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An overview of autoantibodies in rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a systemic auto-immune disease principally effecting synovial joints. RA is characterized by immune cell infiltration in the joint. The presence of autoantibodies is a hallmark for the disease, among these are rheumatoid factor and antibodies against post-translational modified proteins like citrullination (ACPA) and carbamylation (anti-CarP antibodies). These autoantibodies may form immune complexes in the joint, leading to the attraction of immune cells. Based on the presence of these autoantibodies, RA patients can be subdivided in autoantibody positive and negative disease. Both subsets can be associated with genetic and environmental risk factors for RA, like the human leukocyte antigen (HLA) allele and smoking. Autoantibodies can already be detected years before disease onset in a subgroup of patients and at symptom onset a broad isotype spectrum is observed. This suggests that various events occur prior to the development of RA in which the first autoantibodies develop in predisposed individuals. Therefore, the presence of these autoantibodies can be useful in predicting future RA patients. Research on the characteristics and effector function of these autoantibodies is ongoing and will give more knowledge in the inflammatory responses underlying RA. This will give insight in the pathogenic role of autoantibodies in RA. Recent data are suggestive of a role for mucosal surfaces in the development of auto-immune responses associated with (the development of) RA. In conclusion, investigating the potential pathogenic effector functions of autoantibody isotypes and their molecular- and physicochemical-compositions might improve understanding of the disease origin and its underlying immunological processes. This may lead to the development of new therapeutic targets and strategies.

1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a common systemic auto-immune disease principally affecting synovial joints. RA is characterized by immune cell infiltration in the joint [1,2]. Around 0.5–1% of the world population is affected [1,3]. The incidence of RA is higher in women than in men and increases in elderly people [1,3]. Although all joints can be affected, preferably the joints of hands, feet and knees are affected by the disease [4,5]. Main symptoms of RA are pain, joint swelling and stiffness and possibly cartilage and bone degradation which can result in loss of joint function [4,5]. Next to the joints, also other organs can be affected, like blood vessels, kidneys, heart, lungs and liver. Likewise, RA can cause fatigue, malaise and weight loss [5].

Several antibody systems have been identified in RA based on the antigens that these antibodies bind too. Among these are rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), which are currently used as biomarkers for diagnostics, and anti-carbamylated protein (anti-CarP) antibodies (Fig. 1C). These autoantibodies can predominantly be detected in serum and synovial fluid (SF) of RA patients [6]. They may form immune complexes in the joints, leading to the attraction of immune cells through e.g. complement activation or direct activation of immune cells leading to the secretion of chemokines and cytokines [7,8] which can augment the immune response and contribute to chronic inflammation and bone destruction.

Since 2010, the 2010 American College for Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis (2010 ACR/EULAR criteria) are used for the classification of RA [2]. This classification system includes scores for joints involvement, acute phase reactants (inflammatory markers like erythrocyte sedimentation rate and C-reactive protein), symptom duration and serology (autoantibodies RF and ACPA).

For RA patients, the sensitivity of RF and ACPAs are similar (sensitivity ACPA IgG ~67% and RF IgM ~69%), however ACPAs are more specific for RA compared to RF (specificity of ACPA IgG ~95% and RF IgM ~85%) when compared to healthy controls (HC) [9]. The presence of autoantibodies is predictive for the development of RA in undifferentiated arthritis patients [10–15] as well as the development of a more severe disease outcome with more joint erosions over time [16–19].

In the next section, the characteristics of the main autoantibody responses in RA and their risk factors will be discussed. Moreover, possible immune effector functions of these autoantibodies will be described.

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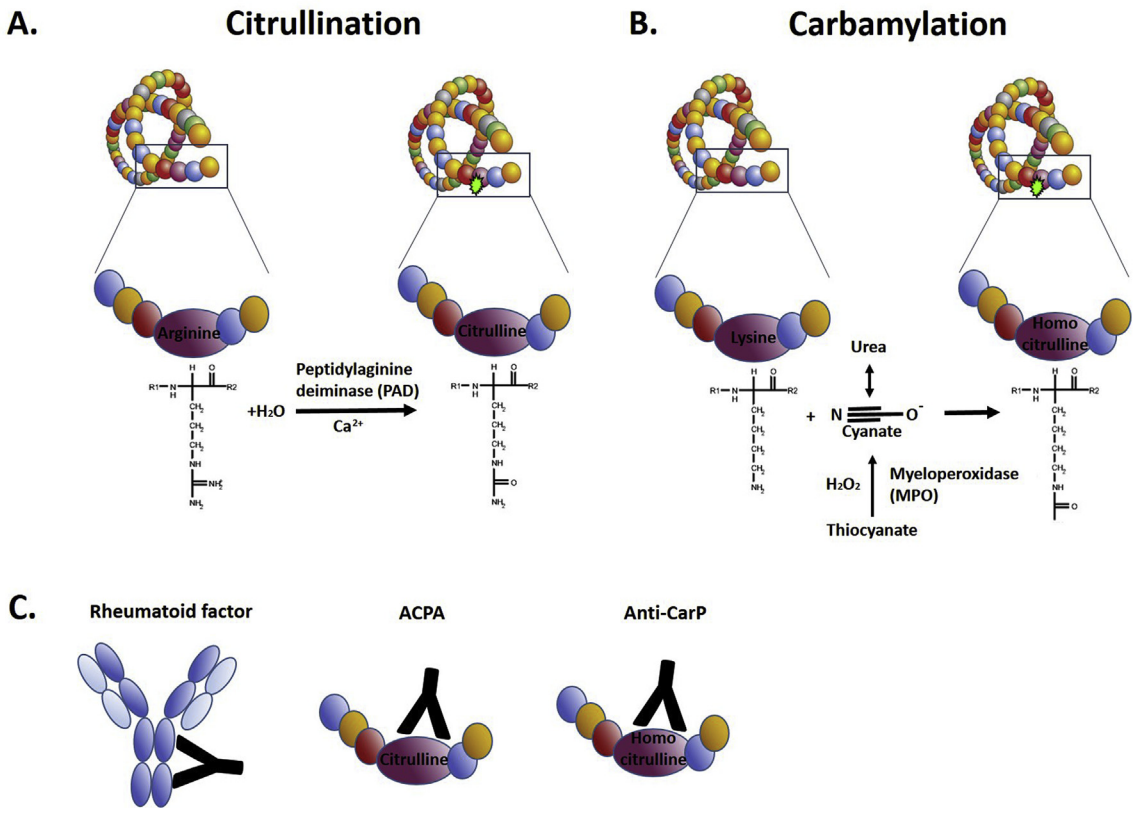


Fig. 1. Post-translational modifications and autoantibodies in rheumatoid arthritis. Citrullination is the conversion of an arginine into a citrulline by an enzymatic reaction with PAD (A). PAD can be released by neutrophils or originate from bacteria. Carbamylation is the conversion of a lysine into homocitrulline by a chemical reaction with cyanate (B). Various conditions can lead to an elevated cyanate level, such as renal disease, inflammation and smoking. Figure adapted from Refs. [86,164]. These PTMs can be recognized by autoantibodies. The best-known antibodies in rheumatoid arthritis are rheumatoid factor, ACPA and anti-CarP antibodies (C). Peptidylarginine deiminase; PAD, Post translational modification; PTM, anti-citrullinated protein antibody; ACPA, anti-carbamylated protein antibody; anti-CarP antibody.

2. Risk factors for rheumatoid arthritis

2.1. Genetic risk factors

Genetic factors contribute for about 60% of the risk for developing RA [20,21]. The most important risk factor for ACPA-positive RA are the human leukocyte antigen (HLA) class II molecule HLA-DRB1-shared epitope (SE) alleles [22]. The risk is 4 times higher in persons carrying a single SE allele and 8 times higher in those carrying two SE alleles compared to SE negative individuals [23]. However, HLA-DR alleles can also be protective in case of HLA-DRB1*13 [24]. Besides the HLA regions, many non-HLA loci are discovered to have a genetic contribution to the development of ACPA-positive RA. The best known in this is protein tyrosine phosphatase N22 (PTPN22) [25–29].

Besides risk factors for ACPA-positive disease, genetic risk factors that contribute to the development of ACPA-negative RA are known as well. In ACPA-negative disease more HLA-DR3 alleles are found compared to controls [30,31]. Interestingly, HLA-DR3 is associated with ACPA-negative anti-CarP-positive RA [32,33].

However, overall it is unknown whether the HLA-gene itself or other genes linked to this locus predispose to the development of the disease. More research is necessary to study the role of the different HLA predispositions to RA pathogenesis.

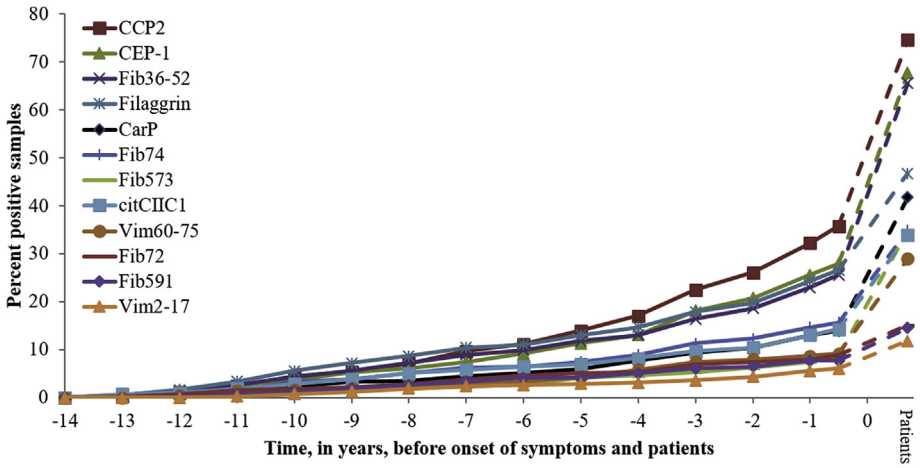
2.2. Environmental risk factors

Besides genetic risk factors, environmental risk factors have a role in increasing the risk for developing RA as well (Fig. 3). The most important and best studied one is smoking, which has a dose dependent association with the susceptibility of developing RA, especially with the combined presence of ACPA and SE [34,35]. For anti-CarP, no association has been found with smoking or the association disappears after correcting for ACPA [32,36]. Moreover, anti-CarP antibody levels are not increased in heavy smokers [37].

Other environmental risk factors are infectious agents, hormones (various roles after menopause or during/after pregnancy, although data are not uniform) and diet, however these are less studied [3,38,39].

2.3. Male versus female

The incidence of RA is higher in female compared to male, with an incidence ratio of about 2:1 to 3:1 [3]. Due to the higher prevalence in female, it is suggested that reproductive and hormonal factors have an influence in the susceptibility, development and perpetuation of the disease (reviewed in Refs. [38–40]. Currently, more and more studies focus on the role of sex hormones, like oestrogens and androgens, though their role in the development of the disease is still far from clear. It has been proposed that oestrogens are more pro-inflammatory and androgens more anti-inflammatory. However, studies find controversial results between female hormones and RA development. Yet, research on this subject only took into account the final phase of RA development. It is still unknown in which stage of the RA development female and male hormones might have an influence and this needs to be studied in more detail in future research.



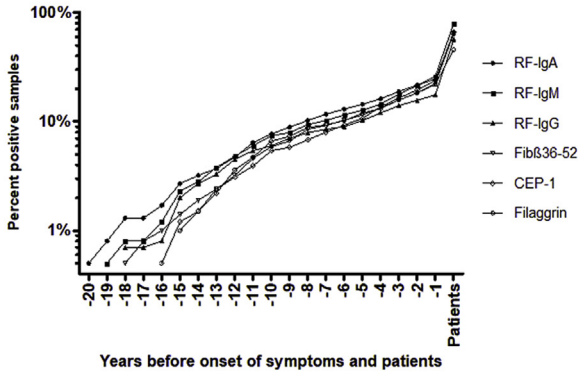


Fig. 2. Presence of autoantibodies in rheumatoid arthritis before symptom onset. Accumulated percentage of positivity of rheumatoid factor isotypes (A, taken from [165]) and anti-CarP antibodies, the different ACPA specificities and anti-CCP2 antibodies (B, taken from [95]). Rheumatoid Factor; RF, fibrinogen; Fibβ, α-enolase; CEP-1, Vimentin; Vim, anti-citrullinated protein antibody; ACPA, anti-carbamylated protein antibody; anti-CarP antibody. Figures republished with author's permission.

2.4. Seronegative rheumatoid arthritis

Autoantibodies are an important hallmark of RA and many data have been generated about the composition of the autoantibody response as well as the etiopathogenetic effects. It has been hypothesized that RA without any autoantibody present is a different disease than RA characterized by presence of autoantibodies. Indeed differences in RA-patients with and without autoantibodies (such as Rheumatoid factor (RF) and anti–citrullinated protein antibodies (ACPA)) have been observed such as a different genetic background [41], different environmental risk factors [42,43], slight differences in the preclinical symptomatic phase and first clinical presentation [44–46], differences in histology [47], differences in the synovial fluid cytokine profile [48] and, when left untreated, more severe joint destruction [44]. When the hypothesis is correct that distinct disease-mechanisms exist, treatment response may also differ. Slight differences in effect of some drugs have been described between autoantibody-positive and autoantibody-negative RA-patients based on trial-data, [49–52]. In summary we feel that all the data together indicate that seronegative disease is a different entity than seropositive disease. Current guidelines for initial therapy still do not promote to treat ACPA-positive and ACPA-negative RA differently. Nonetheless, the outcome of patients with RA, and ACPA-positive RA in particular, has been improved to such an extent that results from the beginning of the century can no longer be replicated in

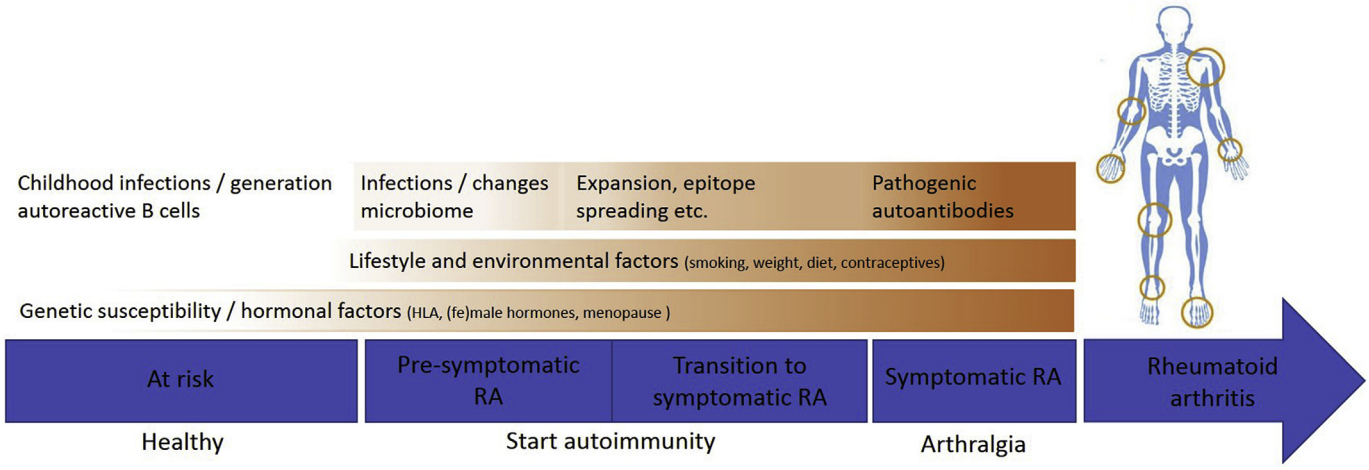


Fig. 3. Overview of the development of RA from health to disease. Rheumatoid Arthritis; RA.

radiographic data collected from patients today. In addition to improvements in disease activity and joint destruction, disease outcomes that are most important to the patients themselves (e.g., pain, fatigue, workability) have improved such that traditional differences between ACPA-positive and ACPA-negative patients have disappeared [53] In other words, with current treatment strategies, the severity of ACPA-positive and ACPA-negative RA has become equal in terms of several outcomes, except that the proportion of patients that achieves drugfree remission seems higher in ACPA-negative RA. Ideally treatment strategies are based on the underlying pathogenesis leading to disease symptoms, most likely the underlying pathogenesis is partly overlapping in seropositive and negative disease which would then lead to identical treatment strategies and partly different which would then lead to different treatment strategies in seropositive and seronegative disease.

3. Autoantibodies in rheumatoid arthritis

3.1. Rheumatoid factor

RFs, antibodies recognizing the Fc-tail of immunoglobulin (Ig)-Gs, were the first type of autoantibodies detected in rheumatoid arthritis and they were used in the 1987 ACR classification criteria for RA. Despite the lack of specificity in the appropriate clinical test situation where there is a high pretest probability for RA, the test can be considered as useful. The antigen binding site of RF, the Fc-part of IgG, has fuelled the hypothesis of infection origin for RA. RF was then supposed to be an anti-idiotypic antibody to e.g. the protein G or protein A (both bacterial proteins) binding site. However, this field of research has not led to new relevant insights in the pathogenesis of RA.

Several studies have indicated that the RF response uses a broad spectrum of isotypes, including IgM, IgG and IgA [10,16,54,55] Fig. 2A). RF IgM and RF IgA are the most studied RFs due to the technical difficulty for detecting RF IgG. Moreover, RF IgA has been shown to be important in the disease feature of RA [15,56,57].

Despite RA, RFs have been identified in non-rheumatoid conditions including leprosy, kala azar, syphilis, pulmonary tuberculosis, chronic liver disease, and sarcoidosis as well as in many rheumatological diseases such as SLE and Sjogren's disease. The frequency of RF in the general (healthy) population is of about 1.3–4% in Caucasians [58,59] to 30% in some groups of some North American Indians [60,61]. The frequency of RF IgM increases in elderly and, surprisingly, RF IgG declines with age [58]. As already stated before, RFs are detectable in non-rheumatic conditions as well. The frequency of RF positive individuals in infectious diseases depend on whether it is a primary or secondary infection and on the duration of the infection. During infections the RF response may be beneficial because it can contribute to the clearance of large immune complexes, as RFs bind pathogens coated with IgG thereby facilitating their removal [62,63]. Moreover, B cells have the capacity to present antigens and stimulate the anti-pathogen response. In case of RF B cells, they will recognize and endocytose IgG coated pathogens. The pathogen will be processed and peptides can be presented to T cells [64].

Yet, it is still conflicting that RFs are able to circulate in blood which is full of their antigen (IgG) without binding to it. Recent published work showed that RFs do not bind to native IgG in solution, but do bind IgG bound to its antigen [65]. Apparently, the native state of IgG seems to be present in a closed form with their Fab arms alongside the Fc tail protecting the RF binding epitopes, thereby controlling RF to bind and probably some other effector functions as well. This discovery will give new insights in understanding antibody structures and functions in health and (auto-immune) diseases.

3.2. Anti-citrullinated protein antibodies

The other well-known autoantibody in RA, also used in diagnostics, are ACPAs. ACPAs recognize the post-translational modification (PTM) citrullination. Citrullination is the conversion of an arginine into a citrulline by an enzymatic reaction with peptidylarginine deiminase (PAD) (Fig. 1A). As described before, smoking is a risk factor for the development of RA especially with combined presence of ACPA. Smoking leads to a higher expression of the PAD2 enzyme, increasing the level of citrullination in the lung [66].

It remains to be seen if a higher load of citrullinated antigens has the effect that tolerance against these antigens is broken earlier. In fact data from three large cohorts from a population-based Japanese cohort (n = 9575) and three early arthritis cohorts from the Netherlands (n = 678), the United Kingdom (n = 761), and Sweden (n = 795) showed no association between smoking and one autoantibody (RF or anti-CCP2). The data showed that smoking was associated with double-autoantibody positivity (OR 2.95, 95% CI 1.32–6.58). In RA patients, there was no association between smoking and the presence of one autoantibody (OR 0.99, 95% CI 0.78–1.26), but smoking was associated with double-autoantibody positivity (OR 1.32, 95% CI 1.04–1.68) and triple-autoantibody positivity (OR 2.05, 95% CI 1.53–2.73). So smoking is associated with the concurrent presence of multiple RA-associated autoantibodies rather than just ACPA. This indicates that smoking is a risk factor for breaking tolerance to multiple autoantigens in RA [67]. Indeed in a Swedish study in which 3645 cases and 5883 matched controls were divided into 4 subgroups based on the presence or absence of RF and anti–cyclic citrullinated peptide 2 (anti-CCP2) antibodies, it was also observed in the RF+/anti-CCP2− patient subset, that there was an increased risk of disease among smokers. So in conclusion smoking seem to induce autoimmunity rather than braking tolerance to citrullinated antigens [68]. However, it still is unclear how tolerance against citrullinated proteins are broken, leading to autoimmunity. The excellent specificity of ACPA for RA and because ACPAs were shown to be predictive for RA development [69], this generated the hope that the research into ACPA could unravel the pathogenesis of RA.

Like RF, also ACPA uses a broad spectrum of isotypes, including IgM, IgG and IgA [10,16,54,55]. ACPAs are present in 50–70% of RA-patients and are known to recognize multiple citrullinated-antigens, such as α-enolase, fibrinogen, filaggrin, vimentin and type II collagen (CII) [70–75] (Fig. 2B). Their recognition profile is generally broad and the serological ACPA-response expands closer to disease-onset (epitope spreading) probably reflecting an escalation in the activation of ACPA-expressing B-cells [76–78].

More recent, autoantibodies recognizing other post-translational modified (PTM)-antigens, anti-carbamylated protein (anti-CarP) antibodies and anti-acetylated protein antibodies (AAPAs), were identified. As citrullination targets arginine residues, and carbamylation/acetylation predominantly lysine residues, the ‘modified’-epitopes are, by definition, unrelated as they occur at different positions within the protein backbone and hence are surrounded by different flanking regions. Likewise, although both modifications of lysine, homocitrullination and acetylation are structurally dissimilar. Consequently, ACPAs, anti-CarP antibodies and AAPAs are often considered as three independent autoantibody classes.

Nonetheless, these autoantibodies often occur concurrently in RA and cross-reactivity between these different AMPA-classes has been reported, both on a polyclonal- and monoclonal-level, within an ELISA setting. These characteristics are in detail discussed in the chapter of dr Scherer, Burmeister and Haupl.

As discussed before, the most important genetic risk factor for RA, the SE, turned out to be a risk factor for ACPA-positive RA [79]. Interestingly the effect of the SE is defined to the maturation of the ACPA response.

Recently it was discovered that ACPAs have a unique physicochemical feature, the extensive glycosylation of the V-domain of ACPA [80]. Interestingly, this extensive V-domain glycosylation is not present on IgM ACPA and is predictive for the development of RA [81,82]. Next

it was reported that the SE alleles associate with ACPA-IgG V-domain glycosylation sites. This suggests that active antigen presentation by the classic risk factors for RA, leads to incorporation of N-linked glycosylation sites, rendering the ACPAs with a unique physicochemical feature of which it is attractive to speculate that this feature is relevant for disease development [83].

3.3. Anti-carbamylated protein antibodies

Besides ACPA, several other autoantibodies recognizing PTM have been identified in RA patients [6]. One of these autoantibodies target carbamylated proteins and these autoantibodies are called anti-CarP antibodies [84]. Carbamylation is the conversion of lysines into homocitrullines by a chemical reaction with cyanate (Fig. 1B) [85,86]. Cyanate is present in fluids of all individuals in equilibrium with urea. In patients with renal diseases, the blood urea levels are increased resulting in an elevated carbamylation level [86–89]. In addition to renal dysfunction, other factors can influence the amount of carbamylation like inflammation, smoking and the inhalation of cyanate. Smoking increases the level of cyanate and the enhanced carbamylation during inflammation depends on myeloperoxidase (MPO), which can convert thiocyanate into cyanate [90,91]. MPO is mainly stored in neutrophils, however during inflammation it can be released, resulting in increased carbamylation during inflammation. Similar to citrullination, carbamylation on itself is not sufficient to break tolerance and induce autoimmunity, as only a small part, ~12%, of renal disease patients harbour anti-CarP antibodies compared to ~44% of the RA patients [37].

The presence of anti-CarP antibodies has been analysed in various cohorts of RA patients [32,36,84,92–99] and other (clinical) conditions (diseases and HC) [37,100–102]. A higher prevalence of anti-CarP antibodies is shown in RA patients compared to controls and other rheumatic diseases [36,84,92,95,97–99,103]. Several observations implicate a role for anti-CarP directed immunity in the pathogenesis of RA as anti-CarP antibodies are present years before disease onset and have a gradual increase just before disease onset [94,95,104]. Moreover, the presence of anti-CarP antibodies is predictive for the progression to RA in arthralgia patients [105] as well as with increased joint destruction overtime, especially in ACPA negative RA patients [84,95–98]. Like ACPA, the anti-CarP antibody response uses a broad spectrum of isotypes and IgG-subclasses, including IgM, IgG_{1-4} and IgA [36]. Moreover, anti-CarP antibodies recognize various carbamylated proteins including self and non-self-proteins [106].

Although citrullination and carbamylation are two rather similar PTMs, yet it seems that they represent two different antibody families in RA as, despite both autoantibodies are often seen together, also ACPA and anti-CarP single positive RA-patients are present [6,32,84].

3.4. Development of autoantibody responses: isotype switching and avidity maturation

During a 'normal' protein derived B cell response, activated B cells will enter the germinal center, where they start to proliferate and undergo, upon receiving T-cell help, somatic hypermutation, isotype switching and avidity maturation, resulting in memory or plasma B cells with improved reactivity towards their antigen. These processes, isotype switching and avidity maturation, are expected to occur side by side and will result in an improved efficacy of the immune response.

A primary immune response (first antigen encounter) results in the secretion of IgM by activated B cells [107]. During subsequent maturation of an immune response isotype switching leads to an increased diversity of the antibody response, including e.g. IgM, IgG and IgA. The different isotypes (IgM, IgG or IgA) and IgG-subclasses (IgG1, IgG2, IgG3 or IgG4) vary in the capacity to trigger immune effector mechanisms. In RA patients, the different autoantibodies can already be detected in sera years before disease onset [14,94,95,104] [10-15] and at baseline several isotypes are detected, including IgM, IgG and IgA [10,16,17,36,103,108]. This indicates that isotype switching already occurs before disease development.

While substantial information is available on the avidity maturation of antibody responses against recall antigens [109–111], less information is available on the avidity maturation of autoantibody responses. However, it has been described that the avidity of IgG and IgA autoantibodies (high, moderate and low) associates with different clinical outcomes in several diseases, like low avidity anti-transglutaminase antibodies are associated with a more severe disease in coeliac patients [112]. Moreover, in RA the avidity of IgG ACPAs and anti-CarP antibodies are low compared to the recall antibodies anti-tetanus toxoid antibodies [113,114]. This indicates that although these B cells underwent isotype switching towards IgG, and apparently attract sufficient signals for survival and proliferation, no or little avidity maturation took place. Strikingly, the anti-CarP IgG avidity is even lower than the avidity of ACPA IgG in serum [114]. When comparing the IgM and IgA avidity of ACPA, RF and anti-CarP antibodies, a lower avidity for anti-CarP and RF IgM and IgA was observed compared to ACPA IgM and IgA [115].

For ACPA, the lowest IgG avidity quartile is associated with more bone damage [113],which could be explained by better complement activation of the low avidity ACPA [113]. However, this pattern is not seen for the anti-CarP avidity. Surprisingly is the absence of anti-CarP avidity maturation before disease onset despite isotype switching [114], whereas for ACPA there is a slight increase in avidity before disease onset [116]. This suggests that the isotype switch and avidity maturation in the anti-CarP (and probably ACPA) B cell response is uncoupled. The mechanism for this is unknown, but probably it is due to a difference in additional stimulation of the B cells; such as the degree of innate or T cell help (reviewed in Ref. [117]) and/or the abundance of its antigen. Probably low avidity antibodies are a marker for chronic antigen overload and chronic antibody responses. Moreover, it could be that anti-CarP antibodies, and probably also ACPAs, cross react with a currently unknown antigen, to which it might have a more "normal" response. Also hypothesized is that autoantibodies develop to a normal temporally protein derived immune response, e.g. after a trauma or infection, however they lead to activation of a chronic response against autoantigens.

3.5. Glycosylation of autoantibodies

All immunoglobulins (IgD, IgM, IgG, IgA and IgE) are glycosylated proteins. IgGs contain a conserved N-linked glycosylation site in the Fc-part [118] which is crucial for maintaining the conformation of the Fc tail and plays a role in immune effector functions like the interaction with Fc-receptors, lectins and activation of complement [119–123]. ACPA IgG_1 Fc glycans are lower in their degree of galactosylation and lack sialic acids. These data might point to an increased pro-inflammatory potential of ACPA IgG_1. Moreover, ACPA IgG_1 Fc glycans are highly fucosylated and these changes are already visible prior to RA onset [124]. However, the functional relevance of this in RA is unknown.

As discussed above, next to Fc-linked N-glycans, IgG molecules in human serum can harbour N-linked glycans in the variable (V)-domain [125] which influences immune functions, yet there role is less defined [126–129]. Recently, our department discovered that ACPAs from RA patients are highly glycosylated in the V-domain, having bi-antennary sialylated glycans and more galactose and fucose residues [80,130]. Moreover, this glycosylation pattern is predictive for the development of RA [82]. Apparently, this extensive V-domain glycosylation is not present on IgM ACPA [81]. This is in contrast to the lower level of galactosylation and sialylation in the Fc part of ACPAs. It remains unclear how this different pattern of ACPA glycosylation exactly arise. Although it is known that before proteins can undergo N-linked glycosylation, they need to express a consensus sequence (N-X-S/T, where $X \neq P$). These consensus glycan sites are typically not germ line encoded

in the Ig V-domain but should be introduced by somatic hypermutation [80]. It has been observed that ACPA-IgGs are highly mutated and able to introduce glycan sites during somatic hypermutation [131]. Because almost all ACPAs have Fab glycosylation, it has been hypothesized that the glycans on the Fab domain are able to give a survival advantage to B-cells producing this Fab glycosylated ACPAs.

The role of V-domain glycans during antigen specific antibody responses remains poorly understood. However, it has been demonstrated that V-domain glycosylation sites emerge close to antigen binding regions [132]. Moreover, the amount of V-domain glycans differs between subclasses of IgG and antigen specificities [132]. This indicates that V-domain glycosylation is not randomly introduced, but rather introduced by antigen associated positive and/or negative selection or is introduced to give a positive selection for a B-cell that produces Fab glycosylated ACPA. Interestingly is the ability of V-domain glycans to modulate (enhancing or reducing) antigen binding and affinity [132]. A recent study also suggested that V-domain glycosylation could be a mechanism to prevent autoimmunity [133]. Although V-domain glycans of ACPAs are not always diminishing the binding to citrullinated peptides [80], it could be hypothesized that ACPAs are a strategy of the immune system to prevent autoreactivity. To confirm this hypothesis, more research will be necessary. In summary it seems that Fab glycosylation of ACPA seem to introduce a selection survival of ACPA producing B-cells who recognize the appropriate antigens.

3.6. Autoantibodies at mucosal sites

Several lines of evidence obtained in recent years indicate a role for mucosal surfaces in the development of auto-immune responses associated with (the development of) RA. Various studies show the presence of RA-associated autoantibodies at several mucosal sites, like the presence of ACPA and RFs in the lung and sputum and ACPA production at the periodontium, intestine and cervical-vaginal sites (reviewed in Ref. [134]). Recently, it is reported that the proportion of IgA plasma blasts is increased in peripheral blood of individuals at risk for developing RA who are already autoantibody positive [135]. This suggest that part of the RA-associated autoantibodies develop from mucosal immune responses and may play a role in early disease pathogenesis. Moreover, dysbiosis has been observed in microbiome studies of the faecal, lung and periodontal microbiota of patients with early or new-onset RA (reviewed in Ref. [134]), also pointing towards a role of the mucosa in the development of RA.

Normally, upon transfer through epithelial cells, antibodies are cleaved of at the luminal site leaving a fragment of the pIgR, known as SC (secretary component) [136]. Although the mechanism is still unclear, SC containing antibodies can be detected in the circulation [137]. Unexpectedly, in serum, the secretory form of the autoantibodies anti-CarP, ACPA and RF were predominantly found in the IgM isotype and not in IgA [115]. Probably, the presence of SC-containing IgM autoantibodies might indicate that autoreactive IgM B cells represent the most prominent B cell subset that can be (re)activated at mucosal surfaces and thereby keeping the immune response ongoing.

Moreover, the group of Scheel-Toelner et al. identified an enrichment of Fc receptor like 4 (FcRL4) positive B cells in the RA synovium. FcRL4 positive B cells are normally a marker for mucosal associated B cells [138–140] and acts as a low affinity IgA receptor [141]. Interestingly, IgA B cells in RA-patients are increased in the FcRL4 positive B cell subset compared to the FcRL4 negative B cells and some ACPA reactivity was only found in the IgA-FcRL4 positive B cell subset [142]. It would be interesting to know whether these FcRL4 positive IgA B cells could be anti-CarP (producing) B cells as well.

Overall, these data suggest a link between the mucosa and RA and the possible mucosal associated origin for autoantibodies in RA. However, more research is necessary to know where the auto-immune response and the production of autoantibodies is started. This is interesting as it will give us more knowledge about the development of antibody responses and the interplay of the mucosal and systemic immune response.

4. Prediction of rheumatoid arthritis development

Clinically symptoms of RA develop around a median age of fifty, roughly half a year before the onset of clinical arthritis. Before reaching the symptomatic phase, people have passed through asymptomatic phases in their “healthy life” (reviewed in Refs. [143,144]) (Fig. 3). The asymptomatic phase includes the subclinical and (early) at risk phases. Each phase has different characteristics. Genetic and environmental risk factors for RA (discussed before) are the primary risk factors and have a role in the earliest onset till clinical RA. During the at-risk phase autoreactive B cells are generated and once they survive, they can expand and mature in the subclinical phage. During this period, which can take a few months to years, autoantibodies can develop and undergo expansion, maturation and epitope spreading (e.g. ACPA, RF and anti-CarP antibodies). It is in this time frame that the prediction for an individual person is possible, as the aspects of autoimmunity and inflammation can be measured.

4.1. Predicting rheumatoid arthritis in ACPA positive individuals

The presence of ACPA (and RF) in the subclinical stage associates with RA risk [12,145–148]. This association was found by studying pre-RA blood donors and previous blood samples from patients that were known to have RA at the time of the study [14,149]. An increase in autoantibodies was found 1–3 years before symptom onset. Further, higher levels of ACPA could even more increase the risk of developing arthritis, however not all studies observed similar associations [12,145,148,150]. In addition to the occurrence of ACPA and ACPA level, other characteristics of ACPA have been studied. The increased amount of ACPA epitope spreading in the pre-clinical phase predicts progression to RA in ACPA positive pre-clinical RA [151–153]. In addition, a decrease in Fc galactosylation and an increase in Fc fucosylation of serum ACPA IgG_1 has been observed prior to the onset of RA [124]. Moreover, the presence of V-domain glycosylation of ACPA IgG has been detected in a subset of predisposed first-degree relatives (FDR) of RA patients and is elevated in FDRs who transitioned to RA [82]. This indicates that this feature substantially increases the risk of RA development.

4.2. Additive value of triple positivity for anti-CarP antibody, ACPA and RF in predicting rheumatoid arthritis

As already discussed earlier, ACPA and RF are used to aid in the diagnosis of RA. Although these antibodies are mainly found in RA patients, their specificity is not optimal. Therefore, it is difficult to predict and diagnose RA patients very early in the disease. A meta-analysis performed by Verheul et al. identified a screening possibility for individuals at risk [154]. An increased Odd Ratio of developing RA was observed for the presence of all three autoantibodies combined (anti-CarP, ACPA and RF) compared to all other combinations [154]. This indicates that the presence of anti-CarP, ACPA and RF together might be helpful in predicting RA development in patients at high risk for RA. However, prospective studies in healthy populations will be important to investigate whether this approach is suitable to detect individuals at risk.

5. Pathogenic potential of autoantibodies

Several features of autoantibody responses in RA, like the autoantibody expansion before disease onset and the association of autoantibodies with joint destruction, suggests that autoantibodies have a role in the disease development and pathogenesis. Moreover, rituximab treatment is effective in RA patients, indicating that B cells, and

probably the antibodies they produce, play a role in the disease pathology. In the next section, several hypotheses regarding the mechanism of autoantibodies to the disease pathophysiology of RA will be discussed.

5.1. Fc receptors

In general, antibodies have an effect on various immune cells via Fc-receptor (FcR) binding. As for recall antigen immune complexes (IC), ICs containing auto-antigen/antibodies (e.g. ACPAs in the presence of RF-IgA or RF-IgM) can induce TNF secretion by macrophages via the FcγR [155–157]. RF-IgM or RF-IgA also enhances the ability of ACPA IC to activate the complements system [157]. More recently it has been shown that IC from RA plasma and SF are able to induce neutrophil activation (Reactive Oxigen Species and release of lactoferrin and LTB4), NETosis and migration [158]. These actions could be, sometimes partially, inhibited using a FcαR blocker, suggesting an important role for IgA autoantibodies in this.

5.2. Complement activation

Another effector function of antibodies is activation of the complement system. There are three pathways to activate the complement system: the classical pathway (by C1q), the alternative pathway (by C3) and the lectin pathway (by mannose-binding lecting). In synovial fluid and blood of RA patients, decreased levels of complement proteins and increased levels of complement activation products are found as well as complement deposition in the joints [8,159]. ACPAs have the ability to activate the complement system via the classical and alternative pathway [8]. Moreover, low avidity ACPAs are better in activating the complement system compared to ACPAs with a higher avidity [113].

6. Conclusion

The field of autoantibodies has brought major insights in rheumatology. It resulted in better understanding of the pathophysiology in RA and the development of the new 2010 ACR/EULAR classification for RA. Although autoantibodies are associated with genetic and environmental risk factors for RA, the origin of the auto-immune response and autoantibody production is currently unknown. This leaves an interesting area for further research, aiming to gain more knowledge about immune responses at various sides and different origins.

Since 1977 Prof Smolen has been active in the autoantibody field in rheumatology [160], both by studying the effects in animal-models as well as by improving the detection of autoantibodies by innovative methods [161]. Interestingly prof Smolen also explored whether removal of autoantibodies was associated with clinical responses [162]. A strategy that was promising and it took the development of the anti-CD20 therapies before more definitive data were generated. The contribution of prof Smolen to the autoantibody field cannot be summarized in a short section of a review article and for the interested readers we refer to a beautiful review published in the Journal of Experimental Medicine [163].

The editor of this issue has asked us to write a personal note as well. What we feel was a beautiful illustration of the intellectual power of prof Smolen was the data-driven way the autoantibody part of the new 2010 ACR/EULAR classification were developed. In a transparent and scientifically sound way both RF and ACPA were integrated in the new criteria, that is for an important part achieved by the dedication of prof Smolen.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2019.102392.

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