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Advanced glycation end products
Key players in skin aging?

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Abbreviations: AGE, advanced glycation end product; ALT-711, dimethyl-3-phenayl-thiazolium chloride; bFGF, basic fibroblast growth factor; CEL, carboxyethyl-lysine; CML, carboxymethyl-lysine; CK10, cytokeratin 10; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FAOX, fructosyl-amine oxidases; FN3K, fructosamine-3 kinase; Glo, glyoxalase; GOLD, glyoxal-lysine dimer; GSH, glutathione; IL, interleukin; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; MOLD, methylglyoxal-lysine dimer; NADPH, nicotinamide adenine dinucleotide phosphate; NFκB, nuclear factor kappa-B; NOX, NADPH-oxidase; RAGE, receptor of AGE; ROS, reactive oxygen species; SOD, superoxide dismutase; sRAGE, soluble RAGE; TNF, tumor necrosis factor; UV, ultraviolet; WB, western blot

Aging is the progressive accumulation of damage to an organism over time leading to disease and death. Aging research has been very intensive in the last years aiming at characterizing the pathophysiology of aging and finding possibilities to fight age-related diseases. Various theories of aging have been proposed. In the last years advanced glycation end products (AGEs) have received particular attention in this context. AGEs are formed in high amounts in diabetes but also in the physiological organism during aging. They have been etiologically implicated in numerous diabetes- and age-related diseases. Strategies inhibiting AGE accumulation and signaling seem to possess a therapeutic potential in these pathologies. However, still little is known on the precise role of AGEs during skin aging. In this review the existing literature on AGEs and skin aging will be reviewed. In addition, existing and potential anti-AGE strategies that may be beneficial on skin aging will be discussed.

Introduction

Aging is defined as the progressive accumulation of damage over time, leading to disturbed function on the cellular, tissue and organ level and eventually to disease and death. Aging is a complex, multifactorial process where genetic, endogenous and environmental factors play a role.[1]

Skin is the largest organ of the human body and also the boundary between an organism and environment. As such, skin is subjected not only to the internal aging process but also to various external stressors, leading to distinct structural changes and affecting not only its youthful appearance, but also its various physiological functions. Aged skin shows disturbed skin permeability, angiogenesis, lipid and sweat production, immune function and vitamin D synthesis, manifesting among others as impaired wound healing, atrophy, vulnerability to external stimuli and development of several benign and malignant diseases (reviewed in Zouboulis et al.).[2]

Endogenously aged skin refers to changes reflecting the internal aging process of the organism and is being observed mainly in ultraviolet (UV) light-protected skin areas, such as the inner side of the arms. Macroscopically it is recognized by fine wrinkles, loss of elasticity, reduced epidermal and dermal thickness, while microscopically epidermal atrophy, decreased mitotic rate of basal keratinocytes, decreased proliferative capacity and cellular senescence, atrophy of the dermal extracellular matrix and change of the physiological properties of the connective tissue are typical characteristics.[2-4] Exogenously aged skin or photoaged skin is the skin where endogenous aging processes are being aggravated by external stressors, mainly UV irradiation,[2,5] but also by tobacco,[6] chemicals and pollution.[2,4] Apart from many similarities with endogenously aged skin, extrinsic aged skin is also characterized by a thickened epidermis and a hyperplasia of elastic tissue (solar elastosis).[2,4]

Until today, more than 300 theories of aging have been proposed, among them the theory of cellular senescence, decreased proliferative capacity and telomere shortening, mitochondrial DNA single mutations, the free radical theory and others, none of which can fully explain all changes observed in aging.[7-11] According to the inflammatory theory of aging, a common characteristic of skin aging factors is their ability to induce or maintain proinflammatory changes and trigger a local inflammatory response which through subsequent immune responses, matrix metalloproteinase (MMP) activation and proinflammatory cytokine production contributes to the structural changes observed in aged skin.[12]

In the recent years, the role of advanced glycation end products (AGEs) has been increasingly discussed in skin aging, and the potential of anti-AGE strategies has received high interest from pharmaceutical companies for the development of novel anti-aging cosmeceutical compounds.

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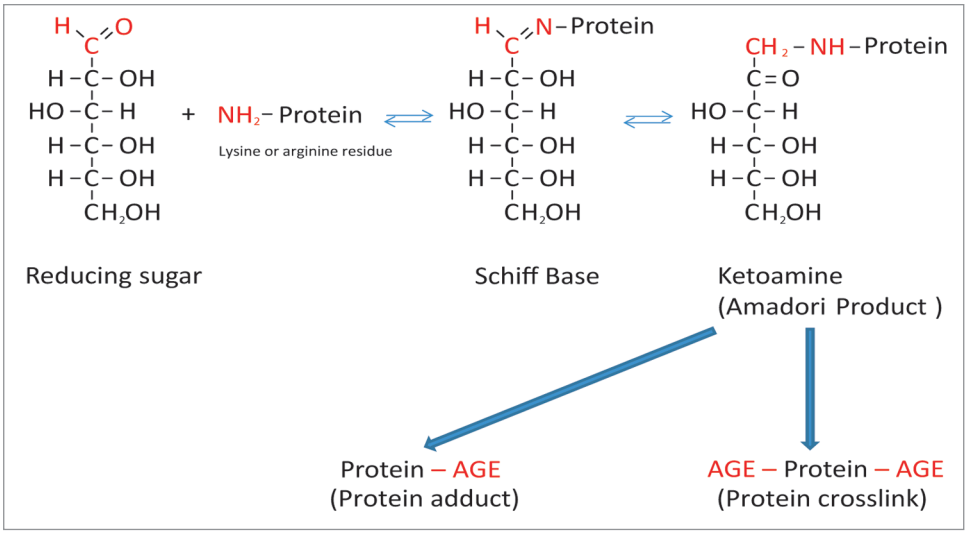

Figure 1. Schematic presentation of the Maillard reaction. Reactive carbonyl groups of a reducing sugar react with neutrophilic free amino groups of proteins to form a reversible Schiff base. Through rearrangement a more stable Amadori product is formed. Dependent on the nature of these early glycation end products, protein adducts or protein crosslinks are formed.

The aim of this work is to critically review the existing literature on AGEs and provide evidence that they play an important role in the pathogenesis of skin aging. Furthermore, existing and potential strategies against the deleterious effects of AGEs on skin aging will be discussed.

Biochemistry of AGEs

Glycation is the non-enzymatic reaction between reducing sugars, such as glucose, and proteins, lipids or nucleic acids.[13] Glycation has to be distinguished from glycosylation, which is an enzymatic reaction. Since its first description by Maillard in 1912 and its involvement in food browning during thermal processing by Hodge 50 years later, its presence in living systems and involvement in various pathologies of the human body, including aging and diabetes, have been an intensive field of research.[14,15]

Formation of AGEs is a complicated molecular process involving simple and more complex multistep reactions. During the classical Maillard reaction electrophilic carbonyl groups of glucose or other reactive sugars react with free amino groups of amino acids (especially of basic lysine or arginine residues), forming a non-stable Schiff base.[16] Further rearrangement leads to formation of a more stable ketoamine (Amadori product) (**Fig. 1**).[13,16] Schiff bases and Amadori products are reversible reaction products. However, they can react irreversibly with amino acid residues of peptides or proteins to form protein adducts or protein crosslinks.[13,16] Alternatively, they can undergo further oxidation, dehydration, polymerization and oxidative breakdown reactions to give rise to numerous other AGEs.[13,17] Oxygen, reactive oxygen species (ROS) and redox active transition metals accelerate AGE formation. When an oxidative step is involved, the products are called advanced glycoxidation end products.[13,17]

AGEs are a very heterogeneous group of molecules. Since the discovery of the first glycated protein, glycated hemoglobin in diabetes, numerous other AGEs have been detected. Some of them have characteristic autofluorescent properties, which simplifies their identification in situ or in vivo.[13] To date, numerous AGEs have been identified. **Table 1** lists the most commonly found ones in the skin.[17-28]

Carboxymethyl-lysine (CML) was first described by Ahmed and represents the most prevalent AGE in vivo.[29,30] It is a non-fluorescent protein adduct. Mechanisms of its formation include oxidative degradation of Amadori products or direct addition of glyoxal to lysine. It seems to be the major epitope of the commonly used polyclonal anti-AGE antibodies.[30]

Pentosidine was first isolated and characterized by Sell and Monnier. It is composed of an arginine and a lysine residue crosslinked to a pentose.[31] Pentosidine is a fluorescent glycoxidation product and forms protein-protein crosslinks.[16]

Dicarbonyl compounds like 3-deoxyglucosome, methylglyoxal and glyoxal derive from oxidative degradation or autooxidation of Amadori products and other pathways.[13,32] These dicarbonyl compounds are very reactive molecules leading to protein crosslinks.[13] Other in vivo characterized AGEs include glucosepane, carboxymethyl-hydroxy-lysine, carboxyethyl-lysine (CEL), fructose-lysine, methylglyoxal-derived hydroimidazolones and pyrraline, which form non-fluorescent protein adducts, while glyoxal-lysine dimer (GOLD) and methylglyoxal-lysine dimer (MOLD) form non-fluorescent protein crosslinks.[13,17]

AGEs can be exogenously ingested (through food consumption) or be endogenously produced. Endogenous AGE formation is increased in diabetes; however, AGEs are also formed at lower rates by normal metabolic processes of the organism.[33] Environmental factors, such as diet and smoking influence the rate of AGE formation.[34] Moreover, it seems that the level of circulating AGEs levels are genetically determined, as shown in a cohort study of healthy monozygotic and heterozygotic twins.[35]

The content of AGEs in the organism is not only defined by the rate of their formation but also by the rate of their removal. Many cells have developed intrinsic detoxifying pathways against accumulation of AGEs.[36] The glutathione-dependent glyoxalase system, comprising of glyoxalase (Glo) I and II, has a key role in the defense against glycation.[37] This system uses reduced glutathione (GSH) to catalyze the conversion of glyoxal, methylglyoxal and other α-oxoaldehydes to the less toxic D-lactate.[37] Other enzymatic systems include fructosyl-amine oxidases (FAOXs) and fructosamine kinases, relatively new classes of enzymes which recognize and break Amadori products.[38] However, FAOXs or "amadoriases" have been found to be expressed only in bacteria, yeast and fungi but not in mammals.

Table 1. Detected AGEs in skin*

AGE	Skin compartments involved	Targets of glycation	Methods of detection
CML	Epidermis[18] Aged and diabetic dermis[19-22] Photoaging–actinic elastosis[20,23]	Epidermis (SC -CK10, SS, SG)[18] Collagen[19-21] Vimentin[22] Elastin[20,23]	LC-ESI-TOF-MS, IF, IB[18] SIM/GC-MS[19,21] IHC[20,22,23] ELISA,[23] confocal microscopy[23]
Pentosidin	Aged and diabetic dermis[19,24,25]	Collagen[19,24,25]	Reversed-phase HPLC,[19,24] ELISA,[25] IB[25]
GO	Aged dermis[21]	Collagen[21]	LC/MS[21]
MGO	Aged dermis[21]	Collagen[21]	LC/MS[21]
Glucosepane	Aged dermis[21,26]	Collagen[21,26]	LC/MS[21,26]
Fructoselysine	Aged dermis[21]	Collagen[21]	LC/MS[21]
CEL	Aged dermis[21,27]	Collagen[21,27]	LC/MS[27] SIM/GC-MS[21]
GOLD	Aged dermis[28]	Collagen[28]	LC/MS[28]
MOLD	Aged dermis[28]	Collagen[28]	LC/MS[28]

ELISA, enzyme-linked immunosorbent assay; GO, glyoxal; HPLC, high performance liquid chromatography; IHC, immunohistochemistry; IB, immunoblotting; IF, immunofluorescence; LC-ESI-TOF-MS, liquid chromatography–electrospray ionization time-of-flight mass spectrometry; LC/MS, liquid chromatography/mass spectrometry; MGO, methylglyoxal; SIM/GC-MS, selected ion monitoring gas chromatography-mass spectrometry; SC, stratum corneum; SG, stratum granulosum; SS, stratum spinosum; all other abbreviations are already explained in the text.

They oxidatively break Amadori products but act mostly on low molecular weight compounds.[39] On the contrary, fructosamine kinases are expressed in various genomes including humans.[38] These intracellular enzymes phosphorylate and destabilize Amadori products leading to their spontaneous breakdown.[39] Fructosamine-3-kinase (FN3K), one of the most studied enzymes in this system, is almost ubiquitary expressed in human tissues including the skin. Thus, it plays an important role in the intracellular breakdown of Amadori products.[40]

Receptors for AGEs

AGEs not only exert their deleterious actions due to their biological properties per se, but also through their interaction with specific receptors. Receptor for AGEs (RAGE) is a multiligand member of the immunoglobulin superfamily of cell surface receptors, encoded by a gene on chromosome 6 near the major histocompatibility complex III. It is a pattern recognition receptor binding in addition to AGEs various other molecules such as S-100/calgranulins, high motility group protein B1 (amphoterine), β-amyloid peptides and β-sheet fibrils.[33,41] The binding of ligands to RAGE stimulates various signaling pathways including the mitogen-activated protein kinases (MAPKs) extracellular signal-regulated kinases (ERK) 1 and 2, phosphatidyl-inositol 3 kinase, $p21^{Ras}$, stress-activated protein kinase/c-Jun-N-terminal kinase and the janus kinases.[33,41] Stimulation of RAGE results in activation of the transcription factor nuclear factor kappa-B (NFκB) and subsequent transcription of many proinflammatory genes.[41,42] Interestingly, RAGE-induced activation of NFκB is characterized by a sustained and self-perpetuating action, through induction of positive feedback loops and overwhelming of the autoregulatory negative feedback loops. RAGE activation leads to new synthesis of the transcriptionally active subunit p65, which overwhelms the newly synthesized inhibitor IκBα. Moreover NFκB increases further expression of RAGE, which itself further stimulates NFκB, forming a vicious cycle of self-renewing and perpetuating proinflammatory signals.[41] RAGE activation can directly induce oxidative stress by activating nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase (NOX), decreasing activity of superoxide dismutase (SOD), catalase and other pathways, and indirectly by reducing cellular antioxidant defenses, like GSH and ascorbic acid.[41,43,44] The reduction of GSH leads furthermore to decreased activity of Glo I, the major cellular defense system against methylglyoxal, therefore supporting further production of AGEs.[37] RAGE is almost ubiquitary expressed in the organism, typically at low levels, and its expression is upregulated under various pathologic conditions.[41,45] In the skin, RAGE expression was observed in both epidermis and dermis, and it was increased in sun-exposed compared with UV irradiation-protected areas. Keratinocytes, fibroblasts, dendritic cells and to a lesser extent endothelial cells and lymphocytes express RAGE.[45] Not only in vivo, but also in vitro, various skin cells types have been shown to express RAGE (**Table 2**).[43,45-51]

RAGE is the most studied receptor for advanced glycation end products. Another group of cell surface receptors, AGER1, AGER2 and AGER3 seem to regulate endocytosis and degradation of AGEs, thus counteracting the effects of RAGE.[52] AGER1 has been further shown to counteract AGEs-induced oxidative stress via inhibition of RAGE signaling.[53,54] Soluble RAGE (sRAGE) is a truncated splice variant of RAGE containing the ligand-binding domain but not the transmembrane domain and has been found in plasma. sRAGE is a soluble extracellular protein without signaling properties and it is considered as a natural decoy receptor of RAGE.[55]

Role of AGEs During Skin Aging

Cutaneous accumulation of AGEs is a feature of skin aging. As mentioned above, AGEs can be directly formed in the organism

Table 2. Expression of human RAGE in skin and skin cells*

Skin in situ	Methods of detection
Young donors:	
High and middle epidermis	
Papillary dermis	
Old donors:	IHC[45,46]
Middle and basal epidermis	
Reticular dermis	
Enhanced expression in sun-exposed skin	
Skin cell types in vivo	
Fibroblasts	
Dendric cells	IHC[45,46]
Keratinocytes	
Endothelial cells	
Mononuclear cells	
Cell types in vitro	
Resident skin cells	
Keratinocytes	qRT-PCR,[46] WB[47]
Fibroblasts	WB,[43,45] qRT-PCR[43,45]
Melanocytes	?
Immune cells and other cell types	
Mononuclear phagocytes[48]	WB,[48] IF[48]
Dendritic cells[49]	FC[49]
T-lymphocytes[50]	qRT-PCR[50]
Vascular dermal endothelial cells	qRT-PCR,[51] WB[51]

FC, flow cytometry; IHC, immunohistochemistry; IF, immunofluorescence; qRT-PCR, quantitative real-time PCR; all other abbreviations are already explained in the text.

or be exogenously ingested. Accumulation of AGEs has been detected in various tissues during aging and diabetes, including articular collagen, skeletal and smooth vascular muscles or glomerular basement membranes.[56-58] Accordingly, deposited AGEs in these tissues have been implicated in various diabetes- or age-associated pathologies such as diabetic angiopathy, age- and diabetes-associated macular degeneration and osteoarthritis.[56-62]

Skin, due to its easy accessibility, offers an excellent opportunity for minimal invasive or even non-invasive investigation of glycation, taking advantage of the characteristic autofluorescent properties of AGEs. Accumulation of AGEs in the skin has been therefore thoroughly studied and is detected not only in diabetes as expected but also during chronological aging.[20,63,64] Glycation-associated skin autofluorescence was shown to correlate with chronological aging in a large number of healthy subjects.[65]

It is a general perception today that AGE accumulation is dependent on protein turnover rate; therefore long-lived proteins are thought to be mainly modified by glycation.[66] Collagen types I and IV, exhibiting a slow turnover rate of about 10 y, and other dermal long-lived proteins like fibronectin mainly suffer from glycation during intrinsic chronological aging.[19,20] The appearance of glycated collagen is first observed at the age of 20. It accumulates with a yearly rate of about 3.7% reaching a 30–50% increase at 80 y of age.[20,67] CML was recently histochemically detected in human epidermis from healthy donors.[18] The upper epidermal layers were mostly involved (stratum spinosum, granulosum and corneum) and the authors identified cytokeratin 10 (CK10) (expressed by differentiated keratinocytes) as a target protein for CML modification. The amount of CML in younger donors seemed to be weak in comparison to the older ones. The latter study had restrictions, as the size of the sample was small and heterogeneous, but indicates a potential involvement of AGEs in epidermal physiology and a possible involvement of more short-lived proteins in glycation chemistry. Moreover, in an in vitro reconstructed organ skin model, both epidermis and dermis, as well as their functions, were modified by glycation.[68]

AGEs also seem to highly accumulate in extrinsically aged skin. Until now, the deleterious effects of UV irradiation have been mainly attributed to proinflammatory changes, apoptosis, oxidative damage, mutagenesis and induction of MMPs.[2,5] However, it has been shown that in young individuals, where typically no significant accumulation of AGEs in sun-protected skin is observed, sun-exposed areas display an increased deposition of these substances.[20,69] Accumulation of AGEs was mainly found in sites of solar elastosis in sun-exposed skin, showing that UV irradiation may also precipitate the formation of AGEs in vivo.[20,23] It is tempting to speculate that formation of AGEs in sun-exposed skin may be one additional mechanism mediating the various structural and functional modifications during photoaging.

Moreover, smoking, a typical aggravating factor of skin aging, accelerates formation of AGEs and increases their deposition in various tissues including skin.[70,71] Another important environmental factor for aging is diet. The content of AGEs in food is highly dependent on the method of preparation, like cooking time and temperature. Fried food contains in general far higher amounts of AGEs than boiled or steamed food.[72] Approximately 10–30% of ingested AGEs are absorbed in the circulation.[73] Dietary AGEs directly correlate with serum levels of AGEs and inflammatory markers in healthy human subjects, respectively.[73]

It has been widely accepted that AGEs, once formed, can be only removed when the modified proteins degrade. However it has now become apparent that in the organism various enzymatic systems seem to be involved in the degradation or removal of AGEs. As mentioned above, Glo I is an enzyme responsible for the removal of reactive α-dicarbonyl compounds. Interestingly, decreased activity of such defense systems against AGEs has been reported during aging.[44] These age-related changes may further increase the extent of deposited AGEs in a living organism over time.

Consequences of AGE deposition in skin. AGEs can be formed intracellularly and extracellularly. Their presence in biological molecules modifies their biomechanical and functional properties. Proteins, lipids and nucleic acids can be targets of advanced glycation, modifying enzyme-substrate interactions, protein-DNA interactions, protein-protein interactions, DNA regulation and epigenetic modulation, thus interfering with numerous physiological functions of the organism. Moreover, AGEs are themselves reactive molecules which through interaction with their receptors activate various molecular pathways in vivo, thus becoming involved in inflammation, immune response, cell proliferation and gene expression (**Fig. 2**).

1. Extracellular matrix proteins. Extracellular matrix (ECM) proteins have been regarded as one of the major target

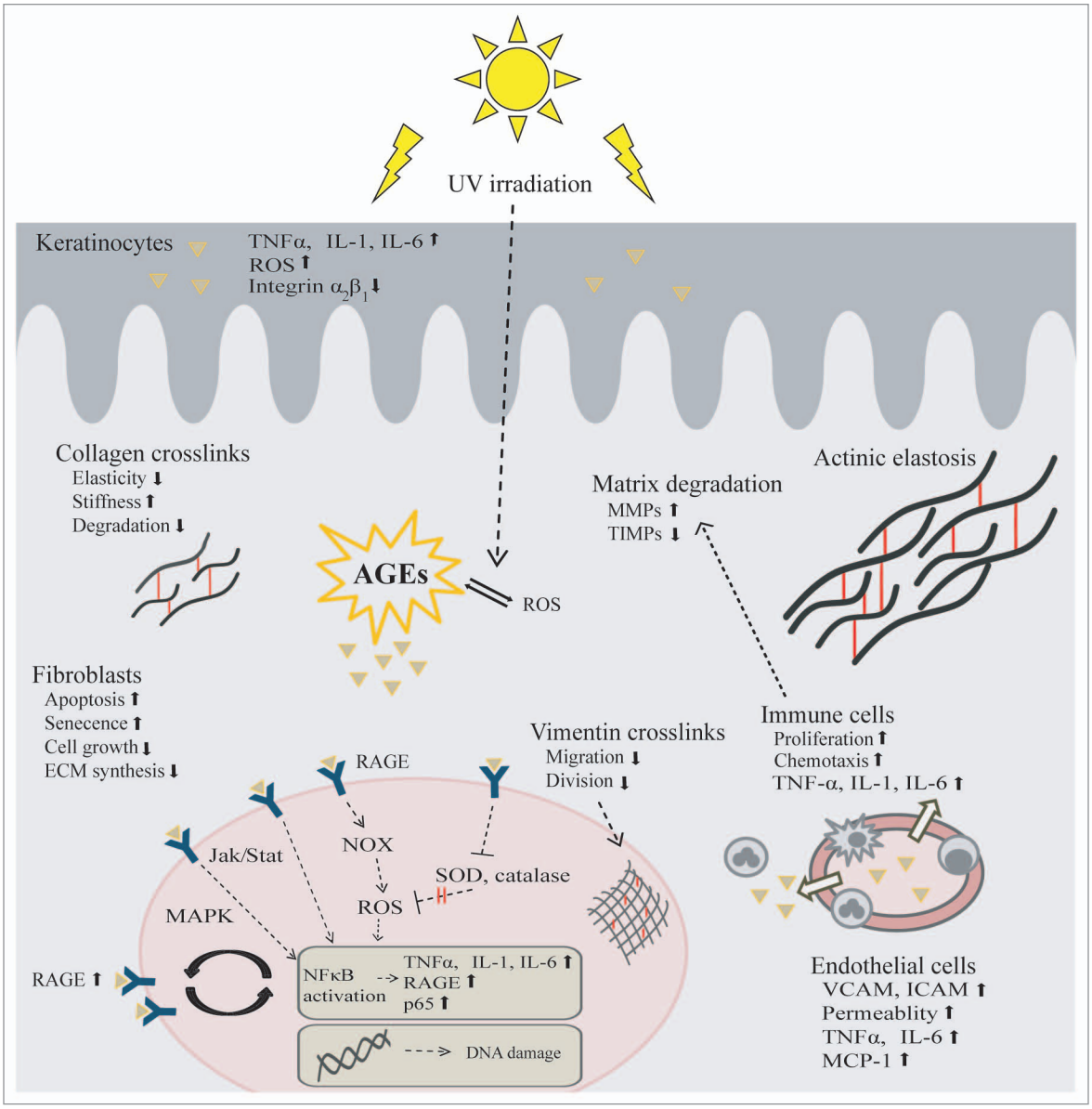

Figure 2. Effects of AGEs on skin. AGEs are formed intracellularly and extracellularly. They can react with proteins, lipids and nucleic acids in almost all skin cells as well as on intracellular or extracellular proteins. Through alteration of the physicochemical properties of dermal proteins, decreased cell proliferation, increased apoptosis and senescence, induction of oxidative stress and proinflammatory mediators as well as other pathways, AGEs contribute to the overall picture of skin aging. Triangles represent AGEs. Abbreviations: jak/stat, januskinase/signal transducers and activators of transcription; MCP-1, monocyte chemotactic protein-1; all other abbreviations are already explained in the text.

structures for glycation. The most abundant collagen type in the skin is type I, whereas collagen IV is being found in the basal membrane. Collagen is one of the strongest proteins. In the skin, it is not only used as a supportive framework for mechanical support for cells and tissues, but represents an active component being able to interact with cells and affect various cellular functions such as migration, differentiation and proliferation.

Collagen glycation impairs its function in various ways. Intermolecular crosslinks of adjacent collagen fibers change its biomechanical properties leading to stiffness and decreased flexibility, thus increasing its susceptibility to mechanical stimuli.[74] The change of its charge and the formation of AGEs on side chains of collagen affect its contact sites with cells and other matrix proteins and inhibit its ability to react with them.[75] The precise aggregation of monomers into the triple helix may be affected as well as the association of collagen IV with laminin in the basal membrane.[16] Modified collagen resists degradation by MMPs, thus inhibiting its removal and replacement by newly synthesized and functional one.[62] Accordingly, tissue permeability and turnover is impaired.[16,76]

Other extracellular matrix proteins suffering from advanced glycation are elastin and fibronectin, contributing further to dermal dysfunction.[19,20,23] Of note, CML-modified elastin has been

Table 3. Effects of AGEs/RAGE on skin morphology and physiology during aging*

Keratinocytes	Proliferation ↓[84] Apoptosis ↑[47] ROS ↑[85] MMP ↑[9], TIPM ↓[84] Senescence ↑[86] NFκB, proinflammatory mediators ↑[81] α2β1-integrin ↓[84]	Cell renewal ↓ Epidermal homeostasis ↓
Fibroblasts	Proliferation ↓[87] Apoptosis ↑[87] ECM synthesis ↓[88] MMP ↑[88] Senescence ↑[89,90] NFκB ↑[87] ROS ↑[43,85,90] Contractile properties ↓[22] NOX ↑[43]	Cell renewal ↓ Dermal homeostasis ↓ Skin contractile function ↓
Melanocytes	?	?
Immune cells	Proliferation ↑[50] Haptotaxis, chemotaxis ↑[48] NFκB, TNFα, IL-1, IL-6 ↑[42,49]	Induction and propagation of inflammation
Extracellular matrix proteins (collagen, fibronectin, elastin)	Crosslinking[16,19,20,23,76] Resistance to MMP degradation[62,76] Impaired assembly of macromolecules to normal 3D structures[16,76-78] Defect cross-talking to cells[75,76]	Elasticity ↓ Stiffness ↑ Resistance to repair mechanisms Tissue permeability ↓
Vascular endothelial cells	VCAM, ICAM, E-selectin ↑[91] Permeability ↑[91] TNFα, IL-6 ↑[91] MCP-1 ↑[91]	Induction of proinflammatory mediators and recruitment of immune cells

ICAM, intercellular adhesion molecule; MCP-1, monocyte chemotactic protein-1; TIPM, tissue inhibitor of MMP; VCAM, vascular cell adhesion molecule; all other abbreviations are already explained in the text.

found almost exclusively in sites of actinic elastosis and not in sun-protected skin, underlining its potential role in photoaging. Indeed, UV irradiation stimulates glycation of elastin in the presence of sugars. Moreover, CML-modified elastin assembled in large and irregular structures, has decreased elasticity and is resistant to proteolytic degradation.[77]

It has been shown that in vitro glycated skin samples have impaired biomechanical properties.[78] In vivo, decreased skin elasticity characterizes diabetic subjects in comparison to healthy controls.[79]

2. Intracellular proteins. Intermediate filaments such as vimentin in fibroblasts and CK10 in keratinocytes have been found to be modified by AGEs.[18,22] Cytoskeletal proteins are important in providing stability of the cytoskeleton and are crucially involved in numerous cellular functions such as migration and cellular division. Various other intracellular proteins including enzymes and growth factors may be targets of non-enzymatic modification by sugars. Glycated basic fibroblast growth factor (bFGF) displays impaired mitogenic activity in endothelial cells.[80] Glycation of enzymes of the ubiquitin-proteasome system and of the lysosomal proteolytic system has been shown to inhibit their action.[81] Antioxidant and other protective enzymes such as Cu-Zn-SOD can be inactivated.[82] Other intracellular components, such as DNA and lipids can be glycated with detrimental effects on their function.[13,83]

3. Receptors for AGEs: RAGE. AGEs do not only act by altering the physicochemical properties of glycated proteins. As mentioned above, AGEs may bind to their cell surface receptor, RAGE, initiating a cascade of signals influencing cell cycle and proliferation, gene expression, inflammation and extracellular matrix synthesis (reviewed in Bierhaus et al.).[41] Interestingly, RAGE is broadly expressed in human skin and in epidermal keratinocytes, dermal fibroblasts and endothelial cells in vitro. It is highly found in sites of solar elastosis, and its expression is induced by advanced glycation end products and proinflammatory cytokines like TNFα.[45] In skin cells RAGE has been shown to decrease cell proliferation, induce apoptosis and increase MMPs production.[47] Many of these effects involve NFκB signaling.[47]

4. Effects of AGEs on resident skin cells. AGEs have been shown to affect various functions of skin cells in vitro (**Table 3**). They decrease proliferation and enhance apoptosis of human dermal fibroblasts, an effect which is at least partly RAGE-dependent and correlates with the activation of NFκB and caspases.[87] In keratinocytes, AGEs decrease cell viability and migration and induce the expression of proinflammatory mediators.[84] Moreover, AGEs are able to induce premature senescence in human dermal fibroblasts and in normal human keratinocytes in vitro.[86,89,90] Collagen and ECM protein synthesis have been also found to be decreased, while the expression of

MMPs is induced.[47] Dicarbonyls such as glyoxal and methylglyoxal impair the signaling of epidermal growth factor receptor (EGFR), a receptor controlling various cellular functions such as proliferation, differentiation, motility and survival, by formation of EGFR crosslinks, blocking of phosphorylation and impaired activation of ERKs and phospholipase C.[92] Various other growth factors or proteins significant for cellular functions, like bFGF, may be glycated inhibiting their functions.[80] In the context of extrinsic aging, AGEs seem to render cells more sensitive to external stimuli, as UVA irradiated fibroblasts and keratinocytes exhibit decreased viability after exposure to AGEs.[85,93]

5. The role of oxidative stress. Oxidative stress has been widely accepted to mediate the deleterious effects of solar radiation in the skin during photoaging. Interestingly, in vitro exposure of AGEs to UVA irradiation leads to formation of ROS, such as superoxide anion, hydrogen peroxide and hydroxyl radicals.[93] AGEs can lead to ROS formation in cells by various ways. They can stimulate NOX to induce production of superoxide anion or they can compromise cellular antioxidant defense systems, e.g. inactivation of Cu-Zn-SOD by cross-linking and site-specific fragmentation of this molecule.[82] Moreover, AGEs are themselves very reactive molecules. As early as during their crosslinking reactions they can act as electron donors leading to formation of superoxide anions.[94] Glycation of proteins creates active enzyme-like centers (cation-radical sites of crosslinked proteins) able to catalyze one-electron oxidation-reduction reactions leading to ROS generation with or without presence of oxygen or transition metals such as iron and copper.[94-96]

Finally, autofluorescent AGEs, such as pentosidine, can act as endogenous photosensitizers leading to increased ROS formation after UVA irradiation of human skin.[97] UV irradiation of human keratinocytes and fibroblasts in the presence of AGEs led to increased ROS formation and decreased proliferation in vitro.[85]

6. Skin AGEs as biomarkers of aging. As AGEs have been etiologically implicated in aging and aging-related pathologies, the idea of using them as biomarkers is appealing. AGEs in the skin have been initially measured by western blots (WB) with polyclonal antibodies or by autofluorescence measurements of skin biopsies, thus restricting the wide use of these measurements. An AGE-Reader (DiagnOptics B.V., Groningen, The Netherlands) has been introduced some years ago as a new, non-invasive method to measure in vivo the skin content of AGEs based on their characteristic autofluorescence.[98-100]

Until now it has been shown that skin autofluorescence positively correlates with various diabetes- and age-related complications such as micro- and macrovascular complications, renal disease, cardiovascular events, overall mortality, age-related macular degeneration and chronic renal disease.[99,101,102] Skin glycation has been proposed as a prognostic factor for the development of diabetic complications.[103] Lately it was shown that skin autofluorescence increases with chronological aging and correlates with skin deposition of AGEs, making this method a potential tool in investigating the effect of various anti-aging products of the cosmetic industry.[104]

Anti-AGE Strategies: Current Knowledge and Future Perspectives

Since the emergence of AGEs as an important pathogenetic factor in diabetes and aging the development of strategies against AGEs has been in the center of scientific interest. Substances able to prevent or inhibit formation of AGEs, as well as agents able to break already formed AGEs or those antagonizing their signaling have been identified. Some of them are already being tested in clinical trials.[105,106]

1. Substances preventing or inhibiting AGE formation. Aminoguanidine was one of the first substances identified limiting the formation of AGEs.[107] Aminoguanidine is a nucleophilic hydrazine and its anti-AGE properties result from trapping of early glycation products such as carbonyl intermediate compounds. It has no effects on more advanced stages of glycation. Despite its potential effects in attenuating various diabetes- and age-related complications in animal models, its use in clinical practice is limited due to adverse effects in clinical trials with diabetic patients.[108] In an in vitro skin aging model it could attenuate collagen glycation, however its effects against AGE-induced collagen modification in vivo have been contradictory.[109-111] Studies on topical application of aminoguanidine in the skin are lacking.

Pyridoxamine, a naturally occurring vitamin B_6 isoform, seems to be another tool in the fight against AGEs. Pyridoxamine traps reactive carbonyl intermediates, scavenges ROS and in addition inhibits post-Amadori stages of AGE formation.[112] It has shown promising results in a phase II clinical trial against diabetic nephropathy.[113] Oral intake of pyridoxamine resulted in potent inhibition of skin collagen CML formation in diabetic rats.[111] However, its potential against skin aging remains to be shown.

2. "AGE breakers." Chemical substances and enzymes able to recognize and break the Maillard reaction crosslinks have been identified. Such chemical AGE breakers are dimethyl-3-phenacyl-thiazolium chloride (ALT-711), N-phenacylthiazolium and N-phenacyl-4,5-dimethylthiazolium.[113] They have been developed to chemically break the prototypical Maillard reaction crosslink via a thiazolium structure.[113] Promising results against cardiovascular complications in diabetes and aging have been reported, although their actual ability to cleave existing protein crosslinks in tissues has been questioned.[114-117] In the rat ALT-711 showed some promising results on skin hydration.[113]

Interference with intrinsic AGE-detoxifying enzymes like FAOXs, FN3K and the enzymatic system of Glo is another interesting strategy to remove AGEs, as enzymes recognize specific substrates and may be associated with fewer side effects.[37,38,118] There are a lot of data supporting the significance of these enzyme systems in aging. As noted above decreased Glo I activity and increased accumulation of AGEs with age have been shown in many tissues and animals.[37] Overexpression of Glo I significantly inhibits hyperglycemia-induced intracellular formation of AGEs in bovine aortic endothelial cells and in mouse mesangial cells by reduction of intracellular oxidative stress and apoptosis.[119,120] A potential in vivo beneficial

effect of Glo I against AGEs could be also shown in transgenic rats.[121] Interestingly, it has been recently shown that Glo I is transcriptionally controlled by Nrf2, and that pharmacological Nrf2 activators increase Glo I mRNA and protein levels as well as its activity.[122] The pharmacological induction of such enzymes could represent a novel future strategy against AGEs. Fructosamine phosphokinases are relatively new enzymes and currently under investigation, and until now no inductors or activators of their expression have been found.[40] FAOXs, on the other hand, are not expressed in mammals, and their potential use in humans by enzymatic engineering remains to be discovered.[39]

3. Nutriceuticals. Since oxidation steps are crucially involved in formation of many AGEs, substances with antioxidative or metal chelating properties, may also have antiglycating activities.[123] Thus, a lot of interest has been directed to nutrients and vitamins, so called "nutriceuticals," as natural tools against AGEs.[106,124]

Accordingly, an increasing list of natural antioxidants and chelating agents such as ascorbic acid, α-tocopherol, niacinamide, pyridoxal, sodium selenite, selenium yeast, trolox, rivoflavin, zink and manganese has been shown to inhibit glycation of albumin in vitro.[125] Alpha-lipoic acid was able to reverse tail tendon collagen glycation in fructose-fed rats, an effect which was attributed to its endogenous antioxidant action, its ability to recycle ascorbic acid, α-tocopherol and GSH as well as to its positive influence on glucose uptake and glycaemia.[126] Green tea, vitamins C and E and a combination of N-acetylcystein with taurine and oxerutin could inhibit skin collagen glycation in mice.[124,127] Another compound, the green tea-derived polyphenol and flavonoid epigallocatechin-3-gallate revealed also promising in vitro effects by antagonizing AGE-induced proinflammatory changes.[128] In healthy human subjects, supplementation of vitamin C significantly decreased serum protein glycation.[129]

Many spices and herbs were shown to inhibit glycation of albumin in vitro, among them ginger, cinnamon, cloves, -marjoram, rosemary and tarragon.[130] Their protective effects correlated with their phenolic content. Recently, in vivo beneficial effects of some of these compounds were shown in zebrafish.[131]

Other promising compounds include blueberry extract and naturally occurring flavonoids, such as luteolin, quercetin and rutin, which can inhibit various stages of AGE formation.[132,133] Recently, blueberry extract, an AGE-inhibitor and C-xyloside, a glycosaminoglycan synthesis stimulator, were tested for 12 weeks in female diabetic subjects. This treatment resulted in significant improvement of skin firmness, wrinkles and hydration although it failed to show a significant decrease in the cutaneous content of AGEs.[132]

4. Caloric restriction and dietary measures. As nutrition is an important factor in skin aging, dietary caloric restriction may be effective in preventing accumulation of AGEs in the human body. In mice restriction of caloric intake increases lifespan and delays many age-related dysfunctions by altering stress response and influencing the expression of various metabolic and biosynthetic genes.[134] Dietary restriction could significantly decrease the levels of AGEs in rat and mice skin collagen.[135,136] Skin collagen glycation and glycoxidation inversely correlated with lifespan whereas caloric restriction led to decreased accumulation of AGEs and increased lifespan.[137] Dietary restriction may not be a pragmatic option in humans; however a restriction in intake of dietary "glycotoxins" may be more feasible. As outlined above these dietary glycotoxins derive from nutrition. In humans dietary glycotoxins significantly increase concentrations of systemic inflammatory mediators like TNFα, interleukin (IL)-6 and C-reactive protein and are thus considered as diabetogenic, nephrotoxic and proatherogenic.[59,138,139] Dietary intake of AGEs correlates with serum AGEs and can induce systemic oxidative stress, increase RAGE expression, decrease antioxidant levels and shorten lifespan in mice.[54] A diet with a low content in AGEs could reduce circulating AGEs and inflammatory biomarkers in patients with diabetes and renal failure thus seeming to be an important supportive therapy in diabetes.[140,141] In mice low dietary AGEs had beneficial effects in wound healing and other diabetes mellitus-associated pathologies.[142] There are no studies investigating the effects of AGE-poor diets on skin aging in humans. However, it has been shown that skin collagen glycation positively correlates with blood glucose levels in diabetes and that intensive treatment can reduce the levels of skin glycation, implicating that a diet low in AGEs may have a beneficial effect on skin glycation.[143,144]

5. Targeting RAGE. Another potential strategy against excessive accumulation of AGEs could be the antagonism of RAGE.[145] Possible approaches include gene knock-down of RAGE by siRNA or anti-sense and antagonism of RAGE with putative small molecular inhibitors against RAGE-induced signaling.[50,145] Promising effects in various systems have been shown in vitro and in vivo with neutralizing anti-RAGE antibodies.[41] Since serum concentrations of sRAGE negatively correlate with AGE-induced pathologies, neutralization of AGEs by these decoy receptors of RAGE may be considered as another anti-AGE strategy. Potential protective effects of sRAGE have been shown in various diabetes and inflammatory models.[41,44,45,146] Interestingly, sRAGE could also attenuate impaired wound healing in diabetic mice. Therefore, studies will be needed to investigate an analogous effect on skin aging.[147]

6. Others. Molecular chaperones like carnosine have lately shown promise in improving skin appearance in various studies at least in part by reducing the amounts of skin AGEs.[148-150]

Conclusion

There is ample evidence that AGEs play an important role in skin aging. There are also numerous studies investigating potential substances against excessive accumulation of AGEs in tissues. Some of these studies have already shown protective effects against diabetic complications. As controlled human studies investigating the effects of these anti-AGE strategies against skin aging are largely missing, this is a hot field for future research.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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