Experimental Section / Mini-Review

Gerontology

Gerontology 2011;57:435–443
DOI: 10.1159/000322087

Received: January 27, 2010
Accepted: August 2, 2010
Published online: October 21, 2010

Reactive Metabolites and AGE/RAGE-Mediated Cellular Dysfunction Affect the Aging Process – A Mini-Review

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Key Words
Advanced glycation endproducts · Advanced glycation endproduct receptor · Methylglyoxal

Abstract
Aging is a dynamic process in which its rate and subsequent longevity of an organism are dependent upon the balance between the reactive intermediates of normal cellular metabolism and the ability of the body to reduce these by-products through a multifaceted antioxidant defence system. Every disturbance of this balance constitutes a clear and present danger to the macromolecular integrity of the body. When defence mechanisms become diminished or impaired, the resulting imbalance results in accumulation of endogenous agents, such as reactive oxygen and carbonyl species, and a state of increased cellular stress, which can accelerate the rate of aging. Glycation is the non-enzymatic glycosylation of proteins, nucleotides and lipids by saccharide derivatives. Glucose and other reducing sugars are important glycating agents, but the most reactive physiological relevant glycating agents, are the dicarbonyls, in particular methylglyoxal. Endogenously formed dicarbonyl compounds can react with proteins to form advanced glycation endproducts (AGEs). Experimental models have recently provided evidence that reduced detoxification of AGE precursors by the glyoxalase system, engagement of the cellular receptor RAGE and RAGE-dependent sustained activation of the pro-inflammatory transcription factor nuclear factor κB might significantly contribute to the rate of aging and the onset of age-related neurodegenerative, musculoskeletal and vascular diseases.

Introduction

Aging is a fundamental and irrevocable characteristic of all living organisms. The process of aging can be viewed as the progressive and irreversible accumulation of damage to the macromolecular integrity of the cell, leading preliminarily to the loss of key regulatory mechanisms within the cell and ultimately to an increased risk for the development of disease. It is generally accepted that the metabolic rate of an organism is a major determinant of life expectancy [1]. The mechanistic link between metabolism and aging has been proposed to be the endogenous generation of reactive oxygen species (ROS; superoxide anions, hydroxyl radicals and hydrogen peroxide). The production of ROS is largely the result of living in an aerobic environment [2]. Within the body, 95% of all inhaled oxygen undergoes a concerted 4-electron reduction to produce water in a reaction catalysed by cytochrome C oxidase of complex IV in the mitochondrial

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electron transport chain [3]. Although the mitochondrial electron transport chain is an efficient system, the very nature of the alternating 1-electron oxidation-reduction reactions, the resulting catalyses (generating a constantly alternating series of caged radicals) can permit side reactions with molecular oxygen, specifically, its reduction to the superoxide (O_2^-). It is estimated from in vitro experiments using isolation mitochondria that 0.12–2% of respiration goes to O_2^- production; however, these values cannot be extrapolated too readily to the in vivo situation, where mitochondrial O_2^- production would be considerably lower [3, 4]. The addition of a second electron and 2 protons generates the reactive species hydrogen peroxide. A third electron produces the highly reactive hydroxyl radical ($HO^\bullet$), which acts as a powerful oxidant and can damage a number of biological macromolecules, despite its short half-life and a limited sphere of influence (approx. 5 molecular diameters before it oxidizes a target) [5].

The 'free radical theory' of aging, as proposed by Harman [6] in the mid-1950s, suggests that aging and aging-associated degenerative diseases could be attributed to deleterious effects of ROS on various cell components. Although initially controversial, this theory gained acceptance following the discovery that mammals have evolved a multifaceted response in reducing the consequences of its own metabolism by implementing an intricate antioxidant defence system composed of enzymatic (superoxide dismutase, catalase, glutathione peroxidase and peroxyredoxins) and low-molecular-mass ROS scavengers (such as glutathione, GSH, and vitamins) [3]. However, when these antioxidant defences become diminished, impaired or overwhelmed, an imbalance will occur resulting in an accumulation of ROS, giving rise to a state of cellular oxidative stress [2, 3].

The formation of toxic metabolites is closely linked to the rate of metabolic flux and/or increased dependence on glycolysis for energy supply within the cells. In situations of increased energy demands (such as aging, tumour development and cancer) and in metabolic disorders with excessive energy supply (such as diabetes), the metabolic flux is enhanced. Under normal physiological conditions, the metabolic flux is controlled by a network of rate-limiting enzymes ensuring energy supply without accumulation of such toxic reactive metabolites. In situations of increased energy availability or energy demand, however, the consequences of increasing concentrations of highly reactive metabolites, such as ROS, which cannot be readily detoxified and/or metabolized by key enzymes of the metabolic network, are the inactivation of additional pathways, a dysregulation of the cellular energy homeostasis and substrate inhibition of the key enzymes. For example, a key enzyme and metabolic switch in glycolysis is glyceraldehyde-3-phosphate dehydrogenase (GA3PDH), which catalyses the reversible oxidative phosphorylation of glyceraldehyde-3-phosphate (GAD3P) in the presence of inorganic phosphate and nicotinamide adenine dinucleotide (NAD^+). An excess of superoxide and/or the increased consumption of NAD^+ due to an excess of NADH inhibits GA3PDH activity. In addition, ROS-induced DNA damage can further reduce the activity of GA3PDH, by activation of poly(ADP-ribose) polymerase. GA3PDH is an acceptor protein for poly(ADP-ribose) polymerase, and following poly(ADP-ribosyl)ation, GA3PDH translocates into the nucleus where it is inhibited [7]. The inhibition of GA3PDH results in accumulation of upstream intermediates and in interconversion of GAD3P to dihydroxyacetone phosphate (DHAP) by the enzyme triosephosphate isomerase. This results in increased flux of DHAP to diacylglycerol, an activator of protein kinase C [8], and in the formation of methylglyoxal (MG), from the spontaneous degradation of triosephosphates. MG promotes posttranslational modification of proteins by glycation, to form advanced glycation endproducts (AGEs) [9, 10]. Furthermore, the increased flux of fructose-6-phosphate to UDP-N-acetylglucosamine, increases modification of proteins by O-linked N-acetylglucosamine (hexosamine pathway) [11], and increased glucose flux through the polyol pathway consumes NADPH and depletes GSH [12]. The mechanistic pathways described have all been implicated in glucose-mediated vascular damage observed in diabetes and are referred to as the 'unifying theory' for the pathobiology of diabetic complications proposed by Brownlee [13] in early 2000. It sets a precedent for the concept that the induction and accumulation of endogenous agents can induce significant damage to the molecular integrity of the cell.

Increased glycolysis also confers growth advantages for tumours and appears to be an adaption to the restricted oxygen supply which occurs as the tumour demands for metabolic energy for growth [14, 15]. As in diabetes, the increased metabolic flux leads to an increased production of endogenous agents, such as ROS (i.e. superoxide anion) and altered cellular function. While there is a general agreement that ROS are contributing factors in tumour development, however, the underlying molecular mechanisms are still unclear. For instance, ROS have been shown to participate simultaneously in both the Ras-Raf-MEK1/2-ERK1/2 and the p38 mitogen-activated

protein kinase pathway. While Ras-Raf-MEK1/2-ERK1/2 signalling is related to oncogenesis, the p38 mitogen-activated protein kinase pathway contributes to cancer suppression, i.e. oncogene-induced senescence, inflammation-induced cellular senescence, replicative senescence, contact inhibition and DNA damage responses [16, 17]. Thus, in the case of tumorigenesis, ROS have a dual role to play.

The disturbances in metabolic flux described for both diabetes and cancer, and the consequences which may arise from increased ROS production, serve to highlight the importance of energy homeostasis within the body, and it is within this context that the examples given can be related to aging. As it has been stated, metabolic rate is a major determinant of life expectancy, and in turn, a major determinant of metabolic rate is dietary intake. In healthy individuals, a poorly controlled diet, such as the western diet, characterized by high intakes of red meat, sugary desserts, high-fat foods and refined grains, can result in similar disturbances in metabolic flux to those described. It is therefore conceivable that prolonged exposure to such a diet will ultimately lead to chronic disturbances in metabolic flux and an increasing pool of ROS. The effect of a reduction in intake without starvation was first shown to increase lifespan in rats in 1935 [18]. This treatment, referred to as dietary or caloric restriction, has been subsequently shown to have similar effects in a wide range of species, from yeast [19] and fruitflies [20–22] to mammals including mice [23, 24], dogs [25] and rhesus monkeys [26, 27]. The use of *Caenorhabditis elegans* as a model organism has allowed for considerable insight into the molecular basis of aging [28, 29]. Studies of mutations affecting the lifespan in *C. elegans* suggest that mitochondria and mitochondrion-derived ROS have a major causative role in the aging process [30–33]. These studies further provide strong evidence that the caloric flux results in increased ROS formation, and caloric restriction prolongs lifespan by decreasing ROS production via increased expression of PHA-4/Foxa, a dietary restriction-specific activator of *sod-1*, *-2*, *-4* and *-5* expression [34].

The increased generation of ROS thus forms a common soil in physiological aging, diabetes and carcinogenesis and underlies further disturbances in cellular energy metabolism, including inhibition of mitochondrial biogenesis, glucose metabolism, cell growth and apoptosis. Although the principles of the 'free radical theory' of aging have been solidified by numerous cell culture, invertebrate and mammalian models, the underlying theory has yet to be proven correct. While it is generally suggested that the aerobic metabolism and the subsequent generation of ROS remains the most widely accepted cause of aging, substantial gaps and unknowns persist. For instance, fundamental questions regarding the variables which regulate the relationship between overall metabolic rate and the production of ROS remain unclear. Furthermore, relatively little is known about what are the relevant intracellular targets for ROS and how oxidative modifications of these targets might influence lifespan. Fundamentally, we know that cells make ROS on a continuous basis, at a steady-state level under normal physiological conditions, but under conditions of excessive production, we are still uncertain as to whether they cause or merely correlate with aging.

Reactive Carbonyl Species

Due to the uncertainties that surround the 'free radical theory' of aging, many researchers have begun to look at alternative mediators to ROS. Reactive carbonyl species (RCS) are a heterogeneous group of low-molecular-weight carbonyls activated by α,β-unsaturation as in 4-hydroxynonenal and acrolein, α-oxo-substitution as in glyoxal and MG, and β-oxo-substitution as in malondialdehyde. These compounds are formed endogenously by lipid peroxidation, carbohydrate metabolism and autoxidation of reducing substrates [35]. RCS exhibit a facile reactivity with various biomolecules, including proteins, DNA and phospholipids, generating stable products at the end of a series of reactions that are thought to contribute to the pathogenesis of vascular diseases such as atherosclerosis and diabetes. In addition, it has recently been found that some of the RCS are responsible for the effects of lipid peroxidation and carbohydrate metabolism on signalling/transcription regulation suggesting that RCS may play a role as regulatory molecules of vascular dysfunction [35]. These effects are similar to the detrimental effects caused with ROS accumulation and have in the past been either mistaken or overlooked. Compared to ROS, the aldehydes are stable and diffuse within or even escape from the cell and attach targets far from the site of their formation. Furthermore, several of the most reactive RCS are derived from glucose metabolism, in particular, glycolysis [35]. As ROS require 3 stages of metabolism before production, RCS can be viewed as providing a more direct insult to the macromolecular integrity of the cell.

MG and glyoxal belong to a class of RCS known as the α-oxoaldehydes. These RCS contain 2 adjacent carbonyl

groups and are therefore referred to as dicarbonyls [36]. This chemical moiety makes the dicarbonyls a highly reactive class of RCS, generated from carbohydrate metabolism and autoxidation, collectively referred to as 'glycation' [37].

Dicarbonyls, Glycation and Glyoxalase System

MG is formed from the spontaneous degradation of triosephosphates (GAD3P and DHAP) and from other non-enzymatic and enzymatic pathways [38]. Glyoxal is formed by lipid peroxidation and the degradation of monosaccharides, saccharide derivatives and glycated proteins [38]. Recent estimates for the concentration of MG and glyoxal in human blood plasma are in the range of 100–120 nM, while cellular concentrations for MG are in the range of 1–5 μM, and 0.1–1.0 μM for glyoxal [38]. As the formation of dicarbonyls is closely linked to the rate of glycolysis within the cell and the presence of glycolytic intermediates, it would be expected that under physiological conditions where there is either an increase in glycolytic flux or an increased dependence on glycolysis for energy, the rate of dicarbonyl formation will be increased [39, 40]. This has been shown to be the case in patients with diabetes mellitus, where complications such as nephropathy, neuropathy and retinopathy can be linked to increases in cellular levels of AGEs [41].

MG and glyoxal are potent glycating agents. Glycation of proteins is a complex series of parallel and sequential reactions, often referred to collectively as the 'Maillard reaction', and occurs in all tissues and body fluids. Historically, the reactions of lysyl side chain and N-terminal amino groups with glucose to form fructosyl-lysine and fructosamines, respectively, have been the major glycation processes studied. The formation of these adducts under physiological conditions is now generally classified as an early glycation process. Later-stage reactions form stable end-stage adducts called AGEs [37, 38]. The formation of AGEs can result from either direct degradation of the fructosyl-lysine or indirectly from the degradation of fructosyl-lysine to either glyoxal and/or MG, both of which can react rapidly with proteins to form AGE residues [37, 38].

To minimize the production of glyoxal and MG and therefore the extent of glycation, the body has evolved a number of enzymatic and non-enzymatic defences. One such defence mechanism involves limiting the availability of triosephosphate which could spontaneously form MG. This is achieved by maintaining low concentrations of triosephosphates during steady-state glycolysis by feedback inhibition of phosphofructokinase 1 and capping the active site in triosephosphate isomerase, preventing the fragmentation of the phosphoendiolate intermediate to MG and phosphate. Although effective in decreasing the formation of MG, some triosephosphate does escape, and as such cells have developed mechanisms for detoxification. MG can be metabolized by MG reductase to lactaldehyde, by aldose reductase to hydroxyacetone and by 2-oxoaldehyde dehydrogenase to pyruvate. However, the system that handles most of the cellular MG is the glyoxalase system [42].

The glyoxalase system is present in the cytosol of all human cells and comprises 2 enzymes: glyoxalase I (GLO-I) and glyoxalase II (GLO-II) and a catalytic amount of GSH. GLO-I catalyses the isomerization of a hemiacetal that is formed spontaneously from dicarbonyls and GSH to *S*-2-hydroxylacylglutathione derivatives; GLO-II then catalyses the conversion of the *S*-2-hydroxylacylglutathione derivatives into α-hydroxyacids and reforms GSH [42]. GLO-I activity prevents the accumulation of reactive dicarbonyls and thereby suppresses dicarbonyl-mediated glycation reactions. It can, therefore, be considered as the key enzyme in antiglycation defences.

The physiological importance of protein glycation remains under investigation. Particularly damaging effects are produced by covalent cross-linking of proteins which confers resistance to proteolysis [38]. Protein modification is also damaging when amino acid residues are located in sites of protein-protein interactions, enzyme-substrate interactions and protein-DNA interaction. Studies looking at the modification of human serum albumin [43] and vascular basement membrane type IV collagen by MG [9] have shown that formation of the respective hydro-imidazolone causes structural distortions, loss of side chain charge and functional impairment.

Direct effects of MG on lifespan have been demonstrated in the model organism *C. elegans*, in which increased detoxification of MG by overexpression of GLO-I increased lifespan by 40%, while RNAi-mediated silencing GLO-I decreased lifespan by 40%. Overexpression of GLO-I also decreased dicarbonyl-derived AGEs as well as the concentration of markers of oxidative and nitrosative damage. Furthermore, MG-derived AGE accumulation was shown in mitochondria to be associated with increased mitochondrial superoxide formation [44, 45].

AGEs are thought to be formed slowly throughout life, accumulating mostly on extracellular proteins. As such, it is supposed that the concentration of AGEs found represents a lifelong accumulation of the glycation adducts.

In a study by Sell et al. [46], the levels of skin AGEs [N^e-(carboxymethyl)lysine (CML) and pentosidine], biopsied from C57BL/6N male mice at the age of 20 months correlated significantly with longevity. In the same study, samples were also taken from mice on a calorie-restricted diet, whereas caloric restriction significantly increased lifespan in these animals and sharply reduced the levels of AGEs present in the skin, further implying that an age-related deterioration in glucose tolerance is a lifespan-determining process [46]. In this context, hydro-imidazolone-derived AGEs (MG-H1) are found in highest concentrations in lens protein of elderly human subjects. Stable AGEs such as CML residues also accumulate on lens capsule, skin and cartilage collagen with age [47, 48]. Such evidence has given rise to the 'Maillard theory of aging', in which it is proposed that the chronic formation and accumulation of AGEs is a determinant for the rate of aging within an organism [49, 50]. While this conclusion was found to apply to chemically stable AGEs formed on long-lived proteins, such as CML or N^e-(carboxyethyl)lysine residue accumulation on skin collagen [38], interspecies comparisons of AGE content versus age showed that this theory is not universal. It was found that the AGEs accumulated at a more rapid rate in the tissues of short-lived mammals, such as mice and rats, compared to humans [51] whereas the rate of accumulation observed in the rodent models correlated inversely with lifespan [46]. In addition, the cumulative damage which was observed in the old, short-lived animals, was in fact decreased due to the shorter lifespan and more rapid turnover of proteins within these animals, and as such the level of AGEs observed in the old, short-lived animals was approximately 10% of those observed in old humans [52]. Due to the lack of a clear relationship between the AGE content of long-lived proteins and an organism's lifespan, these observations challenge the Maillard theory of aging. Despite this conclusion, accumulation of AGEs, either by endogenous formation or from increased dietary intake, can accelerate the multisystem functional decline that occurs in aging. Epidemiological studies have shown that older adults with elevated circulating CML are at a greater risk of arterial stiffness, chronic kidney disease, anaemia, poor skeletal muscle strength and physical performance, as well as cardiovascular and all-cause mortality. In addition, it was shown that the dietary content of AGEs can determine not only serum and urine levels of AGEs, but also inflammatory mediators, such as tumour necrosis factor α, interleukin 6 and C-reactive protein [53, 54]. In experimental animal models, it has been shown that there is a link between AGEs, inflammation and chronic diseases, and that reduction of AGE levels either by pharmacological invention or reduced dietary intake of AGEs reduced the risk of developing chronic kidney disease and aging-associated cardiovascular disease. This is consistent with the recent studies demonstrating that a reduction in AGEs due to dietary restriction extends the lifespan in the model organism *C. elegans* [44, 45]. However, it has yet to be established whether the effect of dietary restriction actually limits the amount of AGEs consumed or rather indirectly limits the amount of glucose consumed, and thereby reduces the amount of MG and glyoxal generated from glycolysis.

However, it can be concluded from such studies that the presence and subsequent accumulation of AGEs within the body is not compatible with a long and healthy life. While the primary contribution of AGE formation is the significant alteration of the structure and function of proteins, the multiple pathophysiological conditions which are associated with elevated AGE concentrations suggest that there is a secondary consequence, resulting from their presence in the body potentiating the functional decline observed in aging. One such consequence is through their interaction with specific cell surface receptors.

AGEs, AGE Receptor and Aging

Protein-bound AGEs are not readily repaired and degraded by cellular proteolysis to release glycation adduct peptide residues (adducts found in peptide fragments) and glycation-free adducts (i.e. glycated amino acids) which are excreted in the urine. AGEs may, therefore, potentate the aging process through activation of cell responses by AGE-modified proteins and glycation adduct peptide residues interacting with specific cell surface receptors, such as the receptor for AGEs (RAGE) [55, 56]. RAGE is a multiligand member of the immunoglobulin superfamily of cell surface receptors with specificity for 3-dimensional structures rather than for specific oligomer sequences. A diverse class of ligands has been identified, including S-100/calgranulins, high-mobility group protein B1, β-amyloid peptides and most important with respect to aging, AGEs. Studies have shown that both glycation adduct peptide residues and glycated proteins (highly modified; 76–89% lysine residues modified), but not glycation free adducts, are recognized and bound by the V domain of RAGE [56–58].

The gene for RAGE is located on chromosome 6 near the major histocompatibility complex III in humans and

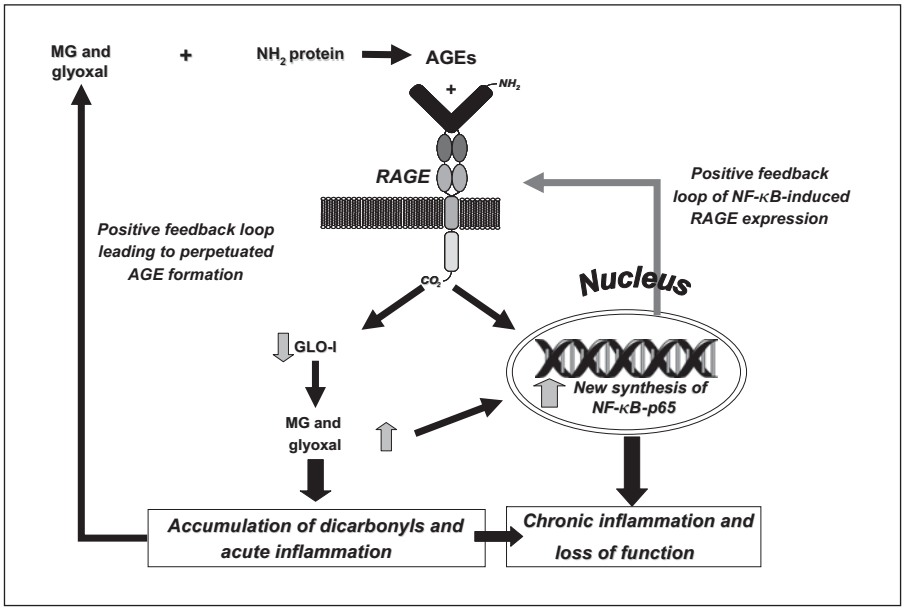

Fig. 1. Proposed cellular activation via RAGE during aging.

mice. The extracellular domain of RAGE consists of 3 immunoglobulin domains: 1 V type and 2 C type domains, which confer the ligand-binding properties. This region is followed by a hydrophobic transmembrane-spanning domain and a short cytosolic tail essential for the RAGE-mediated cellular effects [55, 56] (fig. 1). Upon engagement of ligands, RAGE triggers intracellular signalling pathways via phosphatidylinositol-3-kinase, Ki-Ras, and the mitogen-activated protein kinases ERK1 and ERK2. These pathways culminate in the activation of the pro-inflammatory transcription factor nuclear factor (NF)-κB and subsequent NF-κB-driven pro-inflammatory gene expression. The unique feature of RAGE-mediated NF-κB activation is the prolonged and sustained nature of activation following ligation, which overwhelms the endogenous autoregulatory feedback inhibition loops. De novo synthesis of p65 mRNA results in a constantly growing pool of excess transcriptionally active NF-κB-p65, which subsequently overwhelms the newly synthesized inhibitor κBα, thereby preventing the inhibitor-κBα-dependent retention of NF-κB-p65 within the cytoplasm [59] (fig. 1). The perpetuated activation of NF-κB-p65 following ligation of RAGE converts acute cellular activation into a sustained cellular response, which prolongs pro-inflammatory responses and subsequent cellular dysfunction [55, 56, 59]. Since RAGE itself is regulated by NF-κB, this will further increase, amplify and sustain cellular dysfunction [60].

Expression of RAGE depends upon the cell type and the developmental stage. During embryonic development, RAGE is constitutively expressed and subsequently down-regulated in adult life, but increases during aging [61]. All cells can be induced to express RAGE in situations in which inflammatory mediators and ligands accumulate. Although only little is known regarding the physiological role of RAGE, it has been suggested that it may fulfil the concept of pleiotropic antagonism, in which genes that are beneficial during the reproductive phase of life may become deleterious to development later on. As such, the role of RAGE has been studied in a number of chronic inflammatory diseases, such as diabetes, arteriosclerosis, inflammatory bowel disease, septicaemia, rheumatoid arthritis, inflammatory kidney disease, neurodegenerative disorders and wound healing disorders [55, 56].

Within the context of aging, the involvement of RAGE seems to serve to accelerate and perpetuate the aging process and might shorten lifespan. The most direct mechanism by which RAGE could affect aging is interaction with AGEs, accumulating during aging. As such it is not difficult to envision a situation by which RAGE is upregulated and subsequently activated with time, leading to a perpetuated pro-inflammatory phenotype, a characteristic pathology which is associated with age-related neurodegenerative, musculoskeletal and vascular diseases [3, 56, 59]. An additional mechanism which could indirectly contribute to deleterious effects of RAGE in aging is the

generation of ROS [62]. The increased production of ROS can result in the depletion of GSH and NADPH, which can in turn decrease the in situ activity of GLO-I [63] and thereby increase the concentration of MG and glyoxal and the subsequent formation of AGEs, able to interact with RAGE. Recently, it has been described that the engagement of RAGE is also associated with decreased expression of GLO-I. Induction of diabetes in wild-type mice decreased expression of GLO-I, whereas induction of diabetes in RAGE$^{-/-}$ mice did not [64]. Furthermore, hyperglycaemia, MG, AGEs and other RAGE ligands have been found to significantly reduce GLO-I expression and activity in cultured fibroblasts, endothelial cells and neuronal cells, while inhibition or ablation of RAGE restores GLO-I in these cells [55, 56]. These findings suggest that RAGE is not only a mediator of cell activation and inflammation, but can also directly interfere with the key defence system for detoxification of AGE precursors (fig. 1). As shown in *C. elegans*, impairment of GLO-I is sufficient to limit lifespan at least in this model organism [44].

Furthermore, it has recently been observed that activation of RAGE can lead to epigenetic alterations. The remodelling of chromatin through posttranslational modifications of histone proteins is emerging as a viable determinant of the aging process; proteins maintain the integrity and fidelity of the genome, and corruption of the genetic code will limit its half-life and the lifespan of the related organism. Various posttranslational modifications of histones have been identified, including acetylation, phosphorylation, methylation, poly(ADP-ribosyl)ation and ubiquitination, all of which are involved in regulatory functions in the processing of genetic information, in particularly the activation and/or suppression of gene expression. As aging is associated with changes in patterns of gene expression, epigenetic alterations may therefore provide a suitable explanation for the observed changes [65–67]. Ligation of RAGE has recently been shown to directly induce modifications of chromatin through the thioredoxin-interacting protein, an endogenous inhibitor of antioxidant thioredoxin [68]. Thus, ligand/RAGE interaction does not only induce pro-inflammatory gene expression, but also mediates epigenetic remodelling of histone H_3 lysine K9 by decreasing its trimethylation and increasing its acetylation, which in turn amplifies and sustains pro-inflammatory gene activation [68]. Furthermore, cells cultured under transient hyperglycaemia show increased and persistent NF-κB-p65 gene expression, which could be linked to epigenetic modifications, maintained once the cells were removed from the hyperglycaemic environment [69]. Epigenetic chromatin remodelling therefore provides an additional and novel mechanism by which the activation of RAGE might have a continued and detrimental effect within the aging process.

Conclusion

AGEs are posttranslational modifications that accumulate in long-lived proteins with age. While the rate of accumulation of AGEs in proteins may not necessarily be a primary determinant of an organism's lifespan, the formation of AGEs will undoubtedly contribute to accelerating the gradual decline in tissue and organ function which is observed within the aging body. The interaction of AGEs with the cellular surface receptor RAGE is likely to accelerate and perpetuate the aging process through the maintenance of inflammatory reactions. The RAGE-dependent down-regulation of GLO-I, the key detoxification mechanism of the AGE precursors, would only serve to perpetuate further RAGE up-regulation and activation by increasing the intracellular pool of MG and glyoxal leading to increased AGE formation on various intra- and extracellular macromolecules. This will ultimately lead to further ligation and activation of RAGE, and a continued and self-perpetuated inflammatory response mediated by NF-κB-p65, converting an acute cellular activation into an acute cellular response. Furthermore, the emerging role that RAGE has in regulating epigenetic chromatin remodelling suggests a unique and novel mechanism by which RAGE may further suppress cellular detoxifying mechanisms, by the down-regulation and/or inhibition of those genes key to the antioxidant defence system. Targeting the formation of AGEs and AGE/RAGE interaction may therefore provide a novel therapeutic strategy in the treatment of age-related diseases and help to allow 'successful aging'.

Acknowledgements

This work was supported by grants from the Dietmar-Hopp-Stiftung (to A.B., P.M.H., P.P.N.) and the Network Aging Research (to A.B., P.M.H.).

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