Rheumatoid Arthritis (RA)
Pathogenesis, Prediction and Prevention

DOM Grand Rounds
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Disclosures

Deane
Investigator initiated research grants and consulting with Inova and Janssen
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Consulting with ThermoFisher and Microdrop

Demoruelle
Investigator initiated research funding from Pfizer
Evidence-based reviews

Rheumatoid arthritis: pathogenesis, prediction and prevention – an emerging paradigm shift. Deane KD, Holers VM. Arthritis Rheumatol 2020

Rheumatoid arthritis and the mucosal origins hypothesis: protection turns to destruction. Holers VM, Demoruelle MK, Kuhn KA, Buckner JH, Robinson WH, Okamoto Y, Norris JM, Deane KD. Nat Rev Rheumatol. 2018
Primary Goal

Leave you with enthusiasm that within the next few years, rheumatology will be taking ‘new’ Intent to Prevent* approaches for RA

Overview
Pathogenesis
Prediction
Prevention

Opportunities and challenges, and progress

*Marvin Fritzler, Univ of Calgary
What is RA?

- Systemic, autoimmune disease
- INFLAMMATORY ARTHRITIS (IA) as hallmark
- AUTOANTIBODIES in ~80% of individuals with RA
  
  *Pathogenic, diagnostic, prognostic*

~1% prevalence

~3 to 1 female to male

~Up to 8% in high-risk populations e.g. first-degree relatives, Indigenous North American populations

Smolen et al. Lancet 2016
What is RA? Individual experience

- Joint pain, stiffness and swelling, lack of mobility
- Fatigue, malaise
- Greatly improved treatments with good responses in most individuals

STILL
- Lifelong disease, lots of health-care visits and bloodwork, work loss, expense (~15K+/yr)
- Treatment side-effects
- "Great" disease control doesn’t occur in all individuals
- Comorbid conditions: premature heart disease, osteoporosis, infections, lung disease
- Most people with RA wish they never gotten it, and they don’t want their family to get it!

Gul et al. Rheumatology 2019
Destructive arthritis!
Additional manifestations

Airways disease
Common ~50-70%

Turesson Curr Opin Rheum 2013
RA: Autoantibodies

Rheumatoid factor (RF)
~80% sensitive
80% specific

Good biomarker
Pathogenic

Antibodies to Citrullinated Protein Antigens (ACPA)
Commercially-available = anti—Cyclic Citrullinated Peptide antibody

anti-CCP

~80 sensitive (and typically elevated earlier in disease)

>95% specific

Great biomarker
Pathogenic

Derksen et al Semin Immunopathol 2017
Citrullination: happens in all of us, all the time (e.g. wound healing, apoptosis) – but immune responses to citrulline are highly specific for RA

Many peptide and proteins contain citrullinated residues and are targeted in RA: fibrinogen, vimentin, enolase, histones

Darrah et al Curr Opin Rheum 2018

\[
\text{Arginine} \xrightarrow{\text{PAD}} \text{Citrulline}
\]
How is RA treated NOW?

• We wait until someone is “sick” with clinically-apparent IA

• Apply disease modifying therapy *Ideally start <3 months after onset of symptoms*

• Therapy is based on growing understanding of the biology and natural history of RA

Stack et al BMK Open 2019; Singh et al Arthritis Rheumatol 2015
DMARDS
Steroids
Hydroxychloroquine
Sulfasalazine
Methotrexate
Leflunomide
JAK/STAT inhibition
Anti-TNF
Anti-IL6
B cell depletion
Case Presentation

47 y/o female
Mom had RA
Aches and pains off/on for the past 8 months
Hands and feet, sometimes shoulders
Morning stiffness ~15 minutes some days

On exam, no tender or swollen joints consistent with IA

Autoantibody testing:
anti-CCP 68 units (normal <20)
RF 44 (normal <6)
Overview of RA development: PRE-RA

Ongoing and same/different genetic and environmental factors

Genetic Risk (a)  Environmental Risk Factors (b)

Systemic Autoimmunity (c)  Unclassified Arthritis (e)  Rheumatoid Arthritis Persistent Arthritis (f)

Pre-RA

Arthralgia (d)  Clinically suspect arthralgia (CSA)

Undiff  2010  1987

EULAR Recommendations for Termination and Research in Rheumatoid Arthritis Development

Somewhat controversial politically and biologically

Deane and Holers Arthritis Rheumatol 2020
Gerlag et al Annals Rheum Dis 2014
Van Steenbergen Annals Rheum Dis 2017
How have we learned about Pre-RA?

Well-developed prospective natural history studies

Akimel O'odham (Pima) people *Del Puente 1988* (~20 yr study!)

RA prevalence ~5%

British family study Silman 1991

Fortuitously collected biospecimens

Finnish biobank *Aho multiple 1980s/90s*

Swedish biobank Rantapaa-Dahlqvist 2003

Dutch biobank *Nielen 2004*

US military biobank *Majka 2008 (CU)*
How have we learned about Pre-RA?

Ongoing prospective Studies

Studies of the Etiology of RA (SERA)
Holers/Norris/Deane/Demoruelle (and a cast of thousands...)

First Nations Studies El-Gabalawy multiple
Dutch ACPA+/Arthralgia Cohorts Bos/van Schaardenburg multiple
 Mexican FDR studies Ramos-Remus 2015
UK ACPA+ in clinics Rakieh, Emery multiple
 Others
Pathophysiology: Initiation and propagation of autoimmunity long prior to the first swollen joint!

Autoantibody levels significantly elevated in Cases vs Controls

Anti-CCP
Rheumatoid factor
Other autoantibodies
Cytokines, chemokines
T and B cell reactivities

Kelmenson et al A+R 2020
There is no IA during much of Pre-RA (exam, imaging, biopsy)

**HYPOTHESIS:**
RA-RELATED AUTOIMMUNITY STARTS OUTSIDE JOINTS

Where?
Highly likely to be mucosal site

Holers et al Nature Rev Rheum 2018
Multiple potential mucosal sites where autoimmunity may originate in RA

- Periodontium
- Lung
- Intestine
- Genital Tract

Holers et al. Nature Reviews Rheum 2018
Multiple studies suggest a link between the lungs and RA

In established RA

- High prevalence of airways and parenchymal abnormalities on lung HRCT
  - 66% airways and 54% parenchymal - in early RA

- Increased prevalence of clinically significant interstitial lung disease in RA
  - 5-10% in RA vs. 0.1% in the general population

- Increased prevalence of asthma and COPD in RA
  - RA vs. general population - 17% vs. 14% asthma and 7% vs. 4% COPD

Reynisdottir et al. Arthritis Rheum 2013
Olson et al. Am J Respir Crit Care 2011
Nikiphorou et al. Rheumatology 2020
Airways inflammation in pre-RA

HRCT imaging of the lung in 42 pre-RA subjects and 15 controls
- Inflammatory airways were more prevalent in pre-RA
  - 76% vs. 33%, p=0.005
- Subsequent studies - asthma and COPD are risk factors for RA

Induced sputum in subjects At-Risk for RA, with RA and healthy controls
- At-Risk subjects had more sputum anti-CCP positivity than controls
  - 24% vs. 5%, p<0.01

A portion were sputum anti-CCP+ in absence of serum anti-CCP supporting local generation in the lung

Demoruelle et al. Arthritis Rheum 2017
NETs and anti-CCP in the lung in pre-RA

Neutrophil extracellular traps (NETs) = neutrophils decondense and expel their chromatin
  • Externalize citrullinated proteins
  • Increased in blood and joints in RA

Measured NET formation and NET remnants in sputum

Okamoto et al. submitted

NET formation increased in sputum neutrophils in pre-RA
NET remnants correlate with anti-CCP in sputum
  • Particularly NETs containing citrullinated proteins

Suggesting excessive cit-protein containing NETs may be a trigger of anti-CCP generation in the lung
Going forward – SERA studies

Determine the effect of cytokines and bacteria on sputum NET induction associated with anti-CCP in pre-RA

Determine the role of NET clearance associated with anti-CCP in pre-RA

**Hypothesis:** Distinct factors increasing cit-protein expressing NETs and decreased NET clearance in the lung in pre-RA will be associated with anti-CCP generation and ultimately RA

NET formation and clearance may be novel treatment targets for RA prevention
Female genital tract mucosa in RA

RA more common in women than men (3:1)

Despite decades of research, still unclear why

New concepts may be needed to explain sex differences in RA
  • Mucosal Origins Hypothesis in RA

Cervicovaginal (CV) mucosa may be a mucosal site where inflammation and autoimmunity originate in RA that is unique to women

Uhlig T et al. J Rheumatol 1998
Anti-CCP generation in the female genital tract

CVF anti-CCP is elevated in RA but also in a portion of At-Risk and healthy premenopausal women.

CVF anti-CCP strongly correlates with local inflammation.

Anti-CCP associated with inflammation in female genital tract in women with and without RA.

Demoruelle et al. unpublished
RA and the post partum period

Incidence of RA increases during the first-year after childbirth
  • Up to 6-fold increase
  • Mechanism unknown

We collected breast milk and CVF samples in 9 women without RA who were in the 1st year postpartum

Anti-CCP are present in breast milk and CVF in a portion of healthy women postpartum

Demoruelle et al. unpublished
Oral mucosa in RA

Multiple data link the gingival mucosa, anti-CCP and RA

- Anti-CCP present in gingival crevicular fluid in periodontitis patients without RA
- *Porphyromonas gingivalis*
  - Expresses PAD that can citrullinate human proteins
- *Aggregatibacter actinomycetemcomitans*
  - Expresses a leukotoxin that hypercitrullinates neutrophils

Gut mucosa in RA

Gut dysbiosis and certain bacteria are associated with RA

• *Prevotella copri*
  • Expanded in stool in RA and activates T cells in RA

• Anti-CCP in the stool of subjects with RA and pre-RA
  • Distinct bacteria associated with anti-CCP and pre-RA

Multiple mucosal sites demonstrate RA-related antibody generation in pre-RA

• Often in the absence of serum anti-CCP supporting initial generation at these mucosal sites

• Present in a modest portion of healthy controls suggesting the possibility of a ‘natural’ mucosal response to local inflammation and citrullinated proteins
  • May resolve with resolution of inflammation

Hypothesis: Dysregulation of a natural mucosal immune response could progress to aberrant anti-CCP generation and ultimately RA
Using mucosal site immune dysregulation to predict RA
Using mucosal site immune dysregulation to predict RA

49 serum anti-CCP+ pre-RA subjects were followed for 3 years
• 10/49 (20%) developed RA

Compared baseline factors associated with incident RA

<table>
<thead>
<tr>
<th></th>
<th>Developed RA (N=10)</th>
<th>Did not develop RA (N=39)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum anti-CCP+ or RF+</td>
<td>78%</td>
<td>20%</td>
<td>0.002</td>
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</tbody>
</table>

Sputum RA-related antibodies could enhance prediction of RA in a high-risk population

Perhaps, decreasing inflammation and antibody generation in the lung could be a future therapeutic strategy in the treatment or prevention of RA
Case Presentation

47 y/o female
Mom had RA
Aches and pains off/on for the past 8 months
Hands and feet, sometimes shoulders
Morning stiffness ~15 minutes some days

On exam, no tender or swollen joints consistent with IA

Autoantibody testing:
anti-CCP 68 units (normal <20)
RF 44 (normal <6)
Prediction of future clinically-apparent IA/RA

In case-control and prospective studies, serum elevations of anti-CCP

Positive predictive value of 30-60% for clinically-apparent inflammatory arthritis within 2-6 years

Higher PPV if symptoms are present, RF also positive, HLADR4 allele present

Case Presentation

47 y/o female
Mom had RA
Aches and pains off/on for the past 8 months
Hands and feet, sometimes shoulders
Morning stiffness ~15 minutes some days

On exam, no tender or swollen joints consistent with synovitis

Autoantibody testing:
CCP 68 units (normal <20)
RF 44 (normal <6)

>50% risk for clinically-apparent inflammatory arthritis in 3-5 years
Prevention

Underpinned by:
Prediction models
Established therapies
Growing identification of ‘at-risk’ subjects
Completed RA prevention trials
Stop/delay the first joint with IA on exam

PRAIRI Study

Inclusion
81 subjects
Arthralgia
No examination IA
Anti-CCP and RF

Intervention
Rituximab 1000 mg x 1

37% developed RA over a mean of 29 months (range 0-54): 40% vs. 34%
Rituximab delayed the time at which 25% of subjects had developed IA by ~12 months

Gerlag et al Ann Rheum Dis 2019
# Ongoing RA prevention trials

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Inclusion: Biomarker*</th>
<th>Inclusion: symptoms</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>StopRA</td>
<td>Anti-CCP &gt;2x</td>
<td>-</td>
<td>Hydroxychloroquine x 1 year</td>
<td>RA 2010</td>
<td>USA</td>
</tr>
<tr>
<td>APIPPRA</td>
<td>Anti-CCP+RF or anti-CCP &gt;3x</td>
<td>arthralgia</td>
<td>Abatacept x 1 year</td>
<td>RA 2010</td>
<td>UK</td>
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<tr>
<td>StapRA</td>
<td>RF+anti-CCP or anti-CCP &gt;3x and arthralgia</td>
<td>arthralgia</td>
<td>Atorvastatin 40 mg x 1 year</td>
<td>RA 2010</td>
<td>Dutch</td>
</tr>
<tr>
<td>TreatEarlier</td>
<td>Subclinical joint inflammation on MRI</td>
<td>arthralgia</td>
<td>MTX x 1 year, initial dose of IM methylprednisolone</td>
<td>RA 2010</td>
<td>Europe</td>
</tr>
<tr>
<td>CuPRAA</td>
<td>Anti-CCP any elevated level</td>
<td>-</td>
<td>Curcumin, omega-3, vit D</td>
<td>Anti-CCP levels*</td>
<td>Indigenous/First Nations Canada</td>
</tr>
</tbody>
</table>

*serum levels
StopRA: Study Design

**Enrollment Criteria**
- Anti-CCP
- No IA

**Prescreening**
- FDR
- Clinics
- Population:

30,000+ ‘Prescreened’ in ~3.5 yrs to randomize ~130 so far!

1 year drug

2 years off drug follow-up

100 subjects HCQ/100 placebo (total = 200)

12 visits over 3 years (Pre/Screening included)

**Funding:**
NIH/NIAID
Autoimmunity Center of Excellence

www.stop-ra.org
The trials have different targets and different times in the stages of RA

Where an individual is may dictate intervention: type, risk, cost
Opportunities and challenges

Current preventive interventions: science and convenience – but do we need better?

- **Initiation**
- **Propagation**

NOVEL TARGETS AT AN EARLY AND MALEABLE STAGE
- Sex specific?
- Mucosal?
- ‘unique’ processes e.g. fatty acids/resolvins

This is where we have experience

Move known drugs earlier

Gan et al Rheumatology (Oxford) 2017
Gan et al Ann Rheum Dis 2017
Major Challenges and Opportunities

• What will these current trials tell us? **PREDICTION, RESPONSE TO THERAPY AND NOVEL TARGETS**

• Build infrastructure for trials **TYPE 1 DM AND TRIALNET** (Teplizumab, Herold et al NEJM 2019)

• What is success in prevention? **DRUG-FREE REMISSION? STOP THE FIRST FLARE BUT CONTINUE LIFELONG THERAPY?**

• Individual preferences and delivery **ESPECIALLY TO HIGH-RISK GROUPS** (racial groups, women, family members)

• Expansion to other diseases **E.G. LUPUS, PSORIATIC ARTHRITIS**

• Business model for prevention **PUBLIC HEALTH, INSURANCE, PHARMA, DIAGNOSTICS**
Conclusion

RA
Pathogenesis
Prediction
Prevention
Opportunities and challenges

At-risk populations
Studies of the Etiology of RA (SERA)
Studies of the Etiologies of Rheumatoid Arthritis (SERA)

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9 Health-Fair Resources: Abbvie, Arthritis Foundation

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