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Mini Review

The Importance of Antibodies and other Molecules as Biomarkers in Rheumatoid Arthritis

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Abstract

Rheumatoid Arthritis (RA) is a chronic inflammatory autoimmune disease characterized by synovitis, infiltrated inflammatory cells, cytokine production, and joint destruction. Some typicalbiomarkers are normally used to detect RA. However, these biomarkers are not exclusive of RA, as they might increase with age and gender, in tumours or infections. Therefore, it would be of diagnostic interest to find specific markers for RA.

Keywords: Rheumatoid Arthritis; Biomarkers; Erythrocyte Sedimentation Rate; C-Reactive Protein; Autoantibodies

Abbreviations

ACP: Anti-Citrullinated Peptide; ANA: Antinuclear Antibodies; anti-dsDNA: Anti-Double-Stranded DNA; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; IgG: Immunoglobulin G; miRNAs: microRNAs; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; TNFi: Tumour Necrosis Factor Inhibitor; TNF-α: Tumour Necrosis Factor-Alpha.

Introduction

In many inflammatory disorders, it is well know the profile of cytokines and chemokines locally present in the affected tissues and most times also in the peripheral blood, which holds a significant role in diagnostics or further confirmation of the disease. However, they are not very useful when it comes to a distinctive diagnosis. Clinical serological and proteomic biomarkers, on the other hand, are used to confirm preliminary diagnosis and follow the effect of treatment [1].

In the case of rheumatoid arthritis (RA), –an autoimmune disease whose main feature is inflammation–, the most used biomarkers for diagnosis are acute phase proteins such as erythrocyte sedimentation rate (ESR) [2-4], and C-reactive protein (CRP) [5], and autoantibodies such as rheumatoid factor (RF) [6], anti-nuclear antibodies (ANA) and anti-citrullinated peptide (ACP) –in which arginines are enzimatically transformed into citrullines; this structural change make possible for the IgG antibodies to target the citrullinated peptides [7]. Patients with AR are divided into two different groups –ACP positive or negative– years before the onset of the disease [8,9] and with differential disease progression [10].

These biomarkers are not exclusive of RA, as they might increase in cases of malignant tumours or infections, and in some cases are even related to age and gender.

Autoantibodies to cellular and nuclear antigens, such as ANAs and anti-double-stranded DNA (anti-dsDNA) –which result from the dysregulation of the immune system and can be associated with autoimmune diseases–, deserve a particular mention. Studies in RA suggest an association between therapeutic responses and both ANA and anti-dsDNA autoantibody [11], although some studies display controversial results [12]. Thus, a recent research shows that tumour necrosis factor inhibitor (TNFi) therapy in RA patients can induce ANAs and anti-dsDNA autoantibodies, or can revert from positive to negative these antibodies after treatments with abatacept –a biological therapy that targets T-cell activation [13]-, while RA patients treated with infiximab or adalimumab –antibodies that target tumour necrosis factor-alpha (TNF-α)– develop

higher ANA and anti-dsDNA autoantibodies [14], highlighting the importance of T cells TNF-α in this process.

The use of autoantibodies –which should possess high sensitivity and specificity– in RA and other autoimmune disorders, not only allows for an early detection, but helps in the management of the disease and the right treatment. Things get complicated however, when these antibodies are present not only in affected patients but in healthy people too, which can lead to false positives and consequent unnecessary or incorrect treatments.

Most recently, microRNAs (miRNAs) –small non-coding RNAs involved in the regulation of gene expression at the posttranscriptional level– have also been investigated in RA as possible biomarkers. In a new study, quantitative expression of serum miRNA-146a, miRNA-499 as well as their genotyping rs2910164 (C/G) and rs3746444 (T/C), respectively, were performed in RA patients with active and inactive RA using real-time PCR. Results showed that serum miRNA-146a and were significantly over expressed in RA patients and associated with RA protection and susceptibility respectively. Furthermore, miRNA-146a was negatively correlated with ANA [15]. Although this expression did not correlate with disease activity, results render miRNA-146a and miRNA-499 as diagnostic markers for RA.

Conclusion

Despite the pros and cons of the current antibodies and other type of biomarkers used, the diagnosis of RA is still based in symptoms and physical examination, but the use of biomarkers is a remarkable tool that facilitates and improves the management of RA.

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Conflict of Interest

No financial interest or conflict of interest exists.

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