Editorial

Pharmacogenomics

For reprint orders, please contact: reprints@futuremedicine.com

Pharmacogenetics and psoriasis: is targeted treatment a possibility?

Yiannis Vasilopoulos*,[1]

[1]Department of Biochemistry and Biotechnology, University of Thessaly, Larissa, Greece

* Author for correspondence: iovasilopoulos@bio.uth.gr

"Psoriasis (PS), is amongst the most common autoimmune diseases affecting approximately 2% of people globally, while it can also be a great model disease for the development of pharmacogenetic as well as pharmacogenomic markers of treatment response, with ready access to objectively validated clinical outcome measures as well as ready access to diseased tissue"

First draft submitted: 25 July 2017; Accepted for publication: 25 July 2017; Published online: 27 November 2017

Keywords: autoimmune variation • biological networks • gene–environment interaction • psoriasis • systems biology

Autoimmune disease, characterized by the host's immune response against self-antigens, manifests in more than 100 different types and affects more than 10% of the world's population, causing significant morbidity and high financial burden. Psoriasis (PS), is amongst the most common autoimmune diseases affecting approximately 2% of people globally, while it can also be a great model disease for the development of pharmacogenetic as well as pharmacogenomic markers of treatment response, with ready access to objectively validated clinical outcome measures as well as ready access to diseased tissue.

PS, as is the case for most complex diseases, is the net outcome of genetic and environmental factors whose multilevel interaction is still poorly understood. Intense research efforts to date, had focused on examining these factors in isolation, resulting in hundreds of genetic risk loci identified, many of which are shared between the members of the autoimmune disease spectrum. Such an example are PS, psoriatic arthritis and rheumatoid arthritis (RA), three often related autoimmune disorders, where dysfunction in integrated signaling pathways affecting different constituents of the immune system results in varying clinical features in the three diseases. However, 70% of the PS patients are being affected by psoriatic arthritis [1]. Not surprisingly many identified genetic risk variants are common to all three diseases, with the human leukocyte antigen region on chromosome six being the prominent one. This genetic overlap is an indication of overlap of common causal pathways. Pharmacotherapy is also shared among these diseases, with treatments such as cyclosporine, methotrexate and anti-TNF-α therapies commonly used in daily clinical practice. Notwithstanding their effectiveness, these therapies like the ones which block TNF-α are quite costly while response to treatment is highly variable. In fact, recent cost analyses of these drugs, using real-world drug data on major autoimmune diseases, have yielded estimates from $7993 per year ranging up to $48,000 per year. In addition, there is a wide inter-individual variation in drug efficacy reaching up to 50–70%, which could be partially attributed to the patients' genetic background [2]. Since these diseases share common immunological pathways they could share same pharmacogenetic markers. Indeed, recent work by us and others identified some common and in other cases distinct pharmacogenetic markers that predict efficacy in PS and RA which have been further validated by subsequent meta-analyses in larger cohorts [3,4]. However these studies have been based on candidate gene analysis and may explain some of the inter-individual variation. Both in terms of disease risk causality and prediction to therapy, variation is poorly understood. In all three diseases, genetic background plays a significant role, as twin studies show concordance rates in monozygotic twins ranging from 13% in RA to 60% in PS [5]. Although high, these numbers also reveal that environmental factors are also of critical importance in disease manifestation. Since we have entered the era of systems biology, it is no longer ideal to consider a gene in isolation but rather to explore and identify all possible combinations between genetic and environmental factors that interact in autoimmune disease (as in all complex diseases) which will give us the

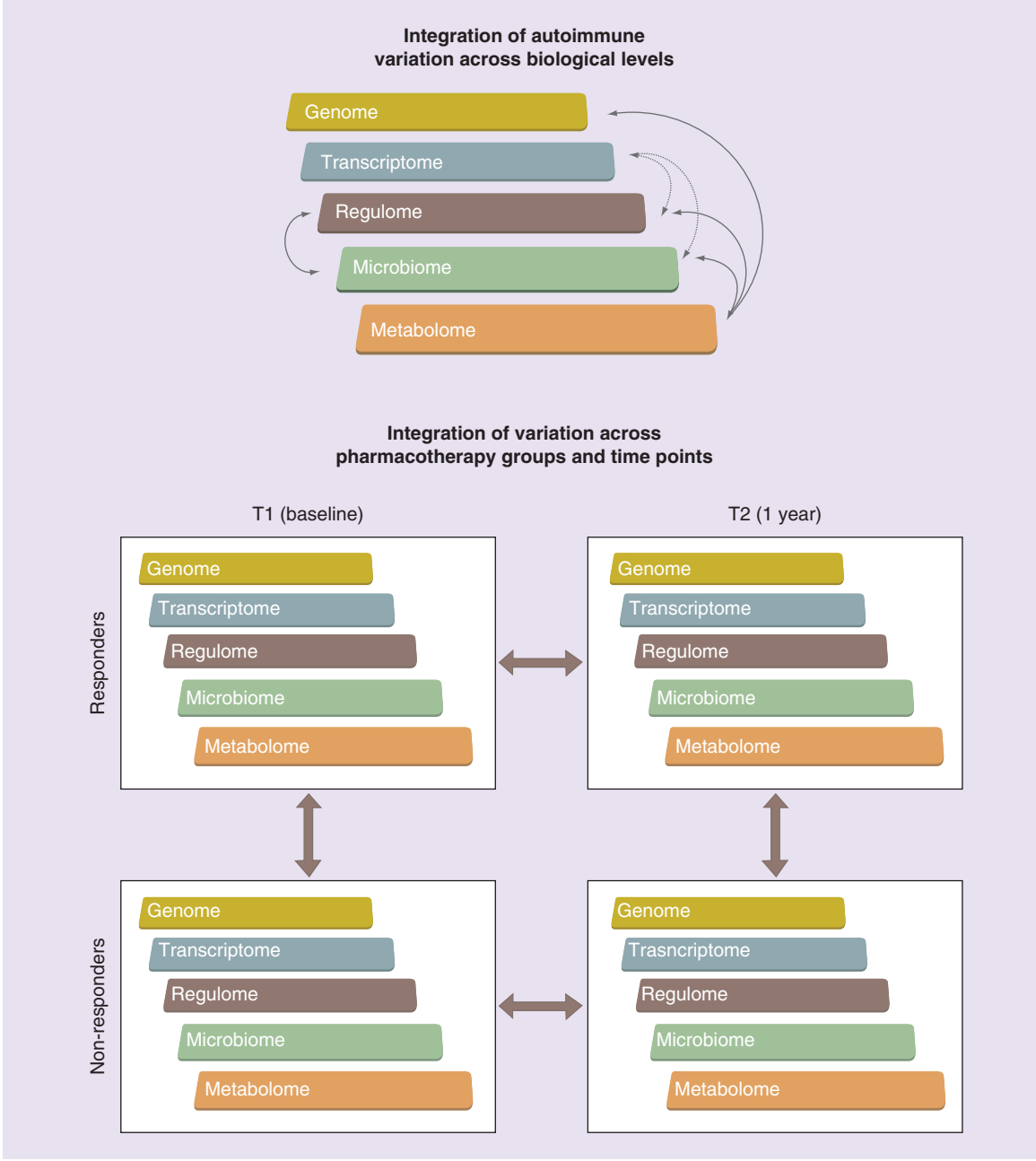

Figure 1. Schematic overview of an integrated trans-omic strategy in studying autoimmune variation in pharmacotherapy of psoriasis and autoimmune diseases.

potential to fully capture disease risk profile and uncover underlying molecular mechanisms contributing to disease pathogenesis but also inter-individual variation to drug therapy.

The microbiome is beginning to emerge as the key liaison in this complex and of dynamic nature, gene–environment interaction. Each and every individual harbors a personalized set of microbial populations whose genome multiplies host's genetic variability by approximately 100-times. The microbiota comprised of commensal bacteria, viruses and other microorganisms are essential to maintain health, as for example some microbiome products allow humans to digest certain plant polysaccharides. However changes in their abundance and composition, a process known as dysbiosis, could be the triggering mechanism in eliciting disease while at the same time underline inter-individual variability as the microbiota composition would have been evolved in response to the individual's unique lifestyle and other genotypic and phenotypic factors. New emerging data suggest that changes in micro-

biome could alter immune homeostasis and trigger proinflammatory processes as it was shown in the case of Crohn's disease and Type II diabetes. For example, lipopolysaccharide is the major component of the outer membrane of Gram-negative bacteria, like the ones of the *Bacteroidetes* phyla, whose changes may elicit a vast proinflammatory immune response [6]. More importantly the microbiota can regulate immune homeostasis by causing epigenetic modifications of the host's DNA [7]. For example, the presence of certain intestinal commensal bacteria can cause DNA methylation of TLR-4, compared to sterile environment [6]. Resident viruses also constitute a big proportion of the microbiome community and examples like the herpesviruses cytomegalovirus (CMV) and Epstein–Barr have an effect in DNA methylation (CMV-IFNγ) and histone acetylation, respectively [8].

Epigenetic modifications of host's genome may indeed function as an integrator of environmental input and the underlying genetic code. This is of particular interest for autoimmune diseases, as the human immune system is composed of a vast and diverse collection of cell types, each of which is adapted to bear a particular role in the organism's defense system against insults that aim to disrupt its homeostasis and under that principle immune cell transcription must be extremely plastic in order to maneuver through the continuous reformatting of the conditions and ensure the proper maintenance of the immune system [9]. Environmental influences as depicted by changes in the microbiota abundance and composition may have a profound effect in the fidelity and variation of the human gene regulatory landscape and thus in inter-individual variability both in terms of disease etiology and progression as well as in prediction of the efficacy/toxicity of therapeutic approaches of autoimmune diseases.

A holistic evaluation of the perturbations of pharmacotherapies in biological systems and thus of integration of variation in autoimmune diseases (Figure 1) could be achieved by the emerging concept of 'pharmacometabolomics informs pharmacogenomics'. The determination of the metabolic state of an individual, defined as the net outcome of genetical (host and microbiome) and environmental (diet, lifestyle, pharmacotherapy and microbiome) or 'metabotype', could reflect the whole molecular variation and thus in combination with other 'omic' data provide novel insights into mechanisms underlying inter-individual differences in disease risk and progression, and drug response phenotypes [10]. Technological advances in the last years have made it feasible to accurately measure large numbers of metabolites in plasma or tissues, which at first could give valuable information regarding what microorganisms do in their complex local communities by a pinpoint identification of the metabolites produced. But they can also be used to guide pharmacogenomic studies that are based on genome-wide association analyses (GWAS), by means of using computational imputation methods that can infer the alleles of hidden variants and use those inferences to test the hidden variants for association [11]. The availability nowadays of open access public databases like the '1000 Genomes Project' and information technologies, coupled with more affordable and reproducible technology with minimal input material further consolidates this approach. It is therefore now possible to merge and integrate large datasets generated by the use of different omics approaches in order to increase our understanding of the molecular basis for variation in disease risk and drug response phenotypes.

Conclusion

Targeted treatment for PS as well as for other autoimmune diseases is feasible when information will be available from all biological levels that constitute the cell's machinery that manifests autoimmune disease. This combined growth in knowledge will ultimately provide novel and high translational value information regarding inter-individual variability towards differential disease diagnosis, progression and response to therapy and will further enhance our understanding of the molecular mechanisms underlying PS and other autoimmune diseases.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Costenbader KH, Gay S, Alarcón-Riquelme ME, Iaccarino L, Doria A. Genes, epigenetic regulation and environmental factors: which is the most relevant in developing autoimmune diseases? *Autoimmun. Rev.* 11, 604–609 (2012).

2 Cheng J, Feldman SR. The cost of biologics for psoriasis is increasing. *Drugs Context* 3, 212–266 (2014).

3 Prieto-Pérez R, Cabaleiro T, Daudén E, Ochoa D, Román M, Abad-Santos F. Pharmacogenetics of topical and systemic treatment of psoriasis. *Pharmacogenomics* 14, 1623–1634 (2013).

4 Márquez A, Ferreiro-Iglesias A, Dávila-Fajardo CL *et al.* Lack of validation of genetic variants associated with anti-tumor necrosis factor therapy response in rheumatoid arthritis: a genome-wide association study replication and meta-analysis. *Arthritis Res. Ther.* 16(2), R66 (2014).

5 Bogdanos DP, Smyk DS, Rigopoulou EI *et al.* Twin studies in autoimmune disease: genetics, gender and environment. *J. Autoimmunity* 38(2), J156–J169 (2012).

6 Takahashi K, Sugi Y, Hosono A, Kaminogawa A. Epigenetic regulation of *TLR4* gene expression in intestinal epithelial cells for the maintenance of intestinal homeostasis. *J. Immunol.* 183(10), 6522–6529 (2009).

7 Ménard O, Butel MJ, Gaboriau-Routhiau V, Waligora-Dupriet AJ. Gnotobiotic mouse immune response induced by *Bifidobacterium* sp. strains isolated from infants. *Appl. Environment. Microbiol.* 74(3), 660–666 (2008).

8 Grossman C, Dovrish Z, Shoenfeld Y, Amital H. Do infections facilitate the emergence of systemic sclerosis? *Autoimmunity Rev.* 10(5), 244–247 (2011).

9 Marques-Rocha JL, Samblas M, Milagro FI, Bressan J, Martínez JA, Marti A. Noncoding RNAs, cytokines, and inflammation-related diseases. *FASEB J* 29(9), 3595–3611 (2015).

10 Neavin D, Kaddurah-Daouk R, Weinshilboum R. Pharmacometabolomics informs pharmacogenomics. *Metabolomics* 12(7), 1–6 (2016).

11 Kaddurah-Daouk R, Weinshilboum RM. Pharmacometabolomics research network. *Clin. Pharmacol. Ther.* 95(2), 154–167 (2014).