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Are There Disease Endotypes in Axial Spondyloarthritis and How Would We Define Them?

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ABSTRACT. Is axial spondyloarthritis (axSpA) one disease or does it comprise multiple types? If the latter, how do we define those types—through clinical or imaging features, HLA-B27 status, or by other immunologic features? Data comparing disease outcomes for individuals with nonradiographic vs radiographic axSpA, or for male vs female patients, demonstrate distinctions. So then, how should we define endotypes? Endotypes are known as the subtype of a health condition defined by a functional or pathophysiologic function. Here, we review the endotypes used for defining rheumatoid arthritis, asthma, and psoriatic arthritis. Taking the lessons learned from these diseases, we discuss how they can be applied to defining endotypes in axSpA. A key unmet need for axSpA is access to affected tissues for interrogation of their pathologic mechanisms, from which tissue-specific endotypes can be defined. These tissue-based features should be combined with clinical data and imaging to inform classification criteria in the future.

Key Indexing Terms: ankylosing spondylitis, endotypes, psoriatic arthritis, rheumatoid arthritis, spondyloarthritis

Introduction

Spondyloarthritis (SpA) is often divided into 2 main groups: axial SpA (axSpA) and peripheral SpA. These divisions are largely based on data from ankylosing spondylitis or psoriatic arthritis (PsA) trials and are generally helpful in making clinical decisions regarding therapy. However, the value of additional subgrouping of SpA, based on clinical or biological definitions, is unclear. Here, we evaluate the lessons learned from the consideration of disease subsets, or endotypes, in rheumatoid arthritis (RA) and PsA.

Endotypes based on clinical features in RA, presented by Dr. Kevin Deane

What works? Endotypes can be defined as a subtype of a health condition that is determined by a distinct functional or pathophysiologic mechanism. In current clinical practice and research in RA, formal determination of endotypes is not commonly done.[1] However, there are a few instances where endotypes have been defined to some extent.

- *Endotypes emerging from classification criteria*. The classification criteria for RA established in 2010 by the American College of Rheumatology and the European Alliance of Associations for Rheumatology includes domains of tender and swollen joints, autoantibodies (mainly anticitrullinated protein antibodies [ACPA] and rheumatoid factor [RF]), and inflammatory markers that, in aggregate, partially define the biology (ie, an endotype) of RA (Table 1).[2] In particular, because this set of criteria requires a certain amount of disease activity for fulfillment, in some ways, this defines an endotype of more severe disease.[3] Further, the criteria give high weight to biomarkers. Specifically, of the 10 possible points in the criteria (a score of ≥ 6 is required for fulfillment), 4 points are possible from autoantibodies and inflammatory markers, which leads to an endotype of RA defined by autoantibody and/or elevated systemic inflammation.
- *Endotypes related to response to therapy*. There are established and emerging findings that suggest autoantibody-positive RA responds better than autoantibody-negative RA to certain therapies, including B cell depletion with rituximab.[4,5] In addition, the presence of the genetic factor known as the shared epitope (SE), as well as positivity for ACPA, appear to be associated with increased responsiveness to the T cell costimulation inhibitor abatacept.[6] Further, there is emerging evidence that endotypes including obesity[7] and tobacco use[8] may decrease drug responsiveness in RA. As such, autoantibody-positive RA (also termed seropositive RA), obesity, tobacco use, and the presence of the SE may be considered endotypes in RA.

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Table 1. American College of Rheumatology/European Alliance of Associations for Rheumatology 2010 rheumatoid arthritis classification criteria.[2]

Feature	Score
Joint involvement	
Large joint	0
2-10 large joints	1
1-3 small joints[a]	2
4-10 small joints[a]	3
≥ 10 joints (≥ 1 small joint)	5
Serology[b]	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
Acute-phase reactants[b]	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of symptoms	
< 6 wks	0
≥ 6 wks	1

Criteria should be applied to individuals who have ≥ 1 joint with definite clinical synovitis (swelling) not better explained by another disease. [a] With or without involvement of large joints. [b] ≥ 1 test result is needed for classification. ACPA: anticitrullinated protein antibody; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor.

- *Endotypes in the natural history of RA, including pre-RA.* There is growing understanding that there is a pre-RA period of disease development in which there are local or systemic immune abnormalities in the absence of clear joint inflammation.[9] In particular, blood elevation of ACPA is roughly associated with ~30% likelihood of developing RA within 3-5 years. The ability to predict future RA has underpinned several clinical trials in RA prevention. Agents that have been trialed include corticosteroids,[10] methotrexate,[11] hydroxychloroquine,[12] and abatacept.[13,14] Of these, corticosteroids and hydroxychloroquine have not significantly delayed or prevented RA, and methotrexate did not delay or prevent RA but may have led to the development of a less severe form of RA. In addition, findings from recently completed trials demonstrate that abatacept may delay or prevent RA in a subset of at-risk individuals within the trial period (EudraCT number: 2013-003413-18 and 2014-000555-93).

What doesn't work? There are currently multiple challenges in the application and development of meaningful endotypes in RA. These are summarized in Table 2.[15-21]

Opportunities. As the concept of endotypes evolves, several considerations should be given to physiologic features of disease in defining such endotypes.

- *Use biology to inform endotypes.* Growing understanding of the biology of the natural history of RA, including the pre-RA state, through observational studies and clinical trials will provide more accurate ways to endotype individuals. Features may include demographic, environmental, and clinical features; genetic, mucosal, systemic, and joint-based factors; artificial intelligence; and "easy use" calculators. Ultimately, endotypes based on biology will improve prognosis, treatment selection (including preventive intervention), and prediction of future disease.
- *Make classification criteria inform endotypes.* Widespread use of endotypes can be facilitated by using endotypes in the development of classification criteria.
- *Integrate imaging into defining endotypes.* Given the growing role of imaging (including ultrasound and magnetic resonance imaging) in defining RA, the role of imaging in endotyping disease will need to be assessed. This may be particularly relevant to SpA, for which imaging of sacroiliac joints is important in diagnosis and classification.
- *Assess tissue.* Synovial biopsy may identify endotypes and, in particular, may inform choice of therapy. As such, synovial biopsy may be integrated into clinical care as a tool to endotype individuals for better biologic classification of their disease, and to help guide the choice of the most effective therapy. This is discussed in more detail in the following section.

Lessons to be learned from recent studies in RA synovial tissue, presented by Dr. Laura Donlin

For many rheumatic diseases, it remains unclear if the pathology fundamentally stems from aberrations in the target tissue or in the infiltrating immune cells, or the interface between the two. Until we come to understand these fundamentals, we are left to consider using more broad pathway level information to guide treatment. Considering that disparate conditions like RA and Crohn disease have achieved therapeutic benefit from targeting the same pathways, like tumor necrosis factor (TNF), there is renewed interest and strong rationale in defining shared immune pathways across disorders.[22,23] Here, we will discuss whether recent work in RA can provide molecular insights for shared therapeutic targets in SpA, as well as practical lessons for enhancing research programs.

The RA field has recently placed considerable emphasis on defining what goes on directly within affected synovial tissue.[24] This includes work from the National Institutes of Health (NIH) and industry-sponsored Accelerating Medicines Partnership (AMP) program, which began with the goal to define the cell types and pathways in the joints across individuals with RA. These efforts have produced a compendium of the cells that can be found in RA-affected joints,[25] representing 77 distinct states across more than 7 cell lineages.[6] Further, and more clinically relevant, this work argues that RA synovial tissue can be stratified into categories based on their composition of cell types. The AMP program has defined 7 distinct synovial subtypes, referred to as cell-type abundance phenotypes (CTAPs).[6] The biologic composition of these types of tissues ranges from proinflammatory, profibrotic, to proangiogenic. Several of these CTAPs overlap in features found independently in the histologic synovial subtyping proposed by Rivellese and colleagues, which defined subtypes as pauci-immune/fibroid, lymphocyte-rich, and myeloid-rich.[26] The AMP program has extended this classification scheme to potentially include more granularity and diversity, and, more importantly, define the specific cellular phenotypes within as well as the pathways. Collectively, this

Table 2. Challenges in endotyping in RA.

Category	Challenges
Use of classification criteria for determining endotypes in RA	Criteria are formally used for classification; they are not diagnostic criteria and have limited use in clinical care. Criteria do not robustly capture prognosis or disease duration/damage and extraarticular disease, guide appropriate therapy, or include rapidly emerging informative biomarkers. Criteria do not formally include a measure of disease activity, although a modestly high level of disease activity is required to meet criteria.
Disease activity	Existing biologic assessments of disease activity have limited efficacy. There is a biomarker panel (multibiomarker disease activity, marketed as Vectra DA) promoted to assess disease activity.[15] However, this assay is not substantially better than other established measures; in addition, it may not be as accurate in individuals treated with certain biologics that may affect the assay, or in situations such as obesity.
Treatment response	Some data indicate that certain features, including autoantibody positivity and/or certain genetic markers, may suggest improved response to certain agents. However, these approaches are not widely used in RA due to limited data, as well as guidelines that recommend a stepwise approach to therapy[16] and payor-driven approaches to medication selection.
Predicting drug tapering/ removal	Some data suggest that features of disease, including low disease activity and negative autoantibodies, identify individuals in whom disease-modifying therapy can be tapered or stopped. However, the duration of follow-up in tapering/ cessation studies is limited, which makes tapering challenging in RA, a typically lifelong disease. Overall, there appears to be rates of flares ≥ ~50% with tapering/cessation of therapy.[17-20]
Predicting future clinical disease in individuals with risk factors for future RA	Certain features, including autoantibody positivity and symptoms, as well as joint imaging studies, can be used to predict the future onset of RA while individuals are in a pre-RA stage without clinically apparent synovitis.[9] However, multiple models only demonstrate positive predictive values of ~20-60% for RA onset within 2-6 yrs. Additional endotyping may help to more accurately identify those who have risk factors for RA and will transition to future clinical RA; such individuals will be particularly important to evaluate in trials for prevention. Blood, mucosal, and other factors in the pre-RA period may determine endotypes related to the pathogenesis of RA.
Preventing future clinical disease in individuals with risk factors for future RA	Thus far, several pharmacologic agents trialed in pre-RA have shown limited effect in delaying or preventing future RA; however, there is emerging data that abatacept may be the most effective in delaying/preventing future RA in individuals with high numbers of autoantibodies.[14-21] This may indicate that certain endotypes may be more responsive than others to certain therapies in terms of prevention.

RA: rheumatoid arthritis.

information forms a foundation for precision medicine targeting of each tissue type. Clearly, understanding which of the cell states may be driving pathology is crucial in such precision approaches and is thus the basis of ongoing studies. Nonetheless, the work described here, which has defined the cell states that interact in distinct tissue environments, suggests unique pathological mechanisms that may represent distinct disease endotypes.

One notable surprise arising from this work has been the identification of tissues in some patients that display more fibrotic or proangiogenic cellular programs with relatively low levels of inflammatory cell types, despite the high levels of systemic inflammatory markers and autoantibodies. Whether these less inflammatory tissue states result from systemic immune system alterations (eg, within the bone marrow hematopoietic niche), or from differences in tissue-resident cell properties, is unclear. Nonetheless, the fact that these cells do not fall into the classical proinflammatory pathways, hallmarked, for example, by nuclear factor- kB (NF-kB) or signal transducer and activator of transcription 1 (STAT1) activation, may suggest individuals with joints in this category would benefit from treatments outside of the antiinflammatory medications, like TNF inhibitor therapies.

Based on these research findings, practical considerations that could be translated for other conditions include the development of a large-scale sample collection of affected tissues within a consortium infrastructure and large-scale funding to support clinical and basic scientist collaborations with cutting-edge technologies. These, together with cross-disease comparator studies—including those of RA, SpA, and checkpoint immunotherapy–induced inflammatory arthritides,[7] as well as seemingly unrelated conditions in the same target tissues—hold promise in improving precision treatment with quantifiable molecular features as therapeutic guides.

Lessons to be learned from PsA, presented by Dr. Christopher Ritchlin

PsA is a highly prevalent, heterogeneous, and complex form of skin disease coupled with joint inflammation that often leads to significant joint pain, disability, and impaired quality of life.[27] Moreover, psoriasis (PsO) and PsA are associated with a number of comorbidities, several of which are linked etiologically to the skin and joint diseases and contribute to decreased response to treatment and lifestyle stress.[28] Further, lifestyle, along with behavioral and metabolic factors—including obesity, type 2 diabetes, lack of exercise, smoking, anxiety, depression, fatigue, and emotional distress—may greatly affect disease activity.[29] Despite the marked increase in the number of therapeutic agents approved to treat PsA, remission is extremely rare and disease flares are common, such that up to 80% of patients cycle through multiple biologic agents within 3 years and still do not demonstrate disease control.[30] Thus, we are faced with a major challenge. How do we improve disease outcomes in a disorder that is highly variable from patient to patient and involves multiple tissues including the skin, peripheral joints, axial skeleton, and entheses? Could use of endotypes be informative?

Asthma as a prototype. Asthma is a disorder that shares the complexity and heterogeneity observed in PsA. Over 20 years ago, the concept of phenotypes and endotypes was applied with the goal of achieving greater individualization and precision in the diagnosis and treatment of this pulmonary disorder.[31] Phenotype, or what can be observed, contrasts with endotype, which is the cellular and molecular pathways involved in pathogenesis.[32] A single phenotype may have several endotypes, and there may exist a range of subphenotypes with distinct and overlapping endotypes. Within a single disease such as asthma, type 1 diabetes, and PsA, many phenotypes and subphenotypes can be identified, and the endotypes underlying these phenotypes often possess distinct mechanisms that require pathway-specific strategies for therapy. Multiple different phenotypes and endotypes of asthma were identified (allergic, intrinsic, aspirin-induced, exercise-induced) and exploration of mechanisms was undertaken to develop more directed and effective therapies. In a recent publication, patients with chronic obstructive pulmonary disease (COPD) and elevated eosinophil counts were treated with dupilumab (an antiinterleukin [anti–IL]-4 receptor antagonist) or placebo in addition to their routine therapy.[33] The group that received the dupilumab showed significant improvement in multiple variables compared to placebo, underscoring the value of identifying subphenotypes within a single disease phenotype such as COPD; these subphenotypes arise through multiple distinct mechanisms that are responsive to a specific therapy. Deciphering endotypes, however, requires investigation of the tissues that are involved in the disease and not just a reliance on cells obtained from the peripheral blood. The optimal approach is to define pathways in target tissues and then to identify actionable biomarkers in the peripheral blood that reflect specific pathologic activity in the end organ or tissue.

Approaching endotypes in PsA. To reveal endotypes in PsA, the Elucidating the Landscape of Immunoendotypes in Psoriasis and Psoriatic Arthritis (ELLIPSS) team in the AMP–Autoimmune and Immune-Mediated Diseases (AIM) program will enroll 3 cohorts of patients with PsO and PsA. Cohort 1 will be patients with different subphenotypes of PsO (vulgaris, palmopustular, guttate, erythrodermic) and PsA (peripheral arthritis, axial, enthesitis, dactylitis) naïve to systemic therapy who will undergo skin biopsy (PsO), skin and synovial biopsy (PsA), and extensive blood profiling of hematopoietic cells, along with microbiome analysis of the skin and gut. Cohort 2 will be patients from cohort 1 who are followed longitudinally on a range of systemic therapies and will undergo skin and synovial biopsies at the time of flare along with blood profiling. Cohort 3 will consist of patients with PsO at increased risk of developing PsA based on ultrasound imaging who will be followed longitudinally for the development of arthritis. The tissues and blood will be examined with single-cell RNA sequencing (scRNAseq), spatial transcriptomics, metabolomics, cytometry by time of flight (CyTOF), microbiome analysis, and epigenetics. The goal of these studies is to link subphenotypes with specific endotypes, define signatures of nonresponse, and reveal the mechanisms that underlie the transition from PsO to PsA.

Additional studies will be carried out by the ELLIPSS team. Uveitis is present in approximately 5% of patients with psoriatic disease, but the pathogenesis is not well understood, and treatment options are limited. We are collaborating with ophthalmologists at our 9 sites to recruit patients with uveitis and collect microbiome specimens from the cornea, tears for proteomic analysis, and, when indicated, anterior chamber fluid for RNA analyses. We will also obtain demographic and clinical data from the patients. Additionally, we are investigating mechanisms of pain in PsO and PsA with a number of pain questionnaires to decipher neuropathic, nocioceptive, and nocioplastic pain phenotypes in these patients. We will correlate these findings with examination of critical nerve fibers in the skin and synovium of patients with PsO and PsA.

Linking phenotypes and endotypes requires a defined strategy to integrate patient-centered variables with data obtained from immunoassays and genomic studies. The palette model for defining endotypes in diabetes involves identifying specific subphenotypes based on a range of patient variables, and then identifying specific genetic, transcriptomic, metabolomic, and microbiome signatures in the blood and tissues that are associated with these phenotypes.[34] Similar approaches are planned for the analysis of data obtained by the ELLIPSS team for patients with PsO and PsA. Ideally, biomarkers in the blood that reflect ongoing pathologies in the tissue will be identified and this will facilitate individualized diagnosis and treatment.

The phenotype of PsA is more heterogeneous and complex than asthma. First, it is highly variable in age at disease onset, genetic susceptibility, disease progression, efficacy, duration of therapeutic intervention, and the number and extent of domain involvement.[35] The different domains involved include peripheral arthritis, axial disease, dactylitis, enthesitis, and PsO. Patients often present with 3 or more domains, which greatly complicates treatment.[36] The dominant contribution of CD8+ T cells is documented in multiple studies in PsO and PsA.[37-39] Key cytokines include TNF, IL-23, IL-17, interferon-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-22.[38] It is highly likely that the endotypes underlying these phenotypes and domains vary considerably, particularly given that the stromal cell and immune cell populations in the skin, joints, entheses, and axial skeleton are quite different. Thus, distinct tissue environments are likely to have specific signatures that require a distinct therapeutic strategy.[40]

With a better insight into the endotypes that underlie the various phenotypes and subphenotypes, the possibility of precision-based diagnosis and treatment may become a reality. Understanding how this new knowledge can be translated to improved outcomes is highlighted in the "Treatable Traits" strategy, which has also been developed in asthma.[32] The complexity of PsA will be addressed, targeting specific phenotypic characteristics (domain involvement) based on validated biomarkers of specific biologic mechanisms or endotypes. These endotypes will be defined by genetics, epigenetics, immune pathways, and metabolomic and microbial features. The first question, of course, remains: Is this really arthritis? This question will be explored in the typical Oslerian manner along with blood

work and imaging. The next step is to investigate the endotypes with blood, imaging, or tissue biomarkers. Yet, we also must address the extraarticular traits (ie, obesity, diabetes, uveitis, colitis, anxiety, and depression). Last, but of equal importance, is addressing treatable behavior and lifestyle risk factors, including smoking, exercise, and food choices.

The advances in basic science, particularly the advent of scRNAseq and spatial transcriptomics, provides unparalleled opportunities to understand pathological events at the tissue level. Admittedly, this type of approach is more challenging in axSpA, for which peripheral tissues are less available. However, cellular analysis of tissues from peripheral joint, anterior chamber fluid in uveitis, and the blood are already providing insights that are establishing new paradigms for HLA-B27–associated diseases.[41] It is anticipated that this momentum will continue in the coming years.

Conclusion

Definitions of clinical and biologic endotypes in RA and PsA have been rapidly evolving over the past several years, yielding valuable information regarding the treatment of patients with these diseases. Nevertheless, a key unmet need for axSpA is access to affected tissues for interrogation of their pathologic mechanisms, from which tissue-specific endotypes can be defined. These tissue-based features should be combined with clinical data and imaging to inform classification criteria in the future.

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