A Review on Role of Advanced Glycation End products (AGEs) in Rheumatoid Arthritis

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Abstract  Rheumatoid arthritis (RA) is a systemic inflammatory connective tissue disease with polyarthritis as a prominent feature; however, extra-articular symptoms and signs are always present. Advanced glycation end products with ability of cross-linking of proteins characteristic fluorescence and reaction with AGE-specific receptor RAGE (receptor for AGEs). AGEs action as well as AGE formation is directly related to both to inflammation and oxidative stress. RAGE is a 35-kDa polypeptide whose gene is located at the junction of the class II and III HLA regions on chromosome. AGE ligation of RAGE has been shown to activate p21ras and mitogen-activated protein (MAP) kinase, and stimulate nuclear translocation of the transcription factor NF-κB, thereby, resulting in the transcription of target genes thus may induce chronic cellular activation and tissue damage.

Keywords: Advance glycated end products, RAGE, Rheumatoid arthritis

1. INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory connective tissue disease with polyarthritis as a prominent feature; however, extra-articular symptoms and signs are always present (Terao, et al., 2014; Megan, et al., 2014). It globally affects up to 0.5-1% of the adult population, with survival rates comparable to coronary artery disease and cancer (Toshio, et al., 2013). RA patients are two to five times more prone to the risk of coronary artery disease, silent myocardial ischemia, sudden cardiac death and overall cardiovascular (CV) mortality risk as compared to general population (Hurlimann, et al., 2002; Miguel, et al., 2005; Gerli, et al., 2005).
RA may act as independent risk for ischemic heart disease. About 50% of atherosclerotic coronary artery disease in community occurs in the absence of “traditional” CV risk factors, including male sex, family history for CV disease, age, dyslipidemia, arterial hypertension, diabetes mellitus, smoking and obesity (Rincon, et al., 2003)

Various factors predicting mortality in RA patients includes:- a) Disease duration: If disease duration is more than 5 years then relative risk for mortality in RA is 3.6 and mortality rate increases ≥ 40% in next 5 years in RA patients with extra-articular features present at baseline; b) Sex: RA reduces life expectancy by approximately 7 years in men and 3 years in women in general but is more in older women; c) Treatment: Treatment with non steroidal anti-inflammatory drugs (NSAIDs) increase 10% mortality in elderly due to risk of peptic ulcers. Glucocorticoids (dose < 7.5 mg/day) act as risk factor for myocardial infarction, cerebrovascular events and transient ischaemic attacks (Arshad, et al., 2005).

Although much new advancement in the treatment plan are available now and a lot of work is in progress, but still DMARDs are the gold standard in the treatment of Rheumatoid Arthritis. But the disease is not fully controllable even with various DMARDs regimens. Triple drug regimen including combination of methotrexate + sulfasalazine + hydroxychloroquine has been used extensively by many rheumatologists since long (Saravanan, et al., 2002, Roberts, et al., 2005), but even then many patients (~ 25%) fail to respond adequately (O’Dell, et al., 1996). Response to even newly introduced biological DMARDs like anti-TNF-alpha agents (Infliximab, Etanercept, adalimumab) alone or in combination with conventional DMARDs is also not complete (Lipsky, et al., 2000, Keystone, et al., 2004, Bathon, et al., 2000). Immune activity has to be controlled at various levels because many other pathways/ factors play role in RA induced inflammation like Advanced Glycation End Products (AGEs), Matrix Metalloproteinases (MMPs), etc.

1.2 Advanced glycation end products

Advanced glycation end products are represented by a heterogeneous group of compounds (e.g. pentosidine, carboxymethyllysine (CML), imidazolone, etc.), some of them with characteristic fluorescence, ability of cross-linking of proteins and reaction with AGE-specific receptor RAGE (receptor for AGEs) (Makita, et al., 1993, Horiuchi, et al., 2002). AGEs formation as well as AGE action is linked both to oxidative stress and inflammation. Apart from non-enzymatic glycation, AGEs can rise via autooxidation of sugars as well as other glycation intermediates—Schiff base and Amadori products (Baynes, et al., 2000).
Figure 1: Schematic representation of the formation of advanced glycation end products (AGEs) through the Maillard reaction. Nonenzymatic reactions of the carbonyl groups of reducing sugars with primary amino groups of the proteins produce their corresponding Schiff bases, which undergo Amadori rearrangements to give protein-derived aminomethyl ketones. Transition-metal-ion-catalyzed glycoxidations of the Amadori compounds, involving reactive oxygen species (ROS) and reactive nitrogen species (RNS), give 1,2-dicarbonyl compounds such as glyoxal. Other sources of 1,2-dicarbonyl compounds include autoxidations of glucose, Schiff bases or the corresponding Amadori products. These highly reactive dicarbonyl compounds further react with surrounding protein amino groups, and undergo further glycoxidations forming a variety of protein crosslinks or protein modifications, and are referred
1.3 Formation of advanced glycation end products (AGEs) through the Maillard reaction

The Maillard reaction is not actually a single reaction, but a series of nonenzymatic reactions involving the reaction between carbonyl groups of reducing-sugars with amino groups of proteins, enzymes, nucleic acids or phospholipids, forming Schiff bases and followed by their Amadori rearrangement and subsequent oxidative modifications (glycoxidations) that are induced by reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Reddy, et al., 2006). The end result of these complex series of reactions is the formation of AGEs. Glycoxidation of the Amadori products, formed in the initial phase of the Maillard reaction, results in the formation of reactive 1,2-dicarbonyl compounds such as glyoxal and glucosone. Autoxidations of glucose, or the corresponding Schiff base and the Amadori products, also give rise to other 1,2-dicarbonyl compounds such as methylglyoxal, 1-deoxyglucosone (1-dG) and 3-deoxyglucosone (3-dG). The increased electrophilicity of these 1,2-dicarbonyl compounds results in their relatively fast reactions with amino groups of proteins, and subsequent glycoxidative modifications result in the formation of the cross linked proteins (Figure 1). Some of the AGEs are intensely colored compounds and have typical fluorescence characteristics (excitation at 330 nm and emission at 400 nm). However, not all of the AGEs are derived from protein crosslinks. N-carboxymethyllysine (CML), for example, is derived from the modification of a lysine residue of a single protein. Such protein modifications can cause enzymes inactivation. (Reddy, et al., 2006).

1.4 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. 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. AGE ligation of RAGE has been shown to activate p21ras and mitogen-activated protein (MAP) kinase, and stimulate nuclear translocation of the transcription factor NF-κB, thereby, resulting in the transcription of target genes (Lander, et al., 1997). 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 AGE on endothelium, smooth muscle cells, mononuclear phagocytes, and neurons when in close proximity to ligands, thus may induce chronic cellular activation and tissue damage (Schmidt, et al., 1999).

1.5 Receptor for advanced glycation end products in rheumatoid arthritis

The multi ligand receptor RAGE functions through amplification of various proinflammatory pathways when interacting with AGEs that enhances the level of cytokines, adhesion molecule and vascular cell expression. (Yaw Kuang Chuah, et al., 2013). (Basta, et al., 2002). In inflamed RA joints, levels of High Mobility Group Box chromosomal protein-1 (HMGB-1) and S100A12, as well as those of AGEs, are strikingly increased (Kokkola, et al., 2002, Miyata, et al., 1998). High levels of RAGE and proinflammatory adhesion molecules are found to be expressed in the RA synovial tissue (ST) endothelium (Basta, et al., 2002). In addition, macrophages established from RA synovial fluid (SF) cells contain large amounts of RAGE protein (Taniguchi, et al., 2003) in RA, targeted site i.e synovial tissue is infiltrated by various inflammatory mediator that is characterized by presence of CD68+ macrophages on RAGE antigen and along with this the level of TNFα, cytokine and IL-1 increased at of the inflammatory site which leads to progression of disease. (Hou, et al., 2002, Yaw Kuang Chuah, et al., 2013). It was shown in a study that RAGE-inducing factors were secreted spontaneously from RA synovial tissue cells, and RAGE mRNA expression in monocytes was initiated by various cytokines, including the two essential proinflammatory cytokines, IL-1β and TNF-α, the Th1 cytokine IFN-γ, and, of interest, the antiinflammatory cytokine IL-10 (Iwahashi, et al., 2004). Studies of the RAGE gene have identified the presence of at least two functional NF-κB sites in the promoter gene (Li, et al., 1997), and RAGE expression is thereby regulated at the transcriptional level by NF-κB activation (Li, et al., 1997, Tanaka, et al., 2000). The NF-κB pathway is believed to play a key role in RAGE induction by both RAGE ligands and the proinflammatory cytokines IL-1 and TNF-α. These cytokines also stimulate HMGB-1 and S100A12 secretion from macrophages and neutrophils (Kokkola, et al., 2002, Taniguchi, et al., 2003. (Hofmann, et al., 1997). There seems to be an intimate relationship between the RAGE–ligand system and the cytokine cascade in RA, forming a positive feedback loop that leads to the propagation of the disease process.
2. ROLE OF AGES IN RHEUMATOID ARTHRITIS

It is now proved that Rheumatoid arthritis generates AGEs, as a byproduct of oxidative stress, in addition to other RAGE ligands as a result of neutrophils 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, in which blockade of RAGE suppressed clinical and histological evidence of arthritis (Hofmann, et al., 2002). AGEs have been shown to accumulate in inflamed RA synovial tissue with RAGE antigen expression overlapping with the distribution of AGE epitopes (Basta, et al., 2002). However, in a small study looking at RAGE staining patterns of synovial tissue, there were no differences has been seen in staining pattern between those patients with RA and those with osteoarthritis (Drinda, et al., 2005).

RA is a chronic systemic disease, although its major clinical consequence is inflammation of the joints and contiguous structures. It is shown in a study that pentosidine is supposed to play an important role in RA (Chen, et al., 1999). Pentosidine level elevated in serum and urine reflects the increased disease activity of RA (Takahashi, et al., 1997). In a study of 20 patients, pentosidine levels in serum and synovial fluid were found to be significant higher in RA than OA patients. Moreover, this was significantly correlated with CRP, ESR and Lansbury Index (LI). When pentosidine was compared between subgroups of RA patients who were divided into high (CRP >20mg/l and LI > 40%) and low (CRP<20mg/l and LI < 20%) activity groups, it was found that pentosidine levels in serum and synovial fluid were significantly higher in high activity group. The levels of pentosidine were found higher in patients with active RA than in those with inactive RA because serum and urine levels of pentosidine are found to be correlated with the activity of RA, thus serum and urinary pentosidine may be act as significant and novel marker for evaluating the disease status and the activity of RA (Takahashi, et al., 1997).

CML is an AGE, which can be used as a marker of oxidative stress (Nerlich, et al., 1999, Nakayama, et al., 1999). In RA, inflammatory changes and destruction of joints are seen (Ames, et al., 1999). The accumulation of CML in RA synovial tissue might be the result of oxidative stress during local and systemic inflammation. Oxidative stress can cause different “metabolic changes”, leading to the mutation of key regulatory genes. This may help to transform inflammation into chronic disease (Tak, et al., 2000). A study showed that in older patients AGES represent new epitopes and contain new antigenic structures (Yang, et al., 1994), thereby possibly contributing to the generation of autoimmune responses (Michaelsson, et al., 1996). This theory is supported by the findings of Miyata et al., 1998 and Takahashi et al, 1997, who found a correlation between the inflammatory activity and concentration of AGES.
measured in the urine and blood of patients with RA. Pentosidine formation is accelerated by oxidative conditions, thus pentosidine is supposed to be implicated in the disease process of RA. It was demonstrated in a study, that pentosidine levels were elevated in cartilage and suggested that oxidative stress was related to the elevation of pentosidine in the cartilage of RA (Takahashi, et al., 1994). It was shown by Takahashi, et al. in a study that Serum levels of pentosidine in RA (mean 150.1 nmol/l) were significantly higher than in controls patients (mean 81.7 nmol/l). Urinary levels of pentosidine in RA (10.7 μmol/mol creatinine) were significantly higher than in controls (3.8μmol/mol creatinine). Serum and urinary pentosidine were significantly related with age in RA, although they were not related with age in controls. In another study, it was shown that the conc. of pentosidine in RA patients is seen to be as high as ≈ 850 nmol/l as compared to ≈ 100 nmol/l in control group. On the other hand the conc. of pentosidine is seen to be ≈ 280 nmol/l and ≈ 300 nmol/l in diabetes and SLE patient groups, respectively, when compared with control groups (≈ 100nmol/l) (Rodriguez, et al., 1997).

These findings implicate AGEs as possible key players in the development of Rheumatoid Arthritis disease and its complications.

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