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Biomarker-guided stratification of autoimmune patients for biologic therapy

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Autoimmunity results from an intersection of genetic and environmental factors that cause patient-specific perturbations in immune homeostasis. Defining autoimmunity-associated genetic factors has led to mechanistic insight into underlying etiologies, and the development of many biologic therapies that target the immune system. However, biomarker-informed pairing of patients with optimal biologic therapy is lacking. Here, we discuss platforms commonly used to find biomarkers that predict response to biologic therapy in autoimmunity and highlight recent biomarker discoveries. We also outline how the lack of assay standardization is a barrier to successful biomarker validation. Finally, we argue that the successful development of companion biomarkers for biologic therapy requires collaborative approaches that integrate multiple platforms and enable comprehensive measurement of multiple immune pathways.

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Introduction

Autoimmunity results when there is an unfavorable intersection of genetic pre-disposition and environmental conditions that lead to a breakdown of immune tolerance. Although the clinical manifestations of autoimmunity may be similar between patients, the underlying immune pathophysiology is patient-specific. Advances in our understanding of autoimmune etiology have led to an explosion of new therapies which target a wide variety of immune pathways. For example, antibodies, recombinant proteins or small molecules that target cytokines, leukocyte trafficking, costimulatory molecules, lymphocyte growth/maturation factors, or specific cell lineages have either recently entered, or will soon, enter the market [1,2]. A common theme for all of these therapies is that they are only expected to be of clinical benefit in a portion of patients; yet, there is a complete lack of tools to couple the right therapy with the right patient. With the increasing choice of therapeutic options there is an urgent need to find effective ways for rational and personalized selection of therapies.

The concept of personalized selection of autoimmune therapy is certainly not new. There have been many attempts to find biomarkers that predict response to therapy, primarily in the context of TNF-α inhibition, but currently none have made it to the point of clinical utility. Here we will briefly review different platforms being used in the search for biomarkers that predict response to therapy in autoimmunity, focusing on studies in the past 2 years in juvenile idiopathic or rheumatoid arthritis (JIA or RA, respectively), psoriasis, and inflammatory bowel disease (IBD) as these are the contexts where most new biologics are being applied. We will then discuss examples of how biomarker research is moving towards more systematic and multi-disciplinary approaches. Of note, many studies have sought biomarkers that measure response to therapy, but these will not be discussed here.

Common biomarker platforms for autoimmune patient stratification

Most of the past work to discover biomarkers to stratify and understand autoimmune diseases has focused on genetic linkage studies, gene expression analyses, and protein quantification. More recently, there is increasing activity in the area of immunologic-and/or metabolomic-based approaches. Responsiveness can also be related to anti-drug antibodies [3], and can be partially captured by current laboratory analyses, such as C-reactive protein [4], but these will not be discussed here.

Genetic association studies

The foundation of our mechanistic understanding of autoimmunity comes from genetic analyses, including the study of rare monogenic forms of autoimmunity [5] and genome-wide association studies (GWAS) for common forms [6]. It logically follows that genetic variation

may also be able to predict patient-specific etiology and thus response to therapy, with much research focused on finding single nucleotide polymorphisms (SNPs) in genes directly related to sensing, binding or effector function of the particular drug of interest. Small hypothesis-driven studies have largely been underpowered and resulted in conflicting data [7–9]. More recently, analysis of a large ($n = 427$) prospective cohort of Crohns disease (CD) patients with the Illumina Immunochip revealed several SNPs associated with non-response versus durable response to anti-TNF therapy. In addition, a composite genetic score predicted response to therapy with greater accuracy than clinical covariate prediction models [10]. Independent replication with well-defined and well-powered cohorts will be critical to determine if these genetic scores are truly suitable for clinical use.

Transcriptome studies

Many studies looking for gene expression-based correlations have focused on analysis of affected tissue. Expression profiling of mucosal biopsies from two cohorts of IBD patients revealed a 5-gene signature that predicted response to anti-TNF with 95% sensitivity and 85% specificity [11]. However, when a similar approach was used on vedolizumab-(anti-α4β7) treated patients, no pre-treatment gene expression profile that predicted response was found [12]. On the other hand, *ITGAE* mRNA expression in pre-treatment biopsies stratified responders versus non-responders to etrolizumab (anti-alphaE integrin) [13], a finding that was confirmed in an independent cohort [14]. In RA synovial tissue, a high baseline myeloid, but not lymphoid, gene signature predicted better response to anti-TNF [15]. In psoriasis, machine-learning with gene expression profiles of skin lesions, created 'molecular phenotypes' that predicted drug efficacy, possibly facilitating shorter and smaller clinical trials in the future [16••]. Cytokine mRNA biopsy profiling identified the IL-6 family cytokine oncostatin M (OSM) as being highly expressed in IBD. Subsequent analysis of >200 IBD patients from multiple cohorts revealed that high pre-treatment expression of OSM was strongly and consistently associated with failure of anti-TNF therapy [17••]; making this one of the most promising biomarkers for predicting response to TNF therapy to date.

In terms of peripheral blood, pioneering work in Systemic lupus erythematosus (SLE) revealed that analysis of coordinately-expressed mRNA transcripts is a powerful way to stratify patients into different disease groups. Specifically, microarray analysis of blood from 62 SLE patients revealed IFN-response modules that classified patients into groups which exhibited different patterns of disease activity, possibly allowing stratification for IFN therapy [18]. A more recent publication from the same group included longitudinal sampling, enabling transcriptome-based separation of SLE patients into 7 distinct disease groups [19••]. Transcriptome analysis of blood has also been fruitful in RA, with a validated 15-gene signature that predicts response to tocilizumab (anti-IL-6R) [20]. Thomson *et al.* used public datasets to develop a blood-based gene expression classifier for RA that can identify likely non-responders to anti-TNF treatment [21], which is remarkable given the differences in microarray platforms and patient populations used for this retrospective study.

Protein-based studies

Protein-based studies have primarily focused on analysis of serum or plasma and include both targeted/hypothesis-driven approaches and unbiased/exploratory studies. Predictive biomarkers found by hypothesis-driven approaches include expression of inflammatory chemokines for response to anti-TNF in RA [22], and low levels of soluble IL-6R for tocilizumab [23]. Analysis of 31 proteins in RA serum revealed predictive algorithms, and confirmed that soluble IL-6R predicts response to tocilizumab [24]. Two studies by Ortea *et al.* used a non-biased, mass spectrometry (MS)-based approach to find serum proteins which were differentially expressed in RA patients pre-treated with anti-TNF [25,26], but there was no correlation between the two datasets, likely because the patient cohorts for each group were very small ($n = 4$). As proteomic-based studies with limited sample numbers can be subject to false positives [27] it is important to verify results in validation cohorts, preferably using a subset of analytes to determine sensitivity, specificity and predictive capacity. Recently, a non-targeted proteomic analysis of serum from psoriasis patients, followed by a targeted MS-based validation study, found a 57 analyte-biomarker panel which predicted response to anti-TNF, and surprisingly also abatacept (CTLA-4-Ig) [28].

Beyond blood-based protein characterization, there are some intriguing studies using confocal laser microscopy to analyze the binding of a fluorescently-labeled biologic in a patient, which is presumably a surrogate measure of the amount of the biologics target at the site of inflammation. This concept was used successfully to measure adalimumab binding to membrane-bound TNF (mTNF), revealing that high expression of mTNF strongly predicts response to treatment in CD [29]. As discussed below, a similar approach is also being tested for predicting response to vedolizumab in Ulcerative Colitis (UC) [30].

Cellular immune-based studies

GWAS studies predict that alterations in immune cell proportions, phenotype and/or function may be associated with patient-specific responses. Although non-heritable influences dominate immune cell frequencies, cytokine responses, and serum proteins [31••], there are many examples of straightforward links between genetic variants and immune phenotypes. For instance, the protective R381Q *IL23R* variant is associated with