Exploring the landscape of rheumatoid arthritis: piecing together risk factors and autoantibodies

Wesemael, T.J. van

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Letter

From phenotype to pathophysiology – placing rheumatic diseases in an immunological perspective

T.J. van Wesemael, T.W.J. Huizinga, R.E.M. Toes, D. van der Woude

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Rheumatic diseases have many overlapping clinical features which can complicate the differentiation between shared and unique underlying immunopathological mechanisms. Fortunately, a wealth of information on the genetic basis of rheumatic diseases has become available due to new research techniques. These genetic data can elucidate common denominators versus unique features of the pathophysiology of rheumatic diseases. We therefore capitalized on the gain of genetic knowledge to make a cutting-edge overview of the immunopathology of rheumatic diseases, and assessed the validity of our model based on its congruence with medication use.

For rheumatic diseases with a prevalence of 1/10.000 or higher, and for which sufficient genetic data were available (gout, rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), familial Mediterranean fever (FMF), systemic lupus erythematosus (SLE), Behçet's disease, primary Sjogren's syndrome (pSS), systemic sclerosis (scleroderma, SSc), and giant cell arteritis (GCA) literature reviews between 2017 and 2019 on genetic risk factors were obtained. Genetic risk factors were classified as contributing to innate and/or adaptive immune responses; contributing to B cell-function or belonging to the human leukocyte antigen (HLA) class I locus. Using the prevalence of autoantibodies as a second key factor, the contribution of innate versus adaptive immunity, of B cell-factors, and of HLA class I alleles was estimated for every illness. Detailed methods, references and the genetic risk factors per disease are provided in the supplementary file.

Figure 1A provides an overview of the location of the various rheumatic diseases in the immunological landscape. The position on the X-axis is determined by the relative contribution of the adaptive versus innate immune system, the position on the Y-axis reflects the contribution of B cell-factors (upper part) and HLA class I alleles (lower part). When the analysis was repeated for genetic factors replicated in different ethnicities, the results were similar (supplementary table three).

This depiction allows us to distinguish three distinct categories of rheumatic diseases (Figure 1B). The diseases in the blue box (SLE, RA, pSS, and SSc) are mainly characterized by the influence of B cells/adaptive immunity on disease pathogenesis. Although the genetic background of these diseases is to some extent quite heterogeneous with innate, adaptive, and B cell-influences, this disease subgroup is unique in the sense that autoantibodies and mutations in genes coding for B cell signaling and proliferation are found in all four diseases. The distinguishing feature of diseases in the yellow box, containing AS, Behçet's disease, and PsA, is the strong association with HLA class I alleles. In AS, an

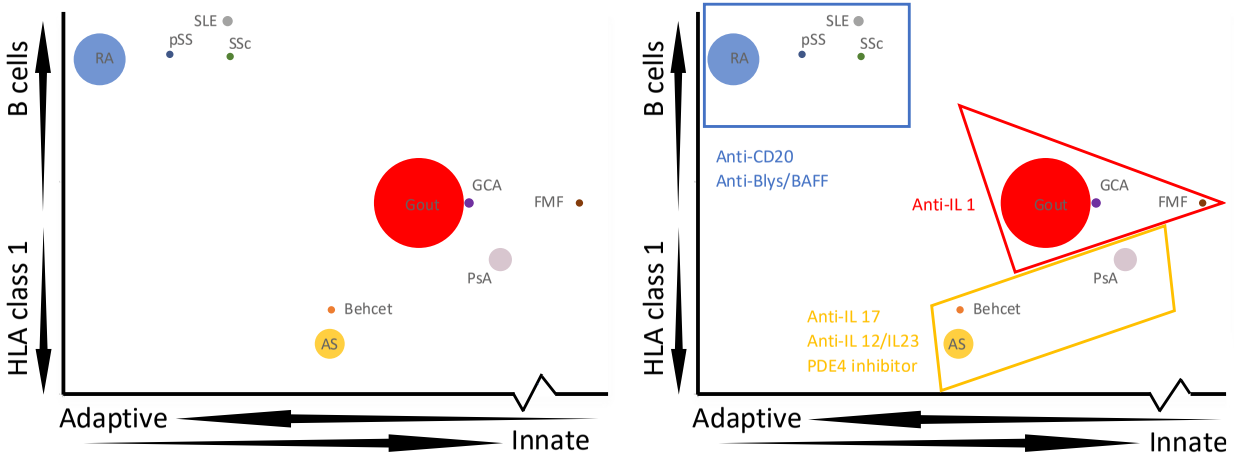


Figure 1. Distribution of rheumatic diseases in the immunological landscape

Figure 1A. The position of a rheumatic disease is determined by the ratio of the sum of genetic predispositions and autoantibody prevalence for innate versus adaptive immunity on the X-axis and for B-cell (+) and HLA class 1 (-) on the Y-axis. The size of each dot is based on prevalence in the Caucasian population, however for diseases with a prevalence lower than 0.2/1000 (pSS, SSc, Behçet's Disease, FMF) the dots are plotted as 0.2/1000. For the sake of legibility of the figure, the symbol depicting GCA was moved slightly to the right to avoid it coalescing with gout.

Figure 1B. As 1A with boxes applied around clusters of diseases.

* GCA prevalence in >=50 year old.

AS – ankylosing spondylitis, Behçet – Behçet's disease, FMF– familial Mediterranean fever, GCA – giant cell arteritis, PsA– psoriatic arthritis, pSS – primary Sjogren's syndrome, RA – rheumatoid arthritis, SSc – systemic sclerosis (scleroderma), SLE – systemic lupus erythematosus (BLyS) – anti-B Lymphocyte Stimulator, PDE4 phosphodiesterase type four, IL – interleukin

association is found with HLA-B27, in Behçet's disease with HLA-B51 and in PsA with an asparagine or serine at position 97 of the HLA-B molecule with the strongest association for HLA-B27.[1-3] Diseases in the red box (gout, familial Mediterranean fever, and giant cell arteritis) are characterized by an aberrant innate immune response which leads to the production of pro-inflammatory cytokines. In these diseases, dysregulation of inflammasome activation plays a role, which ultimately leads to an increased secretion of the pro-inflammatory cytokines interleukin (IL)-1B and IL-18.[4-6]

In each of the groups described above, a unique family of targeted therapy is given: in the blue box: anti-B cell therapy (such as anti-CD20 and anti-B Lymphocyte Stimulator); in the yellow group: IL-17 inhibitors, anti IL12/IL23 antibodies, and phosphodiesterase type four (PDE4) inhibitors; in the red box: targeted therapies against IL-1.

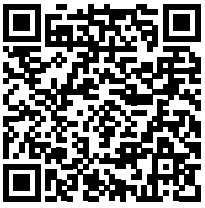
The limitations of this study include, first of all, that data from in vitro (e.g. cellular) studies or in vivo (e.g. murine) investigations were not taken into account. These studies were not included because in vivo and in vitro studies are hard to compare and are difficult to quantify in a numerical way. Secondly, the decision to ascribe the function of a gene influencing the immune system to the innate versus adaptive part of the immune system, can nonetheless be considered debatable, although based on careful consideration. Many genetic risk factors are not classifiable in a black-or-white manner, which is why we have indicated on the axes that all positions are relative, and all diseases (except perhaps FMF and gout) contain innate as well as adaptive features. Another limitation is that the genetic risk factors per disease were compiled using recent literature reviews rather than performing a new systematic literature review per disease for this project. Therefore, some recently described genes may have been missed. However, it appears likely that the most relevant/potent genetic risk factors per disease had been identified prior to the date of our literature search, and omissions will -most probably- not have influenced the overall results. Finally, the post-hoc grouping of disease into three categories could also have been done in another manner, with for example PsA belonging to the group of "innate-like" diseases with gout, GCA and FMF. This grouping is thus not intended to constrain the interpretation of our figure. Instead, we aspired to allow for various insights and interpretations in choosing a topographical lay-out to visualize the relative proximities between many different diseases.

Strengths of the current approach include the empirical evidence afforded by basing the analysis on genetics and the presence of autoantibodies. Secondly, the model appears to be robust, since it does not substantially change when genes found in more than one ethnicity are included in the analysis.

To conclude, we have provided a visual overview of the position of various rheumatic diseases in the immunological landscape based on their association with genetic risk factors and autoantibodies. The congruity with the use of current targeted therapies demonstrates the applicability of our visual model to not only daily clinical practice, but also for the development of new therapeutic agents.

Supplementary material

Supplementary material available at: https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00369-6/fulltext



Author contribution

D. van der Woude: conceptualization, verification of the data, review and editing of the article

T.J. van Wesemael: conceptualization, literature search, figure, data collection and analysis, writing of the article

R. E. M. Toes: conceptualization, review and editing of the article

T.W.J. Huizinga: conceptualization, review and editing of the article

Declaration of interests

T.J. van Wesemael: no conflict of interest
T.W.J. Huizinga: no conflict of interest
R.E.M. Toes: no conflict of interest
D. van der Woude: no conflict of interest

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Not applicable

Data sharing Statement

All data used for this manuscript are already available, since the data that we used for this study are all from published articles (see references).

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