JRD Journal of Rheumatic Diseases Vol. 24, No. 1, February, 2017
https://doi.org/10.4078/jrd.2017.24.1.1

Editorial

Homo-Genius: Homocitrulline Can Be a Better Target than Citrulline as a Biomarker for Rheumatoid Arthritis?

Seung Cheol Shim

Division of Rheumatology, Department of Internal Medicine, Daejeon Rheumatoid & Degenerative Arthritis Center, Chungnam National University Hospital, Chungnam National University College of Medicine, Daejeon, Korea

Rheumatoid arthritis (RA) is not a homogeneous disease including various clinical phenotypes correlated to different genotypes. Therefore, effective treatment of RA has been impeded by a paucity of accurate diagnostic and prognostic tests.

Since the identification of rheumatoid factors (RFs) in December 1937, RFs have been used for 50 years as bio-markers for RA. However, their sensitivity and specificity remain around 70% and the titer of RF is not correlated with disease activity [1]. Therefore, novel bio-markers should be developed not only for higher sensitivity and specificity in the early diagnosis, but also for assessment and prediction of disease severity, selection of therapy, and monitoring of response to therapy.

Post-translational modifications (PTMs) are alternative ways to use for fulfilling the unmet need. A key example of this phenomenon is the conversion of arginine into its polar analogue citrulline by peptidyl arginine deiminase enzymes. Citrullination has been shown to greatly enhance immune recognition of joint-associated proteins, which are selectively targeted by autoreactive T and B cells in patients with RA. Citrullination can increase protein antigenicity by eliciting changes in the tertiary structures of proteins which, in turn, can alter antigen processing, antigen presentation and immune recognition. In cohort studies of patients with early RA, the presence of anti-citrullinated protein antibodies (ACPAs) is associated with higher clinical disease activity and greater progression of structural changes [2-4].

The mechanisms of PTM is solving the puzzle of the pathogenesis of RA in which human leukocyte antigen (HLA)-DR4 is associated with RA developing into the shared epitope (SE) hypothesis based on the observation that the RA is associated with DRB1 alleles [5,6]. Several works of genius have found that arginine is essentially incapable of anchoring within the first binding pocket of all HLA DR proteins but this residue is also poorly accommodated elsewhere because of its charge and relatively large size [7]. Recently, considering crystal structures of citrullinated self-peptides within the binding cleft of HLA-DR0401 (all of which adopt similar conformations), citrulline is more flexible and so is better accommodated than the unmodified arginine residue [8].

Antiperinuclear factor (APF) is the first ACPA described in 1964, which targets a citrullinated variant of filaggrin [9,10], and superseded RFs once the first enzyme-linked immunosorbent assay was developed [11]. After that, anti-cyclic citrullinated peptide (anti-CCP) antibody was developed and is widely used in practice due to its high specificity. The identification of additional citrullinated proteins as potential autoantibody targets has suggested new pathophysiological hypotheses and prompted studies of potential associations with disease severity or specific disease patterns. One of these is anti-citrullinated fibrinogen (ACF) antibodies.

Antibodies against carbamylated protein have been recently studied. Carbamylation is a non-enzymatic PTM that produces homocitrullines, against which newly identified autoantibodies developed. Researchers have focused on the diagnostic performance of anti-carbamy-

Received : January 2, 2017, **Revised** : January 17, 2017, **Accepted** : January 17, 2017

Corresponding to : Seung Cheol Shim, Division of Rheumatology, Department of Internal Medicine, Daejeon Rheumatoid & Degenerative Arthritis Center, Chungnam National University Hospital, Chungnam National University College of Medicine, 266 Munhwa-ro, Jung-gu, Daejeon 35015, Korea. E-mail : slera@yahoo.com

pISSN: 2093-940X, eISSN: 2233-4718

lated protein (anti-CarP) and previous studies have shown that anti-CarP was found in over 15% of patients with RA which is lower than anti-CCP [12,13].

In the previous issue, Lee evaluated the diagnostic performance of anti-CarP and ACF in RA by conducting meta-analyses with analyzing data from 12 studies including 7 studies for anti-CarP antibody and 5 for ACF antibody [14]. The pooled sensitivity of ACF antibody was higher than that of anti-CarP antibody, and the specificity of both antibodies was as high as that of anti-CCP. ACF and anti-CCP showed comparable diagnostic accuracy, however, anti-CarP antibody showed low sensitivity in diagnosing RA. This study has several limitations such as between-study heterogeneity, the cut-off values affecting diagnostic accuracy of anti-CarP and ACF antibodies, and no comparison of diagnostic values between early and long-standing RA. Further research is required to examine the diagnostic accuracy of these antibodies in patients with long disease duration. In addition, several environmental factors should be considered in the analysis of data such as smoking [15], coal particle exposure [16], and periodontal disease [17,18].

The sensitivity and specificity of these new antibodies is not higher than those of anti-CCP that we are using now. However, this study is still worth taking note due to their additive effect in which one of these 2 antibodies has shown positivity in RA patients who were sero-negative on anti-CCP, RF, and the other new antibody. There are more antibodies being developed including antibodies to oxidized type II collagen which reflects immunization against collagen modified by oxidation in relation to intraarticular oxidative stress. We expect these novel autoantibodies to be more sensitive and specific so that those would serve as early disease markers and as useful tools for therapeutic monitoring [19].

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med 2007;146: 797-808.
2. Ursum J, Nielen MM, van Schaardenburg D, van der Horst AR, van de Stadt RJ, Dijkmans BA, et al. Antibodies to mutated citrullinated vimentin and disease activity score in early arthritis: a cohort study. Arthritis Res Ther 2008;10:R12.
3. Vencovský J, Machácek S, Sedová L, Kafková J, Gatterová J, Pesáková V, et al. Autoantibodies can be prognostic markers of an erosive disease in early rheumatoid arthritis. Ann Rheum Dis 2003;62:427-30.
4. Combe B, Rincheval N, Benessiano J, Berenbaum F, Cantagrel A, Daurès JP, et al. Five-year favorable outcome of patients with early rheumatoid arthritis in the 2000s: data from the ESPOIR cohort. J Rheumatol 2013;40:1650-7.
5. Stastny P. Association of the B-cell alloantigen DRw4 with rheumatoid arthritis. N Engl J Med 1978;298:869-71.
6. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum 1987;30:1205-13.
7. James EA, Moustakas AK, Berger D, Huston L, Papadopoulos GK, Kwok WW. Definition of the peptide binding motif within DRB1*1401 restricted epitopes by peptide competition and structural modeling. Mol Immunol 2008;45: 2651-9.
8. Scally SW, Petersen J, Law SC, Dudek NL, Nel HJ, Loh KL, et al. A molecular basis for the association of the HLA-DRB1 locus, citrullination, and rheumatoid arthritis. J Exp Med 2013;210:2569-82.
9. Vincent C, Simon M, Sebbag M, Girbal-Neuhauser E, Durieux JJ, Cantagrel A, et al. Immunoblotting detection of autoantibodies to human epidermis filaggrin: a new diagnostic test for rheumatoid arthritis. J Rheumatol 1998;25: 838-46.
10. Sebbag M, Simon M, Vincent C, Masson-Bessière C, Girbal E, Durieux JJ, et al. The antiperinuclear factor and the so-called antikeratin antibodies are the same rheumatoid arthritis-specific autoantibodies. J Clin Invest 1995;95: 2672-9.
11. Schellekens GA, de Jong BA, van den Hoogen FH, van de Putte LB, van Venrooij WJ. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. J Clin Invest 1998; 101:273-81.
12. van Boekel MA, Vossenaar ER, van den Hoogen FH, van Venrooij WJ. Autoantibody systems in rheumatoid arthritis: specificity, sensitivity and diagnostic value. Arthritis Res 2002;4:87-93.
13. Shi J, van Veelen PA, Mahler M, Janssen GM, Drijfhout JW, Huizinga TW, et al. Carbamylation and antibodies against carbamylated proteins in autoimmunity and other pathologies. Autoimmun Rev 2014;13:225-30.
14. Lee YH. Diagnostic accuracies of anti-carbamylated and anti-citrullinated fibrinogen antibodies in rheumatoid arthritis: a meta-analysis. J Rheum Dis 2016;23:373-81.
15. Makrygiannakis D, Hermansson M, Ulfgren AK, Nicholas AP, Zendman AJ, Eklund A, et al. Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. Ann Rheum Dis 2008;67:1488-92.
16. Miall WE, Caplan A, Cochrane AL, Kilpatrick GS, Oldham PD. An epidemiological study of rheumatoid arthritis associated with characteristic chest x-ray appearances in coal-workers. Br Med J 1953;2:1231-6.

17. Arkema EV, Karlson EW, Costenbader KH. A prospective study of periodontal disease and risk of rheumatoid arthritis. J Rheumatol 2010;37:1800-4.
18. Bingham CO 3rd, Moni M. Periodontal disease and rheumatoid arthritis: the evidence accumulates for complex pathobiologic interactions. Curr Opin Rheumatol 2013;25:345-53.
19. Cantagrel A, Degboé Y. New autoantibodies associated with rheumatoid arthritis recognize posttranslationally modified self-proteins. Joint Bone Spine 2016;83:11-7.