IMMUNE-MEDIATED INFLAMMATORY DISEASES: A NEW MULTIDISCIPLINARY CONCEPT

Dominique Baeten,* Martin van Hagen,** Fernando Magro,*** Paulo Filipe,**** Joao Eurico Fonseca*****

Rheumatology has traditionally been one of the most clinically based disciplines within internal medicine. Careful history and physical examination are the cornerstones of diagnosis, choice of treatment, and follow-up. Not surprisingly, the classification criteria for most of the rheumatic diseases heavily relies on phenotypic features such as poly- versus oligo-articular disease, symmetric versus non-symmetric arthritis, photosensitivity, skin rash, subcutaneous nodules, and sicca symptoms between others. With the exception of specific autoantibodies, most laboratory findings have a poor specificity and can occur in a wide variety of disorders. Imaging abnormalities such as subchondral cysts, pencil-in-cup deformities, and sacroiliitis have a much higher specificity but often appear only in full-blown, established disease. Accordingly, the increasing focus on early diagnosis and treatment confronts rheumatologist with the limitations of the traditional phenotypic approach and raises the question whether alternative approaches can overcome these limitations and thereby create added clinical value.

The field of rheumatic disorders and, more in general, immune-mediated inflammatory diseases (IMIDs), has dramatically changed over the last decade due to rapid developments in cellular and molecular biology. As a prototypical example, the discovery of citrulline as a crucial constituent of the epitopes recognized by rheumatoid arthritis (RA)-specific serum reactivity has lead to major clinical innovations. Not only did anti-citrullinated protein antibodies (ACPA) turn out to be very useful as diagnostic tool in early arthritis but they also allowed for the first time to identify individuals at risk of developing RA and thereby to study the preclinical phase of the disease. Moreover, there is increasing evidence that the presence or absence of ACPA defines two separate RA subgroups with a distinct pathophysiology and response to treatment. ACPA are certainly not the only example of the impact of molecular insights on the daily clinical practice. The identification of mutations in intracellular proteins involved in the inflammatory reactions led to a molecular rather than phenotypic classification of fever syndromes with direct consequences for treatment choice. At a different level, genome-wide association scans (GWAS) in common IMIDs have now identified a wide panel of risk-conferring SNPs. Interestingly these GWAS have taught us two paradoxical lessons. Firstly, the association of specific genes with a variety of IMIDs points toward common or ‘public’ pathways of inflammation shared between different phenotypic entities. Prototypical examples are SNPs in PTPN22 which are associated with multiple autoantibody-associated autoimmune diseases and SNPs in the IL-23 receptor which are associated with ankylosing spondylitis, Crohn’s disease, and psoriasis. Secondly, however, it appears that the multiple genes are associated with a single phenotypic disease entity and that each of them confers only a very modest risk. This emphasizes the pathophysiologic heterogeneity within one single phenotypic disease entity and the presence of ‘private’ pathways of inflammation in subsets of patients. The challenge is now to translate these genetic and molecular patterns into clinical practice in order to rationally redefine disease entities according to pathophysiologic mechanisms rather than phenotype.

The importance of this challenge should be seen
in the context of a second major evolution in the field of IMIDs over the last decade: the successful introduction of targeted therapies with prototypical examples such as cytokine blockade, lymphocyte subset depletion, and costimulation blockade. The availability of these powerful treatments has 3 major implications. Firstly, the potential of targeted therapies to halt disease progression and eventually induce clinical remission has further emphasized the need for very early treatment. Ideally, one would like to treat before the transition from early to chronic disease or even before the transition of preclinical to early clinical disease. This approach implies a molecular rather than phenotypic definition of diagnosis, prognosis, and remission. Secondly, as the biologic treatments target very specific disease pathways, it becomes increasingly important to tailor the treatment to the individual disease process by assessing whether the targeted pathway is really driving the disease in an individual patient. Recent studies have indicated that clinical and phenotypic features fail to predict adequately who will respond well to a specific targeted treatment. In contrast, molecular biomarkers related to the pathogenic mechanisms may prove superior to address this challenge. Thirdly, the targeted therapies also allow for the first time to probe the pathogenesis of IMIDs in vivo and to assess experimentally in our patients whether a particular disease is TNF-, IL-6, IL-1, T cell-, or B cell-driven. As such, these ‘human knock-down models’ provided by the targeted interventions may contribute to redefine the traditional disease concepts based on clinical and phenotypic associations. A prototypical example here is the relationship between skin psoriasis (PsO) and psoriatic arthritis (PsA). Although the phenotypic association between both manifestations did suggest that they are pathogenetically linked, the responsiveness of skin but not joint disease to T cell-directed therapies such as alefacept and efalizumab now indicates that there are clear mechanistic differences which have direct relevance for treatment.

As demonstrated by the latter example, the increasing insights in molecular and cellular processes as well as the use of targeted therapies also pulled down the frontiers between organ-specific disciplines and emphasized the added value of a multidisciplinary approach of IMIDs. Besides the previously discussed link with skin disease, it is striking that PsA displays large cellular and molecular similarities with other peripheral spondyloarthritides (SpA) despite clear phenotypic differences. Interestingly, the same cellular and molecular pathways have been evidenced in the inflamed gut of patients with inflammatory bowel disease (IBD). Taken together with the overlap between gut and joint disease in the HLA-B27 transgenic rat model and the shared responsiveness to TNF blockade, these studies strongly plea for a multidisciplinary translational approach of SpA and IBD by rheumatologists and gastroenterologists. Similar examples can be given for skin, eye, lung, kidney, and/or neurological involvement in systemic diseases such as systemic lupus erythematosus, systemic sclerosis, Behçet’s disease, or sarcoidosis. A multidisciplinary approach will not only contribute to decipher the pathogenetic mechanisms of disease but has direct clinical implications for the optimal treatment of single patients as well as for the rapid implementation of novel therapeutic options to many related IMIDs.

In conclusion, the rapid developments in cellular and molecular biology as well as the emerging therapeutic possibilities with targeted treatments plea for a redefinition of the rheumatic disorders in particular and the IMIDs in general based on their pathogenic mechanisms rather than their phenotype. This challenge requires intimate collaboration between basic scientists and clinicians in a translational perspective as well as a multidisciplinary interaction between different organ-specialists. Defragmentation of the knowledge and efforts in the field using this IMID concept will not only create added scientific and clinical value but will also allow to recruit broad public and political support for chronic inflammatory diseases as a whole at a similar level as for infectious diseases or oncology.

Correspondence to
Dominique Baeten, MD, PhD
Clinical Immunology and Rheumatology, F4-102, Academic Medical Center/University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands.
E-mail: D.L.Baeten@amc.uva.nl

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