# Editorial

## Understanding and Prevention of the Evolution Toward Autoimmune Rheumatoid Arthritis: The New Challenge

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Knowledge of rheumatoid arthritis (RA) has finally reached the stage at which all diseases should be—we have begun to understand its diversity and how some of its variants begin, evolve, and ultimately, in only late phases of a dynamic evolution, manifest. This knowledge provides us with the opportunity to intervene in all phases of RA evolution.

### HOW WAS *DISEASE* ORIGINALLY DEFINED?

The classic classification of a disease is based on the actual symptoms and expected disease course, thus enabling prognostic information for patients and a basis for consistent testing and clinical use of medicines. This classification was the basis for trials and treatment before the era of molecular medicine and still is today.[1]

### HOW SHOULD *INFLAMMATORY DISEASE* BE DEFINED?

The use of molecular science to understand and treat diseases such as RA is currently redefining the concept of *disease* in a fundamental way. The first breakthrough for RA was the molecular characterization of established joint inflammation and the subsequent successful interference with inflammation via blockade of actions of cytokines and interference with functions of various immune cells. Interestingly, many of these therapies work well for several but not all inflammatory diseases, thus suggesting lumping and splitting of diseases into new groups in which different targetable inflammatory pathways are active.[2]

### WHAT WILL A DISEASE BE WHEN WE UNDERSTAND ITS ORIGINS AND LONGITUDINAL EVOLVEMENT?

Understanding of the origins of a disease requires knowledge of how susceptibility genes interact with environment and the resulting emergence of potentially disease-inducing molecular mechanisms. This understanding has classically been reserved for infections in which the interventions are vaccinations to prevent microorganisms to expand and prevent disease or identification and targeting the specific microbes early, preferably before major symptoms have occurred.

Only more recently have we approached such understanding of the gradual evolution of disease for immune-mediated disease such as RA. Three major findings opened the field. The first finding is the identification of immune reactions that are specific to some patients with RA (ie, immunity against molecules posttranslationally modified by citrullination as well as by a number of other modifications).[3,4] Second is the recognition that the development of the autoimmune form of RA is linked to the best known genetic and environmental risk factors for RA (HLA genes and exposure of airways to noxious agents such as smoke), whereas neither the genetic variants in HLA and certain other immune-related genes nor airway exposure such as smoking are risk factors for patients with RA who lack anticitrulline immunity and rheumatoid factor.[5,6] These findings enabled the development of hypotheses of how RA-specific immunity in the HLA-linked RA subset might be triggered at mucosal surfaces in the context of certain HLA and other gene variants.[7] The third major contribution was the discovery that the RA-specific immunity to posttranslationally modified antigens and rheumatoid factors almost always emerge before and not after onset of joint inflammation, hereby providing a classic argument for causality.[8–10] The fourth and so far incomplete fundamental contribution is whether and how these or other related immune reactions actually cause

symptoms that we may observe from the original triggering of immunity. Sometimes such symptoms occur in the context of inflammation at mucosal surfaces, for example, in the lung[11–13] or with periodontitis, sometimes later during the evolution of immunity without joint inflammation (pain, arthralgia, bone loss, and inability to work[14–16]) and finally in some of these individuals as joint inflammation, joint destruction, and the well-known c-morbidities of RA. This is the field, with so many unknowns and so much potential, to which this issue is dedicated.

In this new context, we thus need both a new nomenclature that describes the evolution of the different molecularly related disease states and the outcome measures that capture relevant longitudinal outcomes in these different states. The diagnostic, prognostic, and outcome measures need to be defined well enough to enable guidelines from regulators that can be used in the testing of diagnostics and interventions by industry and academia. Obviously, we also need new tools for patients and health care professionals to identify and monitor evolution of immunology and symptoms in new ways without putting new burdens on already highly stretched rheumatology care. I foresee a revolution in digital tools that will allow information to be captured and shared between patients and health care professionals. Only with such development in patient-driven prevention and care processes will we be able to transform care and prevention of the molecular events and disease symptoms that are described in this book.

Finally, I present an optimistic preview of the future. With the dynamic evolution of symptoms (diseases) from triggering of immunity in organs distant from joints, with an intermediate phase of immunity associated with nondestructive symptoms and with the final destructive attack on joint in a later phase, we will have great opportunities in all these phases. As far as I can see, RA science is in a fortunate situation in these respects compared with many other inflammatory diseases in which it is rarely known when and where disease-specific immunity may be triggered and how it may gradually evolve toward targeting of the end organ. Thus, research and solutions proposed in the current volume may serve as a demonstration example for many other chronic immune-mediated diseases as well.

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