

## Newsletter - May 2011

### *Spotlight: Anti-citrullinated protein/peptide antibodies (ACPA) in RA: Do they measure the same?*

The **2010 classification criteria for RA** that were developed and published by ACR and EULAR ([http://www.rheumatology.org/practice/clinical/classification/ra/2010\\_revised\\_criteria\\_classification\\_ra.pdf](http://www.rheumatology.org/practice/clinical/classification/ra/2010_revised_criteria_classification_ra.pdf)) include the measurement of **anti-citrullinated protein/peptide antibodies (ACPAs)**. Actually, a low ( $\leq 3$  times the cut-off) or high positive ( $> 3$  times the cut-off) ACPA result can make up 33% to 50% of the minimally required score value ( $\geq 6$ ) for definite RA. The criteria do not specify which ACPA could or should be measured, and clinicians often express confusion regarding the different type of ACPAs and their clinical utility. In this essay, we characterize this autoantibody family and clarify the similarities and differences between its members.

**Citrulline** is a nonstandard amino acid originating from a post-translationally modified, deiminated arginine residue. Citrullination is a physiological process that occurs during keratinization of epithelial cells, inflammation, and apoptosis. Antibodies to citrullinated antigens have been identified as diagnostic and prognostic markers in RA.

- From chronological point of view, the first antibodies that now belong to the family of ACPAs were the **antiperinuclear factor (APF)** and the **antikeratin antibodies (AKA)** (both detected with immuno-fluorescence microscopy), and the later discovered **anti-Savoie (anti-Sa)**. These antibodies are rarely measured nowadays, as more specific tests are available.
- **Anti-CCP antibodies** are measured with immunoassays that utilize a synthetic **cyclic citrullinated peptide** as antigen. This peptide was identified by analyzing the epitope reactivity pattern of antibodies directed to filaggrin, the antigenic target of the above mentioned APF and AKA. The currently used anti-CCP assays are second generation tests, sometimes referred to as **anti-CCP2** (as opposed to the originally developed first generation assay). The **TheraTest EL-anti-CCP/2™** assay is a second generation anti-CCP test.
- The **anti-CCP3** assay (marketed by INOVA Diagnostics) contains different synthetic citrullinated peptide antigen, and the **anti-CCP3.1** assay measures not only IgG, but also IgA antibodies against this citrullinated peptide.
- The **anti-MCV** test (marketed by ORGENTEC Diagnostika) detects antibodies against **mutated citrullinated vimentin**. Citrullinated vimentin has been identified as the antigenic target of the above mentioned anti-Sa antibodies.
- Besides of these commercially available tests, research studies have examined the performance of several other ACPA assays, including anti-citrullinated fibrinogen (anti-CF), anti-citrullinated alpha-enolase and anti-viral citrullinated peptide (anti-VCP) antibodies.

**The most widely studied ACPA is the second generation anti-CCP.** An abundance of scientific data supports the strong diagnostic, prognostic and predictive value of anti-CCP2 antibodies. Studies regarding anti-MCV and anti-CCP3 usually could not demonstrate superior performance compared to anti-CCP2 (<http://onlinelibrary.wiley.com/doi/10.1002/art.24720/pdf>). The diagnostic properties (sensitivity, specificity) of various ACPA assays are very similar. However, despite the significant overlap, discrepancy between ACPA test results might occur in a small percentage of patients.

## [What's New in Rheumatology/Immunology?](#)

*Excerpt from a recent publication from A&R:*

In addition to inducing a self-limited myopathy, **statin use has been associated with an immune-mediated necrotizing myopathy (IMNM)**, with autoantibodies that recognize ~200-kd and ~100-kd autoantigens. The identity of the ~100-kd autoantigen was confirmed by immunoprecipitation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) protein. A cohort of myopathy patients was screened for anti-HMGCR autoantibodies by enzyme-linked immunosorbent assay. Anti-HMGCR autoantibodies were found in 45 of 750 patients presenting to the Johns Hopkins Myositis Center (6%). Among patients ages 50 years and older, 92.3% had taken statins. In muscle biopsy tissues from anti-HMGCR-positive patients, HMGCR expression was up-regulated in cells expressing neural cell adhesion molecule, a marker of muscle regeneration. These results suggest that statins up-regulate the expression of HMGCR, the major target of autoantibodies in statin-associated IMNM. These studies demonstrate a mechanistic link between an environmental trigger and the development of sustained autoimmunity.

*Mammen AL, Chung T, Christopher-Stine L, Rosen P, Rosen A, Doering KR, Casciola-Rosen LA. Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. *Arthritis Rheum.* 2011;63:713-21.*

## [TheraTest News: Visit us at upcoming scientific meetings and trade shows](#)

### ***Congress of Clinical Rheumatology***

Sandestin Hilton and Conference Center, Destin, FL; May 12-15, 2011

<http://www.ccrheumatology.com/>

### ***California Rheumatology Alliance 7th Annual Medical & Scientific Meeting***

Omni Hotel Los Angeles, CA; May 21-22, 2011

<http://www.calrheum.org/events.html>

### ***Florida Society of Rheumatology Annual Meeting***

Ritz Carlton, Amelia Island, FL; July 15- 7, 2011

<http://www.floridarheumatology.org/>

### ***American Association for Clinical Chemistry (AACC) Annual Meeting and Clinical Lab Expo***

Georgia World Congress Center, Atlanta, GA; July 24-28 the 2011

<http://www.aacc.org/events/2011am/pages/default.aspx>

### ***National Organization of Rheumatology Managers (NORM) Annual Meeting***

Sanibel Harbour Marriott, Ft. Myers, FL; September 16-17, 2011

<http://www.normgroup.org/documents/2011/norm%20conference%20brochure.pdf>

### ***ACR / ARHP 2011 Annual Scientific Meeting***

McCormick's Place Convention Center, Chicago, IL; November 5-9, 2011

<http://www.rheumatology.org/education/annual/index.asp>

**Look for our previous Newsletters on [www.theratest.com](http://www.theratest.com) !**

### **Gabriella Lakos M.D. Ph.D. D(ABMLI)**

Director of Research & Development

[gabriella@theratest.com](mailto:gabriella@theratest.com)

### **Marius Teodorescu M.D. Ph.D.**

President and CEO

[marius@theratest.com](mailto:marius@theratest.com)