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Review

Molecular portrait of chronic joint diseases: Defining endotypes toward personalized medicine

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ABSTRACT

Joint diseases affect hundreds of millions of people worldwide, and their prevalence is constantly increasing. To date, despite recent advances in the development of therapeutic options for most rheumatic conditions, a significant proportion of patients still lack efficient disease management, considerably impacting their quality of life. Through the spectrum of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and osteoarthritis (OA) as quintessential and common rheumatic diseases, this review first provides an overview of their epidemiological and clinical features before exploring how the better definition of clinical phenotypes has helped their clinical management. It then discusses the recent progress in understanding the diversity of endotypes underlying disease phenotypes. Finally, this review highlights the current challenges of implementing molecular endotypes towards the personalized management of RA, PsA and OA patients in the future.

1. Introduction

Joint diseases, also known as musculoskeletal or rheumatic diseases, encompass over 200 distinct disorders that affect the musculoskeletal system, including joints, bones, muscles, and surrounding connective and soft tissues. These diseases stand as leading contributors to long-term pain and physical disability, impacting hundreds of millions of people worldwide, as well as constituting a huge burden on healthcare systems. While they share common anatomical connections, joint diseases exhibit a wide range of pathophysiological characteristics [1]. Rheumatic disorders such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and osteoarthritis (OA) are three distinct conditions that encompass a spectrum of heterogeneous symptoms ranging from local to systemic clinical manifestations. While RA is a prototypical autoimmune peripheral joint disease, PsA is a complex inflammatory condition which may variably affect the spine, peripheral synovial joints, and entheses. On the other hand, OA has traditionally been considered the strict result of a "wear-and-tear" mechanical phenomenon and categorized as a non-inflammatory arthritis. However, the growing understanding of numerous immune-mediated inflammatory processes occurring within the OA joint has made the distinction between inflammatory and degenerative disease increasingly blurred [2–4]. RA, PsA, and OA partially or almost completely lack therapeutic interventions effective in every patient, hence the importance of better understanding their pathogenic mechanisms to reduce their socioeconomic impact and detrimental effects on patients' quality of life [5].

Hitherto, substantial progress has been made in classifying rheumatic conditions to allow a timely diagnosis through the definition of distinct classification criteria [6–8]. From macroscopic clinical phenotypes, translational research then progressed in describing tissue-specific features, including cellular signatures, which paved the way for further explorations related to the molecular background behind the clinical manifestations, namely endotypes. Despite the recent advances in understanding RA, PsA and OA endotypes, the limited availability of tailored treatment options, as well as the challenges of employing endotype-driven therapeutic

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management in clinical practice currently limit the application of precision medicine in this field [9]. In the future, the design of innovative targeted therapeutic approaches and the implementation, when appropriate, of patient-centric, molecular pathology-driven clinical trials [10] will help reduce the socioeconomic impact and the detrimental effects of rheumatic conditions on individuals.

In this review, we first aim to provide a comprehensive description of RA, PsA and OA epidemiological and clinical features. We then explore how a better definition of clinical phenotypes has improved their management and underline the progress made in portraying molecular endotypes in these conditions from both joint tissue and peripheral blood perspectives. Finally, we highlight some of the challenges represented by implementing molecular endotypes towards the personalized management of RA, PsA and OA patients in the future.

2. RA, PsA, and OA: distinct conditions with various clinical features

RA, PsA, and OA are clearly distinct types of arthritis, though they share some clinical features. All three diseases share their target: the joint. RA primarily manifests in symmetric diarthrodial joints (typically, small joints of hands and feet, wrists, and knees) [11] and currently impacts 0.3 to 1.0% of the general population. Global estimates indicate that RA cases will increase 1.4-fold globally by 2040 [12]. PsA has a prevalence of approximately 1 to 2 per 1000 in the general population [1,13,14] and affects up to 30% of patients with skin or nail psoriasis (PsO)[15]. PsA preferentially involves peripheral joints, including large joints, with an asymmetric distribution [16]. OA, with an age-standardized prevalence of 5.5% in all world regions, is the most common joint disease, affecting almost 600 million people worldwide [17]. The number of adults with clinically diagnosed OA has increased by 134% between 1990 and 2020, along, notably, with ageing populations and the increased prevalence of obesity. OA can occur in any anatomical site, but it most typically involves the hip, knee, hand, foot, and spine [18]. Overall, considering the major individual, economic and societal burden of RA, PsA, and OA, and the constant progression of their prevalence, there is an urgent need to develop efficient clinical management strategies for these diseases.

Common rheumatological features among the three diseases include various levels of synovial inflammation, which leads to the shared "pain, swelling and stiffness" triad and, ultimately, to distinct features of bone and cartilage damage. While RA is archetypically considered synovitis-driven, synovial inflammation in itself is not pathognomonic of RA and can be seen in other rheumatic conditions such as spondyloarthropathies, an umbrella term for various rheumatic inflammatory entities including PsA [19]. Differently from RA, PsA is also characterized by periarticular disease manifestations such as enthesitis and tenosynovitis or dactylitis and soft tissue inflammation [15]. Although OA joints have long been considered as solely characterized by the deterioration of the cartilage, associated with bone hypertrophy (osteophytes and subchondral bone sclerosis), various degrees of synovitis are observed in OA and have been shown to associate with radiographic OA severity. Clinical evidence also suggest that synovitis is observed prior to the development of radiographic OA, therefore highlighting its key role in OA pathophysiology [20]. Therefore, it is now accepted that OA is a disease of the whole-joint, including the capsule or the ligaments. Although RA, PsA, and OA have certain well-defined characteristic clinical features, common presentations at the joint level, and overlapping extra-articular manifestations and comorbidities [21–23] can sometimes make it difficult to precisely define and distinguish these conditions. Overall, current clinical challenges for treating these joint conditions include a timely and accurate diagnosis, better patients' stratification, and the development of targeted therapeutic strategies.

3. Clinical phenotypes of RA, PsA, and OA: current knowledge and perspectives

3.1. The concept of clinical phenotypes

The heterogeneous nature of RA, PsA, and OA, their common association with both joint and systemic inflammation, and the presence of a broad spectrum of acute manifestations, can make an accurate early diagnosis very challenging. In the past, these knowledge gaps highlighted the need for a better classification of these conditions [24] and led to the establishment and subsequent revision of well-defined classification criteria in order to allow a simpler and more specific categorization of patients [6–8], especially in the context of clinical trials. By definition, clinical phenotypes represent the observable and specific set of clinical manifestations that describe a particular subgroup or type of a certain disease. These features can include a combination of symptoms, physical findings, laboratory results, and imaging characteristics. Considerable progress has been made in identifying clinical phenotypes for RA, PsA and RA, and an overview of their variety is presented in the next section.

3.2. Clinical phenotypes in RA, PsA, OA: the basis of patients' classification

The classification criteria for RA are based on joint involvement patterns, serologic features (i.e., rheumatoid factor -RF- and anti-citrullinated protein antibodies -ACPA-), acute-phase reactants (i.e., erythrocyte sedimentation rate -ESR- or C-reactive protein -CRP-), and symptom duration (whether < 6 weeks or > 6 weeks), each criterion being scored and summed to suggest a definite RA diagnosis. Therefore, this classification helps to distinguish patients with undifferentiated arthritis from those with RA, and it is also applicable to people presenting early disease (< 6-months duration) [6]. However, identifying seronegative RA disease, discriminating very early-stage and atypical arthritis, as well as bringing together the clinical and genetic variability seen among different patients still constitute an important gap in the field.

The "Classification Criteria for Psoriatic Arthritis (CASPAR)" criteria, published in 2006 [7], include the presence of inflammatory articular or peri-articular involvement (joint, spine, or entheses), a personal or family history of psoriasis, and specific features like nail dystrophy, dactylitis, or radiologic evidence of juxta-articular new bone formation. Laboratory acute-phase reactants (ESR and CRP) are not listed as part of CASPAR, but a negative RF is included as a serological criterion. Notably, though, these criteria present several limitations and do not account for atypical or subclinical skin involvement, and neither are they precise in distinguishing PsA from undifferentiated arthritis.

While both RA and PsA classification criteria include clinical and laboratory features, OA classification is not as elaborate, although several societies (e.g., European Alliance of Associations for Rheumatology -EULAR-, American College of Rheumatology -ACR-) have started considering the clinical symptoms in this condition as well [25].

Hand, hip, and knee OA-specific criteria have been described, and, for each of these joint areas, they depend on clinical (e.g., joint pain and physical examination findings) and radiographic findings (e.g., bony enlargement). Relying on clinical symptoms occurring in advanced disease and radiographic evidence lack specificity and result in a drop in diagnostic accuracy among early-stage and milder cases.

Beyond strict disease classification, various clinical phenotypes involving additional criteria (e.g., radiographic scores, body mass index, pain, comorbidities) were also defined, although they hardly find consensus in the literature. As an example, six phenotypes of OA have been described following a systematic review of the literature in 2016, and included i. chronic pain, ii. inflammatory, iii. metabolic syndrome, iv. bone and cartilage metabolism, v. mechanical overload, and vi. minimal joint disease phenotypes [26]; however, different phenotypes have also been proposed by other groups. Indeed, further studies identified that pain sensitization, psychological distress, radiographic severity, or body mass index, inflammation and comorbidities, participate in distinguishing clinically distinct phenotypes [27]. Later, it was further emphasized that defining OA phenotypes uniquely based on risk factors was too simplistic, highlighting that socio-demographic factors, clinical, imaging, and biochemical marker measurements, as well as mechanical parameters, should be considered to precisely define clinical phenotypes [28].

Researchers and clinicians should now work together to establish unanimous "phenotypes" within each rheumatic disease. Translating a clinical phenotype into a molecular endotype is an ongoing challenge and will be the topic of the next section.

4. Emerging endotypes of RA, PsA, and OA: deciphering complex molecular pathways

4.1. Moving towards a better histological characterization of diseased tissues: the concept of (histo)pathotypes

The first steps to achieve a tangible application of precision medicine to rheumatic conditions have been uncovered by characterizing novel disease-associated features, enabling a more accurate patients' stratification. As such, synovial "pathotypes" have been initially described at the histopathological level, aiming at finding the relationship between synovial inflammation, including cellular content, and disease severity or response to treatment in RA.

In line with several past studies describing the role of synovitis as a key component of RA disease, three synovial pathotypes have been described from a large cohort of early and untreated RA patients who underwent ultrasound (US) guided synovial biopsies [29,30]: i. lympho-myeloid (characterized by well-organized B cell aggregates, often surrounded by plasma cells, and rich in macrophages); ii. diffuse-myeloid (with predominant macrophages within the sublining tissue and lacking organised B cell aggregates); and iii. pauci-immune (with scant infiltration of immune cells and prevalence of resident fibroblasts). Importantly, these pathotypes have been individually associated with distinct clinical disease features, including level of CRP or ESR, autoantibodies positivity, and disease activity scores (i.e., DAS28) [29]. Moreover, synovial pathotypes seem to predict the requirement for biological therapies in RA [31] and correlate with treatment response [29,32,33]. Although RA and PsA synovial histopathological features differ according to certain criteria, such as the vascular pattern and the level of lining layer hyperplasia at the site of inflammation [34], our group showed the presence of similar pathotypes in PsA synovium, although with a different overall distribution [35]. In addition, the presence of specific cellular subsets, such as $CD117^{+}$ or $CD138^{+}$ cells, differentially distributed among PsA and seronegative RA could help refine disease categorization [36]. Altogether, these results highlight that diagnostic tools could emerge from histological analysis.

Synovial tissue analysis in OA has long been ignored as an additional tool to improve the understanding of the disease pathophysiology, and current OA-synovitis histological assessment has failed to demonstrate a clear association with disease phenotypes; nevertheless, we recently showed that OA synovium, similarly to RA, can be categorized into three pathotypes reflecting distinct levels of peripheral blood inflammation [37], suggesting that synovial pathotypes may be indirectly associate with radiographic severity. Further analyses are now required to confirm these findings.

4.2. From tissue and cellular to molecular perspective: defining common and distinct disease endotypes in RA, PsA, and OA

4.2.1. From pathotypes to endotypes, findings from synovial tissue analysis in RA

In RA, the pathotype-based histological classification was accompanied by a comprehensive molecular characterization of synovial tissues. Synovial pathotypes and their aforementioned clinical phenotypes were found to be associated with specific molecular signatures, as well as with clinical response to conventional synthetic (cs)- and biologic (b)-Disease Modifying Anti-Rheumatic Drugs (DMARDs) [29,32,33]. Recently, a pioneer study of RA synovium using multi-modal single-cell RNA-sequencing and surface protein data coupled with histology, further defined the presence of six cell-type abundance phenotypes characterized by enriched cell-states [38]. In addition to providing a comprehensive atlas of synovial cells, this study highlighted that specific cell states, characterized by distinct cytokine profiles, are associated with specific histologic, serologic profiles, and RA risk genes, and predict the response to treatment.

Overall, these results highlight the powerful insights constituted by molecular biomarkers towards personalized care in RA. Undoubtedly, our comprehension of the intricated relationship between phenotypes and endotypes has recently progressed, but it still requires a better understanding of molecular pathways driving diseases. The next section will briefly highlight examples of shared and distinct key pathways described in RA, PsA, and OA.

4.2.2. Molecular pathways altered in RA, PsA and OA

Over the years, researchers have highlighted numerous molecular pathways involved in the pathophysiology of joint diseases that have led to the pre-clinical and clinical development of various therapeutic agents. This section does not intend to present an exhaustive list of the molecular alterations associated with RA, PsA, and OA, but to highlight a few relevant examples of the variety of pathways involved in their pathogenesis.

Among the molecular pathways altered in rheumatic conditions, especially RA, PsA, and OA, metabolic alterations have been described in distinct tissue compartments. As an example, altered glycolytic processes and lactate production in synovial fibroblasts and macrophages contribute to chronic inflammation and destructive and proliferative disease phenotypes in RA, as described in recent reviews (e.g., [39]). In addition, chondrocytes are also affected by metabolic dysregulation in an inflammatory context [40,41]. Overall, although metabolic disturbances may generally affect joint tissues and RA, PsA, and OA share common metabolic defects, clinical features sometimes correlate with the presence of distinct metabolites in the serum, which may serve as disease biomarkers [42], a concept further developed in the next section (4.2.3).

Cellular senescence is another critical molecular pathway reflecting the changes observed in rheumatic joint tissues. Senescent cells, especially fibroblasts in the synovium and skeletal cells in the cartilage/bone, accumulate in rheumatic tissues and participate in tissue damage and the production of inflammatory mediators through their senescence-associated secretory phenotype (SASP) [43,44]. For instance, senescent T cells have been shown to promote osteoclastogenesis and contribute to bone loss and osteoporosis in RA [45]. Cellular senescence is often linked with defective auto-

phagy in the context of joint diseases, and targeting this axis has been investigated, for example, in the context of OA [46].

Of note, the importance of molecular pathways related to bone turnover, such as the ones involving bone morphogenetic proteins (BMPs) or Dickkopf (DKK)/Wnt, is widely acknowledged in rheumatic conditions. For instance, in the context of RA, the presence of $DKK3^{+}$ fibroblasts in the synovium has been associated with refractoriness to treatment [47].

Moreover, abnormally active inflammatory and catabolic pathways constitute a hallmark of RA, PsA, and OA, representing promising molecular targets in these diseases. As an example, a specific fibroblast inflammatory phenotype, characterized by the expression of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), was associated with proliferative features and mediate joint inflammation in obese OA patients [48]. Accordingly, the inflammatory landscape of synovial fibroblasts has been recently linked to obesity, highlighting that this molecular endotype may serve OA patients stratification [49]. Though the identification of relevant disease endotypes from dysregulated molecular pathways in the tissue has progressed in recent years, it has also been held back due to intrinsic limitations. Indeed, the limited accessibility to synovial biopsies, and even more to cartilage or bone tissue sampling, the relative invasiveness these procedures may require, and the potential challenge of dynamic molecular changes over time strongly impact the current implementation of endotype-based clinical care in daily practice. However, as numerous rheumatology centres around the world are progressively introducing synovial biopsies and further large biopsy-based clinical trials are completed [50] or undergoing (https://www.qmul.ac.uk/whri/emr/clinical-trials-emr/3tr-precis-the-ra/), we expect significant developments in this field.

Nevertheless, to overcome some challenges related to the availability of the diseased tissue in less accessible sites, and because tissue alterations observed in RA, PsA, and OA may lead to the subsequent production of soluble factors that propagate systemically, understanding how peripheral blood biomarkers ("liquid" biopsy) correlate with clinical phenotypes is of critical importance in the journey toward precision medicine.

4.2.3. Systemic alterations: from biomarkers to the refinement of endotypes characterization

In addition to soluble acute phase reactants markers of inflammation (e.g., ESR, CRP) or the circulating antibodies (e.g., RF, ACPA) cited above that help distinguish some subtypes of RA ("seropositive") from PsA and OA and are somehow associated with disease severity, other specific systemic alterations may be observed and could improve disease monitoring and treatment design or allocation. For instance, a recent study revealed that a panel of seven serological biomarkers of bone changes, cartilage and matrix degradation, or macrophage activity, identified pathological RA endotypes reflecting tissue state [51].

Interestingly, in PsA patients, red cell distribution width and mean platelet volume have been linked to the incidence of major adverse cardiac events following treatment and their monitoring could help prevent such complications [52].

In OA, by measuring serum and urine biomarkers (such as type II collagen degradation fragment, or high-sensitive CRP), Angelini and colleagues identified three dominant clusters of patients (low tissue turnover, structural damage, and systemic inflammation). Importantly, patients belonging to each cluster exhibited distinct clinical characteristics (e.g., pain, disease progression), opening novel avenues for the study of systemic alterations in OA [53]. In addition, as described by our group and others [37,54], the distribution of circulating immune cells may reflect joint pathology in OA and requires further investigation before being translated to clinical practice.

5. Treatment options in rheumatic diseases: progressing towards personalized medicine

5.1. Treatment options for RA, PsA, and OA: current clinical approaches

Currently, RA as well as PsA and OA, together with most of the rheumatic conditions, do not have a definite cure. The pharmacological management aims, in the case of RA and PsA, to reach disease remission or, at least, a low disease activity state and the prevention of bone damage progression and long-term disabilities. OA management primarily focuses on pain relief, but, to date, there is no treatment able to slow-down or reverse the progression of the disease.

Historically, the first line of treatment, usually while waiting for confirming the diagnosis of inflammatory arthritis, aims at targeting the general pain and inflammatory features of the disease. Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (oral, parenteral, or intra-articular injections) can provide pain relief and locally control some symptoms related to inflammation (e.g., swelling). As soon as the diagnosis of RA is made, along with these drugs, csDMARDs (methotrexate–MTX, unless contraindicated) should be started. csDMARDs are widely used as initial treatment also for PsA. Although csDMARDs are not used in clinical practice for OA, recent studies suggested that MTX may significantly reduce the pain in selected cases of hand OA [44].

Numerous bDMARDs have been introduced and widely used in the last two decades for the treatment of RA and PsA. They embrace several mechanisms of action, ranging from cytokine inhibition (e.g., anti TNF, anti-IL-6, anti-IL-17, anti-IL-23), cell targeting (e.g., anti CD20), co-stimulation modulation (anti CTLA-4) or molecular pathways inhibition (e.g., JAK inhibitors). Although these therapeutic strategies have revolutionized the treatment of rheumatic diseases, they have been and are still used according to a "trial and error" approach to treatment allocation. Such clinical use leads to variable responses and, through the multiplication of molecules employed, to the increase of potential adverse events, impacting patients' quality of life [10].

5.2. Recent successful proof of concept for the personalized management of rheumatic diseases

Altogether, following successful examples in cancer and as recently proposed in other contexts like asthma, the field of rheumatology should move towards targeting endotypes, which, conversely to phenotype-based therapeutic strategies, would likely lead to the complete resolution of clinical manifestations [55]. This overall strategy is illustrated in Fig. 1. Importantly, recent work has highlighted that considering synovial tissue molecular features for drug allocation ameliorates the effectiveness of treatment in RA [47,56]. In the context of PsA, we have also provided the first evidence that synovial molecular pathology could help identify patients with a greater probability of responding to IL-23 inhibitors [57].

Integrating synovial tissue molecular signatures into clinical algorithms should, therefore, be optimized for future development. Notably, the use of novel multi-omics technical approaches in biofluids (e.g., blood, urine, synovial fluid) or at the synovial tissue level, implemented with artificial intelligence and machine learning tools, could help uncover biomarkers for patients' stratification, predict treatment response, disease course, or potential for adverse events. This challenge could become achievable with the increased accessibility to such technologies and their future implementation in daily care for rheumatologic patients [58]. It should also be noted that, although beyond the scope of this review, the exploitation of Genome-Wide Association Studies (GWAS) could

Fig. 1. The twisting road of precision medicine.

help refine disease taxonomy and revolutionize the identification of candidate targets for personalized treatment of rheumatic conditions [24].

6. Conclusions

Diverse phenotypes, pathotypes, molecular endotypes, and underlying aetiologies standing behind the development of RA, PsA, and OA make both the disease classification and the design of effective therapeutic strategies rather complex. Moreover, the possibility of overlapping endotypes underlying disease phenotypes further complicates our understanding and management of rheumatic conditions. The improved, but still incomplete, knowledge about disease endotypes paves the way towards more personalized healthcare approaches. The improvement of high-throughput multi-omics approaches, and its progressive democratization, associated with a precise clinical assessment will, in the future, help reconcile all current challenges for better patients' care.

Disclosure of interest

The authors declare that they have no competing interest.

Authors contributions

Writing and original draft: G.M.G., C.A.D; Writing, reviewing, and editing: A.N., M.-A.B.

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