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EXPLORING THE PATHOGENESIS OF RHEUMATOID ARTHRITIS: A REVIEW OF THE EVIDENCE.

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Abstract

RA is estimated to affect a significant percentage of the world population. Although the pathophysiology of RA remains unclear, studies suggest that it involves a complex interplay of genetic predisposition, environmental triggers, and dysregulation of the immune system. In this paper, it has conducted an extensive literature review to summarise various RA concepts. it reviewed RA's pathophysiology by analyzing its pathological immune and inflammatory mechanisms and inter-related processes that lead to tissue damage. Also, discussing the role of autoimmunity in RA, where the body's immune cells mistakenly target healthy tissues, particularly the synovium, leading to chronic inflammation and joint damage. Additionally, we reviewed literature to understand how autoimmunity in RA can be triggered by various factors such as infections, hormonal changes, and environmental exposures. Furthermore, we discussed the genetic component in RA where genetically susceptible individuals, certain alleles, such as HLA-DRB1, are strongly associated with RA development. we described how RA-specific biomarkers such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP) aid in diagnosis and monitoring disease progression. We analyzed how pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1) promote synovial inflammation, cartilage degradation, and bone erosion, contributing to joint damage and functional impairment. Finally, we analyzed literature to describe the treatment

and management of RA to alleviate symptoms, suppress inflammation, and prevent disease progression. Disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents targeting TNF-α, IL-6, and other inflammatory pathways are the mainstay of RA therapy. Early diagnosis and aggressive treatment strategies, including combination therapies and treat-to-target approaches, have been shown to improve outcomes and prevent long-term joint damage. Regardless of RA's complex nature, advances in understanding RA pathophysiology, biomarkers, and treatment strategies have improved clinical outcomes and quality of life for affected individuals.

Keywords: Rheumatoid Arthritis, Autoimmunity, Synovium, Inflammation, Joint damage, Genetic predisposition, Environmental triggers, Biomarkers, Rheumatoid Factor, Anti-cyclic citrullinated peptide antibodies, Pro-inflammatory cytokines, Disease-modifying anti-rheumatic drugs (DMARDs), Biologic agents, Treat-to-target approach, Functional impairment.

Introduction

Rheumatoid arthritis (RA) is an autoimmune (AI) disease characterised by progressively deteriorating joints affecting the synovium, articular cartilage and bone (Firestein, 2005; J. Smolen & Keystone, 2012). While the pathogenic effects of RA are primarily exerted at the joints, particularly those connecting small bones of the hands and feet, systemic effects often arise following the onset of RA (Choy, 2012; Firestein, 2005). Ensuing disability often results if the chronic joint destruction is left untreated (Firestein, 2005). RA has an estimated prevalence of 1% of the total population and combined with its deleterious effects, the disease represents a significant economic burden (Dunlop, Manheim, Yelin, Song, & Chang, 2003; Sangha, 2000). The economic burden extends beyond the tangible resources expended in delivering healthcare to RA sufferers as they begin to suffer the plight of osteoarthritic-related losses of function and productivity, subsequently leading to a reduced quality of life (Firestein, 2005).

The aetiology of RA is yet to be cohesively elucidated. However, both genetic and environmental causes are thought to play a contributory role in the diseases pathogenesis (Choy, 2012; McInnes & Schett, 2011). Notwithstanding this, the literature points to a plethora of interactive biological factors and immunological mediators involved in RA pathogenesis and the manifestation of symptoms. In addition, curative therapy for RA is not yet on the horizon, with many mono-therapeutic strategies such as disease-modifying antirheumatic drugs (DMARDs) proving ineffective with many RA patients. In light of this, eventual need for polypharmacological treatment has become the best method for preventing RA progression and alleviation of symptoms (Breedveld & Combe, 2011).

The goal of this literature review is to collate and summarise the complex spectrum of current perspectives surrounding RA pathogenesis at a cellular, genetic and environmental level and the current clinical management including the inherent failures of various treatment regimes. Additionally, development of DMARDs will be briefly discussed in conjunction with therapeutic targeting of aforementioned cellular pathways.

Overview of RA Pathophysiology:

The pathological immune and inflammatory mechanisms of RA are complicated and appear to include several intimately interrelated pathophysiological processes causing systemic articular damage. Despite the rapidly expanding pool of scientific knowledge about RA, a single accurate cause is yet to be demonstrated. Furthermore, the ultimate link between both immune and inflammatory involvement also remains obscure. Speculative theories of infectious triggers have been described but not yet confirmed (Ebringer & Wilson, 2000; Silman & Pearson, 2002; Toivanen, 2001). Likewise, evidence is yet to establish clear logic behind the localised joint effects that are characteristic of the condition. Several genetic links to RA have been established, however there is a gap in the research regarding the development of the disease and the interplay between genetics and other factors.

In a study unlikely to have passed ethics committees in the current day, (Hollander, McCarty Jr, Astorga, and Castro-Murillo (1965)) demonstrated the development of arthritis in relation to self-reactive antibodies. This was a landmark study in illustrating the autoimmunity involved with RA. First, a patient with a seropositive joint for RA underwent IgG extraction and purification before re-injection into the joint causing the development of acute arthritis with existing IgG antigen (aggregated) and IgM antibody. The authors then demonstrated the opposing effect in relation to purified IgG injection into a RA seronegative joint with no subsequent development of arthritic symptoms because only IgM antibody was present. Moreover, the purified IgG from diagnosed RA sufferers elicited no arthritic effects when injected into seronegative joints because only the IgG antigen was present. Hollander et al. (1965) demonstrate that RA is a disease caused by immune complexes however the underlying autoimmune mechanisms were not discussed. Subsequent to this, the cause of joint damage was widely accepted—as remains—as being of an inflammatory origin caused by the autoimmune reactions and antibody complex deposition.

Autoimmunity related RA causes and effects

IgG rheumatoid factor (RF) is an IgM autoantibody that plays a significant role in initiating the inflammatory process by binding denatured IgG or Fc IgG fragments to form immune complexes (Hui et al., 2014). RF is detected in over 80% of RA sufferers and up to 10% of non-RA sufferers, therefore providing a reasonably helpful diagnostic biomarker in the clinical context (Dörner, Egerer, Feist, & Burmester, 2004; McInnes & Schett, 2011). Self-aggregation of small IgG-RF dimers result in joint damage, however the ability of the small dimeric units to instigate a systemic complement mediated response is questionable due to their size (Weissmann, 2004). Instead, it may the dimmer may be further aggregated due to its hydrophobic properties upon entry into the circulatory system through blood vessel fenestrations (Mitnick, Hoffstein, & Weissmann, 1978; Weissmann, 2004; Weissmann, Brand, & Franklin,

1974). Hence leading to the entrapment of larger immune complexes within the synovial tissues and manifestation of bilateral symptoms.

Further along the pathogenesis continuum, synovium localised self-aggregating immune complexes cause numerous sequelae, virtually all of which are the result of complement activation and ligand binding to facilitate phagocyte activation (Brown, Nardella, & Mannik, 1982; Chen, Daha, & Kallenberg, 2010; Neumann et al., 2002). Several studies have confirmed that complement is present in the synovium either in fragmented or full form. C5 and MAC were detected by immunohistochemical analysis, showing their upregulation in RA patients (Kemp et al., 1992). Likewise, C5 was identified within synovial fluid using radioimmunoassay (Jose, Moss, Maini, & Williams, 1990). Such findings hold a magnitude of systematic possibilities in relation to further pathological mechanisms. An indication of the systemic inflammatory process is the detection of C5a and C5b in serum as well as synovial samples (Jose et al., 1990; Moxley & Ruddy, 1985).

A plethora of inflammatory mediators and signal transducers are involved in the pathogenesis of RA. TNF-α being one of the most implicated cytokines in RA as it is an essential inflammatory mediator. TNF-α has been subject to therapeutic targeting that is later discussed. Of particular importance is the ability for TNF-α to cause downstream effects including additional cytokine production, chemokine production and bone-damaging effects such as activation of synovial fibroblasts, matrix enzymes and osteoclasts (Choy, 2012). Interleukins (IL) 1 (IL-1) and 6 (IL-6) are also critical in activating leukocytes, endothelial cells and synovial fibroblasts which have various locally and diffusely damaging effects (Choy, 2012; McInnes & Schett, 2011). They also promote B-cell differentiation, which is perhaps the reason why its inhibitory drug remains as one of the most clinically effective drug available. IL-7 and IL-15 are underlying activators of T-cell and natural killer (NK-cells), as well as T-memory cells (McInnes & Schett, 2011). It is thus also conceivable that the apoptotic inhibitory action of these cytokines may also play a role in T-cell tolerance in the manifestation of the disease. Other ILs are also stimulated to varying effect. Intracellular signaling molecules such as JAK that regulates leukocyte maturation and stimulation in addition to releasing cytokines and playing a role in immunoglobulin release is also substantially implicated, and is being investigated closely as a disease modifying therapeutic (Fleischmann et al., 2012). Meanwhile the downstream effects of Syk, PI3K and BTK are all linked to immune cell regulation, proliferation or survival (McInnes & Schett, 2011). The perplexing interplay between these inflammatory come immunomodulatory molecules and factors substantiates the fragmented approach to drug development and hence clinical treatment.

RA Specific Biomarkers

Notwithstanding the current clinical importance of RF, the prevalence of RF among the general healthy population (10%), as well as in others diagnosed with rheumatic and autoimmune diseases, renders it widely non-specific to RA. Since the first discovery of the

immune complex producing RF, other more RA specific antigens have been identified. One such antigenic determinant of RA in individuals is the anticycliccitrullinated peptide (anti-CCP) antibodies, which represent highly predictive biomarkers for RA even years prior to symptom onset (Ärlestig et al., 2012; Kokkonen et al., 2011). Interestingly, many anti-CCP proteins are readily identifiable using anti-CCP assays. These include keratin, α-enolase, fibriniogen, fibronectin, collagen and vimentin (McInnes & Schett, 2011). The anti-CCP targets intrinsic citrulline protein components (Gassid, Daoud, & Al-Osami, 2012; Kokkonen et al., 2011). Anatomically, radiographic visualisation of articular damage in anti-CCP positive individuals with RA is much more extensive than anti-CCP negative individuals (Kroot et al., 2000). Perhaps more fascinating however, is the immunoregulatory role of anti-CCP in nuclear factor κB (NF-κB) dependent pro-inflammatory signalling cascades as well as the activation and differentiation of T-cells (Kurreeman et al., 2007; McInnes & Schett, 2011).

Potential Causes of autoimmune effects in RA

One explanation of local effects of RA is arthrotropic cross-reactivity between a triggering agent and joint tissue structures (J. S. Smolen & Steiner, 2003). The mechanism would resemble an autoimmune hyper-reactive event leading to inflammatory cell infiltration at the site and therefore local affects. It is possible that exogenous antigens could trigger an innate immune response due to toll-like receptor (TLRs) or CD14 activation (Armant and Fenton (2002); Choy (2012); Dobrovolskaia and Vogel (2002)) that could generate an innate immune response with T-lymphocyte and dendritic cells activation with input from various other cell signaling pathways (proinflammatory interleukins and cytokines), which may then turn into a humoral response with B-lymphocyte involvement (Choy, 2012; J. S. Smolen & Steiner, 2003). TLR activation and subsequent T-lymphocyte differentiation into T-helper 1 (T_H-1 cells) and T-helper 2 (T_H-2 cells) is crucial in determining the immune processes thereafter (Choy, 2012; J. S. Smolen & Steiner, 2003). T_H-1 cells and T_H-2 cells generate varying effects, the former of which may be pro-inflammatory leading to diffuse humoral responses, and the latter of which may initiate anti-inflammatory changes and diffuse humoral responses such as immunoglobulin E (IgE) production (J. S. Smolen & Steiner, 2003). Following activation of dendritic cells and other antigen presenting cells (APCs) such as macrophages and mature B-lymphocytes it is likely that external arthritis associated presentation would facilitate T-lymphocyte activation and further inflammatory mediator release (Choy, 2012).

Smoking and other injurious bronchial events have been discussed in relation to RA manifestation. The relationship between smoking and the pathogenesis of the disease appears to be of a genetic origin (Di Giuseppe, Orsini, Alfredsson, Askling, & Wolk, 2013; Källberg et al., 2011; Klareskog, Malmström, Lundberg, Padyukov, & Alfredsson, 2011). Particularly, environmental stressors appear to increase the risk of developing RA, particularly those with the HLA-DR4 susceptibility gene (Symmons et al., 1997). This may be related to post-translational modifications to local respiratory and mucosal tissue proteins altering either the quality or quantity of the citrullinated proteins (Källberg et al., 2011; McInnes & Schett, 2011). Källberg

and colleagues (2011) estimated that smoking was the causative agent in 35% of anti-CCP antibody positive individuals.

Genetic Associations with RA

Mounting evidence is beginning to illustrate a significant genetic basis of the rheumatic disease (Choy, 2012; Silman & Pearson, 2002). There is a long-standing association of RA and the human-leukocyte antigen DRB1 (HLA-DRB1 loci), which has been confirmed in numerous RF positive and anti-CCP positive RA patients (Hui et al., 2014; Lubbers et al., 2012; McInnes & Schett, 2011). Moreover, it has been suggested that varying HLA class II peptide presentations could affect the development of T-cell tolerance in the thymus hence conferring resistance or susceptibility to autoimmunity (Nicholson, Hahn, & Wucherpfennig, 2005). Another HLA study indicated that constituent residues of the HLA-DR peptide-binding groove are decisive in conferring RA susceptibility (Raychaudhuri et al., 2012). Additional explanations for the connection between HLA-DRB1 and RA is the aforementioned molecular mimicry by microbial proteins with shared residues (De Almeida et al., 2010; McInnes & Schett, 2011).

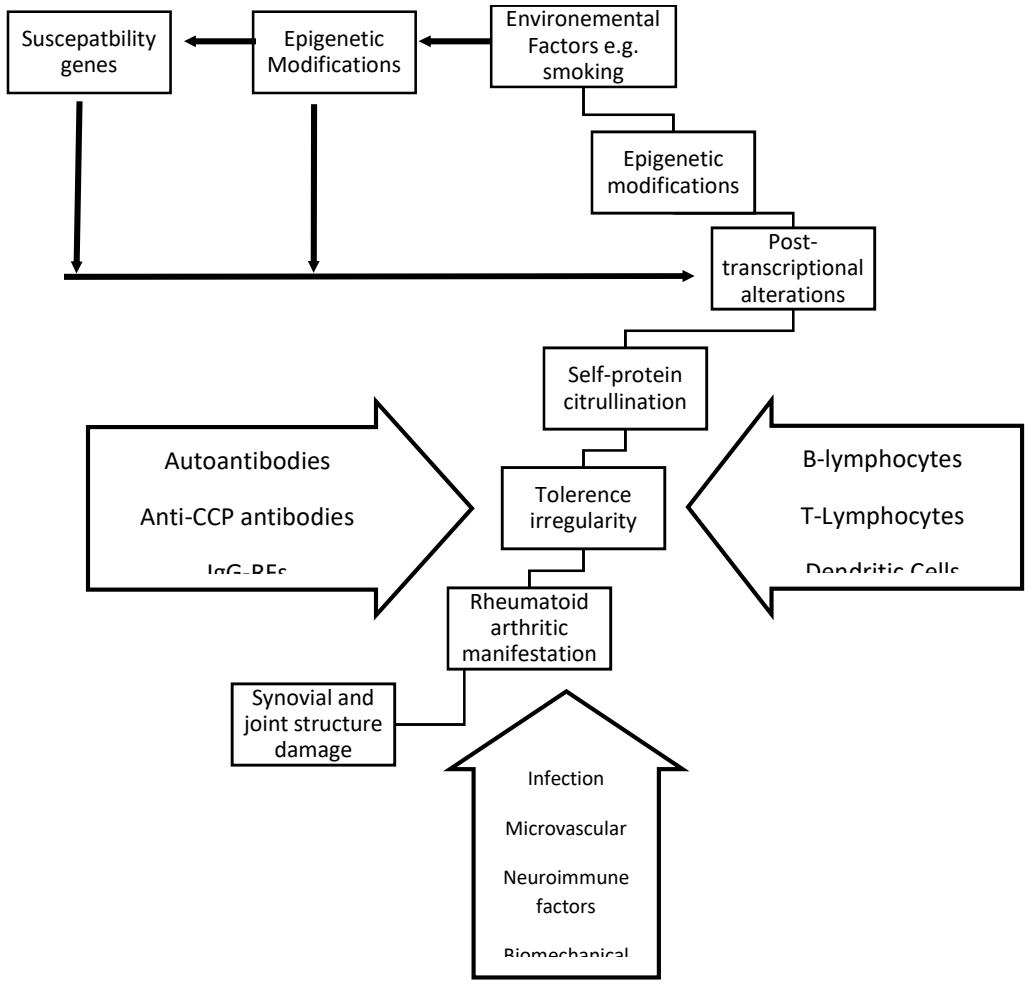

Figure 1. Outline of RA pathogenesis.

Clinical Treatment and Management of RA

The armamentarium available in the treatment of RA has been expanding. The overall modes of clinical care for RA including diagnosis, pharmacological treatment, surgical treatment, education and self-management strategies have been developed over the previous decade (Fernandes et al., 2013; Petersson et al., 2014; J. S. Smolen et al., 2014). Developments of new treatments and treatment optimisation have guided the improvement of patient outcomes nevertheless remains hit and miss. Although in-depth discussion of clinical management is outside the scope of this review, it is important to briefly consider the clinical relevance of the aforementioned pathological pathways as pharmacological targets.

RA is a complicated disease to treat clinically. Its multifactorial pathogenesis makes treatment of one pathway widely ineffective. Likewise, the individual variability in disease manifestation is a significant barrier facing the development of remission seeking therapies. Immune targeted therapies are mainly directed towards the attenuation of cytokine inhibition. Tumour necrosis factor (TNF-α) targeted blockers were the first biological mediators utilised to inhibit cytokine action (McInnes & Schett, 2011). These drugs include those such as adalimumab, certolizumabpegol, etanercept, golimumab and infliximab most of which target TNF-α in some manner in order to actively reduce inflammatory. Other cytokines that are targeted include IL-6 and IL-1. Another approach is to CD20 targeting utilising rituximab in order to reinforce humoral immunity in the disease (McInnes & Schett, 2011).

Perhaps the most recent influential development has been the blockade of IL-6 by the binding of the humanized monoclonal antibody cytokine inhibitor, tocilizumab, to the IL-6 receptor is profoundly successful treating systemic RA effects, as well as acute-response RA and synovial inflammation (Nishimoto et al., 2007; Josef S Smolen et al., 2008). Fascinatingly, monotherapy with tocilizumab has shown effectiveness gross radiological assessment, illustrating its diffuse anti-inflammatory benefit, more than the commonly administered DMARD group (Nishimoto et al., 2007). Furthermore, athree year prospective study conducted by Nakashima and colleagues (2014) demonstrated that the drug was successful in both patients who had and had not been administered biological agents such as TNF-α. The study showed that 65% of those who attained remission within one to three years remained in remission, in addition to high remission rate overall.

Conclusion

The pathological mechanisms that govern the effects of RA are complex and multifaceted. This has led to a clinical inability to treat the disease with success in individuals who are subject to a discrete pathogenic pathway unlike all others. In saying this, treatments for RA are being rapidly developed and with many in the final stages of testing, changes on this front are probable. Understanding the dynamics between the microbiological agents and their consequential disease effects is crucial to furthering the clinical capacity to treat RA. Collectively it appears that the additional treatment options and further research into these

options will lead to increasing remission rates and the transformation of RA into an acute rather than chronic condition. Notwithstanding this, addressing the logic behind the loss of immune tolerance and therefore development of joint-damaging autoimmunity remains the most notable challenge in tackling this disease.

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