Rheumatoid Arthritis & Periodontal Disease

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Outline

- Periodontal Disease (PD)
- Pathogenetic Mechanisms of PD
- Epidemiological Correlations with RA
- Pathogenetic Correlations with RA
- Anti-CCP Antibodies
- RANKL/OPG System
- Animal Models
- Treatment Issues
- Conclusions
Periodontal Disease

Affects one or more of the periodontal tissues
(Alveolar bone/ Periodontal ligament/ Cementum/ Gingiva)

Majority plaque-induced

Gingivitis → Periodontitis

Necessary but not sufficient
Periodontitis

- Destructive inflammatory disease of the supportive tissues of the teeth
- Consequence of an infectious trigger

**Stages of Periodontitis**

- **Gingivitis**, Chronic inflammation
- Colonization by pathogenic organisms - Biofilm formation
- Loss of connective tissue attachment to the teeth
- Bone resorption
- Tooth loss

*P. gingivalis, P. intermedia, A. actinomycetemcomitans, B. Forsythus etc*
Healthy Gingivitis

Moderate Periodontitis

Severe Periodontitis
Epidemiology of PD

- **Periodontal Disease**
  - Leading cause of tooth loss in the US

- **Estimates of Prevalence of Periodontal Disease**
  - NHANES III 35% of adults > 35 years (10 - 60%)
  - 30% of these are moderate to severe (13% total)
  - Substantial proportion of severe PD is progressive

- **Risk factors**
  - Cigarette smoking, medications, systemic diseases

- **Twin studies** \(\approx 50\%\) heritability

- **Genetic Associations reported**
  - HLA-DR4, TNF, IL1\(\beta\), IL6, IL10, TLR4, CD14 polymorphisms

*De Pablo, J Rheumatol 2008
**Detert et al, Arthr Res Ther 2010
Pathogenesis of PD

- Bacteria necessary but not sufficient
- Bacterial eradication does not necessarily lead to resolution
- Antibody response to bacteria predicts progressive disease and bone loss (e.g. IgG Anti- *P. gingivalis*)
- T-cell component (CD4:CD8 = 2:1, Tregs)
- B cell component (plasma cells, Ag presentation, RANKL)
- Cytokine-mediated damage (TNF, RANKL, etc)
- Genetic Associations (HLA-DR4, IL1b, etc)

*Bertelot et al, J B Spine 2010
**Ohlrich et al, Aust Dent J 2009
PD Classification

Based on histopathologic and immunopathogenetic features [*Page & Schroeder, Lab Invest 1976]

- **Initial lesion (0 - 4 days)**
  - PMN accumulation, complement activation, TNF-α, ↑vascular permeability, initiation of tissue damage

- **Early lesion (4 - 7 days)**
  - PMN turn to lymphocytes & macrophages, perivascular infiltrates, ELAM-1, ECAM-1, IL-8, collagen degradation, T cell CD8:CD4 1:2

- **Established lesion (non-reversible)**
  - B cell predominance, IL-1, IL-6, TNF-α, PGE$_2$, bone destruction

- **Advanced lesion**
  - Clinically obvious loss of attachment, MMPs by fibroblasts & macrophages
Bacterial plaque and biofilm

Tooth

**Gingiva**

- LPS
- PMN
- IL1
- IL6
- IL8
- RANKL
- IL17
- PGE2
- TNF
- IL1, PGE2, TNF, IL6, IL8, RANKL, IL17

**Bone**

- MMPs
- Connective Tissue Matrix
- Fibroblast
- Osteoclast

**Macrophage**

**Plasma cell**

**T cell (Th1, Th2, Th17)**
Porphyromonas Gingivalis

- Gram-negative anaerobic bacteria
  One of terminal “red complex” group of organisms
- Express LPS and activate through TLRs
- Express numerous proteolytic enzymes
  - Arginine, lysine, and cysteine metabolism
    - Peptidyl Arginine Deiminase (PAD)
  - Collagenolytic enzymes
  - Tryptic and chymotryptic peptidases
  - Glycylpropyl peptidases
  - Gingipains
  - Exotoxins
- Express enolase with overlapping sequence to human α-enolase susceptible to citrullination
- Antibodies to *P. gingivalis* are a marker of periodontal disease

*Detert et al, Arthr Res Ther 2010*
PD correlations

Increased PD seen in various systemic conditions

- Rheumatoid Arthritis (RA)
- Diabetes Melitus (*)
- Atherosclerotic Cardiovascular Disease (**)
- Low birth weight infants and preterm labor (†)

*Salvi et al, J Clin Periodontol 2008
**Detert et al, Arthr Res Ther 2010
†Piscoya et al, Pediatr Int 2011
Epidemiological Associations with RA

- **NHANES III (*)**
  - Subjects ≥60 yrs old with musculoskeletal and single quadrant dental exams
  - RA more likely edentulous (OR=2.27) and having PD (OR=1.82) compared with non-RA subjects
    - Adjusted for age, sex, race/ethnicity, and smoking

- **NHEFS (**)**
  - Subjects 25-74 yrs old, 20 yr follow-up
  - Even though >5 missing teeth led to higher prevalence & incidence of RA, most associations were not statistically significant

- Small case-control studies have reported similar results (**)
  - OR 2.3-4.0 for PD in RA patents vs. controls

* De Pablo P et al, J Rheumatol 2008
** Demmer et al, J Clin Periodontol 2011
‡ Mercado et al, J Clin Periodontol 2001
Epidemiological Associations with RA (2)

- RA pts in higher risk for PD (*, ¥)
  - 2-8 fold higher PD risk, higher percentages of attachment loss and probing depth

- Marotte et al (**)  
  - High association between periodontal bone loss and wrist X-ray damage (P<0.001)  
  - RA shared epitope associated with both periodontal bone loss and wrist damage (OR=2.2)

*Kasser et al, Arthr Rheum 1997  
**Marotte et al, Ann Rheum Dis 2006  
¥Pischon N et al, J Periodontol 2008
Limitations of Epidemiological Studies

- Most studies in established longstanding RA
- Poor characterization of RA disease activity
- Influence of medications unclear
- Sjögren’s contribution unclear (*,¥)
- Poorly controlled for smoking

*Kuru et al, J Clin Periodontol 2002
¥Marotte et al, Ann Rheum Dis 2006
Shared Mechanisms in PD & RA

Mediators
- IL-1β
- TNF-α
- IL-6
- IL-8
- IL-17
- MMP
- Nitric Oxide
- Lipoxins
- PGE₂

Cells
- T cells
- B cells
- Plasma cells
- Macrophages
- Neutrophils
- Fibroblasts
- Osteoclasts
- Angiogenesis
Pathogenetic Associations of PD & RA

1. Smoking is a risk factor for both conditions  
   [Van Winkelhoff et al, J Periodontol 2001]

2. HLA-DRB1-04 are a risk factor for both conditions  
   [Stein et al, J Periodontal Res 2003]

3. Key role for B cells and plasma cells in chronic inflammation of gingival and synovial tissues (B cells > T cells, plasma cells)

4. Mechanism underlying alveolar resorption similar to the mechanism involved in joint erosions (RANKL, IL-17)

5. TLRs in Animal Model Arthritis & in PD  
   [Hirschfeld et al, Infect Immunol 2001]  
   [Drexler et al, Int J Biochem Cell Biol 2010]
Pathogenetic Associations of PD & RA

(2)

- DNA from oral bacteria (e.g. P. gingivalis) in the gingiva of PD pts & in the synovial membrane from RA pts
  

  & may promote citrullination of various self-antigens
  
  [Routsias et al, Rheumatology 2011]

- Strong correlation (2.6-fold risk increase) between presence of anti-CCP antibodies & periodontitis in RA pts
  
  [Molitor et al, Arthr Rheum 2009]

- Antibodies to P. gingivalis are more common in RA subjects than controls, although lower than in PD, & Correlate with certain anti-CCP antibody isotypes
  
  [Mikulis et al, Int Immunopharmacol 2009]
Peptidyl Arginine Deiminase (PAD)

- Human Peptidyl Arginine Deiminase (PAD) 1,2,3,4,6
  - PADI2, PADI4, PADI6 expressed in RA synovium
  - **PADI4** polymorphisms in some RA patients (17 SNPs)
  - PAD2 up-regulated with cigarette smoke
  - Expressed by T cells, B cells, NK cells, neutrophils, monocytes, eosinophils
  - PAD activation due to oxidative stress or apoptosis

- **P. gingivalis** has endogenous PAD
  - The only bacterium known to express PAD
  - Hypothesized release of NH$_3^+$ → Buffering of crevicular fluid
    → Evasion of host defense

*Mangat et al, Arthr Res Ther 2010*
Citrullination

Peptidylarginine deiminase (PAD) catalyzes the conversion of L-arginine to L-citrulline by removing a calcium ion (Ca\(^{2+}\)). This reaction is a post-translational modification that results in neo-epitope formation.

L-arginine residue (+charged) → L-citrulline residue (neutral)

Human PADI-4 Mutations

Peptidyl Arginine Deiminase

Arginine → Citrulline + NH3

Citrullinated Peptides (e.g. vimentin, vitronectin, keratin, filaggrin, fibronectin, collagen, α-enolase)

Innate immune responses, inflammation, other immunologic activation

In Proper Context: MHC HLA-DR4*0401

Antigen Presenting Cell

T Cell

Cytokines

MΦ

FLS

B Cell

Plasma cell

Anti-CCP Antibodies
Early RA marker
98% spec/ >80% sens

Effector cell-mediated joint inflammation and destruction
Shared epitope of RA:

**HLA-DRB1** region 70-74 of the 3rd hypervariable region (0401, 0404, 0405, 0408)

- Correlates with both RA & rapidly progressive PD
- Correlates with smoking and ACPA(+) RA

The (+) charged pocket P₄ of the epitope does not react with the (+) charged Arginine, but does with the neutral Citrulline

*Citrullination of HLA binding peptide* $\rightarrow$ *100-fold increase in peptide-MHC affinity* $\rightarrow$ *CD4⁺ T cell activation in HLA DRB1 0401 transgenic mice*

*Routsias et al, Rheumatology 2011*

**Hill et al, J Immunol 2003**
Pathogenetic Hypothesis

Gingiva: infection, inflammation, immune activation

Joint: trauma, apoptosis, PAD activation

peptidyl arginine

P. gingivalis PAD

peptidyl citrulline

Human PADs

self-proteins

ANTIPETIDYL CITRULLINE ANTIBODIES

CITRULLINATED SELF-PROTEINS

intramolecular epitope spreading

intermolecular epitope spreading

ANTI-CIT PROTEIN ANTIBODIES
RANKL/OPG System

- RANKL/OPG ratio up-regulation in PD (*)
- RANKL/OPG ratio up-regulation in RA (**) 
- Further up-regulation by Smoking & Diabetes Melitus 
- P. gingivalis is a strong RANKL inducer (¥)

**Fonceca et al, Clin Exp Rheumatol 2005
¥Belibasakis et al, Microb Pathog 2007
Animal Models

- Primates
- Dogs
- Miniature pigs

Naturally induced PD, practical & ethical issues

- Rodents: Experimentally induced PD- Immunopathogenetic Correlations

- Murine model of A. actinomycetemcomitans induced PD
  - Mice lacking the p55 TNF receptor → ↓Bone resorption & ↓levels of RANKL expression, but also ↓Migration of lymphocytes, macrophages, and neutrophils → ↑Proliferation of A. actinomycetemcomitans (*)

- Chronic Ag-Induced Arthritis (AIA) (Methyl-BSA injection in the knee joint of immunized mice) → Periodontal disease (**)

** Queiroz-Junior et al, J Immunol 2011
PD Treatment & RA

- Patients receiving PD treatment showed a significant decrease in the mean DAS28, ESR (P <0.001), and serum TNF-a (P <0.05), regardless of the medications used to treat RA
  
  [Ortiz et al, J Periodontal 2009]

- A meta-analysis also showed a significant decrease in DAS28 (P=0.03), due to PD therapy
  
  [Lü Zu et al, 2011]

- PAD blockade has the potential to switch off autoimmunity at the point of initiation and could inhibit the maintenance of RA pathology (Paclitaxel, Cl-amidine in CIA)
  
  [Mangat et al, Arthr Res Ther 2010]
Anti-RA Agents & PD

- Anti-TNF agents can ↓RANKL/OPG ratio, thus slowing bone damage
  - [Havaardsholm et al, Ann Rheum Dis 2006]
  - [Mayer et al, J Periodontol 2009]

- Infliximab Study/40 RA subjects [Pers, J Periodontol 2008]
  - 20 IFX (mean 22.2 infusions) vs. 20 non-IFX treated
  - No difference in baseline RA disease activity
  - PD and AL not affected by IFX Tx in Group 1 vs. 2
  - Gingivitis and bleeding index actually increased in 9 patients

- Exogenous OPG reduced bone loss in a rodent model of PD [Jin et al, 2007]

- Denosumab (RANKL monoclonal Ab) could be beneficial in PD [Culshaw et al, J Clin Periodontol 2011]
**Periodontal Disease**

- **P. gingivalis**

**Innate immune responses, inflammation, immunologic activation**

- **↑PAD-2**
- **↑PAD-4**

**Peptidyl Arginine Deiminase**

- **Arginine** → **Citulline + NH$_3^+$**

**Citrullinated Peptides** (e.g. vimentin, vitronectin, keratin, filaggrin, fibrinogen, enolase)

**Anti-CCP Antibodies**

**Effector-cell mediated inflammation and tissue destruction**

- **Macrophage**
- **Fibroblast**
- **Osteoclast**
- **PMN**

**TNF-α, (LPS)**

**Apoptosis**

**Smoking**

**Inflammation**

**Rheumatoid Arthritis**
Ευχαριστώ