Cross-reactivity of anti-modified protein antibodies is also present in predisease and individuals without rheumatoid arthritis


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Cross-reactivity of anti-modified protein antibodies is also present in predisease and individuals without rheumatoid arthritis.

The presence of anti-citrullinated protein antibodies (ACPAs), anti-carbamylation protein antibodies (Anti-CarPAs), and anti-acylated protein antibodies (AAPAs) is a hallmark of rheumatoid arthritis (RA). ACPA and anti-CarPA can play a role in the development of RA before RA develops. Recently, it has become clear that ACPA can display cross-reactivity to other post-translational modifications (PTM), more specifically homocitrullination and carbamylated protein antibodies (anti-CarPAs).

Cross-reactivity of ACPAs can expand years before RA develops. However, it has been shown that the citrullinated epitope recognition profile of ACPA and anti-CarPA is a hallmark of early and active RA. ACPA can display cross-reactivity to other post-translational modifications (PTM), more specifically homocitrullination and carbamylated protein antibodies (anti-CarPAs).

The presence of anti-citrullinated protein antibodies (ACPAs), anti-carbamylation protein antibodies (Anti-CarPAs), and anti-acylated protein antibodies (AAPAs) is a hallmark of rheumatoid arthritis (RA). ACPA and anti-CarPA can already be detected years before RA develops. Moreover, it has been shown that the citrullinated epitope recognition profile of ACPA and anti-CarPA expands before RA develops. Recently, it has become clear that ACPA can display cross-reactivity to other post-translational modifications (PTM), more specifically homocitrullination and carbamylated protein antibodies (anti-CarPAs).
Stand the evolution of anti-progression to disease, it is relevant to obtain more insights. Given the association of ACPA epitope spreading with responses. Therefore, we analysed cross-reactivity in pre-disease samples and ACPA-positive individuals without RA. To this end, ACPA, anti-CarPA and AAPA in different cohorts were measured using modified peptides as described in online supplemental materials. First, we analysed the AMPA-IgG response in samples from 19 different Swedish subjects who later developed RA. As expected, ACPA could be detected years before disease onset with a rise in antibody level over time (figure 1A). We detected a similar pattern for anti-CarPA and AAPA. Interestingly, for most patients with detectable ACPA, anti-CarPA and/or AAPA, these antibodies could be detected at the same timepoint, indicating their simultaneous appearance years before disease onset. Next, we analysed ACPA levels in samples from ACPA-positive and ACPA-negative Japanese individuals without RA, derived from the community-based Nagasaki Island study (figure 1B, online supplemental figure S1). Intriguingly, a strong correlation between levels of the different individual ACPA-reactivities was observed, pointing to cross-reactivity of the antibodies (figure 1C). To experimentally confirm cross-reactivity, we selected six samples from ACPA-positive non-RA individuals with high ACPA values, isolated ACPA, anti-CarPA and AAPA and determined the reactivity of the isolated antibodies to the three different PTMs. Isolated ACPAs were highly reactive to the homocitrullinated and acetylated antigen and vice versa, showing that AMPA in individuals without RA are also cross-reactive towards different PTMs (figure 1D). These results were confirmed on post-translationally modified fibrinogen and FCS (online supplemental figure S2). Interestingly, the reactivity to citrullinated/homocitrullinated peptides was higher when AMPA were isolated with a citrullinated or homocitrullinated antigen than with an acetylated antigen. This suggests cross-reactivity between ACPA and anti-CarPA is stronger than between either of them and AAPA. Together, our data show that ACPA, anti-CarPA and AAPA already coexist before disease onset. Moreover, ACPA can be cross-reactive towards homocitrulline and acetylysine in ACPA-positive individuals without RA. These results indicate that cross-reactivity towards different PTMs emerges when AMPA responses become detectable and provide evidence that cross-reactivity towards different PTMs is an intrinsic characteristic of ACPA responses. This finding is in line with the observation that (germline) ACPA-IgM can be cross-reactive towards other PTMs as well. Although cross-reactivity seems to be an intrinsic feature of AMPA, it is tempting to speculate that the most cross-reactive B cells are selected during progression towards RA, explaining the increase of the ACPA epitope recognition profile in time towards disease onset. Although cross-reactivity is already present before disease onset, the further increase in AMPA cross-reactivity and level could be a valuable biomarker in predicting transition towards disease.

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