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Rheumatoid arthritis: links with cardiovascular disease and the receptor for advanced glycation end products

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Rheumatoide Arthritis: Zusammenhänge zwischen kardiovaskulären Erkrankungen und dem „Advanced Glycation End Product Receptor“

Zusammenfassung. Kardiovaskuläre Erkrankungen treten bei Patienten mit chronischen entzündlichen Erkrankungen wie zum Beispiel der Rheumatoiden Arthritis (RA) gehäuft auf. Aus der Sicht der Pathophysiologie hat die Atherosklerose mit Autoimmunerkrankungen verblüffende Ähnlichkeiten. Diese Erkenntnis wurde zu einer Zeit des Paradigmenwechsels im Management der chronischen Polyarthritis mit Biologika gemacht. Diese Übersicht beschreibt mögliche Ursachen für das gehäufte Auftreten von Gefäßerkrankungen der Rheumatoiden Arthritis einschließlich der Rolle von traditionellen kardiovaskulären Risikofaktoren. Potentielle Mechanismen wie das C-Reaktive Protein (CRP), Veränderungen im Gerinnungssystem und Cyclooxygenase (COX)-2 Inhibitoren werden kurz behandelt. Der Advanced Glycation End Product Receptor (RAGE) wurde als Kandidatenmolekül, welches laufende Entzündungen und Autoimmunprozesse beeinflusst, identifiziert. Ein Schwerpunkt dieser Übersichtsarbeit ist die Rolle von RAGE bei kardiovaskulären Erkrankungen und der chronischen Polyarthritis. Wie es bei vielen neuen Molekülen der Fall ist, wird angenommen, dass funktionelle Polymorphismen die Krankheitsexpression verändern und zur Aufklärung der biologischen Aktivitäten des ursprünglichen Moleküls beitragen können. Diese Übersichtsarbeit schließt mit einer Diskussion der möglichen Rolle des RAGE Glycine 82 Serine Polymorphismus.

Schlüsselwörter: Rheumatoide Arthritis, kardiovaskuläre Erkrankungen, Advanced Glycation End Product Receptor, Polymorphismus, Genetik, Entzündung, C-Reaktives Protein, Hyperlipidämie, Blutgerinnung.

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Summary. Cardiovascular (CV) disease is increased in patients with chronic inflammatory disease, including rheumatoid arthritis (RA). Furthermore it has become clear at a pathophysiological level, that atherosclerosis has striking similarities with autoimmune disease. This realization has come at a time of paradigm shift in how rheumatologists manage RA, with the availability of biological agents targeting key inflammatory cytokines. This review will focus on the possible causes of increased vascular disease in RA, including the role of traditional CV risk factors. Mechanisms potentially at play, such as C-reactive protein (CRP), altered coagulation, and cyclooxygenase (COX) -2 inhibitors will be covered in brief. The Receptor for Advanced Glycation End Products (RAGE) has been identified as a candidate molecule influencing response to ongoing inflammation and autoimmunity. There will be a focus on the role of RAGE in CV disease and RA. As has been the case with many novel molecules, functional polymorphisms are thought to alter disease expression and assist us in coming to terms with the biological activities of the parent molecule. The review will conclude with a discussion of the potential role of the RAGE Glycine 82 Serine polymorphism.

Key words: Arthritis Rheumatoid, Cardiovascular Diseases, Advanced Glycation End-Product Receptor, Polymorphism, Genetic, Inflammation, C-Reactive Protein, Hyperlipidaemia, Coagulation.

The mortality of patients with RA is increased compared to the general population [1, 2], with much of this increase attributable to excess CV deaths [2–5]. It is also known that CV disease accounts for much of the comorbidity of RA [6–9]. The known risk factors have been shown to account for about 50% of CV events in the general population [10, 11]. Many novel factors contributing to vascular disease pathogenesis have been described, but their clinical utility is still under investigation. These include hyperhomocysteinaemia [12, 13] (which occurs in RA patients taking methotrexate [14]), various prothrom-

botic factors (many of which are elevated in RA [15]) and serological markers of inflammation such as C-reactive protein (CRP), interleukin (IL)-6 and serum amyloid A [16–25].

Traditional CV risk factors have been studied in RA cohorts. However, the incidence of CV disease is high in RA, even when accounting for traditional risk factors [6, 26, 27]. Furthermore three studies, so far reported only in abstract form, have shown that RA is an independent predictor of ischemic heart disease (IHD) with half of patients having clinically silent disease, and many not even presenting with pain when suffering an acute coronary syndrome [28–30]. This suggests that IHD may be far more widespread in RA than is clinically apparent. In keeping with these clinical findings, silent ischemia has also been noted on 24 hour Holter monitoring in RA patients [31]. Furthermore echocardiography and Doppler have shown a high frequency of sub-clinical left ventricular diastolic dysfunction [32].

Patients with RA have signs of vascular dysfunction even when newly diagnosed [33, 34]. Across RA patients of all disease durations, endothelial dysfunction inversely correlates with markers of inflammation [35]. In a small study, vascular dysfunction could be reversed, at least in the short term, with successful RA therapy [34]. Even accounting for adverse effects of anti-rheumatic drugs present in long term RA, the implication of these studies is that the pathogenesis of RA and of atherosclerotic vascular disease may be similar. Very recently the results of a ten year follow up study of inflammatory polyarthritis patients, has revealed that 38.5% of patients died of CV causes. Baseline level of inflammation (CRP) was found to be an independent predictor of future CV death, supporting the hypothesis that inflammation occurring in patients with RA may play a direct role in CV disease pathogenesis [36]. Results from laboratory, clinical, and epidemiological studies all support the hypothesis that immune dysregulation as well as ongoing systemic inflammation in RA are likely to be pivotal factors in the early vascular disease of RA [37, 38]. The response to an insult is remarkably similar whether it is in the lung (pulmonary fibrosis), kidneys (glomerulosclerosis), liver (cirrhosis), pancreas (pancreatitis), joints (pannus) or arteries (atherosclerosis) [39].

Dyslipidaemia

There is known to be an inverse relationship between lipid levels and any form of inflammation as measured by the acute phase response [40, 41]. It has been known for some time that RA sufferers have low levels of total cholesterol [40, 42]. Closer analysis of lipid profiles reveals that high density lipoprotein (HDL) is disproportionately lowered, giving rise to an adverse lipid profile [43–45].

The mechanisms at play that induce lipid changes in RA and other proinflammatory states have been the object of some research. It has been shown that interleukin-1 receptor antagonist (IL-1ra) gene deficiency and associated IL-1 excess promotes autoimmunity and joint-specific inflammation in animal models [46, 47], and it is clear that relative IL-1 excess exists in human RA [48–50]. Animal models have also shown that IL-1ra gene deficiency leads to pro-atherogenic changes in lipid metabolism with elevated levels of total cholesterol and reduction of HDL under inflammatory conditions [51]. The implication is that relative IL-1 excess, be it constitutional or induced by the inflammatory state, promotes the pro-atherogenic lipid profile in RA, due to IL-1-mediated induction of enzymes critical for cholesterol metabolism. There is good evidence implicating proinflammatory effects of IL-6 on progression of atherosclerosis, with hepatic synthesis of CRP largely regulated by this cytokine [52], however knockout animal models suggest that IL-6 is important in regulating body composition, probably via hypothalamic mechanisms, and treatment with agents that block IL-6 leads to hyperlipidaemia in animals and humans [53, 54]. Circulating levels of IL-6 are increased by Tumour Necrosis Factor (TNF) α and IL-1, but IL-6 also regulates the level of TNFα, and of IL-6 indirectly, via inducing the release of IL-1ra [52]. This plethora of interactions is somehow likely to be responsible for the dyslipidaemia of inflammatory diseases, however the changes in lipid profile seen in RA, are not in themselves sufficient to account for the increased risk of CV disease.

There is some evidence that controlling disease activity with conventional disease modifying agents, including corticosteroids and hydroxychloroquine, may reverse some of the abnormalities in lipid profile [44, 55–58]. TNFα blockers may also improve the CV risk profile of patients with RA [59] however not all reports have been favourable [60]. A humanized anti-IL-6 receptor antibody has been recently trialled for the treatment of refractory RA, with significant reduction of disease severity. However almost half of patients had an increase in blood cholesterol at both treatment doses, an effect that has been seen in other human trials, and there was significant elevation of triglycerides at the higher dose. HDL cholesterol also increased, but to a lesser degree suggesting an overall adverse effect [53]. Of interest, mice deficient in IL-6 develop mature onset obesity and insulin-resistance, associated with reduced energy expenditure [54]. The clinical observations provide further evidence of positive and negative roles of inflammatory cytokines on CV disease risk, and highlight an important area to scrutinize with the increasing use of anti-cytokine therapy.

Smoking

Smoking dose-dependently increases the risk of RA [61–63]. Smokers with RA are more likely to be rheumatoid factor (RF) seropositive [64]. RF is generally associated with more severe rheumatoid disease and also with a greater incidence of extra-articular disease, thus it has been hypothesized that smoking may be a co-morbid dependent risk factor for CV disease. However, at least one study indicated that smoking was not a predictor of CV events or mortality in a cohort of seropositive RA patients [58].

Hypertension

Hypertension is common in RA [8, 65] and diastolic BP levels are elevated compared to controls [27]. It seems

likely that the widespread use of non-steroidal anti-inflammatory drugs (NSAIDs) may be partly to blame for the high incidence of co-morbid hypertension in RA patients, and perhaps some of the increase in CV mortality [66–73]. Both traditional NSAIDs and the newer cyclooxygenase (COX)- 2 inhibitors have been found to aggravate blood pressure through their effects on reduced renal function and fluid retention [74]. Clinically the elevation is likely to be important, as even small decreases of 5–6 mmHg in diastolic blood pressure were shown to decrease the risk of CV events by 20–25% and cerebrovascular events by 35–40% in a non-RA population [75].

Diabetes mellitus

The prevalence of diabetes was not found to be increased in RA [27] and even when present, failed to predict CV events [58]. However, insulin resistance is prevalent in RA [76] and increasingly it is believed that this prediabetic phase has similar pathophysiological consequences to diabetes itself [77, 78].

C-Reactive protein

CRP is the major acute phase protein which rises rapidly in response to inflammatory stimuli, and may remain elevated for prolonged periods in chronic inflammation. Smoking, aging, abdominal obesity, steato-hepatitis and subclinical vascular disease also increase levels [52, 79]. The biologic activities of CRP include activation of the classical complement cascade, enhancing phagocytosis and binding Fcγ receptors (FcγR), resulting in cytokine production [80, 81]. In addition to recognition of microbial antigens, CRP and the related molecule serum amyloid P (SAP), react with and clear dying and apoptotic cells from sites of tissue injury [82, 83] indicating that CRP is involved in regulation of the immune system [84].

The highly sensitive CRP (hsCRP) test detects small elevations in the CRP which are not usually detectable by standard assays. There is accumulated evidence that minor elevations in CRP are identified in almost every step of atherogenesis and predict poor outcome [16–19, 21–23, 85, 86] and CRP has been found to correlate with intima-media thickness (IMT) a marker of vascular disease [87–91]. Thus, CRP is an independent determinant of the risk of atherosclerotic disease. The relative risk of future events in both men and women for those with values of CRP in the highest quartile compared with the lowest quartile has been shown to be between 2 and 4 [21, 23, 86]. The clinical utility of monitoring CRP levels to establish vascular disease risk in patients with RA has been difficult to clarify, with high levels as a result of arthritis clouding the picture. However, Goodson et al have provided evidence that even a single elevated CRP, early in the inflammatory polyarthritis disease course, is predictive of future CV death [36].

CRP may actively participate in promoting the proinflammatory component of atherosclerosis. It induces expression of cellular adhesion molecules (CAMs), IL-6, and endothelin-1 by endothelial cells [92, 93] and has been shown to mediate monocyte chemoattractant protein (MCP)-1 induction [94] and uptake of low density lipoprotein (LDL) by macrophages [95]. In addition to this, smooth muscle cells and macrophages in arterial tissue have been shown to produce CRP, a process that is substantially upregulated in the atherosclerotic plaque [96]. Given the direct activation of complement by CRP, and that activated complement is pathogenic to cells in plaques, suggests that there is a self-sustaining autotoxic mechanism operating within the plaques as a precursor to thrombotic events [96]. As further evidence of a direct role of CRP in angiogenesis, there are data to suggest that CRP is responsible for a reduction of NO [97], which may result in inhibition of angiogenesis, an important compensatory mechanism in chronic ischemia [98]. Whether it does in fact have a direct role remains a subject of debate.

In RA, due to the high levels of systemic inflammation, it has been difficult to use CRP alone for the detection and monitoring of vascular disease. However, other potentially useful markers of vascular activation are currently being investigated [99]. Obviously if CRP plays a causative role, this has major implications for risk of vascular disease in sub-optimally treated autoimmune diseases. However, since a single elevated CRP at baseline presentation is predictive of CV death, CRP may have a direct role in CV disease pathogenesis in patients with inflammatory disease and may be a useful marker even if levels are higher in RA than in atherosclerosis in the general population [36].

Other novel risk factors

CAMs and selectins are essential in mediation of adhesion and transendothelial migration of leukocytes, one of the earliest processes in atheroma formation, the absence of which results in a reduction of disease in murine models [39]. Local expression of intercellular adhesion molecule-1 (ICAM-1), vascular cellular adhesion molecule-1 (VCAM-1), and E-selectin has been described in both rheumatoid synovium and atherosclerotic lesions [39, 100, 101], suggesting a similar pathogenic mechanism for both. Furthermore biomarkers of endothelial dysfunction, including VCAM-1, ICAM-1 and endothelial leukocyte adhesion molecule (ELAM)-1, are higher in RA than in control subjects and correlate with markers of inflammation [102].

Coagulation and cardiovascular disease in RA

Inflammation in under-treated RA may have significant prothrombotic effects, contributing to the severity of CV disease. Fibrinogen, tissue plasminogen activator (tPA), D-dimers and Von Willebrand factor (vWF) have all been found to be elevated in RA compared to controls [27], and tPA and plasminogen activator inhibitor (PAI) -1, may be associated with CV events in RA [103].

Evidence has accumulated that highly COX -2 specific inhibitors (such as rofecoxib and celecoxib) increase CV risk [67, 69–73], however these agents have only been in use relatively recently, and the contribution by selective COX blockade is unlikely to explain much of the excess morbidity seen in previous years, despite some degree of selectivity by conventional NSAIDs. COX -2 specific inhibitors impair endothelium-dependent vasod-

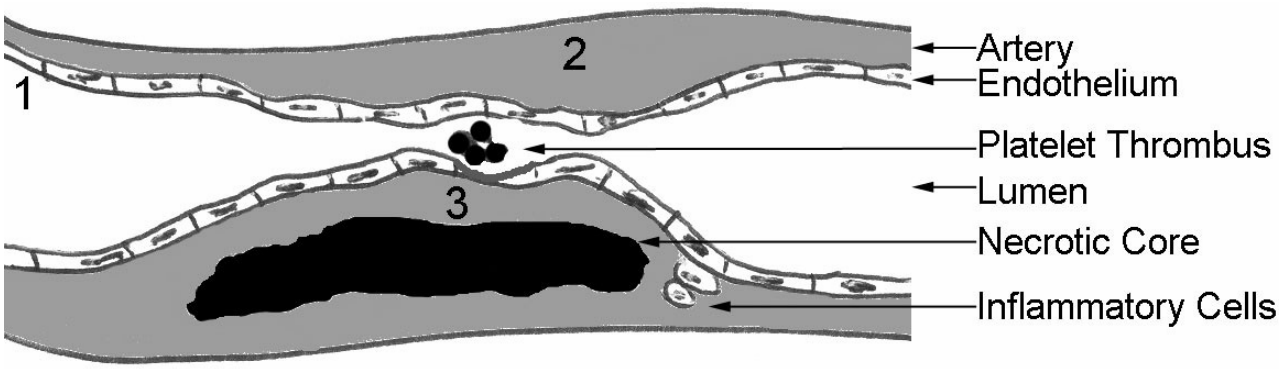

Fig. 1. Stages in Vascular Inflammation
1. Endothelial dysfunction, induced by factors such as oxidized LDL and smoking, results in increased permeability, leukocyte and platelet adhesion and a procoagulant tendency.
2. An increase in smooth muscle cell volume results in an intermediate lesion. At this stage compensatory dilatation can occur.
3. A fibrous cap overlies a core of lipid and necrotic tissue. This can further erode and lead to thrombosis and complete vessel occlusion.
Modified from Adams et al [114].

ilatation [104] primarily by negatively shifting the balance of prostacyclin (PGI2) to thromboxane (TXA2), which has pro-thrombotic effects. Specific inhibition of the COX-2 enzyme decreases systemic PGI2 [105] resulting in the loss of a natural inhibitor of platelet activation [106]. The effects of COX- 1 and COX- 2 selective inhibitors on thrombosis are almost certainly related to their divergent effects on the balance between PGI2 and TXA2. The release of PGI2 by ischemic tissue, contributing to protective reactive hyperaemia was first demonstrated by McGiff in 1970 [107]. Animal studies have confirmed that this occurs in the coronary vasculature [108] and that the COX-2 enzyme plays an essential role in cardio protection post ischemia [109]. The CV risk of these drugs may also be present for less COX-2 selective NSAIDs [70].

Clinically it is imperative to know whether the co-administration of a COX-1 selective inhibitor (such as aspirin) may dampen these negative vascular effects. A previously observed increase in time to occlusion with aspirin in a coronary thrombosis model was abolished with celecoxib, suggesting that co-treatment with these agents neutralizes the protective effects of COX-1 selective inhibitors [110]. Such studies have important clinical implications, given the widespread use of these agents in RA, particularly for those patients with prior vascular events or multiple risk factors who require aspirin for coronary heart disease and stroke prophylaxis.

The role of inflammation in cardiovascular disease

Atherosclerosis is now acknowledged to be an inflammatory disease [39]. Endothelial dysfunction is the initial step in atheroma formation, and may be caused by elevated and oxidized LDL, free radicals (generated for instance, by smoking [111]), hypertension, diabetes mellitus, elevated plasma homocysteine, and perhaps infectious micro-organisms [39]. This dysfunction is accompanied by increased permeability and adhesiveness (with respect to leukocytes and platelets) and a procoagulant state as the endothelium is bathed in cytokines, chemokines, and growth factors. Within the enlarging inflammatory focus, smooth-muscle cell volume increases to form an intermediate lesion, whilst the artery thickens and compensates by gradual dilation [112] (remodelling). Continued inflammation recruits greater numbers of monocyte-derived macrophages and T-lymphocytes, and release of hydrolytic enzymes may eventually induce focal necrosis. With continuation of the process, a fibrous cap is formed over a core of lipid and necrotic tissue (advanced, complicated lesion). At some time point the artery loses its ability to compensate by dilation, the lesion intrudes into the lumen and the flow of blood is impaired. Plaque rupture and thrombosis can occur, resulting in acute coronary syndromes [39] (Fig. 1).

In atherosclerosis, most of the normal anticoagulant defences are impaired. There is loss of the vasodilator NO [113], abnormal heparin formation, local thrombin activation, relative lack of tPA and thrombomodulin, of all which favour local coagulation. In addition, increased tissue PAI and lack of tPA impair clot lysis. Thrombin activation, membrane bound platelet adhesion molecule expression, exposure of collagen, increased production of tissue factor (TF), and loss of NO also favour increased platelet adhesion and aggregation. Coagulation is greatly accelerated with endothelial erosion or plaque fissure [114].

Monocyte-derived macrophages and the related dendritic cells are scavenging and antigen-presenting cells that secrete cytokines, chemokines, growth-regulating molecules, metalloproteinases and other hydrolytic enzymes. Activated macrophages and smooth muscle cells express MHC class II antigens, allowing them to present antigens to T lymphocytes [115, 116]. Activated T-cells secrete cytokines; including interferon γ, TNFα and lymphotoxin; all of which amplify the inflammatory response [115]. One possible antigen may be oxidized LDL, which can be produced by macrophages [117]. Cell-mediated immune responses are likely to be involved in atheroge-

nesis, since both CD4 and CD8 T-cells are present in the lesions at all stages of the process.

Given the pathogenesis of atherosclerosis as described, research has delved into the possibility of an HLA-associated genetic predisposition to accelerated CV disease; however findings have been less than overwhelming. Although HLA- associations have been reported in patients with atherosclerosis [118–120], it is not clear whether the HLA tissue antigens are involved directly in pathogenesis or whether they are markers for some other genetic factor. Lipoprotein (a) has been found to be independently associated with early atherosclerosis and its sequelae, and a link between inherited high levels of lipoprotein (a) and certain HLA class II genotypes has been suggested but not proven [121, 122].

The Receptor for advanced glycation end products

RAGE is a 35-kDa polypeptide whose gene is located at the junction of the class II and III HLA regions on chromosome 6 [123]. It is a multiligand member of the immunoglobulin super-family of cell surface receptor molecules [124, 125]. This cell surface *r*eceptor is known as RAGE as it was initially found to bind AGEs (*a*dvanced *g*lycation *e*nd products) which are nonenzymatically glycated adducts of proteins and lipids [126]. In addition to AGEs, RAGE was found to bind EN-RAGEs (*e*xtracellular *n*ewly identified *RAGE*-binding proteins), or RAGE-ligands. These include the S100/calgranulin chemokine family [127], β pleated sheet fibrils of amyloid [128], and amphoterin, also known as high mobility group box chromosomal protein 1 (HMGB-1) [129].

AGEs accumulate in disorders such as diabetes [130], amyloidoses [131], Alzheimer's disease [128] and renal failure [132], as well as at sites of oxidative stress, and in normal aging [133]. In rat models, RAGE expression is high in the developing nervous system (in association with amphoterin), at a time when little AGE formation would be occurring, however levels tend to decrease as the animals mature. This suggests that RAGE may have a physiological role in development [129].

The proximity of cells expressing RAGE to lesions rich in AGEs, and the activation that results, suggests that the AGE-RAGE interaction may trigger intracellular signal transduction mechanisms that alter properties of vascular and inflammatory effector cells. This may then contribute to dysfunctional repair in AGE rich tissues, as occurs in diabetes. Given that RAGE also serves as a cell surface receptor for amyloid-β peptide [128], which accumulates in Alzheimer's disease, it has been hypothesized that the RAGE receptor converts proteinaceous deposits into bioactive substrate [127].

AGE ligation of RAGE has been shown to activate p21ras and mitogen-activated protein (MAP) kinase, and to stimulate nuclear translocation of the transcription factor NF-κB thereby resulting in the transcription of target genes [134]. Ligation is believed to enhance receptor expression and to initiate a positive feedback loop, in which receptor occupancy triggers increased RAGE expression, followed by further cellular activation. Ongoing expression of RAGE on endothelium, smooth muscle cells, mononuclear phagocytes, and neurons when in close proximity to ligands, thus may induce chronic cellular activation and tissue damage [135].

RAGE and cardiovascular disease

Increased expression of RAGE and the presence of AGEs have been described at sites of vascular lesions and in blood vessel walls [135, 136]. In diabetic retinopathy and renal glomerulosclerosis, microvascular lesions correlate with the accumulation of AGEs [137, 138]. In a murine model, after the induction of neointimal expansion of smooth muscle, the process was strikingly suppressed by blockade of RAGE by using a truncated soluble form of RAGE (sRAGE), RAGE antibodies or in RAGE-/- mice [136]. Recently the importance of endogenous sRAGE in human health has been shown, with low levels independently associated with the presence of coronary artery disease in nondiabetic men [139].

Ligation of RAGE expressed by endothelial cells diminishes vascular barrier function [140], enhances expression of VCAM-1 [141], quenches NO [142], induces the expression of cytokines such as IL-6 and MCP-1 [135], and changes the balance of coagulation, partly by induction of procoagulant TF [143]. RAGE has also been shown to upregulate the COX-2 enzyme, resulting in monocyte activation and vascular cell dysfunction [144].

Diabetes provides a model of widespread chronic vascular disease. As further evidence of the role of RAGE in atherosclerosis, sRAGE has been shown to prevent the accelerated progression of atherosclerosis usually seen in diabetic apoE null mice [145], and diabetes associated vascular dysfunction in vivo can be prevented by blockade of RAGE [146]. A murine model implicated RAGE as central to diabetic neuropathy, with prevention and even reversal demonstrated with RAGE blockade [147].

RAGE and rheumatoid arthritis

Given that rheumatoid arthritis generates AGEs, as a by-product of oxidative stress, in addition to other RAGE-ligands as a result of neutrophil activation, the role of RAGE and its ligands in the pathogenesis of inflammatory joint disease has been studied. In a murine model of inflammatory arthritis, blockade of RAGE suppressed clinical and histological evidence of arthritis [148].

AGEs have been shown to accumulate in inflamed RA synovial tissue, with RAGE antigen expression overlapping with the distribution of AGE epitopes [101]. However, in a small study looking at RAGE staining patterns of synovial tissue, there were no differences in staining pattern between those patients with RA and those with osteoarthritis [149].

Members of the calgranulin family of proteins are key molecules involved in signal transduction, differentiation, and cell cycle control, and are ligands of RAGE [150]. S100A12 (calgranulin C) is one of several RAGE ligands that is expressed and secreted by granulocytes [151]. Murine models of collagen-induced arthritis demonstrate the ability of S100A12 to trigger synovial inflammation [127]. Serum levels of this cytokine have been shown to be raised in several autoimmune diseases including adults with RA, seronegative and psoriatic arthritis, inflammatory bowel disease, and in children and

adolescents with Kawasaki disease and juvenile RA (JRA) [151–153]. In systemic onset JRA, levels of S100A12 are higher than in health. There is a gradient in serum levels, those with polyarticular joint involvement having higher levels than those with oligoarticular JRA. Levels decrease in response to treatment of inflammation and increase prior to clinical flares. High concentrations in synovial fluid indicate release of the cytokine at this site [151]. Other calgranulins include S100A8 and S100A9. These RAGE ligands are also known as macrophage migration inhibitory factor-related proteins 8 and 9 (MRP8 and MRP9) and like S100A12, have been shown to accumulate at sites of inflammation, including the synovial membrane lining layer adjacent to the cartilage-pannus junction of rheumatoid arthritis [154]. Serum levels are also representative of inflammation in JRA [155].

The last of the currently known ligands for RAGE, HMGB-1 / amphoterin, has been implicated in the pathogenesis of arthritis. This molecule was first thought to function only as a nuclear factor that enhanced transcription, but it is now known to be a crucial cytokine mediating tissue response to infection, injury and inflammation [156]. Murine models have demonstrated high levels of immunohistochemical staining in collagen- or adjuvant- induced arthritis [157], a five fold elevation in the synovial fluid of rheumatoid compared to osteoarthritis patients [158], and increased serum levels during active RA [157]. Taken together, the available data strongly suggest that various RAGE ligands are proinflammatory, mediated by the RAGE receptor.

Functional polymorphisms have been described in coding and non coding regions of the RAGE gene, several may be associated with vascular disease [159–162], however most are beyond the scope of this review, which will cover only one.

RAGE: Glycine 82 Serine polymorphism

The location of the RAGE gene in the HLA region on chromosome 6 [123] has implications for RA. Like many HLA genes implicated in genetic control of the immune response, the RAGE gene has a number of polymorphisms described in the recognition coding regions [161] one of which, a Glycine to Serine substitution at position 82 (82Ser; SNP: rs2070600)**,** has a significant prevalence and results in a functional amino acid change in the RAGE molecule [163]. This amino acid shift occurs at a predicted N-linked glycosylation site in the same immunoglobulin variable domain as the AGE binding site [163]. The tertiary structure of the RAGE molecule however, is unknown, and thus structural effects of this polymorphism are unable to be predicted [163]. However Hofmann et al have presented evidence that 82Ser may upregulate the immune response. Amongst other effects, they demonstrated human mononuclear phagocytes of healthy subjects bearing 82Ser, when exposed to S100A12, secreted significantly greater levels of TNFα than subjects bearing the Glycine82 allele [148].

The allele frequency of 82Ser varies between 0 to 29%, with significant differences between ethnic groups [163–165]. Allele frequencies do not vary in type I or II diabetics compared with non-diabetic controls [161, 163], however 82Ser has been shown to be increased in subjects with RA [148]. The location of the gene within the HLA suggests that linkage disequilibrium with known RA-associated DR genes is likely. When Hofmann et al sub-analysed their cohort for the presence or absence of DRB1*0401, they were unable to demonstrate a statistically significant association between the 82Ser allele and RA [148], suggesting the RAGE polymorphism was in linkage disequilibrium with DRB1*0401, and thus accounting for its prevalence in the RA population. The TNFα gene is also located in the MHC class III region, and likewise variant alleles have been demonstrated to be in strong linkage disequilibrium with certain RA associated haplotypes, making it highly unlikely that individual polymorphisms in the TNFα gene would be of primary importance in RA [166, 167]. Of interest, given the close proximity of RAGE to TNFα, these two genes may be linked. However, given the ability of RAGE signalling to control TNF production, they may also be linked functionally.

Several studies have addressed whether the polymorphism is associated with risk of micro- or macro- vascular disease in type I or type II diabetes [160, 161, 163, 164, 168, 169]. Prevost et al found that 82Ser is significantly associated with risk of developing advanced nephropathy in Caucasian type I diabetic patients [160], whilst Kumaramanickavel et al found it was significantly associated with a low risk of developing diabetic retinopathy in Asian Indian patients who have type II diabetes [169]. Since DR4 is also associated with development of type I but not type II diabetes, it is possible that other genes in the same HLA region may influence the response of RAGE.

Summary

Patients with RA have a considerably increased risk of cardiovascular morbidity and mortality, which is likely to be at least partly explained by inflammation and altered immune mechanisms, although RA patients may be carriers of a higher load of conventional risk factors. RA and cardiovascular disease have some striking similarities. The RAGE receptor has a role in sustaining chronic inflammation and in autoimmune disease. A polymorphism of RAGE that is enriched in RA could potentially have a role in CV disease expression, as well as on RA itself. As yet, the exact role of RAGE in perpetuation of rheumatoid arthritis, vascular inflammation or perturbed immunity is unclear, but is the subject of ongoing research.

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