (16). Under normal conditions our immune system does not attack readily accessible cardiac self-proteins such as myocyte surface proteins. On a susceptible genetic background, however, this self-inhibition of immune effector cells may be hampered after cardiac injury. It is still unclear, whether this auto-reactivity is related to the amount or "dose" of myocardial self-antigens presented to the respective immune-competent cells (i.e., the extent and severity of myocyte damage/inflammation), or to the kind and quality of subsequently activated immunologic paths (5, 6, 16). Moreover, its seems conceivable that only presentation of myocardial self-antigens that were previously hidden to the immune system may induce an autoimmune response, which in the worst case might result in a kind of "perpetuation of immune-mediated myocyte damage" involving either cellular (e.g., T-cell), or humoral (e.g., B-cell) immune responses, or both (52, 53). In this regard the specific epitopes targeted by GPCR-aabs appear of paramount importance: most functional GPCR-aabs so far described target the second extra-cellular loop domain (EC_{II}) of the respective receptors, which in most GPCRs represents the largest of the existent EC-loops which is, however, thought to be shielded from the immune-system in most (conformational) receptor-states (16).

All GPCRs consist of seven transmembrane (TM) α-helices, which are linked together by three extra-cellular (EC_{I-III}) and three intra-cellular loops (IC_{I-III}) and form a kind of hydrophobic "ligand pocket" (54). The amino-acid composition of the (often largest) EC_{II}-loops allows for the formation of a β-hairpin in almost all GPCRs, which dips down partly into the ligand-binding site. As a consequence, the conformation and stability of EC_{II} (and - depending on the respective GPCR - possibly also EC_{I} and/or EC_{III}) may influence basal receptor activity as well as GPCR–ligand interactions to some extent; at least for the β_1AR and the β_2AR it has been shown, that that the correct folding of EC_{II} and/or EC_{I} is essential for the formation of the ligand-binding pocket (54). This might explain why GPCR-aabs that recognize and bind to these loops can (a) interfere with ligand binding, (b) alter receptor conformation and, as a consequence, also (c) affect receptor activity ((8, 16, 55); see also Figure 1).

Potentially antigenic components of cardio-myocyte membrane or sarcolemmal proteins which are normally shielded from the immune-system (see above) may get accessible following myocyte injury. Apoptosis and/or necrosis may result in the liberation and presentation of previously unknown myocardial self-antigens and then induce an autoimmune response (8, 16, 23, 52). To serve as an auto-antigen cardiac membrane GPCRs must be degraded by proteolysis into small oligo-peptides, which then must be able to form a complex with one of the MHCs or HLA class II molecules (47, 52). In case of the human β_1AR, more than two decades ago a comparative analysis of short β_1AR-fragments *versus* peptides known to be immunogenic under a mouse MHC-haplotype has been performed by employing a comprehensive homology scanning algorithm (47, 56). At that time, the only β_1AR-fragment containing B- and T-cell epitopes and, beyond that, protruding from the membrane into the (for autoantibodies readily accessible) extra-cellular space, was in fact the EC_{II}-fragment of the β_1AR. Several years later this finding could be confirmed by *in vitro* B- and T-cell experiments (57).

Taken together, β_1AR-directed autoimmunity might serve as a "general model" to derive the immunologic frame-conditions and activated paths that might result in the formation of autoantibodies also in case of other cardiac GPCRs, and – dependent on the respective target-epitope(s) – perhaps even to derive the potential (allosteric) functional effects of other GPCR-directed autoantibodies which might be stimulatory, inhibitory, or neutral (16, 17, 58). In this context it is important to note, that the EC_{II}-loop appears to represent a major target-epitope also for functionally active autoantibodies directed against other GPCRs involved in the regulation of the cardiovascular system: Autoantibodies directed against the muscarinergic M2-receptor (detected in patients with CHF due to Chagas' heart disease or DCM) recognize and bind to an EC_{II}-epitope, thereby activate the M2-receptor and lead to a decrease in the cardiac beating rate (32, 59). Autoantibodies directed against the α_1-adrenceptor were found in malignant and in refractory hypertension (31, 60), and together with autoantibodies against the endothelin 1 receptor type A in pulmonary hypertension, suggesting a potential functional relevance mainly through the modulation of the contractile status of major vessels next to the heart (34, 61). Similarly, activating autoantibodies against the AT1-receptor targeting the EC_{II}-epitope mediate their functional effects predominantly by modulating arterial stiffness in patients with (primary or secondary) malignant hypertension and with renovascular diseases (17, 58, 62, 63).

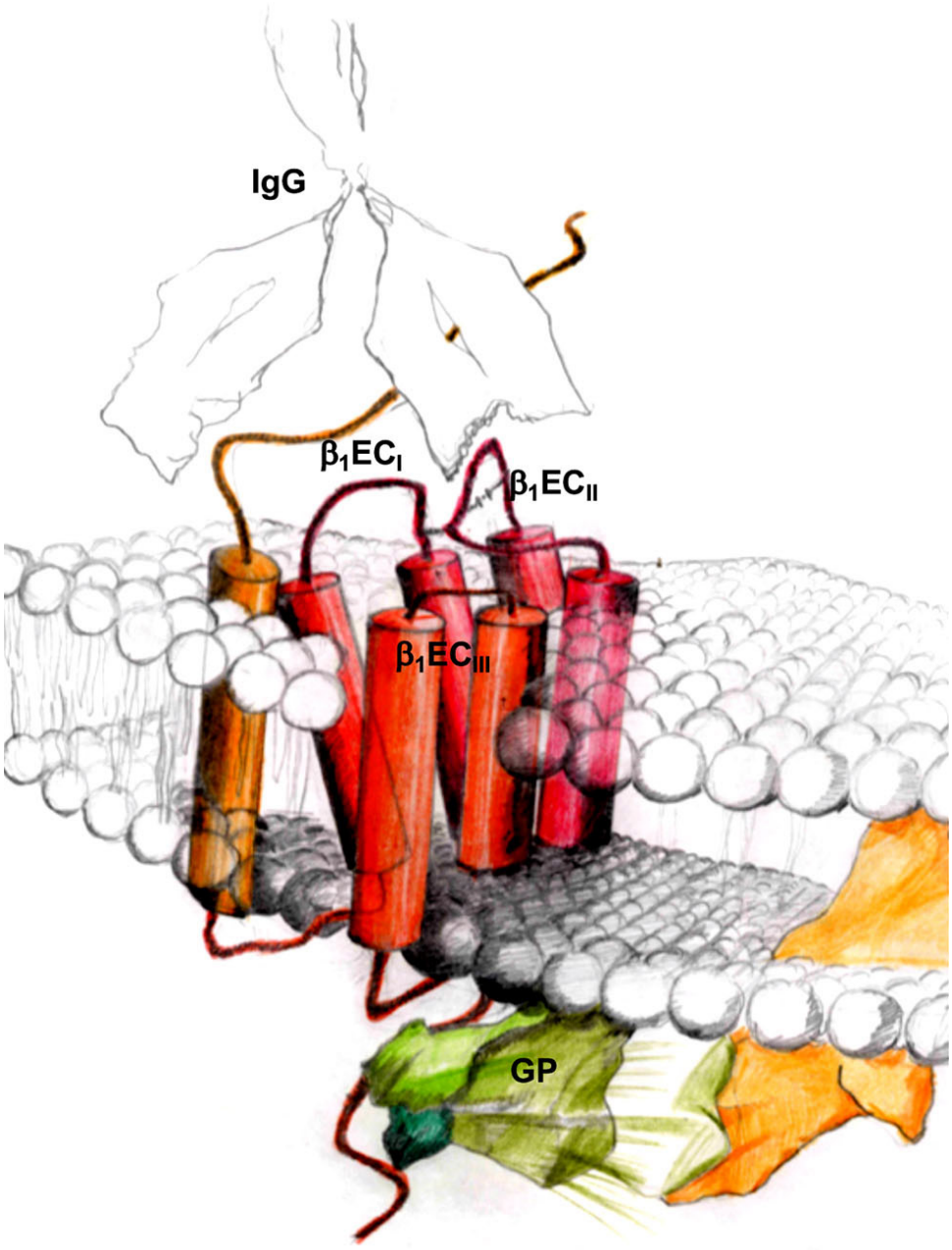

Figure 1. Cartoon showing a GPCR-autoantibody (IgG) targeting the second extracellular loop domain (β_1-EC_{II}) of a β_1-adrenergic receptor situated in a cell membrane (the seven β_1AR transmembrane (TM)-domains are represented by red columns). Three extracellular loops linking the TM-domains II/III, IV/V, and VI/VII are depicted (β_1-$EC_{I/II/III}$). Intra-cellularly, the C-terminal portion of the receptor protein couples to a (hetero-trimeric) G protein (green), *drawing adopted from* (8).

3.2. Epidemiology of GPCR autoantibody-associated heart failure

As mentioned before, low titres of autoantibodies to several housekeeping antigens can also be detected in healthy subjects as a part of the natural immunological repertoire (37, 52). However, in recent years a growing number of “non-natural” GPCR-aabs have been described that might, indeed, have the potential to play an important role in the pathogenesis of CHF, but only a few of them have been studied more in detail (16, 17). The potential pathophysiological and, thus, clinical relevance of autoantibodies directed against GPCRs depends on their potential to induce or worsen CHF which is supposed to be associated on the one hand with (a) the accessibility and on the other with (b) the functional relevance of the targeted GPCR-epitope(s) (8, 16). However, regarding the detection of functionally relevant GPCR-aabs, the use of different screening-techniques renders direct com-

parisons of the different clinical reports rather difficult. Hence, so far reported prevalences must always be read in the context of the respective detection method employed (30, 64-66). In the last decade several research groups have independently demonstrated that second loop GPCR-aabs, in particular those directed against the β_1AR, preferentially recognize intact native GPCRs in various immunological assays (whole cell-ELISA, immuno-precipitation, immuno-fluorescence), indicating that they are "conformational" (8, 16, 17, 67, 68). Functional testing revealed that the same antibodies also affected receptor function, such as intracellular cAMP-production and/or cAMP-dependent protein kinase (PKA) activity, suggesting that they may act as "allosteric regulators" of GPCR-activity (16, 30, 55, 67-70).

Regarding functionally active anti-β_1AR aabs it has been shown that their prevalence is almost negligible in healthy individuals (<1%) provided that a screening procedure based on cell-systems presenting the target in its natural conformation is employed (30, 69, 70). By using the latter screening method, the prevalence of functionally stimulating anti-β_1AR aabs was ~10% in ischemic (ICM) and ~30% in dilated cardiomyopathy (DCM) (30), which was significantly higher than in healthy controls, but in the lower range of previous reports on similar CHF patient collectives (33%-95% prevalence) (27, 28, 50, 64). It seems conceivable that differences in screening methods aiming to detect functionally active GPCR-aabs most likely account for the wide range of prevalences reported in the past (64, 67). In fact, for anti-β_1AR aabs it has been repeatedly shown that only a minor fraction of ELISA-defined human autoantibodies recognized and activated human β_1AR expressed in the membrane of intact eukaryotic cells (30, 65-68, 70, 71). Therefore, cell systems presenting the antigenic target in its natural conformation are essential when screening for functionally relevant GPCR-aabs in CHF (65, 66, 68-70).

However, taking all available clinical data together – even against the latter methodological background – it seems quite clear now that the prevalence of GPCR-aabs in the general (healthy) population is very low (< 5%) (17, 30, 58, 69, 71), whereas in certain cardiac disorders, particularly in non-ischemic CHF due to Chagas' heart disease (> 80% anti-M2 receptor aabs, anti-β_1AR aabs and anti-β_2AR aabs (59)) and in chronic autoimmune myocarditis and/or DCM the prevalence of distinct GPCR-aabs may amount to 80% (~70-80% anti-β_1AR aabs, ~30% anti-M2 aabs (28, 30, 33, 68, 70, 72, 73)). Lower levels of GPCR-aabs have been observed in ischemic CHF (~15% anti-β_1AR and anti-β_2AR aabs (30)), in malignant and refractory hypertension (~40% anti-α_1AR aabs (31, 60, 61)), pulmonary hypertension (anti-α_1AR and anti-ET-1A receptor aabs (34)), and in (primary or secondary) malignant hypertension (anti-AT1 receptor aabs, (33, 58, 62, 63, 74)), as well as in certain reno-vascular diseases (anti-AT1 receptor aabs, (17, 58, 63, 75). By contrast, no GPCR-aabs could be detected in CHF due to valvular heart disease or (general primary) hypertensive heart disease (71).

From an immunological point of view, the two most suspicious and thus most intensively studied GPCR-antigens in CHF are the cardiac β_1AR (representing the predominant adrenoceptor-subtype in the heart) and the muscarinic M2-receptor; autoantibodies directed against both receptors have been detected in patients with non-ischemic CHF (17, 28, 30, 32, 58). Whereas anti-M2 aabs (exhibiting an agonist-like action on the cardiac M2-receptor) have been mainly associated with a decrease in cardiac performance due to negative chronotropic effects at the sinu-atrial level (e.g., sinus node dysfunction, atrial fibrillation (76-79)), agonistic anti-β_1AR aabs have been associated with both the occurrence of severe arrhythmias at the ventricular level (80-82) and the development of (maladaptive) cardiac hypertrophy, followed by cardiac remodelling, dilatation, and finally progressive CHF (30, 83-85). The true prevalence and prognostic impact of functionally active GPCR-aabs in human cardiac disease and CHF remain to be clarified, however, as are the trigger-events leading to their formation, their frequency of *de novo* appearance, and their patterns of clearance and/or persistence in the course of the respective cardiac disease (8, 17, 86).

3.3. Evidence from clinical studies: GPCR-autoantibodies and CHF

In the last three decades, much knowledge has accumulated regarding the pathophysiological and clinical implications of GPCR-aabs in CHF (7, 8, 16, 17, 38, 58). Since the first reports in the late 70s/early 80s on sera or γ-globulin fractions from patients with Chagas' cardiomyopathy (45) or idiopathic cardiomyopathy (27, 72) binding to and having stimulatory effects on GPCRs *in vitro*, it took less than 10 years before larger, clinically well characterized patient collectives suffering from different cardiovascular diseases were systematically analyzed for the presence and potential pathogenic as well as clinical relevance of GPCR-aabs (28, 30, 31, 35, 42, 55, 59, 62, 71, 87). In particular, the presence of anti-β_1AR aabs in CHF patients suffering from DCM has been shown to be clinically associated with a more severely compromised cardiac function (30), the occurrence of more severe ventricular arrhythmias (79, 81), and a higher incidence of sudden cardiac death (81). Thus, stimulating anti-β_1AR aabs appear to accelerate and aggravate both structural remodelling (comprising changes in cardiac tissue architecture, fibre disarray, myocyte-alterations, and fibrosis) and subsequent cardiac dysfunction (16, 84), as well as electric remodelling of the heart (comprising

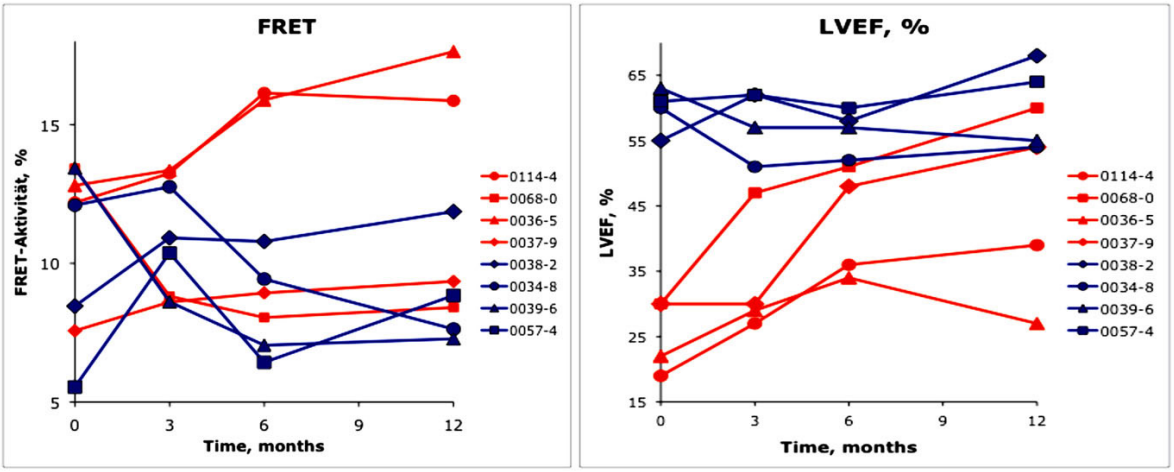

Figure 2. The large majority of cases of non-ischemic CHF are thought to be triggered by acute or sub-acute myocarditis which then progresses to chronic myocarditis and autoimmune DCM, characterized by fibrotic replacement of previous infiltrates, cardiac remodelling, dilatation, and finally chronic heart failure (CHF). Progression of DCM to CHF occurs particularly, when associated with the development of autoantibodies against distinct cardiac membrane GCPRs, in particular the cardiac b_1AR. Left: FRET-activity of human IgG-preparations of sequential blood samples from patients with a first (transmural) myocardial infarction (FAMI, blue lines) or from patients with acute myocarditis (AMitis, red lines) included into the ETiCS-study (time= 0, 3, 6 and 12 months, pseudonyms of study-patients with completed follow-up are given). For better readability only mean-values of 3-5 FRET-measurements are shown (92). Right: Time-course of the corresponding left ventricular ejection fractions (LVEF, in %), as determined by echocardiography (time= 0, 3, 6 and 12 months).

molecular remodelling of gap junctions that affect cell-to-cell propagation of electrical impulses and changes in distinct ion-channels that modify cardiac excitability) facilitating development of malignant arrhythmias (79, 80). Recent data comparing anti-β_1AR aab–positive with aab–negative DCM patients over a follow-up period of more than 10 years not only confirmed a higher prevalence of ventricular arrhythmias in the presence of stimulating anti-β_1AR aabs, but also revealed that aab–positivity predicted an almost three-fold increased cardiovascular mortality-risk (82). These findings were recently confirmed by other clinical follow-up studies in human CHF underscoring the pathogenic (70, 88-90) and prognostic relevance of anti-β_1AR aabs, at least in CHF due to DCM (70, 91).

The still ongoing Etiology, Titre-Course, and effect on Survival (ETiCS) of cardiac autoantibodies study is the largest diagnostic European multicenter study initiated in the field of cardiac autoimmunity. The ETiCS-study will prospectively analyse the time-course and sequentially engaged immunologic processes in autoimmune-mediated CHF (86). Based on the rationale that presentation of cardiac membrane GPCRs and other cardiac components following inflammation and/or necrosis may amongst others induce the formation of stimulating anti-β_1AR aabs, in total 13 European centres (9 in Germany) recruited 200 patients with a first acute myocardial infarction (FAMI), and 120 patients with acute (biopsy/MRI-proven) myocarditis (AMitis) into the ETiCS-study. Inclusion was stopped in December 2016; follow-up of the last study-patients will be completed by the end of 2017. At baseline (inclusion) and after 3, 6, and 12 months patients received thorough clinical evaluation (including sequential echocardiograms and cMRI's at baseline and 12 months). At all visits blood was sampled to follow the *de novo* formation and titer-course of different cardiac autoantibodies including selected GPCR-aabs. Although some study-participants still need to accomplish their final follow-up examinations, preliminary results of the first ETiCS-patients with complete follow-up indicate that acute microbial-induced rather than post-infarction myocardial inflammation triggers the formation of GPCR-aabs, in particular the formation of clinically relevant anti-β_1AR aabs (92). Whereas most of the so far analysed FAMI-patients did not develop significant anti-β_1AR aab-titres over time, in the AMitis-group about half of the patients developed functionally stimulating anti-β_1AR aabs three to six months after cardiac injury (cut-off: ≥ 17% FRET-activity, as a surrogate for aab-induced cellular cAMP production; Figure 2, left). In the latter patients' cardiac function did not recover, whereas left ventricular ejection fraction (LVEF) almost fully recovered in AMitis- and FAMI-patients who did not develop stimulating anti-β_1AR aabs within 12 months of follow-up ((92); see Figure 2, right). Once available, the results of the ETiCS-study will contribute to a number of important diagnostic, pathophysiological and probably also prognostic issues in autoantibody-mediated CHF (38). The role of inflammatory or ischemic cardiac damage as a potential trigger for heart-directed autoimmune reactions will be explored, as will be the relevance of such autoimmune reactions for the initiation and/or progression of CHF (8, 16). In particular, we might learn and better understand

whether the specific target-domain of a heart-directed autoantibody, its titre, its functional activity and/or its kinetics (aab-persistence or clearance over time) relate to the complex process of cardiac wounding, healing (recovery) and/or (pathological) remodelling (86). Thereby, novel prognostic markers for patients with an unfavourable course of autoimmune CHF might be unravelled; as a consequence, conventional treatment could be intensified, and/or novel treatment-strategies exploited earlier in such patients (16).

3.4. Evidence from animal experiments: may GPCR-autoantibodies cause CHF?

To generate an autoimmune response, myocyte membrane proteins (e.g., GPCRs) must be degraded to small oligopeptides able to form a complex with a MHC or HLA class II molecules of the host (37, 47, 53). In case of the human β_1AR computer-based analysis for potential immunogenic fragments revealed that the only portion of the receptor molecule containing B- and T-cell epitopes was, in fact, the second extracellular receptor loop (β_1EC_{II}) (47). This could explain the successful use of β_1EC_{II}-peptides for the generation of β_1-specific receptor antibodies in different animal-models (28, 55, 83, 93).

To investigate the pathogenic potential of anti-β_1AR antibodies, in our laboratory we chose an experimental *in vivo* approach that met the Witebsky' criteria of "direct evidence" for an autoimmune disease: Monthly immunization of Lewis rats with fusion proteins containing the human β_1EC_{II} (100% sequence-identity human/rat) gave rise to functionally stimulating anti-β_1EC_{II} antibodies. Within 8 months anti-β_1EC_{II}–positive rats developed progressive left ventricular dilatation, wall thinning, and downregulation of cardiac β_1AR, a feature typical for human CHF (*indirect evidence*). Subsequent monthly isogenic transfer of anti-β_1EC_{II} (auto-)antibodies from cardiomyopathic rats (intravenously) into healthy littermates within 8 months also transferred the cardiac disease (*direct evidence*) (94). These pioneering key-experie ments were later on confirmed by other groups using linear β_1EC_{II}-peptides as an antigen together with a similar experimental approach in mice (95, 96); these isogenic transfer-experiments equally added value to previous experiments having transferred IgG and/or lymphocytes from human CHF-patients (97) or anti-β_1EC_{II}–positive cardiomyopathic rabbits into immunodeficient SCID-mice (98), in order to circumvent naturally occurring anti-species (!) immune-reactions. However, the 2004 published landmark transfer-experiment in the Lewis rat furnished the long time desired proof-of-principle for a possible pathogenic role of anti-β_1EC_{II} aabs in the development and/or worsening of CHF (93), most likely caused by the mild but sustained agonist-like stimulation of cardiac membrane β_1AR (7). The latter hypothesis is supported by the ample body of data available on the cardio-toxic effects of excessive and/or long term β_1AR-stimulation induced by genetic or pharmacological manipulation (17, 99-101): Transgenic mice with cardiac over-expression of membrane β_1AR showed progressive left ventricular fibrosis starting at the age of four months accompanied by a decrease in both contractility and relaxation, ultimately leading to CHF (89). Isolated cardiomyocytes from these animals displayed markedly altered calcium transients with a significant prolongation of the intracellular calcium transient compared to non-transgenic littermates. Although the expression of sarcoplasmic reticulum proteins like calsequestrin, triadin, and phospholamban (involved in calcium trafficking) was not altered, the authors observed a progressive decrease in junctin abundance in β_1AR transgenic mice (101). In conclusion, anti-β_1AR aab-induced immune-cardiomyopathy (iDCM) and subsequent CHF since the proof-of-concept in the human-analogous Lewis model can be regarded as a proper disease entity, together with other well established receptor-directed autoimmune diseases such as myasthenia gravis and/or Graves' disease (7, 94, 102, 103). However, in clinical routine efficient and specific therapeutic strategies to combat such harmful receptor-autoantibodies in CHF are still lacking (16, 17, 104).

Conceived as a novel therapeutic approach specifically directed against harmful anti-β_1EC_{II} aabs (104), we synthesized β_1EC_{II}-mimicking cyclic peptides (β_1EC_{II}-CP) and intravenously injected 1 mg/kg β_1EC_{II}-CP into immunized Lewis rats (a) either shortly after the induction of stimulating anti-β_1EC_{II} antibodies (*preventive approach*), or (b) in anti-β_1EC_{II} antibody-induced manifest CHF (*therapeutic approach*) (105). In our experimental Lewis model β_1EC_{II}-CP either (a) prevented the development of CHF when administered shortly after the first antigenic boosts, or (b) inhibited the progression of and even partially reversed CHF when administered after 8-9 antigenic boosts (and development of the full cardiomyopathic phenotype); moreover, in anti-β_1EC_{II}–positive cardiomyopathic rats (intravenous) application of the β_1EC_{II}-CP was by far more efficient in recovering LVEF than an (oral) application of the clinically used β_1-receptor blocker bisoprolol alone (105).

3.5. Therapeutic approaches in GPCR autoantibody-associated heart failure

Despite available treatment guidelines, the recent progress in conventional pharmacotherapy (106), and promising novel device-based therapeutic approaches the outcome of patients suffering from CHF remains unsatisfactory (1). This has stimulated the search for causal treatment strategies aiming to block or neutralize factors thought to play a role in CHF progression (17, 85, 104). In a large number of neurologic, rheumatologic, and endocrine disorders

autoimmune phenomena have been recognised as main disease-causing factors. Their relevance in human heart disease and CHF, however, still needs to be substantiated (8, 38) albeit first clinical data clearly suggest that the presence of certain functionally relevant GPCR-aabs worsens the prognosis of patients suffering from CHF (82).

Therapeutic strategies known from other autoimmune disorders, such as application of peptide-ligands (for multiple sclerosis (107)) or immunoadsorption of disease-causing aabs (for myasthenia gravis (108)) might also offer treatment options for certain cardiac disorders including non-ischemic CHF (102). In this regard, recent *in vitro* experiments with functionally active anti-β_1EC_{II} aabs isolated from a smaller number of DCM-patients indicate, that aab-induced activation of cardiac β_1AR might be abrogated by incubation with β_1EC_{II}–mimicking peptides (70). The latter *in vitro* findings and the above described experiments in the human-analogous Lewis rat model together with the first clinical *in vivo* data achieved with epitope-derived autoantibody-scavengers (clinical phase I and IIa trials (109, 110)) and, of course, the expected results from the ETiCS-study (86) should further stimulate research in the field of specifically antibody-directed therapeutic strategies.

Besides conventional standard treatment of CHF patients according to current guidelines (ESC, AHA, ACC) (1) including AT1-receptor blockers, ACEI, beta-blockers, aldosterone-antagonists, and -more recently- neprelysin-inhibitors (111) - all of them considered to positively affect cardiac remodelling, currently some novel promising drugs are at the horizon having the potential to further promote reverse-remodelling in CHF, particularly in GPCR-autoantibody-associated CHF:

3.5.1. Grehlin, a growth-hormone releasing peptide-analog

Grehlin, a growth-hormone releasing peptide-analog, was found to have anabolic effects, but also to prevent cardiac remodelling and fibrosis both in rodent models of DCM (mice and rats) and in a pilot-study with CHF-patients, resulting in an increase in LVEF and exercise capacity. In addition, Grehlin-treatment of DCM-mice resulted in the suppression of sympathetic and a recovery of parasympathetic nerve activity (112, 113), which might be beneficial also in anti-β_1AR aab–positive human DCM-patients.

3.5.2. β1ECII-CP, a cyclic peptide neutralizing anti-β1AR-antibodies

β_1EC_{II}-CP, a cyclic peptide neutralizing anti-β_1AR-antibodies, was found to act through scavenging of cardio-noxious anti-β_1EC_{II}–abs from the circulating blood and to specifically reduce the amount of anti-β_1EC_{II}–antibody-specific early memory B-cells producing such antibodies without affecting overall B-cell count (103). Pre-clinical studies in the rat demonstrated that injection of β_1EC_{II}-CP every 4 weeks for a period of 6-8 months either prevented or efficiently treated anti-β_1EC_{II}–antibody-induced myocardial damage along with an almost complete reversal of the cardiomyopathic phenotype; such reversal was not achieved with the cardio-selective β_1-blocker bisoprolol alone, however (105). A clinical development program was initiated, demonstrating that a slightly modified β_1EC_{II}-CP (termed COR-1) was safe in human volunteers (109). More recently, a double-blind clinical phase II pilot-study enrolling only anti-β_1AR aab–positive CHF-patients has been set up in order to assess the dose-dependent effects of COR-1 (given intravenously every 4 weeks as an add-on to standard CHF-therapy). Cardiac function increased (increase in LVEF > 5%) only in patients receiving 1.0. mg/kg COR-1 along with a non-significant reduction in anti-β_1EC_{II} antibody-titers, suggesting a stoichiometric optimum for anti-β_1EC_{II}–antibody/β_1EC_{II}-CP interactions (110). As a consequence, the concept of cyclic peptides to treat anti-GPCR-directed autoimmune diseases has recently been extended to an experimental treatment of Graves´ disease (114).

3.5.3. Specific or non-specific immunoadsorption (IA)

Specific or non-specific immunoadsorption (IA) represents another experimental GPCR–aab-directed strategy consisting in their removal from the circulation by a kind of dialysis-approach using either matrix-coupled peptides derived from β_1EC_{II} (specific) or protein A columns (non-specific) (102, 104, 115). A meta-analysis showed promising results with excellent survival rates after treatment with specific β_1AR–peptide-coated columns (116, 117). However, this approach is rather invasive, expensive, time-consuming, and (in a slightly modified fashion with IgG-substitution after four IA-courses) is currently being validated in a larger randomized still ongoing clinical trial (Felix S., Staudt A., *et al.:* Multicenter study of immunoadsorption in DCM, Clinical Study www.clinicaltrials.gov NCT00558584).

3.5.4. Aptamer BC007

Aptamer BC007 represents another novel treatment approach attempting to inactivate and/or neutralize anti-β_1AR aabs. Aptamers are a recently introduced new molecule class consisting of (target-specifically) selected short single- or double-stranded RNA or DNA sequences, which bind to and neutralize diverse molecule species, including antibodies (118, 119). By employing Monolex® selection-technology, more recently a single-stranded DNA aptamer could be identified with high affinity for anti-β_1AR aabs. The

neutralizing potential of this aptamer (called *BC007*) was then tested with anti-β_1AR aabs isolated from CHF-patients (DCM, Chagas' cardiomyopathy, and peripartum cardiomyopathy) in a functional bioassay using cultured neonatal rat cardiomyocytes. Aptamer BC007-addition virtually reversed anti-β_1AR aab-induced positive chronotropic responses in a dose-dependent manner whilst (in the given experimental setting) the cardiomyocytes remained fully responsive to standard agonists and antagonists. As a consequence, aptamer BC007 is currently tested in a phase I clinical study (Müller J., Göttel P., *et al.*: A study to investigate the safety, tolerability, pharmacokinetics, and efficacy of BC 007 in healthy subjects, Clinical Study www.clinicaltrials.gov NCT02955420) in order to assess its potential to neutralize human anti-β_1EC_{II} aabs also *in vivo* (120).

4. SUMMARY AND PERSPECTIVE

In conclusion, anti-β_1AR autoantibody-induced immune-cardiomyopathy (iDCM) and subsequent CHF since the landmark isogenic anti-β_1AR-transfer reproducing cardiac dilatation and failure (94) can be regarded as a disease entity for its own, together with other well-established receptor-directed autoimmune diseases such as myasthenia gravis and/or Graves' disease (7, 94, 102, 103). Although some participants of the ETiCS-study still await their final follow-up examinations, preliminary results indicate that in the human acute microbial-induced rather than post-infarction myocardial inflammation triggers the formation of GPCR-aabs, in particular the formation of anti-β_1AR aabs (92). After a first (transmural) myocardial infarction most of the patients do not develop persistent anti-β_1AR aab-titres over time, whereas –apparently– about 50% of the patients with a first episode of acute myocarditis developed functionally stimulating anti-β_1AR aabs. In the latter, cardiac function did not recover, whereas it almost fully recovered in patients, who did not develop stimulating anti-β_1AR aabs within one year of follow-up after the initial myocardial damage.

However, in clinical routine efficient and reproducible (validated) tests to diagnose (65, 66, 68) as well as efficient and specific therapeutic strategies to combat cardio-noxious GPCR-aabs in CHF are still lacking (16, 17, 104); in addition to established anti-adrenergic drugs like cardio-selective beta-blockers and standard CHF-therapy according to current guidelines (1) such strategies might comprise (a) the aforementioned β_1EC_{II}-CP as antibody-scavengers (probably also targeting and thereby suppressing the autoantibody-producing early memory B-cells themselves (121), see above point 3.5.2.), or (b) an elimination of functionally active GPCR-aabs by selective or non-selective immunoadsorption (studies currently under way; see above point 3.5.3. and (122, 123)), or (c) the administration of aptamers like the aptamer BC 007, which is thought to neutralize even different GPCR-aabs and is currently tested in a (first-in man) clinical phase I study (see above point 3.5.4.). At least in animal models of antibody-induced immune-cardiomyopathy and -nephropathy some of these novel therapeutic approaches have already obtained promising results (104, 105, 121, 124). Whilst the aptamer-approach uses i.v.-application of small DNA-fragments interacting with the respective autoantibodies and, thus, appears similarly easy-to-use as we have demonstrated for β_1EC_{II}-CP, the *in vivo* effect of aptamers in patients still needs to be explored. In contrast, a slightly modified β_1EC_{II}-CP, termed COR-1, has successfully accomplished a clinical phase I (110) and a clinical phase II pilot study (111), with no safety concerns, encouraging further assessment of tailored cyclic peptides for the treatment of anti-β_1AR–positive human CHF in larger clinical trials.

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