

## 14-3-3 $\eta$ in “Seronegative” Rheumatoid Arthritis

To the Editor:

Serum 14-3-3 $\eta$  is a novel joint-derived proinflammatory mediator implicated in the pathogenesis of rheumatoid arthritis (RA)<sup>1</sup>. Unlike rheumatoid factor (RF) or anticitrullinated protein antibody (ACPA), which can arise as a consequence of disease in sites distinct from inflamed joints, 14-3-3 $\eta$  hyperexpression in RA is restricted to synovial joints with a significantly higher expression in synovial fluid than matched serum<sup>2</sup>. In our recent report by Maksymowych, *et al* in *The Journal of Rheumatology*<sup>3</sup>, we demonstrated increased sensitivity of detection in subjects with early RA (< 6 months of disease) by the addition of serum 14-3-3 $\eta$  to the traditional serological markers, RF and ACPA. However, we did not explicitly identify the subset of patients who were “seronegative” by traditional markers. Of the 99 subjects with early RA, 71 patients were positive for RF or ACPA. Of these, 57 (80%) were also 14-3-3 $\eta$ -positive. Six (21%) of the 28 patients who were seronegative for RF and ACPA were 14-3-3 $\eta$ -positive. The mean serum 14-3-3 $\eta$  level in these 6 patients was 3.98 ng/ml with a range of 0.35–12.65 ng/ml (normal < 0.20 ng/ml). Receiver-operation characteristic curve analysis comparing early RA with all controls indicates that with increasing 14-3-3 $\eta$  levels, the likelihood of identifying patients with RA increases significantly. Consequently, 14-3-3 $\eta$  together with RF and ACPA can aid in the early detection of RA.

Because RF and ACPA are used in the 2010 American College of Rheumatology/European League Against Rheumatism RA classification criteria, we anticipate that future studies will reveal that the complementarity of 14-3-3 $\eta$  is underestimated in this study<sup>3</sup> because of the reliance on RF and ACPA in the criteria. Because immediate early referral to a rheumatologist is a central tenet in mitigating the debilitating aspects of this disease, the testing of 14-3-3 $\eta$  together with RF and ACPA may assist in identifying those patients who require an immediate early referral to a rheumatologist. Further, of the 124 subjects with established RA, 10 (67%) of 15 seroneg-

ative for RF and ACPA were 14-3-3 $\eta$ -positive. Therefore, 14-3-3 $\eta$  has clinical use beyond RF and ACPA in patients with RA because 14-3-3 $\eta$  confirms joint-specific inflammation in the absence of traditional serological markers.

STANLEY J. NAIDES, MD, FACP, FACR, Medical Director, Immunology R&D, Quest Diagnostics Nichols Institute, San Juan Capistrano, California, USA; ANTHONY MAROTTA, PhD, Chief Scientific Officer, Augurex Life Sciences Corp., North Vancouver, British Columbia, Canada. Supported by Quest Diagnostics Incorporated, Augurex Life Sciences Corp. Address correspondence to Dr. S.J. Naidcs, Immunology 101A, Quest Diagnostics Nichols Institute, 33608 Ortega Highway, San Juan Capistrano, California 92629, USA.  
E-mail: stanley.j.naides@questdiagnostics.com

## REFERENCES

1. Maksymowych WP, van der Heijde D, Allaart CF, Landewé R, Boire G, Tak PP, et al. 14-3-3 $\eta$  is a novel mediator associated with the pathogenesis of rheumatoid arthritis and joint damage. *Arthritis Res Ther* 2014;16:R99.
2. Kilani RT, Maksymowych WP, Aitken A, Boire G, St-Pierre Y, Li Y, et al. Detection of high levels of 2 specific isoforms of 14-3-3 proteins in synovial fluid from patients with joint inflammation. *J Rheumatol* 2007;34:1650-7.
3. Maksymowych WP, Naidcs SJ, Bykerk V, Siminovitch KA, van Schaardenburg D, Boers M, et al. Serum 14-3-3 $\eta$  is a novel marker that complements current serological measurements to enhance detection of patients with rheumatoid arthritis. *J Rheumatol* 2014;41:2104-13.

*J Rheumatol* 2015;42:10; doi:10.3899/jrheum.150330