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Translational Research in Immune and Inflammatory Diseases: What are the Challenges, Expected Advances, and Innovative Therapies?

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Abstract – Despite very different aetiologies and clinical expressions, advancing knowledge in the physiopathology and treatment of immune and inflammatory diseases (IID) prompts us to consider them as a whole. These are chronic, often incapacitating and painful illnesses that progress and destroy organs. Management by discipline too often leads to erroneous diagnoses and sometimes inappropriate treatment. More integrated translational research would further understanding of the complex relationships between cytokines and organ damage, which vary with the conditions and patients, making it possible to develop new biomarkers and personalize treatment. The research in France has very many strengths but its organization is fragmented. Better coordinated research into IID, which could be based on creating a strategic valorization field (*domaine de valorisation stratégique*, DVS) and thematic multi-organization institute (*Institut thématique multi-organismes* ITMO), would advance patient management.

Abbreviations: see end of article.

1. Introduction

Immune and inflammatory diseases (IID) are a family of a large number of chronic, incapacitating and painful illnesses, that progress and destroy organs. Phenotype expression is extremely varied and dependent on the autoimmune and autoinflammatory target organs. These targets may be single organs or more often several. These diseases share an unfavourable organ function and life-threatening

† Articles, analyzes and proposals from the Giens Workshops are those of the authors and do not prejudice the position of their parent organization.

prognosis, partly related to the lack of aetiological or definitively curative therapy. They are a heavy burden on the lives of patients and their families, and to a greater degree, on the use of health resources.

Each of these diseases affects a relatively limited population and their prevalence is very widely distributed, but together, they represent a significant population and include the majority of chronic illnesses. An initial approximation indicates an overall prevalence of 3% to 5% of the population, namely around 2 to 3 million people in France. By way of example, IID include rheumatic diseases, spondyloarthritis, chronic inflammatory bowel diseases (Crohn's disease and ulcerative colitis), psoriasis, sclerosing cholangitis, scleroderma, multiple sclerosis, lupus, autoimmune cytopenia, vesical and bullous illnesses, etc.

The available treatments are non-specific, more often symptomatic, and in all cases, administered long term. They involve different types of immunosuppressants, oral or injections, such as glucocorticoids, standard immunosuppressants (cyclophosphamide, azathioprine, mycophenolic acid) or biopharmaceuticals like interferons and anti-cytokine monoclonal antibodies. Patient management is often complex, multidisciplinary and requires adapted coordination between non-hospital and hospital settings. Faster progress in researching treatment solutions for these patients is a priority at the beginning of this 21st century. The round table focused its thoughts on possible changes in the organization of research structures in France.

2. Disease classification diversity but physiopathological similarities

The various phenotype presentations of these diseases have led to a classification, semiological, diagnostic and therapeutic approach that has been fairly organic over the past few decades. Management by discipline too often causes erroneous diagnoses and consequently delays appropriate treatment. In particular, organ classification of tissue lesions observed in these patients has long prompted the different medical specialities to consider the management of IID as too segmented, and thereby limiting the lessons one discipline can offer the other.

More recently, the multidisciplinary management of some diseases and the exchanges of interdisciplinary experiences, for example in rheumatology and gastroenterology, or in dermatology, have contributed to improving both the individual and collective management of these patients. These experiences were based of course on practical observations, but also on a physiopathological approach. In particular, IID share the involvement of epigenetics, cytokines and microbiota.

Indeed, autoimmune rheumatic diseases, beside a strict genetic determinism, are governed by epigenetic regulations on several levels, such as chromatin remodelling, transcription factors, alternative splicing, and micro-ribonucleic acid (microRNA). The significance of epigenetic abnormalities in developing autoimmunity has been studied mainly in systemic lupus erythematosus[1] and rheumatoid arthritis, but other studies also indicate the existence of deregulations in other diseases like scleroderma. In particular, overall deoxyribonucleid acid (DNA) hypomethylations, methylation changes to several gene promoters, histone modifications and abnormal microRNA expressions like miR-146 have been observed. Similarly, some molecules like hydralazine behave like epigenetic factors that can cause drug-induced lupus. While we are unsure whether these epigenetic aberrations are secondary to the development of these illnesses or whether they contribute to their triggering, the reversible nature of some observed changes does pave the way for new therapies.

IID also share some physiopathological mechanisms and notably the involvement of common cytokines, including tumour necrosis factor-alpha (TNF), interleukin-17 (IL-17), interleukin-6 and vascular endothelium growth factor (VEGF). We know for example that TNF is involved in interactions between T-lymphocytes, macrophages and endothelial cells in different diseases.[2] In addition, TNF is responsible for the activation of synovial fibroblasts in rheumatoid arthritis and intestinal fibroblasts and neutrophils in Crohn's disease. Similarly, we know of the pleiotropic nature of IL-17, which, whether it affects macrophage, dendritic cell, endothelial cell, fibroblast, osteoblast or chondrocyte, may induce from a same signal, a different biological and clinical response, possibly leading to infections, psoriasis, thrombotic disease, Crohn's disease or arthritis.[3]

Better knowledge of the biological factors involved, thanks to overall awareness of IID, should improve the development of therapies.

3. Challenges of a globalised research in IID-Quality of knowledge but many shortcomings

A number of problems common to these IID still need to be resolved before we move on to researching treatment solutions, including:

- lack of aetiological treatments, ultimate major challenge of any research;
- poorly known physiopathology, but with shared aspects;
- difficulty of developing animal models, which are still imperfect;
- complex implementation of *ex vivo* studies;
- lack of diagnostic, prognostic, response or relapse biomarkers;
- lack of feedback from the clinical setting to research laboratories, with an empirical use of available therapies;
- imperfect knowledge of the dose-response relationship of biopharmaceuticals.

More integrated research on this consistent set of diseases would enable progress on several points of difficulty, namely: