J Clin Periodontol 2011; 38 (Suppl. 11): 106–113 doi: 10.1111/j.1600-051X.2010.01669.x

Journal of Clinical Periodontology

What can the periodontal community learn from the pathophysiology of rheumatoid arthritis?

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Culshaw S, McInnes IB, Liew FY: What can the periodontal community learn from the pathophysiology of rheumatoid arthritis? J Clin Periodontol 2011; 38 (Suppl. 11): 106–113. doi: 10.1111/j.1600-051X.2010.01669.x

Abstract

Aim: The aim of this paper is to provide a narrative review of the aetiopathogeneis and treatments of rheumatoid arthritis (RA), focusing on aspects that may share commonality with periodontitis.

Results: A myriad of cell types, cytokines and pathways have been investigated in both periodontitis and RA. Chronic inflammatory diseases, including RA, psoriatic arthritis, ankylosing spondylitis and periodontitis are likely to share pathogenic mechanisms of inflammation-mediated solid tissue destruction. The aetiopathogenesis of these diseases has been extensively researched over the last several decades and advances in understanding have revolutionized arthritis therapeutics.

Conclusion: The rational, targeted inhibition of mediators in RA has provided clinically useful therapeutics and shed light on mechanisms underpinning disease pathogenesis. RA should be considered a prototypic disease revealing how understanding disease pathogenesis may transform therapeutic options and patient outcomes.

Key words: bone destruction; host response; periodontitis; rheumatoid arthritis

Accepted for publication 7 November 2010

Rheumatoid arthritis (RA) is a systemic autoimmune disease encompassing breach of self-tolerance, chronic inflammation and joint destruction. RA affects approximately 1% of the population and is associated with significant morbidity and mortality (Firestein 2003). In addition to debilitating joint destruction, patients with RA demonstrate substantial co-morbidity, including significantly accelerated atherosclerosis, psychological disease and socioeconomic decline. Clinical presentation is preceded by a ''pre-articular'' phase of up to 10 years, which is characterized by elevated serum autoantibody titres directed against citrullinated peptides or immunoglobulin (rheumatoid factor) (McInnes & Schett 2007) and intriguingly with lipid dysregulation suggesting some integration with metabolic processes. Although primary aetiological differences seem likely, periodontal destruction and the articular destruction of RA share common pathogenic mechanisms of host-response driven hard tissue destruction arising from chronic dysregulated inflammatory cascades in adjacent tissues.

Conflict of interest and source of funding statement

None of the authors have financial conflicts of interests.

F. Y. L. and I. B. McI. received funding from Medical Research Council, UK; The Wellcome Trust; Arthritis Research UK; The European Commission; Chief Scientists Office, Scotland; The British Heart Foundation and the Oliver Bird Rheumatism Program. SC received funding from Medical Research Scotland, and is supported by The University of Glasgow. This supplement was supported by an unrestricted grant from Colgate.

Aetiopathogenesis of RA

Currently the triggers that initiate breach of immune tolerance and the subsequent progression to clinically relevant autoimmunity, and in particular articular localization leading to the clinical symptoms of RA are unknown. A number of recently reported genome wide scans have provided insight to many novel disease-associated loci. The majority thus far identified clearly implicates the immune system in inci-

dent risk and progression. It has long been recognized that MHC class II alleles (e.g. *DR0401*, *0404*) are associated with RA. Although discrete alleles are linked to RA in different geographical regions, all share a common capacity to bind distinct peptide sequences – the so called shared epitope hypothesis (Stahl et al. 2010). A variety of additional candidate genes that exhibit plausible biologic effects are now evident. Many point to regulation of adaptive immunity, including *ptpn22* (protein tyrosine phosphatase, non-receptor type 22, which regulates lymphocyte activation), *ctla4* and *cd40* (both implicated in co-stimulation of T cells). Other loci suggest modulatory influences on wider immune regulatory potential e.g. *stat4*, *tnfa20*, *c5* (which in general regulate leucocyte activation and inflammatory signaling) and Fc receptors (Plant et al. 2009). Cytokine genes too have been implicated including *interleukin* (*IL*)*-1*, *tumour necrosis factor* (*TNF*), *IL-10* and *IL-18* (van der Helm-van Mil et al. 2005) although their functional correlates are not as yet resolved. Overall, genetic factors may account for around 30% of disease risk in RA, and although this has been debated it is generally accepted that environmental factors are crucial (Klareskog et al. 2008). A substantial recent advance therefore has been the identification of gene environmental interactions between the MHC class II locus, *ptpn22* and smoking upon disease risk (Kallberg et al. 2007, Klareskog et al. 2008). The mechanisms underlying these interactions, and particularly how oral/pulmonary exposure and local citrullination in turn promote a localizing arthropathy, are unclear but will likely be highly informative for future preventative therapeutics. It is significant that smoking is a shared risk factor common to periodontitis (AAP Position Paper 1999, Baka et al. 2009). Other risks associated with RA include exposure to other environmental triggers e.g. mineral oils, carbon products and to significant life stress events (Klareskog et al. 2002). Thus far no clear relationship to any particular infectious agent has been confirmed although associations with a variety of bacterial and particularly viral infections have been variously offered including EBV, CMV and parvovirus (Costenbader & Karlson 2006, Colmegna & Alberts-Grill 2009).

A contextual framework for the pathogeneses of RA and periodontitis is outlined in Fig. 1. Treatment strategies for RA have evolved to include successful, specific targeted, biological therapies, which in their development have provided valuable insights into the pathogenesis of arthritis. RA and periodontitis likely have aspects of aetiopathogenesis in common and this provides lessons for both diseases.

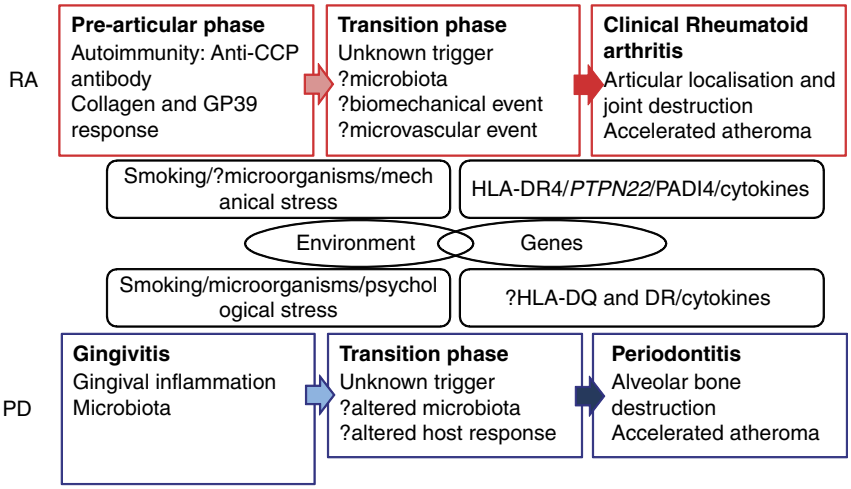

Fig. 1. A contextual framework for the pathogenesis of rheumatoid arthritis, and periodontitis. In RA, autoimmune processes are predicted to have been active for an undetermined time – up to several years – before clinical presentation. The transition phase remains poorly defined. Once the rheumatoid arthritis is established, inflammatory pathways may take president over autoimmunity.

Cells Involved in RA

Normally the synovial membrane is relatively acellular comprising a loose fibroblast/macrophage lining layer overlying adipose cells supported by a modest capillary structure. In RA the synovial membrane becomes heavily infiltrated with leucocytes of many subsets and mediating numerous effector functions. This is in turn supported by extensive angiogenesis but not by lymphangiogenesis thereby promoting accumulation and aggregation of cells within the joint. Germinal centre formation is observed in around 30% of tissues examined and thus the synovial membrane often acquires the properties characteristic of a secondary lymphoid organ – so called ectopic germinal centre formation. A ''pannus'' of proliferating cells forms over the cartilage, consisting of fibroblast-like synoviocytes and macrophages. The cartilage-pannus junction is the site of predominant cartilage destruction. The synovial environment is also a rich maturation milieu for osteoclasts, which develop from locally invading monocyte precursors and thereby mediate destruction of mineralized cartilage and bone. Osteoblast expression is reduced and the net effect is towards bone damage with failed repair. This ''solid phase'' of the RA lesion is bathed in protease and cytokine-rich synovial fluid (SF), which is also heavily infiltrated by leucocytes, primarily neutrophils.

The hierarchical organization of leucocytes in the joint has been hotly debated and remains unclear. Synovium removed at joint replacement surgery provides an ex vivo system for investigation. Fibroblast-like synoviocytes thus derived, have been extensively studied and in the rheumatoid joint these cells demonstrate an invasive phenotype, capable of destroying cartilage. Their phenotype is semi-autonomous characterized by anchorage independence, loss of contact inhibition and the capacity for high levels of prostanoid, MMP and cytokine production. Although unlikely to initiate joint destruction, these synoviocytes perpetuate joint damage (Bartok & Firestein 2010) and have recently been shown to exhibit migratory activity within patients and in vivo arthritis models (Lefevre et al. 2009). Synovitis thus contains high numbers of macrophages, mast cells, $CD4^+$ and $CD8^+$ T cells and B cells, plasmablasts and plasma cells. As noted above, organized lymphoid tissue is apparent within the synovial membrane that may be associated with poorer treatment outcome (Dorner &

Lipsky 2006). It is likely that lymphoid regulatory activity is also ongoing in adjacent lymph nodes and bone marrow (Jimenez-Boj et al. 2005, Rudnicka et al. 2009). In addition to autoantibody production and subsequent immune complex formation, B cells contribute cytokines including IL-6, IL-10 and LTβ. B cell depletion reduces ectopic germinal centre formation suggesting B cells may have significant antigen presentation and T-cell regulatory functions (Edwards et al. 2004). T cells are strongly implicated in RA by their abundance in the inflamed joint and the associations of the disease with Class II MHC alleles, and other genes associated with T-cell regulation including *ctla4*, *ptpn22*. T cells appear essential for some animal models of arthritis. Conversely, T-cell-derived cytokines, including IL-17A, IL-17F and interferon-γ (IFN-γ) are sparsely expressed in the joint and T-cell-targeted therapy has proven ineffective in treatment of RA thus far (Keystone 2003). These observations initially challenged the role of these abundant cells in disease pathogenesis. Targeting the T-cell costimulatory molecule CTLA4, however, proved clinically effective, suggesting inhibition of T-cell activation, rather than elimination of T cells, may ameliorate disease (Genovese et al. 2005). Macrophages residing in synovitis may initiate and perpetuate inflammation both through cytokine production, auto-antigen presentation, and cell-contact-dependent non-antigen specific T-cell activation (McInnes et al. 2000). These multiple cell types, in a defined, architecturally complex environment, are bathed in SF in which there are high concentrations of cytokines and abundant activated neutrophils (Edwards & Hallett 1997). SF-derived neutrophils display evidence of in vivo priming and activation. The SF contains numerous neutrophil-derived factors (including IL-1, IL-8, TNF-α and LTB_4), which may exert autocrine priming and activation of neutrophils. Additionally, immunoglobulin G (IgG)-containing immune complexes found within the joint are potent neutrophil agonists. Histological examination of the cellular composition of the cartilage pannus junction revealed the presence of neutrophils (Mohr et al. 1981) and an activated neutrophil adjacent to cartilage may release reactive oxygen and degradative enzymes; a process termed ''frustrated phagocytosis''. In the fluid phase, potential for neutrophil damage includes release of products that break down hyaluron (Grootveld et al. 1991), reducing its viscosity and mediators which saturate the SF anti-proteinase and antioxidant activity (Abbink et al. 1993). In a rat arthritis model, administration of a neutrophil depleting antibody reduced neutrophil accumulation within the joint, concomitant with ameliorated arthritis (Santos et al. 1997).

The Cytokine Cascade in RA

Cytokines are central to immune regulation and are key to all stages of RA from initiation of autoimmunity to bone destruction. The function of individual cytokines is detailed below and their role in periodontitis has been recently reviewed (Yen-Chun et al. 2010). Therefore, observations described below pertain mainly to studies of arthritis.

TNF family

In the rheumatoid joint TNF-α is produced by monocytes, T cells, B cells, NK cells, neutrophils, mast cells, fibroblasts and osteoblasts. Overall, it activates these cells and promotes inflammation and tissue degradation. Inhibition of TNF-α in vitro reduced IL-1 activity, and production of GM-CSF, IL-6 and IL-10. These observations placed TNF further up the hierarchy, making this cytokine an attractive target for therapy (Brennan et al. 1989). Other members of the TNF-α family whose role has been studied in RA include LT-β, which promotes ectopic germinal centre formation (Takemura et al. 2001). B lymphocyte stimulator (BLyS) and a proliferating inducing ligand (APRIL) are believed to promote autoantibody production (Takemura et al. 2001). Receptor activator of NFκB ligand (RANKL) is expressed by T cells, stromal cells and osteoblasts, and stimulates bone resorption by directly activating osetoclasts. Its expression can be enhanced by TNF-α (Schett et al. 2005).

IL-1 family

The cytokine hierarchy model places IL-1 downstream of TNF-α and this is confirmed by the disappointing clinical response to IL-1 inhibition in RA (Furst et al. 2005). However, IL-1 receptor antagonist–deficient mice develop spontaneous arthritis suggesting this may have key influence at certain stages of disease, possibly through amplification of T-helper type 17 (Th17) cells (Nakae et al. 2003). IL-18 is detected in the synovium and promotes Th1 cell differentiation against an IL-12-rich backdrop via IFN-γ induction, and promotes Th2 differentiation in the presence of IL-4 (Arend et al. 2008). IL-18 also induces IL-32, which causes TNF-α independent matrix degradation and IL-32 is therefore of interest as a novel target in RA (Joosten et al. 2006). IL-33 has been detected in the RA joint and appears to play an exacerbating role, likely mediated by mast cells (Liew et al. 2010).

IL-6

IL-6 is probably the most abundant cytokine in the diseased joint where it regulates activation of B cell proliferation and autoantibody production, influencing T-cell differentiation, as well as exerting broad effects on other cells residing in the joint. IL-6 has bone marrow modulating effects, and increases the hepatic acute phase response. IL-6 binds its receptors, IL-6Rα and the accessory molecule gp130 which can form a functional receptor with either transmembrane or soluble IL-6Rα (Jazayeri et al. 2010); an observation that was key to appropriately directed therapy.

IL-17

The IL-17 family encompasses IL-17A–F, and IL-17A is currently the most extensively characterized. A potent role for IL-17 in joint damage has been proposed (Miossec et al. 2009). IL-17 is produced by T cells, synovial fibroblasts and mast cells and promotes osteoclastogenesis and fibroblast activation (van den Berg & Miossec 2009, Hueber et al. 2010).

IL-15

Of the common gamma chain binding cytokines, IL-15 has received most recent attention in RA. IL-15 is produced by monocytes, synovial fibroblasts, mast cells, DCs, neutrophils and B cells. The elevated presence of IL-15 in the joint accounts for the ongoing T-cell activation in the absence of high levels of IL-2, as IL-15 promotes T-cell expansion and maturation (McInnes et al. 1996, 1997, Zhang et al. 1998).

Cytokines operate in hierarchical networks, the nature of which is dependent on the stage of disease. The complex kinetics of cytokine network function are exemplified by the observation that patients with early rheumatic disease express high levels of IL-4 and IL-13 in their SF, but these cytokines are undetectable in established disease (Raza et al. 2005). As investigations continue into earlier stages of disease, the role of cytokines in disease initiation remains to be fully elucidated and the limitations of studies using human ex vivo tissue from end stage disease become more apparent. However, clearly, there is therapeutic benefit in understanding cytokine networks in established disease.

The role of Th1/Th17/regulatory T cells (Tregs)

The Th1/Th2/Th17 paradigm and its role in both periodontal diseases (PD) and arthritis have been extensively reviewed (Gaffen 2008, Miossec et al. 2009). The Th17-derived cytokine IL-17 has been identified in the diseased joint (van den Berg & Miossec 2009), and the discovery of these Th17 cells provided some explanation for the lack of IFN-γ but apparent Th1 features of the rheumatoid joint. The main cytokine growth factors for synovial T cells are likely to be IL-7 and IL-15, but they do not directly modulate their cytokine effector phenotype (McInnes et al. 1997). The cytokines in the joint, IL-1, -6, -7, -12 -15, -18, -23 and transforming growth factor-β (TGF-β) are all capable of supporting Th17 or Th1 differentiation. Studies in animal models suggest a Th1 predominance favouring disease progression, even though IFN-γ is lacking or expressed at low levels in RA synovium. Th17 cells share some characteristics of Th1 cells, and appear capable of producing IL-17, IFN-γ, IL-22, RANKL and GM-CSF. Arthritis models demonstrated reduced severity in the absence of IL-6 or IL-23, both of which drive Th17 differentiation. Direct inhibition or over-expression of IL-17 ameliorates or exacerbates rodent models of arthritis respectively (Lubberts et al. 2005). Naturally occurring FoxP3$^+$ Treg are present in the rheumatoid joint, but appear not to have normal regulatory function. However, neutralizing TNF-α in rheumatoid patients appears to promote regulatory cell secretion of IL-10 and TGF-β, which may be clinically beneficial (Ehrenstein et al. 2004).

The paucity of Th1 cells in the synovium suggests that this cell type is unlikely to play a key role in the pathogenesis of RA. Furthermore, a recent study shows that IL-17 contributes to the Th1 defect in RA through the down regulation of Th1 differentiation (Toh et al. 2010). Although Th17 cells are clearly important in animal models of arthritis, their role in clinical RA remains uncertain. The presence and the pivotal role of IL-17 in RA have been supported by several studies (Miossec et al. 2009). However, most of the IL-17 producing cells in the joints are found to be mast cells rather than T cells (Hueber et al. 2010). Thus, further studies are clearly warranted.

The role of Toll-Like Receptors (TLRs)

TLRs have been implicated in the triggering and perpetuation of synovial events in RA. Expression of TLR 2, 3, 4, 6, 7 and 9 has been demonstrated in the rheumatoid joint, in macrophages and fibroblast-like synoviocyte lineages. Diseased joints express elevated endogenous ligands such as hyaluron oligosaccharides, fibronectin fragments, heat shock proteins and antibody-DNA complexes. Whilst conditioned media from explant cultures activated macrophages in a MyD88-dependent, IL-1R-independent fashion, the precise ligand(s) have not been confirmed. No association with TLR polymorphisms has been detected, but using gene knock-outs, TLRs have a well-documented initiating and exacerbating role in animal models of arthritis, including models mediated or exacerbated by LPS, peptidoglycan and streptococcal cell wall. TLR2 and 4 seem to show most effect in these models. A number of studies documented bacterial DNA in the diseased joint. However other studies have failed to find muramic acid, used as a bacterial marker (reviewed in (Drexler & Foxwell 2010).

Therapeutic Intervention in RA

The traditional approaches to controlling RA relied on Disease Modifying Antirheumatic Drugs (DMARDS), including methotrexate (MTX), leflunomide and sulphasalazine. These drugs demonstrate partial clinical benefit but at a cost of significant toxicity and progression of erosive articular damage over time. Since the latter is closely correlated with functional loss and long-term disability it has become a major focus for clinical therapeutic objectives. Use of MTX alone achieves approximately 50% improvement in clinical signs and symptoms in 30–50% of patients (Smolen et al. 2007). Advances in understanding key events in the pathogenesis of RA have identified numerous novel therapeutic targets. RA was the first disease in which the benefit of such targeted anti-cytokine therapy proved efficacious (Elliott et al. 1994) and subsequently a large range of biological therapeutics has emerged. Findings from numerous pathological studies have been successfully translated into therapies, which have improved patient outcomes and shed further light on some aspects of disease pathogenesis. Current biological therapies are summarized in Table 1.

Anti-TNF therapies

Five TNF-α inhibitors, infliximab, a chimeric monoclonal antibody; etanercept, a soluble TNF receptor (TNFR2) with an Fc portion of immunoglobulin; adalimumab, a fully humanized monoclonal antibody; golimumab, a fully humanized monoclonal antibody; and certolizumab, a PEGylated Fab fragment are now available for clinical use. In combination with methotrexate, a 20% reduction in composite measures of clinical signs and symptoms is achieved (reflected in the American College of Rheumatology Response criteria) in approximately 50–70% of patients and this improvement is often accompanied by inhibition of joint destruction measured by reduced Sharp score progression on plain radiographs (Smolen et al. 2007). These TNF inhibitors have documented efficacy in a number of other autoimmune inflammatory disorders including Ankylosing Spondylitis, Psoriatic Arthritis and psoriasis. Intriguingly, only the monoclonal antibodies and not the soluble receptor are effective in Crohn's disease (Sandborn & Targan 2002). One hypothesis to explain such observations is that etanercept may not neutralize LPS induced IL-1 as effectively as infliximab (Nesbitt et al. 2007) – observations such as this may prove valuable if targeting TNF was considered for PD. Wider beneficial effects on co-morbid risk in RA, especially in the cardiovascular area are also

Table 1. Currently licensed biological therapeutics in RA

Target	Benefits of target	Risks of target	Therapeutic agent
TNF-α	Well validated in vitro and in vivo Effective in 70% of recipients	Infection (tuberculosis) Malignancy	Infliximab (Remicade) Etanercept (Enbrel) Adalimumab (Humira) Golimumab (Simponi) Certolizumab (Cimzia)
IL-1	Biologically plausible target	Limited efficacy in clinical trials Infection risk	Anakinra (Kineret)
IL-6	Biologically plausible Good efficacy in clinical trials so far	May have essential role in host defence May modulate serum lipids	Tocilizumab (Actemra)
T-cell activation (CTLA4-Ig)	Biologically plausible Effective in 50% of patients	Risk of infection	Abatercept (Orencia)
Depletes B cells	Biologically plausible Effective in 34% or patients	Risk of infection	Rutiximab (Rituxan/MabThera)

TNF-α; tumour necrosis factor-α; IL, interleukin; RA, rheumatoid arthritis.

now emerging (McKellar et al. 2009). The documented side effects of neutralizing TNF-α include increased risk of infection, particularly reactivation of tuberculosis and a possible increased risk of malignancy (Smolen et al. 2007). Rarer events include demyelination, and emergence of paradoxical autoimmune features and psoriasis. These findings await mechanistic explanation and confirmation in other patient cohorts. Other members of the TNF cytokine superfamily have also received attention. RANKL inhibition with a fully human RANKL specific monoclonal antibody, denosumab, has demonstrated promising results in Phase II clinical trails in RA (Lewiecki 2009). Neutralizing BLyS or APRIL has proved unsuccessful thus far (Brennan & McInnes 2008).

Anti-IL-1 family therapies

Anakinra, a recombinant IL-1 receptor antagonist, has limited efficacy in RA. An anti-IL-1 antibody, AMG108 also failed in Phase II clinical trials in RA. However, Anakinra has proved efficacious in potentially lethal, febrile disorders such as Still's Disease and Muckle Wells Syndrome and monoclonal anti-IL-1 strategies are being actively pursued in this area (Furst et al. 2005). IL-18 has been targeted in Phase I clinical trials (Tak et al. 2006) but is not being developed at this stage as a therapeutic in this RA.

Anti IL-6 therapies

An anti-IL-6Ra monoclonal antibody, Tocilizumab, neutralizes the activity of both membrane bound and soluble IL-6Ra and prevents IL-6 signalling. This antibody has shown similar efficacy to TNF inhibitors (Smolen et al. 2008) in patients with RA. It is also being used in Still's disease and is being tested in a variety of other inflammatory disorders.

Anti-IL-15 therapies

A fully human IgG1 anti-IL-15 antibody, AMG 714, has shown some efficacy in Phase II clinical trials (Baslund et al. 2005) but is not being taken forward in the clinical context.

Anti-IL-17 therapies

Anti-IL-17 antibodies have proved effective in Phase 1 clinical trials (Genovese et al. 2010). Larger Phase II studies are underway and it is too early to determine whether this will be a beneficial approach. Targeting up stream cytokines such as IL-12/23 via anti-p40 monoclonal antibodies has proven efficacious in psoriasis (ustekinumab) and is being tested in psoriatic arthritis (Kuhn & Luger 2010).

Cellular targets

$CD20^+$ B cells, but not $CD20^-$ plasma cells, are depleted with the anti-CD20 antibody, Rutiximab. This therapy is effective in MTX and TNF-α non-responder populations and is now used routinely in RA (Emery et al. 2006). Both anti-inflammatory effects and articular damage prevention have been demonstrated. Abatacept, a construct of CTLA4Ig, prevents T-cell activation by antigen presenting cells through harnessing the ability of CTLA-4 to bind CD80 and CD86 and prevent the co-stimulatory effects of T-cell membrane-associated CD28. This is now in clinical use in patients with RA and brings about both reduction in disease activity measures and retardation of radiographic damage (Kremer et al. 2006).

These novel, targeted, biological therapies have shown outstanding results. Drug-free disease remission rates are increasing. However, overall only 10–40% of patients show clinical improvement of 70% or more even with the best of therapeutics (Goekoop-Ruiterman et al. 2008). Combinations of biological agents show no increased efficacy but increased risk of side effects such as infection or anti-idiotype responses (Scheinecker et al. 2008). There remains an urgent need for therapeutic and toxicity prediction via either biomarker profiling or pharmacogenomic approaches.

What can the periodontal community learn from advances in understanding qthe pathophysiology of RA?

The above discussion highlights the advances made in treatment for RA, which are the direct result of an improved understanding of disease aetiopathogenesis. Both RA and PD are complex, multi-factorial, diseases and incomplete understanding of both renders an accurate portrayal of their similarities and differences nearly impossible. The most striking discrepancy is that RA is of autoimmune aetiology, whereby a specific adaptive immune response is mounted against self-antigen. Inflammation is perpetuated and ultimately results in joint destruction. Inflammation is critical to PD pathogenesis, but this inflammation occurs in a unique ecological niche in

which the microbial plaque biofilm is central to pathogenesis. It remains debated whether the local inflammatory state dictates the composition of the biofilm or vice-versa. Nonetheless, both RA and PD cumulate in inflammation mediated pathological hard tissue destruction. Therapeutic strategies common to both diseases may include targeting bone turnover; or targeting inflammation, using either non-steroidal anti-inflammatory drugs (NSAID), inflammation resolving or specifically targeted biological therapies.

Bone turnover provides a potential target for both diseases and as such the use of bisphosphonates has been reported in both RA and PD (Reddy et al. 2003, Breuil & Euller-Ziegler 2006). However, neither the indications for use, nor the efficacy of bisphosphonates as adjuncts in either periodontal or RA treatment are well defined. Similarly, the RANKL-OPG axis has proved a successful target for both diseases. Inhibition of RANKL by exogenous OPG reduced alveolar bone destruction in a rodent model of PD (Jin et al. 2007). As discussed previously, the anti-RANKL antibody, denosumab, has been used in human trials for RA treatment (Lewiecki 2009).

NSAIDS have been used to provide symptomatic relief for RA. A systematic review of the use of NSAIDS for PD concluded that arachidonic acid metabolite inhibition may be a useful adjunct to mechanical debridement, although the indications for the use of NSAIDS are not clear (Reddy et al. 2003).

Endogenous mediators which orchestrate the resolution of inflammation have demonstrated promising results. These ''resolvins'' mediate active processes, regulating neutrophil trafficking and cytokine production. Topical administration of resolvin E1, a derivative of eicosapentaenoic acid, mediated significant healing and tissue regeneration in established PD in a rabbit model (Hasturk et al. 2007, Van Dyke 2007). Recently, resolvin E1 was found to provide striking relief of inflammatory pain behaviours in a number of rodent models of inflammatory pain (Xu et al. 2010).

Therapies targeting IL-1 and TNF-α, which have proved effective in RA, have also demonstrated efficacy in animal models of PD (Oates et al. 2002, Di Paola et al. 2007). At the time of preparation of this manuscript, no studies were identified which target TNF-α or IL-1 specifically in treatment of human PD. However, a small number of small studies report on periodontal health in RA patients undergoing treatment. TNF-α inhibition in patients with RA was reported to either enhance (Pers et al. 2008), or have no effect on gingival inflammation, but reduced alveolar bone loss (Mayer et al. 2009). Moreover, it has been suggested that treatment of periodontitis in patients with RA improved response to their arthritis therapy (Ortiz et al. 2009).

The recent explosion of studies into IL-17 might highlight some of the potential discrepancies between RA and PD. Targeting IL-17 in RA appears to be a promising strategy for treatment (Genovese et al. 2010). Given the osteoclastogenic potential of IL-17, it could therefore be speculated that this may translate to periodontitis. However, a protective role for IL-17 signaling was documented in a murine model of PD (Yu et al. 2007). These findings have not been confirmed in human studies of PD but suggest that although PD may share a number of common pathways with RA, it would seem that some aspects of the host defense remains critical to protection against the periodontopathic biofilm, whilst being predominantly pathogenic in established RA.

Conclusion

A number of useful therapies for RA have emerged from extensive studies into disease pathogenesis. Currently, anti-TNF-α, anti-IL-6, anti-IL-1, CTLA4 and anti CD20 therapies are licensed for treatment (Table 1) and a there are a number of other targets undergoing human trials. As the detailed understanding of RA initiation and progression expands, so do the therapeutic options. Although total disease prevention may prove elusive, the combination of predictive biomarkers and a wide armamentarium of targeted biological therapeutics offer a real possibility of early intervention and induction of disease remission. So what can be learned from studies into RA? Extensive, high quality research in the aetiopathogenesis of RA has transformed patient treatment, and although not all putative targets have proved successful, overall there have been concrete benefits for patients. Periodontal destruction and the articular destruction of RA share common pathogenic mechanisms. There are already data hinting that certain therapeutic strategies may be beneficial to both diseases and a number of the mediators that have been effectively targeted in RA may have therapeutic potential in periodontitis. Although there have been extraordinary advances in periodontal regeneration techniques, with numerous products available; there are currently no targeted biological therapeutics for the treatment of periodontitis. There are considerable ongoing efforts to understand the aetiology and pathogenesis of PDs, both individually and related to systemic disease. Perhaps such efforts will, eventually, inform safe host-modulating approaches, which can offer early intervention and prevention of further alveolar bone destruction. Nonetheless, currently both RA and periodontitis share an unmet need for improved prognostics and therapeutics.

Acknowledgements

We thank Mr. Lee Savarrio for critical reading of the manuscript

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Clinical Relevance

Scientific rationale for the study: To provide a narrative review outlining lessons from advances in RA pathogenesis and treatment, which may have relevance to PD.

Principal findings: Significant changes in the treatment of patients with RA have directly resulted from advances in understanding disease pathogenesis. Total disease remission has been achieved in some patients and, as the enquiry to pathogenesis and search for novel targets rapidly expands, the goal of disease remission becomes closer for more patients.

Practical implications: Careful investigation into the parallels and links between arthritis and periodontitis may ultimately yield improved treatment outcome for both patients groups.