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Diagnostic, Prognostic and Theranostic Genetic Biomarkers for Rheumatoid Arthritis

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Abstract

The identification and adoption of diagnostic and prognostic biomarkers for rheumatoid arthritis has informed and improved the clinical management of this disease. With the advent of biologic treatments such as anti-Tumour Necrosis Factor (anti-TNF) therapy, achieving disease remission has become a realistic endpoint for clinicians. The life-changing efficacy of these therapies however is restricted to the 60-70% of patients who respond. The immune reaction to anti-inflammatory therapy is thought to be influenced by many genes which cumulatively contribute to a threshold for response. There is an inherent clinical need to provide theranostic biomarkers which could determine treatment outcome. The current role of genetic biomarkers in diagnosis, prognosis and predicting response to anti-TNF therapy are discussed.

Introduction

The field of biomarker research has expanded dramatically in the past 5-7 years coinciding with the advancement of high-throughput technologies such as genomic and proteomic arrays. A biomarker can be generally defined as a measurable indicator of either normal or pathogenic processes or pharmacological responses to therapeutic interventions [1]. Clinically, biomarkers are commonly used for diagnostic (disease identification) and prognostic (predicted outcome or progression) purposes. However the availability of biomarkers which support treatment choice (theranostic biomarkers) remains limited. A theranostic biomarker could identify the most appropriate treatment for an individual, indicate the correct dose, or predict response to treatment. This approach attempts to maximise drug efficacy, minimise toxicity and provides a more informed treatment choice.

Rheumatoid arthritis (RA) is a chronic inflammatory disease which affects up to 1 % of the population world-wide [2]. RA is particularly suited and consequently one of the more developed disease areas where biomarkers have been applied. The genetic basis of diagnostic, prognostic and potential theranostic biomarkers of RA are discussed in this brief review.

RA Diagnostic and Prognostic Biomarkers

The association of RA with the Major Histocompatibility Complex (MHC) has been well documented, in particular the HLA-DRB1 locus is thought to account for around 30% of RA genetic risk [3,4]. HLA-DRB1 alleles such as HLA-DRB1*0401 and HLA-DRB1*0404 share a similar amino acid sequence, known as the shared epitope (HLA-SE), which may be specific to particular peptides related to disease [5,6]. RA patients with the HLA-DRB1*0401 and DRB1*0404 alleles have been shown to have increased radiological erosions and joint replacement compared to individuals without these alleles [7]. The genetic complexities of the HLA complex in RA are further reviewed by Jawaheer et al. [8]. Multiple studies of genes within and outside the MHC region have been carried out to identify and validate RA risk markers. These concerted efforts in over 40,000 samples have led to confirmation of 31 loci associated with RA risk [9]. While HLA-SE detection remains the most common genetic variant which is tested for in RA patients, incorporation of these relatively new loci into genetic tests for RA may become commonplace in the near future.

RA can be serologically characterised by the presence of autoantibodies such as Rheumatoid Factor (RF) or Anti-cyclic Citrullinated Protein Antibodies (ACPA), which are present in about two thirds of individuals with the disease [10]. Rheumatoid factor are circulating autoantibodies (predominantly IgG and IgM) released by B cells directed against the Fc fragment of IgG molecules forming immune complexes. These immune complexes are known to activate the complement pathway thereby contributing to inflammation. Although widely used, the diagnostic specificity and sensitivity of RF is limited as it may also be present in other connective tissue or infectious disease states [11]. ACPA such as anti-CCP antibodies directed against peptides such as fillaggrin, keratin and vimentin have been shown to be highly specific (>95 %) to RA [12]. Anti-CCP antibodies have similar sensitivity to RF but display much greater specificity to the disease [13]. The American College of Rheumatology (ACR) guidelines for RA classification, revised in 2010, now requires that at least one serological test such as RF or ACPA is included in the clinical evaluation for 'definite RA' diagnosis [14]. In addition to their use as diagnostic markers, RF and/or ACPA antibodies also carry prognostic value in RA. In early RA, the presence of RF is an independent predictor of erosive disease as shown in cohorts followed up for 5-12 years [15,16]. The presence of anti-CCP has also been identified a predictor of poor prognosis in terms of disease severity and joint damage [17-19]. Many studies have identified that anti-CCP positivity and higher titres are associated with MHC genes such as the HLA-SE alleles [20-25]. Conversely, HLA-DRB1-*03 alleles have been associated with lower anti-CCP titre [26,27]. The presence of genetic factors which influence the production and titre of autoantibodies are therefore potential indicators of a more aggressive phenotype in RA and could find utility in informing treatment decisions.

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Treatment in RA

Methotrexate (MTX) has long been considered the 'gold standard' disease modifying anti-rheumatic drug (DMARD) for RA. However, in the past decade treatment paradigms have been dramatically changed by the introduction of biologic therapies which specifically target molecules involved in disease pathogenesis. Biologic therapies for RA have revolutionised clinical outcomes where disease remission has become a realistic goal for individuals with moderate to severe RA.

Current biologics available or in development for RA have mechanisms of action which interfere with pivotal chemical mediators or cell types which are involved in the RA inflammatory response. These include those directed against cytokine actions such as anti-TNF, anti-IL-1 and anti-IL-6 and also those directed against cell surface receptors involved in T and B cell activation, such as anti-CD28 and anti CD-20 respectively. The anti-TNF therapies such as adalimumab (Humira®, a fully human monoclonal antibody), infliximab (Remicade®, a chimeric monoclonal antibody) and TNF receptor protein etanercept (Enbrel ®) have been available for more than 10 years. Certolizumab (Cimzia ®, a pegylated humanized monoclonal antibody) and Golimumab (Simponi ®, a fully human monoclonal antibody) are newer alternative options within this drug class.

In the UK, anti-TNF therapy is recommended in patients who have failed at least two other DMARDs including MTX and have active disease defined by a disease activity score in 28 joints [DAS28]of >5.1 [28]. Although anti-TNF therapies have demonstrated remarkable efficacy there are a subset of patients (30-40%) who do not achieve clinical response to therapy. The reasons for this remain unknown; however given the heterogeneous nature of RA, response is likely influenced by many different pathways. The associated expense, the detrimental effect of inefficacious therapy in terms of progressive joint destruction and exposure to potentially harmful side-effects has led to an influx of studies to identify biomarkers to predict response to therapy. Many different pathways have been examined for potential biomarkers including the inflammatory, immune response, protein synthesis, apoptotic and mitochondrial oxido-reduction pathways. Within these pathways, genetic, cellular, and protein factors have been investigated as potential theranostic biomarkers which could enable informed treatment decisions at an individual level. It is likely that a genetic predisposition promoting restoration of the immune system balance is advantageous for response to therapy. The remainder of this review examines some of the genes which may be involved in this process and have been associated with response.

Theranostic biomarkers and response to anti-TNF therapy

There are two main types of genetic approaches to look for biomarkers of treatment response. These are candidate gene studies and genome wide association studies (GWAS). Candidate studies generally involve genes which have already been related to RA (such as disease risk / susceptibility genes) or pathways involved in the RA process or pathogenesis. The first investigations were thus based on probable involvement of polymorphisms affecting the gene function and signalling pathways of cytokines involved in RA pathogenesis, such as TNF. There has been considerable data accumulated here, in particular with regard to single nucleotide polymorphisms (SNPs) which effect the TNF promoter such as -308G>A, and -857C>T. Reports on TNF–308G/A have indicated that a genetic predisposition toward increased TNF expression (carrying the A allele) can be associated with non-response to anti-TNF therapy [29-32]. These findings however have been disputed in a recent meta-analysis by Pavy et al and so the role of this SNP remains unclear [33]. In addition to studies of TNF, SNPs within other cytokine genes such as IL-10, TGF-B1, IL-1B and the IL-1 receptor antagonist IL-RA have also been examined where opposing associations as biomarkers for response and non-response are reported [34,35]. These conflicting data highlight the need for studies examining the functional role of identified SNPs in RA pathogenesis.

Signalling pathways involved in the propagation of chronic inflammatory processes are also potential sources of biomarkers for response to anti-inflammatory therapies such as anti-TNF. These include mechanisms driving and regulating the immune cell responses such as Toll- like receptor (TLR), NF kappa B (NFκB) and P38 mitogen activated protein kinase (MAPK) signalling pathways.

SNPs located within the TLR and NF-κB pathways such as rTLR signalling protein MyD88 (rs7744) and kinase CHUK (rs11591741) have been demonstrated to be associated with good response to anti-TNF therapy [36]. MyD88 and CHUK play integral roles in the NFκB signalling system, effecting TNF production and chronic inflammatory processes [37,38]. Interestingly, these two SNPs (rs7744 and rs11591741) remained significant against DAS28 or European League Against Rheumatism (EULAR) response criteria, where others lost significance.

The P38 signalling pathway which plays a major role in cytokine production, inflammation, and apoptosis has also been a pathway of interest for possible biomarkers. Response to anti-TNF therapy has been associated with SNPs within the genes coding for MAP3K1 (rs96844), MAP3K14 (rs4792847) [39] and MAP2K6 (rs11656130) [40] proteins. These findings demonstrate a likely importance of this pathway for understanding response.

Receptor-ligand interactions which can influence the magnitude and duration of immune responses also warrant consideration as biomarkers. Inherited predisposition to an activating or inhibitory immune capacity for response to any insult could critically influence the restoration of balance and tolerance required for therapy to be effective.

Killer-cell immunoglobulin-like receptors (KIR) are expressed on NK cells and T-cell subsets and play a role in balancing the activation/inhibition thresholds for these cells in response to HLA antigens. The importance of HLA ligands and KIR in influencing susceptibility, immune response and outcomes to infections and inflammatory diseases are well documented. In a recent candidate gene study a KIR-HLA combination that favours NK cell activation through the presence of activating KIR2DS2 and homozygosity for HLA-C1 or HLA-C2 was associated with responders to anti-TNF therapy [41]. These KIR and HLA-C biomarker findings require replication in larger cohorts, however the NK cell activating biomarker signature in responders is in agreement with a recently reported observation of an expanded population of activated NK cells in responders compared to non-responders [42]. Interestingly, an allele (HLA-C.*0701) attributed to the responder population in this study, has also recently been identified as a RA susceptibility gene [43].

The exponential increase in RA susceptibility genes in recent years has also led to examination of newly identified risk genes as potential biomarkers for response to therapy. It is possible that RA risk alleles may play a functional role in RA and response to therapy but they

could also simply be in linkage disequilibrium with another gene which actively contributes to RA or response. There are several risk genes however which given their function may also play important roles in response to therapy. CD226 is a membrane protein expressed on the surface of NK, T-cell and B cell subsets and plays a role in their activation and inhibition. A Gly307Ser substitution in the CD226 gene caused by SNP (rs763361) has been associated with autoimmune susceptibility, including RA, and also poor response to anti-TNF therapy [44,45]. It is possible that the cytoplasmic tail location of this SNP could alter the expression or signalling capability of this protein, effecting inflammatory responses. In the same study susceptibility gene AFF3 was investigated. AFF3 encodes a family of transcription factors which are preferentially expressed on lymphoid cells [46]. Carriage of the G allele (rs10865035) has recently been weakly associated with good response to anti-TNF therapy [45].

Currently one of the forerunners for theranostic biomarkers is the Protein tyrosine phosphatase receptor–C (PTPRC) gene also known as CD45. PTPRC performs essential modulation of T and B-cell responses by negatively regulating cytokine receptor signalling [47]. PTPRC is an RA susceptibility gene [48] which has been demonstrated to play a dual role in both risk and response to anti-TNF therapy in RA. In a large study of 9 RA cohorts carriership of the G allele (rs10919563) at the PTPRC locus was associated with good response to anti-TNF therapy [49]. The association of the PTPRC locus with response to therapy has since been replicated in an additional large cohort which appears to confirm the biomarker potential of this SNP [50].

Chronic inflammation is the net result of many genetic influences and thus the multiple effects of an anti-inflammatory drug such as anti-TNF are unlikely to be altered by a single gene or pathway. This is supported by the current failure to identify a single dominant gene which can predict response to therapy in RA. The attentions of many research groups now focus toward multi-gene/pathway panels and GWAS. With these approaches it may be possible to produce gene-panels will provide the most powerful predictive combination for response to therapy and enable theranostic solutions in RA.

Considerations

It is difficult to ascertain if a biomarker for response to therapy affects treatment outcomes through effecting disease risk, diagnosis, prognosis or directly undermines treatment efficacy. Currently accepted biomarkers for RA appear to have influence in each of these categories. This is demonstrated by HLA allele carriage which can influence disease susceptibility, the production of autoantibodies- effecting prognosis and also influence response to therapy. For example the HLA-SE, HLA-DRB1*03 alleles and HLA-DRA/BTNL2 SNP (rs1980493) have all been associated with the presence or absence of anti-CCP antibodies [26,27]. Subsequently, anti-CCP positivity and titre have been shown to adversely influence disease activity and response to anti-TNF treatment [51,27]. The precise functional role of these genes in each of these disease stages still remains to be determined. Perhaps genes such as the HLA loci which are known to influence RA from presentation to outcome will prove the most robust biomarkers and provide clues as to the aetiology of RA.

The discovery of theranostic biomarkers is confounded by differences in the methods which are used to determine clinical response to therapy. The most commonly employed being DAS, ACR, EULAR, Simplified (SDAI) or Clinical (CDAI) Disease Activity Index criteria to assess disease activity and therefore treatment outcomes. Each method involves all or a combination of joint evaluation to varying degrees, and laboratory analysis of acute phase proteins such as Erythrocyte Sedimentation Rate (ESR) or C - reactive protein (CRP), and patient/physician subjective measures for disease activity or pain. The clinical use of these methods have been reviewed and recommended by the ACR [52], however their adoption and translation is known to vary across rheumatology centres. Perhaps for a theranostic biomarker to be truly clinically useful, it should retain predictive value for response irrespective of the methods used to assess improvement in disease activity.

The majority of studies for response biomarkers to date have incorporated several anti-TNF drugs within the 'treated' group, which carries potential for bias normally avoided in studies with cohort allocation. This collation of treated patients is likely driven by the necessity to sample large numbers of patients required for genetic analysis, from often financially limited patient populations. In fact, such studies which truly reflect 'real life' clinical practice, are perhaps the most likely to derive biomarkers which will remain useful as additional anti-TNF drugs join the treatment paradigm. Anti-TNF therapy was the first biologic class to come to market in RA. With the addition of alternative mechanism of action drugs such as rituximab and abatacept, the rheumatologist and patient now have options beyond anti-TNF therapy, making it even more valuable to have the ability to predict response to therapies. This will ensure the most appropriate treatment in a timely manner for each individual patient.

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