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The role of 14-3-3 η as a biomarker in rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic multisystem inflammatory disorder with significant morbidity and mortality. Making an early diagnosis and providing appropriate treatment decisions based on clinical and other parameter results in good disease control. Biomarkers, such as C reactive protein (CRP), anti-cyclic citrullinated peptides (anti-CCP), and erythrocyte sedimentation rate (ESR), have been traditionally used. Recently novel biomarkers are described. This article reviews the evidence behind a novel biomarker 14-3-3 η that has been found to provide additional diagnostic and prognostic information as well as predicting response to treatment. A systematic literature review is presented showing the evidence behind this molecule.

Background

Rheumatoid arthritis (RA) is a chronic multisystem disease causing significant morbidity and mortality with a prevalence of between 0.5% and 1% in different parts of the world.[1] It is associated with increased disability, deformity, and damage and is a significant health burden.[2]

Predicting who will develop the disease and who would do well has long been the objective of the researchers. Classic biomarkers have been described for diagnosis such as rheumatoid factor (RF) and antibodies to cyclic citrullinated peptides (anti-CCP). The former has been used as part of the original 1988 criteria[3] and both are now considered as part of the new 2010 European league against rheumatism and American college of rheumatolog (EULAR/ACR) Classification criteria.[4] More recently they are advocated as biomarkers for severity of damage,[5, 6] indicating that they could correlate with disease severity. This is important as the perceived wisdom has been that disease severity over time = damage[7] and therefore, it is being able to detect not only the presence of disease but also the severity of disease is vital.

Recently there has been an emergence of new biomarkers that have been explored with different populations to predict severe disease and response to therapy: the two that had the most amount of evidence in the literature are multi biomarker disease activity (MBDA) score[8] and 14-3-3 η which is the subject of this review.

The 14-3-3 is a family of proteins consisting of seven isoforms found in the bloodstream with biological activity linked to the inflammatory process. 14-3-3 η has been found to be elevated in both the blood and synovial fluid in RA patients and a diagnostic biomarker for RA was first described in 2007.[9] It was reported to add to the diagnostic sensitivity of the disease and is useful in early disease prediction.[10, 11]

This article will review this markers ability to predict both the disease and the response to treatment from the evidence that has been shown to date.

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Methods

A search strategy that included the terms "14-3-3η", "Rheumatoid arthritis" and "diagnosis", "treatment" or "DMARDS", "Biologics", "tsDMARDS", "Small molecules", "TNF inhibitors" was performed. Articles published up to April 2021 were included.

Papers were excluded if they were not published in English, were comprised of reviews, editorials, or opinion pieces.

The ability of 14-3-3 η to differentiate RA from non RA and its utility to predict response to treatment was scrutinized in each of the publications and the results compared.

Results

After applying the search criteria, the results were grouped into predicting who will develop RA with a history of polyarthralgia and having elevated protein levels, and whether it could distinguish RA from non RA and whether the sensitivity and specificity of the diagnostic process is above that or RF and anti-CCP.

Regarding 14-3-3 η studies in predicting disease, 16 reports were found and they all used a similar enzyme linked immunosorbent assay (ELISA) to quantify the levels of 14-3-3 η

and had various serum cut offs. The studies with sensitivity and specificity are described in Table 1.

All studies either had cut off levels of the protein not described (tan) or had low levels <0.5 ng/ml, but three studies had a higher cut off (Guan et al.[15] 1.44, Zeng et al.[19] 1.89, and Huang et al.[16] 2.60) making comparisons difficult. The Arab study[20] compared levels between cases and controls and correlated the levels with radiographic severity.

Despite the large amount of heterogeneity between the studies, we appear to have a high sensitivity and specificity to diagnose RA. When comparing 14-3-3 η with other novel antibodies including mutated citrullinated vimentin (MCV) and anti-CCP, Hu et al. found and odds of 5.1 (95%CI 2.1–12.5) for RA using 14-3-3 η levels in addition to anti-CCP and anti MCV antibodies making the diagnosis more certain. This seemed to indicate that precision of diagnosis can be significantly enhanced.

As can be seen from the table, the sensitivity and specificity vary widely but are consistently good with a meta-analysis of all studies estimating that a pooled sensitivity was 73% (95% CI: 71, 75) and the pooled specificity was 88% (95% CI: 87, 90).[21] This provides evidence that it could be a very useful biomarker for diagnosis. Another pooled meta-analysis [22] showed that a pooled sensitivity of 14-3-3 η as 0.63 (95% CI: 0.60–0.66) and the pooled specificity as 0.90 (95% CI: 0.88–0.91). All these

Table 1: Performance of 14-3-3 η in the classification and diagnosis of RAs in different populations

Authors	Number of patients: Comparators	Ethnicity	Study design	Sensitivity	Specificity
Maksymowych et al. (2014)	234:385	European	Cohort	71	86
Kadavath et al. (2014)[12]	91:37	European	Retrospective	54	73
Maksymowych et al.[13]	249:251	European	cohort	69	80
Mohamed et al. (2017)	92:74	African	Cohort	90	95
Gong et al. (2018)	259:80	Asian	Case-control	97	95
Tan et al. (2018)	128:254	Asian	Cohort	52	93
Elshahaly et al. (2018)	30:60	African	Case-control	80	87
Shovman et al. (2018)	96:167	Asian	Cohort	50	95
Mohamed et al. (2019)	20:20	African	Case-control	90	90
Salman et al.[14]	45:45	Asian	Cross-sectional	89	92
El_Sherif et al. 2019	50:144	Arab	Case controls	100	78.6
Guan et al.[15]	94:80	Asian	Cohort	79	74
Huang et al.[16]	108:192	Asian	Case-control	63	91
Zang et al. (2020)	113:289	Asian	Case-control	73	92
Yarlagad et al.[17]	61:20	Asian	Case controls	74	90
Tu et al.[18]	45:44	Asian	Case control	79.3	75
Hussin et al 2021	40:40	Arab	Case control	NA	NA

RA: Rheumatoid arthritis.

meta-analyses had patient populations overlapping with different regions, which could partially explain these differences.

14-3-3 η as a Prognostic Biomarker

14-3-3 η has had a number of studies analyzing its ability to predict clinical and radiographic outcomes. In an analysis of 331 patients with 5 years of follow-up from the longitudinal Sherbrooke Early Undifferentiated PolyArthritis (EUPA) cohort[23], it was shown that 14-3-3 η was linked to radiographic progression and markers of disease severity including the Simplified disease activity index. In a Japanese study with 149 patients[24], the levels of 14-3-3 η predicted worse disease and better response to tocilizumab. In a small case control study of 35 patients starting with tofacitinib, 14-3-3 η showed that a decrease in levels is linked to better response to the drug.[25]

Discussion

In this contemporary period, the management of RA is dictated not only by "treat to target principle" but also treating with multiple agents including five distinct modes of action to date post DMARDS (tumor necrosis factor inhibition, Interleukin 6 therapy, B cell treatment, co-stimulator blockade, and small molecules), and it is crucial that we have a method of predicting not only the presence of disease but also the response to therapy or at least who will not do well.

Combining RF and anti-CCP, especially high titers of both[26] have already alluded to this specifically when treating with drugs like abatacept. It could be conceivable that further work looking at using both these and adding 14-3-3 η further would enable a approach to the idea of personalized medicine, whereby the patient would have all these biomarkers measured and thus allocated a specific treatment regimen.

This review shows that 14-3-3 η has now got adequate evidence for helping in assessing the veracity of the diagnosis and severity of early RA. It can be combined with existing markers for severity and provide a possible way of stratifying patients to more effective treatments and could be the route to a more personalized approach to treatment.

This molecule might also enable us to further sub-classify the disease and provide information for treatment decisions and so it is a welcome new addition for a rheumatologists diagnostic, treatment, and strategy in RA. Further work will only hone these abilities and provide for more effective and targeted patient care.

Further work using this and new biomarkers will be forever our overarching principles in treating disease and it might become a more standard way of classifying our patients and perhaps lead to an even bigger rethink of RA as single disease entity as it is well known that patients with RA have different disease trajectories over time,[27] it therefore could be envisaged that we then have subcategories of disease that would have different guidelines.

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