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Biomarkers for rheumatoid and psoriatic arthritis

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Abstract Rheumatic diseases, such as rheumatoid and psoriatic arthritis are systemic inflammatory conditions characterized by a chronic form of arthritis, often leading to irreversible joint damage. Early treatment for patients with rheumatic diseases is required to reduce or prevent joint injury. However, early diagnosis can be difficult and currently it is not possible to predict which individual patient will develop progressive erosive disease or who may benefit from a specific treatment according to their clinical features at presentation. Biomarkers are therefore required to enable earlier diagnosis and predict prognosis in both rheumatoid arthritis and psoriatic arthritis. In this review we will examine the evidence and current status of established and experimental biomarkers in rheumatoid and psoriatic arthritis for three important purposes; disease diagnosis, prognosis and prediction of response to therapy.

1. Introduction

1.1. Rheumatic musculoskeletal diseases

The term rheumatic musculoskeletal diseases (RMD) encompasses a large and varied group of diseases, that share a number of features such as the involvement of connective tissues, muscles and the joints. In addition to similarities, there is also significant variety across the RMD spectrum including inflammatory and non-inflammatory diseases. Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are two of the most prevalent inflammatory RMD while diseases such as osteoarthritis and fibromyalgia represent the main non-inflammatory conditions. RMD can also be classified

Abbreviations: ACPA, anti-citrullinated protein antibodies; Anti-CarP, anti-carbamylated protein; CASPAR, Classification of psoriatic arthritis; CCP, cyclic citrullinated protein; DAS, Disease activity score; DMARD, disease modifying anti-rheumatic drug; FDA, US Food and Drug administration; IFN, interferon; MAA, malondialdehyde-acetaldehyde; MBDA, multiple biomarker disease activity; MDA, malondialdehyde; MMP, matrix metalloproteinase; NIH, US National Institute of health; NSAID, non-steroidal anti-inflammatory drug; PAD, protein arginine deiminase; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor; RMD, rheumatic musculoskeletal diseases; SLE, systemic lupus erythematosus; TNFi, TNF inhibitor.

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according to duration of symptoms or impact on function. The duration may be acute, remitting or chronic persistent and the impact on the subject may vary from mild to severe, often depending on the level of inflammation or tissue damage. The level of inflammation is often quite different in patients with RA and PsA even though both may result in joint damage while fibromyalgia, which is painful, is not associated with inflammation or tissue damage. The signs and symptoms of RA and PsA may be quite similar especially at the earlier phases of disease, so it may be difficult to distinguish between them on clinical grounds, although early treatment may prevent the development of disability in both conditions if introduced appropriately [1,2].

RA occurs in 0.5–1% of the adult population globally [3]. The main characteristics of RA are stiffness and swelling of the joints as a result of inflammation of the synovium, which normally is a thin translucent membrane lining the non-articular surfaces of the joint. The synovium may proliferate and invade surrounding structures leading to damage of the articular cartilage and erosions of the periarticular bone. The cause of RA is not clear, although both genetic and environmental factors have been identified to play a role in disease initiation and progression. RA patients exhibit an increased frequency of cardiovascular disease, a higher susceptibility to infections and have an increased risk for certain malignancies [3].

PsA occurs in 10–40% of psoriasis patients [4,5]. Psoriasis is characterized by red, thickened and inflamed skin lesions and affects up to 3% of the general population. In addition to the skin lesions, patients may develop a chronic arthritis of the peripheral and/or axial joints, characterized by inflammation of the synovium and erosions similar to but distinct from RA. Classified as one of the spondyloarthropathies, due to axial joint involvement similar to ankylosing spondylitis, patients may also exhibit enthesitis, uveitis and nail disease [4,5]. PsA patients, similar to RA, have an increased mortality due to cardiovascular disease, however there is no evidence of increased susceptibility to infections or lymphoma when compared to the general population [6].

The signs and symptoms of RA and PsA patients, including systemic features such as skin and eye manifestations, appear to respond well to anti-inflammatory drugs (corticosteroids and non-steroidal anti-inflammatories (NSAIDs)) and disease-modifying anti-rheumatic drugs (DMARDS) such as tumour necrosis factor inhibitors (TNFi). For some other biological agents there may be a differential response when comparing RA and PsA patients [7,8].

1.2. Biomarkers

Biomarkers may be defined in several ways. A simple definition proposed by the US Food and Drugs Administration (FDA) is; 'Any measurable diagnostic indicator that is used to assess the risk or presence of disease'. However the US National Institutes of Health (NIH) has suggested a more comprehensive definition of a biomarker—'A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic intervention'. The NIH definition encompasses the concept of response to therapy, which is becoming more relevant and therefore more important in the context of RA and PsA.

Therapies for RA and PsA patients have developed rapidly in the past decade such that great improvements in signs and symptoms, but also in quality of life and function, have been realized. However, many patients do not respond to the first treatment that is offered, leaving room for substantial improvements [7,8]. Also, in both RA and PsA, early treatment is important in order to prevent irreversible joint damage [1,2]. In order to treat patients in an early stage of the disease, it is essential to determine which of the patients that visit the doctor with psoriasis or joint pain will eventually develop PsA or RA respectively. Only the patients that do acquire PsA or RA will benefit from the treatment, while people who do not develop severe disease might suffer from unnecessary side effects. Furthermore, not all treatments are effective in each patient and treatments are often given on basis of trial and error [7,8]. It would therefore be useful to predict which RA and PsA patients will benefit from a specific treatment.

In this review, we describe the biomarkers that are generally accepted for PsA and RA, after which we will discuss a selection of interesting biomarkers that are still under investigation. This will include biomarkers that are used to improve diagnosis, to predict prognosis and to identify response to treatment.

2. Autoantibodies

For RA patients, one of the most important types of biomarkers at the moment is autoantibodies. The most recent criteria for the diagnosis of RA were described in 2010 [9]. Besides joint pain and inflammation, several serological biomarkers are used to classify RA patients. Serological biomarkers, described in the new criteria, include autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA).

Currently there is little evidence for a role of autoantibodies in PsA, as rheumatoid factor is mainly absent in PsA, so that the CASPAR classification of PsA includes rheumatoid factor negativity as an independent diagnostic criterion [10]. Indeed, also the autoantibodies to citrullinated proteins are mostly absent in 90% of the PsA patients [11,12]. There is one recent report of autoantibodies, against fibrillin 3 and desmocollin 3, crossreacting with a shared epitope common to both the skin and the joints that may suggest some as yet unidentified autoantibodies may be associated with PsA [13]. Since the role of autoantibodies as a biomarker in PsA is almost non-existent, we will now discuss the different autoantibodies that have been discovered in RA and shortly explain the relevance of these antibodies as a biomarker.

2.1. ACPA and RF

The first autoantibody that was discovered in RA patients is RF, which is present in 60–80% of the RA patients. The antigen that RF binds to is the Fc-region of an IgG molecule [14]. RF has a low specificity, since it can also be found in healthy controls and patients with other rheumatic diseases [15]. But even though RF has a low specificity, it has been used extensively to diagnose RA for a long time, since no better alternatives were available. At least, not until ACPA were discovered. ACPA bind to a different type of antigen than RF; proteins that contain the amino acid citrulline.