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The author has no conflicts of interest to disclose
Rheumatology in the 21st century uses current cellular, biochemical and immunologic techniques to explain the etiology of rheumatic diseases. While it is unlikely that molecular biology will differentiate rheumatic diseases into subsets based on their etiology, the genome revolution does provide us with new diagnostic tools, which are already beginning to have an impact.
Molecular Weight Comparison

- Aspirin: 180 Daltons
- Insulin: 5,700 Daltons
- mAb: 150,000 Daltons
For many years, polymorphisms in drug metabolizing enzymes have been associated with both reduced clinical response and adverse effects of treatment. Proteomics and genomics offer new opportunities to identify biomarkers that provide surrogates of disease activity and response to therapy.
Micro RNAs are small, imperfectly paired, double-stranded RNAs expressed in all cells regulating the expression of hundreds of genes by inhibiting the translation and promoting the degradation of messenger RNAs. MicroRNAs act as master regulators of how a cell responds to changes in its environment, including growth factors and environmental stressors.
There have been substantial advances in the field of rheumatology in the past 20 years in the management of rheumatoid arthritis (RA), spondyloarthritis (SpA), psoriatic arthritis (PsA), systemic lupus erythematosus (SLE) and vasculitis.
Pathogenesis of rheumatoid arthritis

Environment (pathogens, smoking, etc.)
Genetics (HLA-DR, PTPN22, PADI4, etc.)

Citrullination of proteins
Anticitrulline antibodies

- Innate immunity
- Antigen loading into DCs

Migration to central lymphoid organs

- Local inflammation
- Local antigen presentation

Antigen presentation
T and B cell activation

- Antigen presentation
- Cytokine production
- Autoantibodies

Osteoclast activation
Epigenetic changes
Complement activation

B
T
DC
OC
MΦ
PMN
FLS

Synovium
Lymph nodes
Spleen

T and B cell migration to joint
Autoantibodies
Pathogenesis of rheumatoid arthritis

Macrophage

Th1/Th17 cytokines
IL-17A and F

IL-10
IL-1Ra

IL-1
TNF
IL-18

Fibroblast

IL-8
IL-6
GM-CSF

TGF-β

Metalloproteinases
Prostaglandins
Complement

Th2 cytokines
IL-4, IL-10, IL-13

Kelley’s Textbook of Rheumatology, 2012, p. 1093
### 2010 ACR/EULAR Classification criteria for Rheumatoid arthritis

<table>
<thead>
<tr>
<th>Joint Involvement*</th>
<th>(0-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 medium to large† joint</td>
<td>0</td>
</tr>
<tr>
<td>2-10 medium to large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small‡ joints (with or without involvement of large joints)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints (with or without involvement of large joints)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints§ (at least one small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

| Serology|| (0-3) |
|-----------------|-------|
| Negative RF AND negative ACPA | 0 |
| Low-positive RF OR low-positive ACPA | 2 |
| High-positive RF OR high-positive ACPA | 3 |

<table>
<thead>
<tr>
<th>Acute Phase Reactants###</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CRP AND normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP OR abnormal ESR</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of Symptoms**</th>
<th>(0-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

* Joint Involvement

† Medium to large joints include: knee, ankle, hip, and shoulder.
‡ Small joints include: small joints of the hands and feet.
§ More than 10 joints include at least one small joint.
** Duration of Symptoms

### Kelley’s Textbook of Rheumatology, 2012, p. 1127
Rheumatology in the 21st century

Following the introduction of the treatment recommendations for RA in 2013 by the European League Against Rheumatism (EULAR) and the introduction of biological agents in the management of RA, there is a need to consider the selection of the most appropriate therapy for an individual patient and to review how and when to switch treatment in those patients who do not show an optimal response. On 6 November 2012 FDA approved inhibitor of kinases to RA treatment.
Inhibitors of TNF alpha are the standard therapy in RA, PsA and SpA
Abatacept is also a standard therapy in RA, JIA
Tocilizumab is a standard therapy in RA, JIA
Rituximab is standard therapy in RA, GPA, MPA
The Janus kinase, the signal transducer and activator of transduction (JAK–STAT) pathway is the signaling target of a multitude of cytokines, including INF gamma, IL–2, IL–4, IL–6, IL–7, IL–10, IL–12 and IL–15, all of which are thought to have biologically significant roles in rheumatoid synovial inflammation.
JAK inhibitors
JAK inhibitors

Nature Reviews | Cancer

Activation of genes important in proliferation and survival

4.03.13
Assessment of SpondyloArthritis in ternational Society Classification Criteria for Axial Spondyloarthritis (SpA)

For patients with back pain for $\geq 3$ mo and aged $< 45$ yr:
Sacroiliitis on imaging $+ \geq 1$ SpA feature

or

HLA-B27 $+ \geq 2$ other SpA features

Sacroiliitis on imaging defined as:
- Active acute inflammation on magnetic resonance imaging
  highly suggestive of sacroiliitis associated with SpA

  or

- Definitive radiographic sacroiliitis according to the modified New York criteria

SpA features comprising:
- Arthritis
- Enthesitis (heel)
- Inflammatory back pain
- Dactylitis
- Uveitis
- Psoriasis
- Inflammatory bowel disease
- Good response to nonsteroidal anti-inflammatory drugs
- Family history of SpA
- HLA-B27
- Elevated C-reactive protein

*Kelley’s Textbook of Rheumatology, 2012, p. 1223*
Assessment of SpondyloArthritis in ternational Society Classification Criteria for Axial Spondyloarthritis (SpA)

For patients with:
Periphera l arthritis (usually asymmetric, lower limb)
*or*
Enthesitis
*or*
Dactylitis
+ 1 of:
  - HLA-B27
  - Genitourinary or gastrointestinal infection
  - Psoriasis
  - Inflammatory bowel disease
  - Magnetic resonance imaging sacroiliitis
*or*
+ 2 of:
  - Arthritis
  - Enthesitis
  - Dactylitis
  - Inflammatory back pain
  - Family history of spondyloarthritis

*Kelley’s Textbook of Rheumatology, 2012, p. 1093*
Psoriatic arthritis (PsA) is a chronic inflammatory disease associated with multiple and variable clinical features.

• Patients with PsA suffer from inflammatory peripheral arthritis and may also suffer from extra-articular manifestations and axial disease.¹
• Patients with PsA have a range of disease burden.²,³
• Estimates of the prevalence of PsA among general adult populations range from 0.17% to 0.42%.⁵,⁶

PsA

Pain
Overall Reduced Quality of Life
Skin Manifestations
Psychosocial Problems
Fatigue and Sleep Disturbance
Difficulty Working
Interference with Personal Life
Stiffness & Decreased Function

² Lee et al. P & T. 2010;35:680-689
Psoriatic Arthritis

Five overlapping clinical patterns are observed in PsA

- **Axial disease**
  - Peripheral joints may or may not be involved in these cases
  - ~Up to 40%\(^3\)

- **Symmetrical polyarthritis**
  - ~12–70%\(^4\)

- **Asymmetrical mono-/oligo-arthritis**
  - ~37–70%\(^1,2\)

- **Arthritis mutilans**
  - ~5%\(^1\)

- **DIP joint involvement**
  - ~5%\(^1\)

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## Classification criteria for Psoriatic Arthritis (CASPAR)

Inflammatory articular disease (joint, spine or enthesal) with ≥3 points from the following 5 categories:

<table>
<thead>
<tr>
<th>Points</th>
<th>Inflammatory articular disease (joint, spine or enthesal) with ≥3 points from the following 5 categories:</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Psoriasis</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Current psoriasis</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>History of psoriasis</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Family history of psoriasis</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Psoriatic nail dystrophy</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Onycholysis, pitting ad hyperkeratosis</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>A negative test for rheumatoid factor</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>By any method except latex but preferably by enzyme-linked immunosorbent assay (ELISA) or nephelometry, according to the local laboratory reference range</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Dactylitis</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Swelling of entire digit or A history of dactylitis recorded by a rheumatologist</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Radiological evidence of juxta-articular new bone formation</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Ill-defined ossification near joint margins (excluding osteophyte formation) on plain X-rays of hand or foot</td>
<td></td>
</tr>
</tbody>
</table>

Specificity 0.987, Sensitivity 0.914
GRAPPA recommendations for the management of PsA

Peripheral arthritis
- Initiate therapy: NSAID, IA steroids, DMARD (MTX, CsA, SSZ, LEF), Biologics (anti-TNF)

Skin and nail disease
- Initiate therapy: Topicals, PUVA/UVB, Systemics (MTX, CsA, etc.), Biologics (anti-TNF)

Axial disease
- Initiate therapy: NSAID, PT, Biologics (anti-TNF)

Dactylitis
- Initiate therapy: NSAID, Injection, Biologics (anti-TNF)

Enthesitis
- Initiate therapy: NSAID, PT, Biologics (anti-TNF)

Reassess response to therapy and toxicity

EULAR recommendations for the management of PsA
EULAR recommendations for the management of PsA
EULAR recommendations for the management of PsA
EULAR recommendations for the management of PsA

* Because of the variable nature of the disease, not all situations can be covered by this figure; therefore it is important to consult the full text to which the numbers or letters in parenthesis refer; dotted lines refer to situations where deleting a phase is recommended.
** Active disease: 1 or more tender and inflamed joint and/or tender enthesis point, and/or dactylitic digit, and/or inflammatory back pain; adverse prognostic factors: ≥5 active joints; or high functional impairment due to activity; or damage; or past glucocorticoid use.
***The treatment target is clinical remission or, if remission is unlikely to be achievable, at least low disease activity; clinical remission is the absence of signs and symptoms.
Rheumatology in the 21st century

New treatment of PsA

TNF alpha inhibitors, IL-17 inhibitor Ixekizumab, Ustekinumab (Stelara) – a fully human IgG 1k monoclonal antibody that binds to the common p40 subunit shared by interleukins 12 and 23

45 mg sc initially and 4 weeks later, followed by 45 mg every 12 weeks

Apremilast (Otezla) – a phosphodiesterase 4 inhibitor

Day 1 – 10 mg, day 2 – 2 x 10 mg, day 3 – 10 mg + 20 mg, day 4 – 2 x 20 mg, day 5 – 20 mg + 30 mg, day 6 and thereafter 2 x 20 mg

Phosphodiesterase 4 inhibitor degrades cAMP into AMP. Elevated intracellular cAMP down-regulates the inflammatory responses through inhibition of the expression of inflammatory cytokines and increasing the expression of anti-inflammatory interleukin 10
Pathogenesis of SLE

Genetic susceptibility

Gene variants promoting innate immune activation
- IRF5
- TNFAIP3

Gene variants increasing self-antigen
- C4
- TREX1

Gene variants promoting adaptive immune response
- PTPN22
- BLK

Apoptotic cells and microparticles
Viruses
Environmental triggers

Nucleic acids
Toll-like receptors

Type I IFN

Proinflammatory cytokines
Vascular target

ROS
Immune complexes

Kelley’s Textbook of Rheumatology, 2012, p. 1270
Pathogenesis of SLE

Kelley’s Textbook of Rheumatology, 2012, p. 1276
### Treatment of SLE

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Induction Therapy</th>
<th>Maintenance Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>High-dose GC (0.5-1 mg/kg/day prednisone ×4-6 wk, tapered to 0.125 mg/kg every other day within 3 mo) alone or in combination with AZA (1-2 mg/kg/day)</td>
<td>Low-dose GC (prednisone ≤0.125 mg/kg on alternative days) alone or with AZA (1-2 mg/kg/day)</td>
</tr>
<tr>
<td></td>
<td>If no remission within 3 mo, treat as moderately severe</td>
<td>Consider further gradual tapering at the end of each year of remission</td>
</tr>
<tr>
<td>Moderate</td>
<td>MMF (2 g/day) (or AZA) with GC as above; if no remission after the first 6-12 mo, treat as severe</td>
<td>MMF tapered to 1.5 g/day for 6-12 mo and then to 1 g/day; consider further tapering at the end of each year in remission</td>
</tr>
<tr>
<td>Severe</td>
<td>Pulse IV-CYC alone or in combination with pulse IV-MP for the first 6 mo (background GC 0.5 mg/kg/day for 4 wk, then taper)</td>
<td>Alternative: AZA (1-2 mg/kg/day)</td>
</tr>
<tr>
<td></td>
<td>If no response, consider adding RTX or switch to MMF</td>
<td>Quarterly pulses of IV-CYC for at least 1 year beyond remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alternative: AZA (1-2 mg/kg/day), MMF (1-2 g/day)</td>
</tr>
</tbody>
</table>
Belimumab, a fully human monoclonal antibody that inhibits B−lymphocyte stimulator BLYSS, was approved for the treatment of SLE in 2011. There is also a number of other novel therapies in development. The clinical data for these agents and their impact on the management of lupus is an important topic.
Classification of vasculitis by blood vessel size

- Aorta
  - Giant cell arteritis
  - Takayasu’s arteritis

- Large- to medium-sized artery
  - Polyarteritis nodosa
  - Kawasaki disease

- Small-sized artery
  - Henoch-Schönlein purpura
  - Cryoglobulinemic vasculitis

- Arteriole
  - ANCA-associated vasculitis: microscopic polyangiitis

- Capillary
  - ANCA-associated vasculitis: granulomatosis with polyangiitis
  - Churg-Strauss syndrome

- Venule
  - Anti-GBM
  - Leukocytoclastic vasculitis

- Vein

*Kelley’s Textbook of Rheumatology, 2012, p. 1455*
## Classification of Vasculitis by the Chapel Hill Consensus Conference

<table>
<thead>
<tr>
<th>Classification</th>
<th>Histopathology</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Large Vessel Vasculitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giant cell (temporal) arteritis</td>
<td>Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery</td>
<td>Often involves the temporal artery Usually occurs at &gt;50 yr of age Often associated with polymyalgia rheumatica</td>
</tr>
<tr>
<td>Takayasu’s arteritis</td>
<td>Granulomatous inflammation of the aorta and its major branches</td>
<td>Usually occurs at &lt;50 yr of age</td>
</tr>
<tr>
<td><strong>Medium-Sized Vessel Vasculitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyarteritis nodosa(^1) (classic polyarteritis nodosa)</td>
<td>Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules Arteritis involving large, medium-sized, and small arteries, associated with mucocutaneous lymph node syndrome</td>
<td>Coronary arteries often involved Aorta and veins may be involved Usually occurs in children</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Small Vessel Vasculitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulomatosis with polyangiitis(^2)</td>
<td>Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels (capillaries, venules, arterioles, arteries)</td>
<td>Necrotizing glomerulonephritis common</td>
</tr>
<tr>
<td>Allergic granulomatosis with polyangiitis(^3)</td>
<td>Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels, associated with asthma and blood eosinophilia</td>
<td></td>
</tr>
<tr>
<td>Microscopic polyangiitis(^4)</td>
<td>Necrotizing vasculitis with few or no immune deposits affecting small vessels (capillaries, venules, arterioles)</td>
<td>Necrotizing arteritis involving small and medium-sized arteries may be present Necrotizing glomerulonephritis very common Pulmonary capillaritis often occurs Typically involves skin, gut, and glomeruli Associated with arthralgia or arthritis</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>Vasculitis with IgA-dominant immune deposits affecting small vessels (capillaries, venules, arterioles)</td>
<td>Skin and glomeruli often involved</td>
</tr>
<tr>
<td>Essential cryoglobulinemic vasculitis</td>
<td>Vasculitis with cryoglobulin immune deposits affecting small vessels (capillaries, venules, arterioles) and associated with cryoglobulins in serum</td>
<td></td>
</tr>
<tr>
<td>Cutaneous leukocytoclastic angitis</td>
<td>Isolated cutaneous leukocytoclastic angitis without systemic vasculitis</td>
<td></td>
</tr>
</tbody>
</table>
# VASCUITIDES

## Biopsy Findings in Major Vasculitic Syndromes

<table>
<thead>
<tr>
<th>Vessel Size</th>
<th>Fibrinoid</th>
<th>PMNs</th>
<th>Lymphocytes/monocytes</th>
<th>Eosinophils</th>
<th>Giant cells</th>
<th>Granulomas</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takayasu's arteritis</td>
<td>aorta, main branches, pulmonary</td>
<td>−</td>
<td>++</td>
<td>++++†</td>
<td>±</td>
<td>++++ †</td>
<td>During inactive stage lesions are primarily fibrotic</td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>large arteries</td>
<td>+</td>
<td>rare</td>
<td>+++</td>
<td>±</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Polyarteritis</td>
<td>medium to small arteries, venules, arterioles</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>−</td>
<td>rare*</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
<td>small&gt;medium arteries, veins, arterioles, venules</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++++</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Wegener's granulomatosis</td>
<td>medium-large arteries, small arteries, veins, capillaries</td>
<td>+++</td>
<td>+++</td>
<td>++++</td>
<td>+</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>medium arteries, small arteries arterioles, venules</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>±</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>medium arteries, small arteries arterioles, venules</td>
<td>+</td>
<td>+++ (early)</td>
<td>+++ (early)</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Behçet's syndrome</td>
<td>arterioles, venules&gt;medium-sized vessels</td>
<td>±</td>
<td>+++ (early)</td>
<td>+++ (late)</td>
<td>rare</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Hypersensitivity vasculitis</td>
<td>arterioles, venules&gt;capillaries</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>−</td>
<td>+*</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>arterioles, venules&gt;capillaries</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>rare</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

* In variants † During active phase

*Kelley's Textbook of Rheumatology, 2012, p. 1483*
Rituximab has been found to be an alternative to cyclophosphamide in the treatment of vasculitis. The general consensus was that cyclophosphamide continues to have a role while rituximab may be considered a valid option to cyclophosphamide for remission induction in newly diagnosed patients with severe ANCA-associated vasculitis. In 2011, the FDA approved rituximab in combination with glucocorticosteroids for the treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), two forms of ANCA-associated vasculitis.