# Synovial heterogeneity in rheumatoid arthritis: the key for rational patient stratification?

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Rheumatoid arthritis (RA) is one of the most frequent chronic inflammatory disorders, affecting nearly 1% of adults worldwide[1]. It is an immune mediated inflammatory disease that mainly targets the synovial tissue, leading to pain, deformaty, functional disability and, if untreated, to destruction of the affected joints[2,3]. RA causes considerable direct (e.g., joint replacement) and indirect morbidity (e.g., cardiovascular, infection and cancer risk), reduces quality of life and increases mortality, resulting in large medical and societal costs[3,4].

From a clinical perspective RA is characterised by the typical symmetric polyarticular involvement, frequently of hands and feet, and variable extra-articular manifestations. However, the spectrum of the rheumatoid disease is quite broad, with patients exhibiting very aggressive disease despite treatment, while others have a milder, slowly progressive phenotype with little damage and preserved function over time[3,5,6]. In the last decades, it has been shown that introduction of early effective therapy improves long-term outcomes including joint damage and disability[7]. The advent of biologic therapies and its inclusion in the RA therapeutic arsenal have further maximised clinical response in patients refractory to conventional synthetic disease-modifying antirheumatic drugs (DMARDs)[8,9]. However, biologics represent a significant cost (€10--12,000/patient/year)[10] and treatment response is far from uniform, with 30-40% of patients not responding to these drugs and optimal improvement being seen only in 20-25% of patients[11,12]. This clinical heterogeneity is still a reality in current management of RA patients and the inability to effectively treat a significant proportion of patients and prevent them from progressing to disability remains a clear unmet need.

With this in mind, and despite the considerable experience already accumulated in RA management, clear-cut predictors of prognosis and particularly of treatment response are indeed missing[2,13]. In daily practice, the clinician currently lacks valid tools to rationally select the most appropriate management strategy, as the available predictive algorithms perform poorly at the individual patient level and, most importantly, therapeutic choice remains empirical, as it cannot be determined in advance what will be the response to a given treatment [14]. Thus, both synthetic and - mainly - biologic DMARDs are chosen on a *trial-and-error* approach, with sequential use defined by historical and licensing reasons (e.g., TNF inhibitors commonly used as first-line biologics) rather than by established precise biomarkers translating different molecular pathology underlying mechanisms[8,9].

Significant progress has been made regarding the pathogenesis of RA and, although a clear aetiology cannot be established, it is thought that on a genetically-predisposing background a number of diverse triggers (e.g. microorganisms, smoking) can lead to breach of tolerance in secondary lymphoid organs or mucosal--associated lymphoid tissue and autoimmunity documented by autoantibodies production (e.g., rheumatoid factor, anti-citrullinated protein antibodies)[2,3]. While autoantibodies are found in the majority of RA patients and have been associated with poor disease outcomes, a causal pathogenic role has not yet been clearly established as they can be found years before disease onset without significant clinical or synovial changes and also in a proportion of healthy individuals[2,15].

Despite the several systemic features of autoimmunity in RA, the disease mainly localises to the synovial tissue as a result of a second hit, which has not been determined until now[16–18]. In fact, synovitis is the hallmark of rheumatoid disease and represents the driving force that leads to bone erosion and joint destruc-

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tion[19–21]. Still, significant heterogeneity has been reported in RA synovitis, both in terms of clinical outcomes, with some patients experiencing little progression despite persistent synovitis, and, most importantly, regarding pathobiological characteristics[19,22–25]. Distinct cellular and molecular synovial signatures have been described in the recent years, with around 30-40% of patients presenting either a strong lymphoid response with formation of B cell-rich ectopic lymphoid-like structures (ELS) or a diffuse myeloid infiltrate, with upregulation of specific genes associated with these inflammatory pathways[23,25]. Moreover, an additional 20--30% of patients exhibit little local inflammation, with a predominantly fibroblast-like signature, despite comparable levels of clinical activity[23,25].

It is thus apparent that, as for clinical features, RA is an heterogeneous condition also at the disease tissue level, linked to diverse molecular mechanisms that would require an appropriate specific therapeutic approach. The concept of *pathotype* emerges as the logical corollary of such pathobiological heterogeneity and better understanding of its relationship with clinical data and disease outcomes is likely to be crucial for moving one step closer to personalised therapy[23]. As an example, it would perhaps make more sense to start intense immunosuppressive therapy or even cell--targeted therapies such as B cell depletion with rituximab in a patient with intense lymphoid infiltrate and abundant ELS formation in the synovium, than if a pauci-immune fibroid synovial pattern was present. It is at this stage that routine synovial biopsies may play a pivotal role in the selection of the most appropriate treatment for individual patients. With the introduction of minimally invasive techniques such as mini--arthroscopy or ultrasound-guided synovial biopsies, the collection of synovial tissue has become significantly more tolerable, effective and accessible and can virtually be performed in any rheumatology centre[26,27]. Ultimately, every RA patient could have a pre-treatment synovial biopsy that would be informative of the most advisable treatment for each case. Albeit this may seem somewhat of a challenging paradigm to aim for, it was not until recently that in other areas such as oncology routine biopsy for tissue characterisation was adopted as standard procedure for every cancer patient, after major breakthroughs pointed the way to molecular diagnostics led therapies. It is precisely this gap that needs to be filled and it is exciting to be part of a time where important research is ongoing and substantial increment of the body of knowledge can be achieved, leading to better care and more effective and personalised treatments.

In summary, astonishing progress has been seen over the last two to three decades in the area of RA mechanisms of disease, prognosis and drug response. However, current treatment modalities are still ineffective and have a poor cost-effectiveness in a considerable number of patients, with individual treatment selection being done with little rational basis. Clinical variability might reflect the synovial pathobiology heterogeneity and understanding the complex interplay between systemic immunity, local tissue factors and bone/cartilage homeostasis is key to establishing this relationship. Synovial biopsies can, in this sense, constitute a valuable tool for the translation of research findings into the optimisation of RA patient care.

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