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REVIEW

Maillard reaction and immunogenicity of protein therapeutics

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Abstract

The recombinant DNA technology enabled the production of a variety of human therapeutic proteins. Accumulated clinical experience, however, indicates that the formation of antibodies against such proteins is a general phenomenon rather than an exception. The immunogenicity of therapeutic proteins results in inefficient therapy and in the development of undesired, sometimes life-threatening, side reactions. The human proteins, designed for clinical application, usually have the same amino acid sequence as their native prototypes and it is not yet fully clear what the reasons for their immunogenicity are. In previous studies we have demonstrated for the first time that interferon-β (IFN-β) pharmaceuticals, used for treatment of patients with multiple sclerosis, do contain advanced glycation end products (AGEs) that contribute to IFN-β immunogenicity. AGEs are the final products of a chemical reaction known as the Maillard reaction or glycation, which implication in protein drugs' immunogenicity has been overlooked so far. Therefore, the aim of the present article is to provide a comprehensive overview on the Maillard reaction with emphasis on experimental data and theoretical consideration telling us why the Maillard reaction warrants special attention in the context of the well-documented protein drugs' immunogenicity.

Key words: Maillard reaction; Glycation; Advanced glycation end products; Protein therapeutics; Interferon-β; Immunogenicity

Core tip: The Maillard reaction occurs spontaneously in host cells and causes covalent modifications, proteolysis and crosslinking of therapeutic proteins. These are gross structural changes, which upon administration may provoke in patients classical type innate and adaptive

immune responses. The consequences of the Maillard reaction, however, reach far beyond. Specific and non-specific cellular receptors for the advanced products of the Maillard reaction may further enhance the immune response and elicit inflammation. All together the Maillard reaction actions are expected to result in drug neutralization and side effects in treated patients such as inflammatory and hypersensitivity reactions.

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INTRODUCTION

Protein pharmaceuticals are the major group of biopharmaceuticals used today in medicine for treatment of a large number of diseases. Accumulated clinical experience indicates that protein drugs can elicit an immune response especially when applied in multiple doses over a prolonged period. The antibodies (Abs) in treated patients are produced either by a classical immune response against non-self-antigens or by distortion of the immune tolerance[1]. The development of anti-drug Abs is a slow process, in which the frequency of occurrence and the titer of the antibodies vary widely from low levels in most cases to very high, for example during treatment with some interferon-β pharmaceuticals (IFN-β)[2]. The anti-drug Abs may have no clinical consequences[3-5]. However, some studies show that Abs may neutralize drug activity and that of the endogenous drug counterparts thus provoking severe complications in patients[6-8]. The most frequent side effects are flu-like symptoms and injection-site reactions[9,10], although cases of allergy, anaphylaxis and serum sickness have also been reported[11-16].

The amino acid sequence of therapeutic proteins may differ from that of the native human prototypes and such proteins are therefore recognized by the immune system as non-self. This was the case with porcine insulin used nearly 60 years (from 1920 to 1980) for treatment of diabetes. Porcine insulin differs by only one amino acid from human[17] but all patients treated with porcine insulin developed anti-insulin Abs[18]. To compensate for drug neutralization in such cases drug dosages are increased thus further boosting the immune response. The final result of such a vicious cycle is loss of therapeutic efficacy[19,20]. The deviation from the native protein structure may explain why insulin and other therapeutic proteins of animal origin are immunogenic. However, the production of human insulin by the recombinant DNA technology did not fully solve the problem with the immunogenicity. Interestingly, the deletion of Tyr-19 in human insulin resulted in reduced immunogenicity[21]. We suppose that this Tyr-residue might be involved in covalent aggregation of insulin *via* the formation of dityrosine crosslinks.

To date, the reasons for the immunogenicity of human proteins are not fully understood. The dose and duration of treatment, the route of drug administration and patients' inborn characteristics may modulate the immune response[22]. Excipient substances, used in drugs to stabilize proteins, may also be of particular relevance[23-25]. However, the reasons for immunogenicity are mainly attributed to protein structural changes occurring during fermentation, purification, drug formulation and storage, including amino acid substitutions, non-native (or lack of) glycosylation, proteolysis, aggregation (both covalent and non-covalent), denaturation, deamination and oxidation. Some of these structural alterations (covalent aggregation and proteolysis) may occur during the Maillard reaction, which relation to drugs' immunogenicity is poorly studied and has inspired us to write the current review.

MAILLARD REACTION AND MAILLARD REACTION PRODUCTS

At the beginning of the past century the French chemist Louis Camille Maillard conducted research on peptide synthesis[26]. At that time, when the mechanisms of protein biosynthesis were still a mystery, his far reaching goal was to understand the natural way of amino acid polymerization under mild physiological conditions. For this purpose Maillard used D-glucose, a widespread sugar in biological systems, as a soft condensing agent. Thus he realized that glucose, through its aldehyde group, is capable of reacting with amino acids[26]. In this way Maillard did not only make a contribution to basic organic chemistry but ingeniously predicted that "The consequences of these facts appear… interesting in various fields of science: Not only in human physiology and pathology"[26].

The significance of the Maillard reaction, known also as non-enzymatic browning reaction or carbonyl-amine reaction, for food chemistry was recognized soon. However, it took many years for biologists and physicians to grasp the physiological role of the Maillard reaction. Studies in the late 1960s revealed the existence of an abnormal fast-moving hemoglobin band in diabetic patients during routine electrophoretic screening for hemoglobin variants[27,28]. In the same year, it has been shown that the fast-moving hemoglobin subfraction HbA_{1c} can be prepared *in vitro* by incubation of hemoglobin with glucose in the absence of enzyme catalysts[29]. Later on, in the scientific lexicon were introduced the terms "non-enzymatic glycosylation" and "glycation" in order to distinguish the Maillard reaction, proceeding in biological systems, from

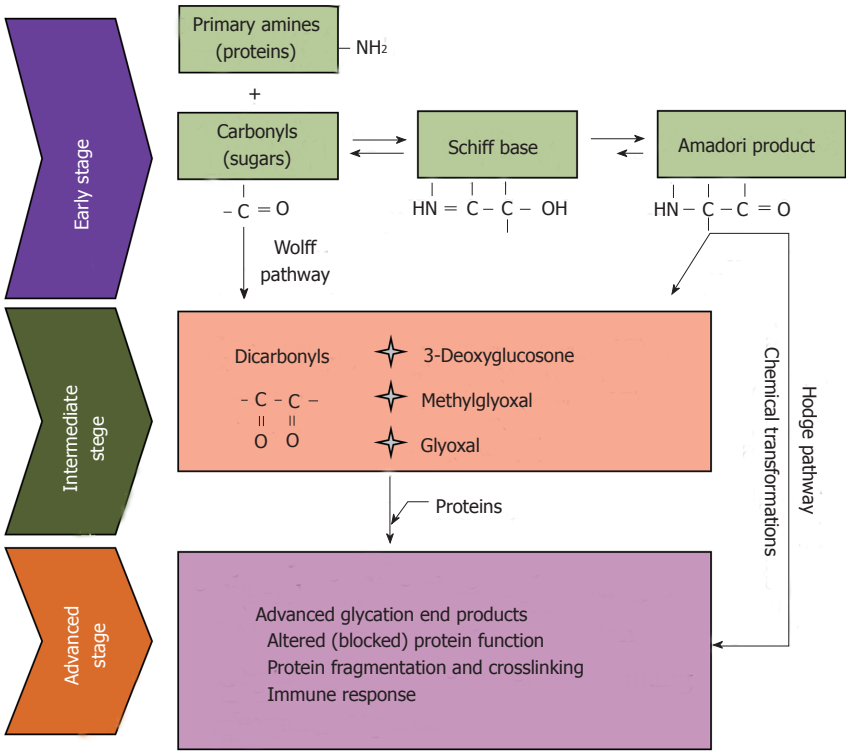

Figure 1 Maillard reaction.

the enzymatic glycosylation, which is a quite different, genetically programmed process. In the early 1980s, it has been hypothesized that glycation plays an important role in the pathogenesis of diabetic complications and aging[30,31]. Subsequently, this hypothesis found a plethora of experimental support, and many reviews have been dedicated to the link between glycation, diabetes and aging[32-38]. Although the carbonyl-amine reaction was discovered a century ago, its chemistry remains a still growing avenue of research. Two well defined stages can be distinguished in the Maillard reaction - early and advanced. The early stage includes reversible formation of Schiff bases between carbonyl and amino groups of the reactants, followed by a rearrangement of the Schiff bases to significantly more stable aldoamines (Amadori products) or ketamine (Heyns products) (Figure 1).

The early stage of the Maillard reaction is relatively well understood[39,40]. However, the same does not hold true for the chemical transformations of the Amadori and Heyns products into the so called advanced glycation end products (AGEs)[41]. Generally, these are dehydrogenation, dehydration, cyclization, condensation, isomerization, oxidation, and fragmentation reactions, taking place in the advanced stage of Maillard reaction. Under anaerobic conditions, AGEs are derived directly from the Amadori product. However, under aerobic conditions, oxidative degradation of the Amadori products takes place, leading to the generation of highly reactive dicarbonyl compounds such as glyoxal (G), methylglyoxal (MG) and 3-deoxyglucosone (3DG)[42,43]. This "interruption" between the early and the advanced stage is what we call the intermediate step of Maillard reaction. In turn, the intermediate products, which are small, diffusible and highly reactive species, again attack amino compounds, thus propagating the initial chemical burden. The formation of AGEs, either directly from the Amadori product or through its degradation intermediates, is known as the classical, or Hodge pathway[40]. The Schiff base, formed early in the Maillard reaction, may also undergo non-enzymatic fragmentation to α-oxoaldehydes, which initiate another chain of chemical transformations known as the Namiki pathway[44]. In addition, under physiological conditions free monosaccharides undergo a transition metal ions catalyzed autoxidation to H_2O_2 and the corresponding ketoaldehydes, which are precursors for AGEs formation in the Wolff pathway, also recognized as a separate reaction chain in the Maillard chemistry[45-47]. The picture becomes increasingly colorful, pasting therein the carbonyl products released during lipid peroxidation, which also react with amines to form AGEs-like structures called Advanced Lipoxidation End Products (ALEs)[48,49]. AGEs/ALEs are covalent adducts with diverse stability and physicochemical characteristics such as blue fluorescence, brown color and crosslinking properties. When accumulating in biological amines such as proteins, DNA and amino-lipids, AGEs may significantly impair their structure and physiological function. The chemical structure of a number of AGEs formed *in vitro* as well as in human plasma and tissues has been determined so far[50-57].

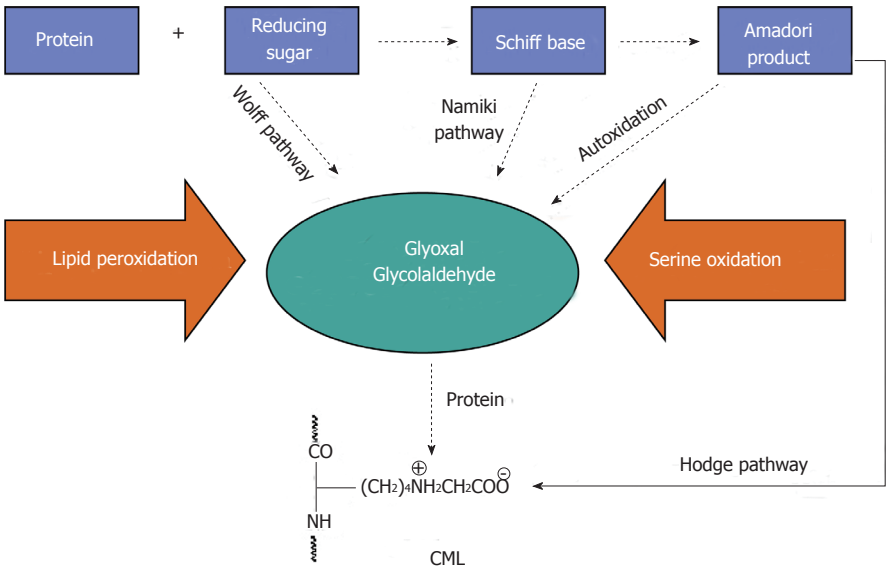

Figure 2 Pathways of N$^{\varepsilon}$-(carboxymethyl)lysine formation. CML: N$^{\varepsilon}$-(carboxymethyl)lysine.

N$^{\varepsilon}$-(carboxymethyl)lysine

N$^{\varepsilon}$-(carboxymethyl)lysine (CML) is one of the best-characterized AGEs[58]. It is formed in the advanced stage of the Maillard reaction and always accompanies the formation of brown and fluorescent AGEs, although *per se* it is colorless and non-fluorescent. If proteins are glycated with either ribose or 3DG, then CML is formed only when the reaction is carried out under aerobic conditions[52,59]. This is why the detection of CML is an indication that protein modifications have occurred in the presence of oxygen. CML is formed by different oxidation mechanisms *in vitro*, involving not only reducing sugars. It may also be a product of lipid peroxidation[48] and serine oxidation[60] (Figure 2), and because of that CML should not be considered a typical glycation marker. In most cases of *in vitro* glycation CML is the main product found in proteins[61], and is also a dominant AGEs antigen in tissue proteins[62]. Direct formation of CML from the Amadori product through its autoxidation has been reported by Miki Hayashi *et al*[63]. The authors used as a model of Amadori compound glycated human serum albumin (HSA) and found that CML is formed by heat treatment of glycated HSA over 80 ℃ in a time-dependent manner. Further rise in the temperature to 100 ℃ resulted in the formation of the glycation intermediates G, MG and 3DG. The formation of CML in HSA was inhibited in the presence of a reducing agent (sodium borohydride), a chelator of transition metal ions (diethylenetriamine pentaacetic acid), or a trapping reagent for a-oxoaldehydes (aminoguanidine), which indicates that CML (AGEs) accumulation in proteins is manageable.

Hydroimidazolones

Hydroimidazolones are formed in a reaction of the guanidino group of arginine with G, MG and 3DG[64-66]. The resulting products undergo structural and stereochemical isomerization, which were extensively studied by Ahmed *et al*[54,65]. The authors found that hydroimidazolones formed in the reaction of arginine with methylglyoxal (MG-H) are composed of three structural isomers designated as MG-H1, MG-H2 and MG-H3. The reaction of arginine with G and 3DG yielded similar structural isomers (Figure 3)[67]. Due to racemization in the hydroimidazolone ring, each structural isomer may exist in two epimiric forms, which cannot be resolved without prior derivatization. As a rule, the stability of hydroimidazolones decreases with increasing pH and each structural isomer has a distinctive stability and half-life. The half-life of the individual stereoisomers of MG-H increases in the following order: MG-H1 > MG-H2 >> MG-H3. Under physiological conditions (pH 7.4, 37 ℃) the half-life of MG-H1 is approximately 12 d. Ahmed *et al*[65] suggested that in contrast to CML, hydroimidazolones are not accumulating in long-lived proteins over time *in vivo* but rather reflecting short episodes of enhanced protein glycation under conditions of abnormal rise in the concentration of α-oxoaldehydes. The authors also assumed that Nω-(1-carboxyethyl)arginine and Nω-(1-carboxymethyl)arginine, which are more stable and found in *in vivo* glycated proteins, are probable degradation products of hydroimidazolones.

AGEs crosslinks

The Maillard reaction not only yields sugar adducts on proteins but also results in gross structural changes such as proteolysis[68-70], and intra- or inter-molecular crosslinking[71,72]. Proteolysis of glycated proteins usually occurs at lysine and arginine residues[73] but may also happen randomly as a result of transition metal ions catalyzed oxidation[68,69]. In contrast, covalent crosslinking of polypeptide chains involves exclusively lysine and arginine residues. Lysine residues on the

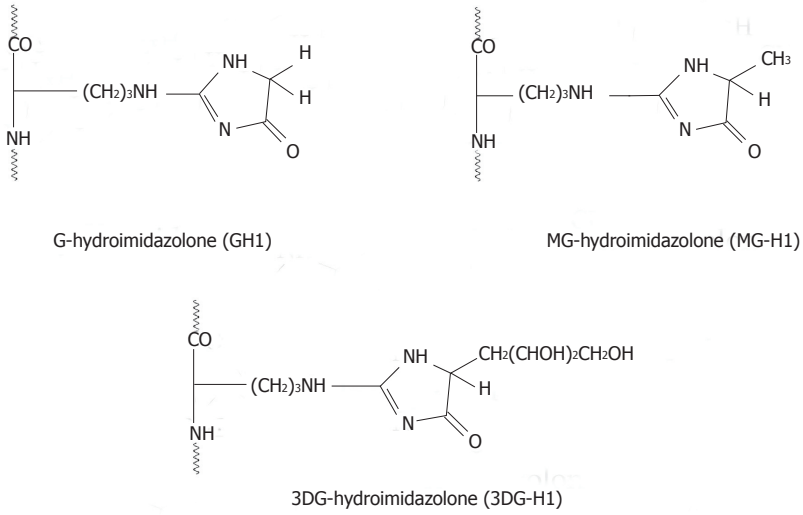

Figure 3 Hydroimidazolones[67].

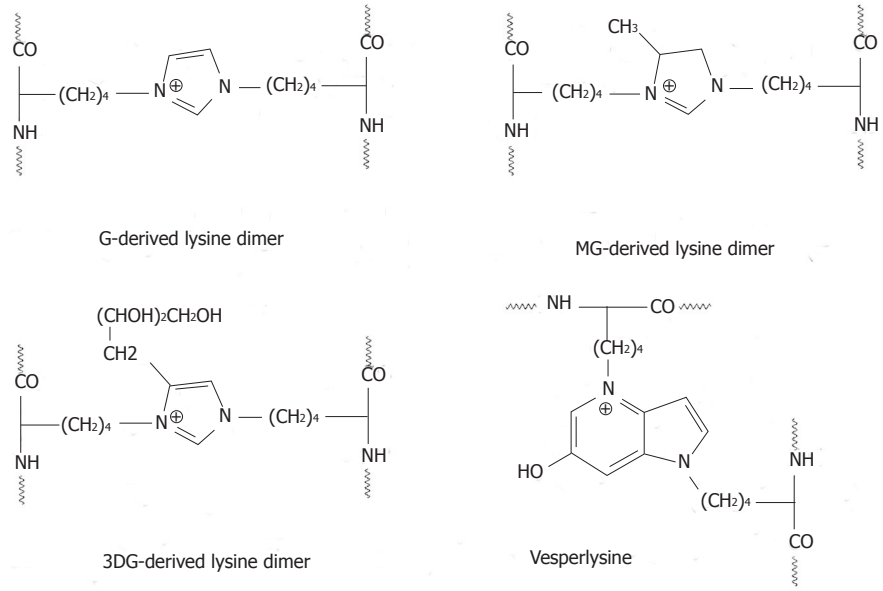

Figure 4 Lysine-lysine advanced glycation end products crosslinks[67].

same or on different polypeptide chains become involved in the formation of shared AGEs structures such as G-derived lysine dimer (GOLD)[74], MG-derived lysine dimer (MOLD)[75], 3DG-derived lysine dimer (DOLD)[76], G-derived lysine-lysine crosslinks GOLA and GALA[77,78], glucose lysine dimer GLUCOLD[79], crossline[80,81] and vesperlysines[82] (Figure 4)[67]. AGEs crosslinks formed between lysine and arginine residues are G-derived arginine-lysine dimer (GODIC), MG-derived arginine-lysine dimer (MODIC)[83], 3DG-derived arginine-lysine dimer (DOGDIC)[84], pentosidine[78] and glucosepane[84]. To the best of our knowledge, to date crosslinks formed between two arginine residues or between arginine/lysine residues and other amino acids have not been detected neither *in vivo* nor in *in vitro* glycation reaction, although the possible involvement of the cysteine thiol group in the formation of such crosslinks has been proposed[85].

MAILLARD REACTION PRODUCTS IN THE HUMAN BODY

Endogenous formation of glycation products

Early and advanced glycation products are formed in the human body throughout its existence. Many glycation adducts, appearing on proteins in model reactions *in vitro*, have been detected also in physiological systems. Fructoselysine (FL), the Amadori product formed by glucose on the ε-amino group of lysine, has a relatively short half-live (2-6 wk)[86]. As a rule, early glycation in healthy subjects is not age-dependent, although some rise in the physiological FL concentration has been observed during aging. For example, the concentration

of the collagen-bound FL increases from 5 mmol/mol Lys in 20-year-old individuals to 7 mmol/mol Lys in 70-year-old subjects[87]. Short-lived proteins such as albumin (half-life *ca.* 20 d) and even hemoglobin (half-life *ca.* 120 d) accumulate *in vivo* predominantly early glycation products. Approximately 10% of HSA of healthy subjects is modified by FL at Lys-525[88], and incubation of HSA with glucose under physiological conditions *in vitro* leads to glycation of the same Lys residue[89]. Other Lys residues in HSA including Lys-439, Lys-199 and Lys-281 are also involved in FL formation *in vivo*[90] and it has been reported that glycation impairs HSA binding to physiologically important ligands such as bilirubin and *cis*-parinaric acid[89]. The historically crucial hemoglobin HbA_{1c} contains glucose-derived Amadori product at the amino group of the hemoglobin β-chain N-terminal valine (βVal-1) and amounts 4%-6% of the total hemoglobin in healthy individuals. Except the N-terminal valine, some internal Lys residues in HbA_{1c} also become glycated[91]. Under hyperglycemia HbA_{1c} levels increase several times and correlate positively with the chronic diabetic pathology[92].

Most AGEs are either not formed at physiological glucose concentrations (5 mmol/L) or their levels are quite lower (ten to thundered times) compared with hyperglycemic conditions. This makes AGEs relevant biomarkers of the glycation status of individuals, which changes with age and in disease state such as diabetes and kidney failure. Because of their great diversity, AGEs cover a wide concentration range *in vivo* (0.001 to 15 mmol/mol modified amino acid)[86]. Physiologically important AGEs are those having long half-life (CML, CEL and pentosidine) and/or high concentration (hydromidazolones). Stable AGEs accumulate on long-lived proteins such as skin and cartilage collagen[93-96], and lens proteins[97], although CML has also been detected in the short-lived HSA of diabetic patients[98]. Hidroimidazolones, albeit relatively unstable, may also appear on long-lived proteins such as human lens proteins[99].

Maillard reaction products (MRPs), which are found in the body, are classified into three groups - MRPs in proteins (> 12 kDa), MRPs in peptides (< 12 kDa) and free MRPs in amino acids. The term MRPs is more general than AGEs and applies to both early glycation products and AGEs. Peptide MRPs are detected mainly in the portal venous plasma and in the urine, and are most likely degradation products of glycated proteins. Free MRPs are formed during proteasome/lysosome degradation of glycated cellular proteins, then released into the bloodstream and excreted in the urine, which ensures efficient functioning of the cell proteome[100,101]. Free MRPs may appear *in vivo* also as a result of amino acids glycation though this latter source of free MRPs is disputable[55].

The impact of glycation on human physiology depends on many factors including the target amino compound and its half-life, the adduct stability and its location. Especially harmful are the consequences of the formation of covalent cross-links in proteins that render them resistant to proteolysis[102]. Both early glycation products and AGEs can cause damage *via* various mechanisms such as (1) release of oxygen radicals by early products[103]; (2) altered (blocked) activity of enzymes[104,105], receptors[106] and regulatory proteins[107,108]; (3) crosslinking of structural proteins[78,109]; (4) damage of signaling pathways[110,111], (5) damage of protein recycling[112,113]; and (6) induction of an immune response[114].

Dietary intake of glycation products

Sugar-rich and processed foods are also a source of FL and AGEs in the human body[115]. The biodistribution and metabolism of these products have not been systematically studied, except the dietary intake of FL in humans[116]. Among foods rich in FL and AGEs are bread, biscuits, chocolate, breakfast cereals and hot milk. It has been reported that lactulose-lysine, an Amadori product formed during heat treatment of milk, is poorly digested in the gastrointestinal tract[117]. Some microorganisms can hydrolyze FL in the intestine. For example, an enzyme has been discovered in *E. coli* that degrades N^{ε}-fructoselysine-6-phosphate to lysine and glucose-6-phosphate[118]. FL ingested with food and resorbed by the intestine, enters the circulatory system and then penetrates liver and muscle cells by passive diffusion. It is not clear yet whether lysine and glucose can be recycled from FL, because no human enzymes have been identified so far catalyzing the breakdown of FL to free lysine and glucose. In rats, about 60% of dietary FL is excreted in urine[119], whereas in humans this percentage is only 3%. In newborns, however, 16% of FL is found in the urine, and 55% is recovered in the feces[116] (Figure 5).

Foods with high FL and AGEs content are poorly digestible, because glycated proteins are resistant to proteolysis. In addition, some AGEs inhibit intestinal proteases[120]. It is thought that dietary AGEs are absorbed mainly in the form of free and peptide MRPs. The highest concentration of absorbed food AGEs is expected in the plasma of the portal vein, where MG-H1 is detectable mainly in peptides[121]. Although CML is formed *in vivo*, it is hypothesized that urinary CML is mostly of exogenous nature[122]. Studies with rats have shown that another product of the advanced glycation, 5-Hydroxymethyl-2-furaldehyde (HMF), administered *per os* or intravenously is present in the liver but is mostly in the kidney and the bladder. Also, HMF or its metabolites are rapidly eliminated in the urine with a recovery of 95%-100% after 24 h[123]. Only 10% of dietary AGEs are absorbed, of which only 30% are excreted in the urine of healthy individuals with unimpaired renal function[124]. Some dietary AGEs, after entering blood circulation, interact with low density lipoprotein (LDL) and tissue proteins (*e.g.,* collagen) or bind to cellular receptors for AGEs to trigger intracellular oxidative stress, endocytosis and degradation of AGEs.

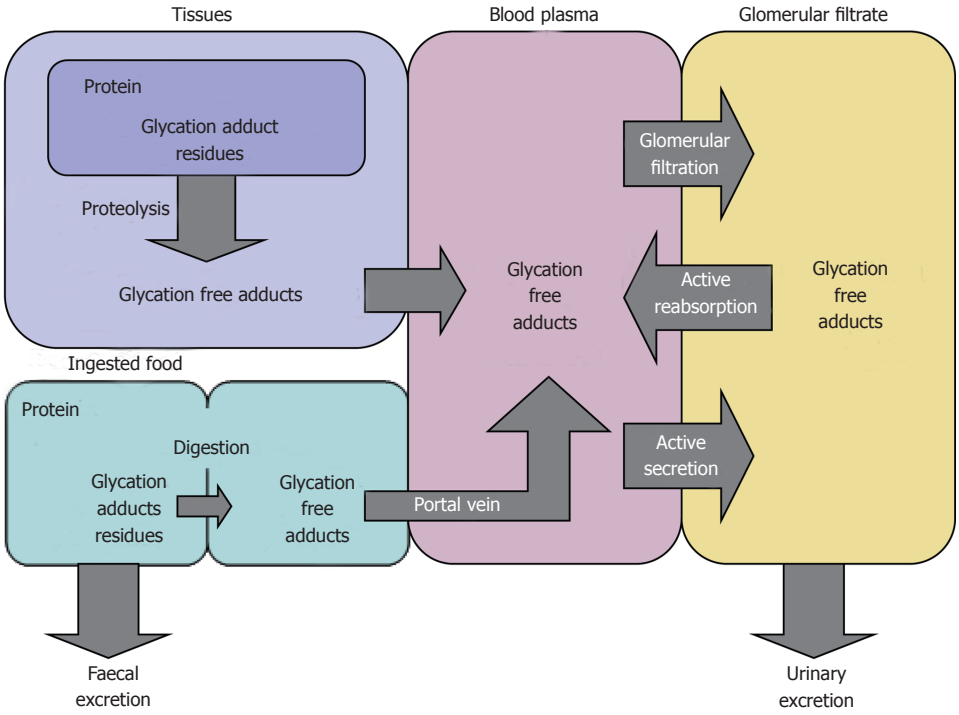

Figure 5 Biodistribution scheme illustrating flows of formation and removal of protein glycation free adducts[86].

ROLE OF THE IMMUNE SYSTEM IN THE ANTI-GLYCATION DEFENSE

Cellular receptors for AGEs

Many cellular receptors are capable of binding AGEs. The AGE-receptor complex consists of AGE-R1 (oligosaccharyl transferase-48), AGE-R2 (80K-H phosphoprotein)[125,126] and AGE-R3 (galectin-3)[127]. Some receptors belonging to different classes of the scavenger receptor (SR) supergroup[128,129] also bind AGEs. These are SR-A1 (SCARA1)[130] and SR-A1.1 (SR-AII)[131], SR-B1 (SR-BI)[132] and SR-B2 (CD36)[133], SR-E1 (LOX-1)[134], SR-H1 (FEEL-1) and SR-H2 (FEEL-2)[135]. These receptors are involved in detoxification of AGEs by intracellular degradation (endocytosis). Best characterized is the specific receptor for AGEs called Receptor for Advanced Glycation End Products (RAGE)[136]. RAGE is a multi-ligand receptor of the immunoglobulin superfamily, which plays a key role in inflammatory responses. Its extracellular domain is composed of three immunoglobulin-like domains - one V (variable) type Ig domain followed by two C (constant) type Ig domains[137]. RAGE also possesses a transmembrane domain and a cytoplasmic tail of 43 amino acids. Crucial for ligand binding is the V-domain, while the cytoplasmic tail is implicated in further transduction of captured signals[138]. RAGE is expressed weakly on a number of cell types and tissues under physiological conditions, however, an increased expression is observed in sites of ligands' deposition. RAGE exists also in a soluble form (sRAGE)[139], which is hypothesized to participate in detoxification of circulating ligands.

Apart from AGEs, ligands for RAGE are pro-inflammatory cytokine-like mediators from the S100/calgranulin family[140], the β-amyloid peptide[141] and amfoterin also known as High Mobility Group Box 1 (HMGB1) - a nuclear protein released during cell necrosis[142-144]. AGEs and non-AGEs ligands bind to RAGE on endothelial cells, neurons, smooth muscle and immune cells to activate a variety of signaling pathways including expression of NF-κB - a transcription factor, which plays a key role in regulation of the immune response[145]. While expressed inducibly on T-cells of healthy subjects upon T-cell receptor activation, RAGE is constitutively synthesized in diabetics' T-cells, and a role for RAGE in the adaptive immunity has been proposed[146,147]. In has been demonstrated that ovalbumin (OVA) modified with AGEs (pyrraline), but not native OVA, induces SR-A mediated uptake of the antigen by dendritic cells and enhances $CD4^+$ T-cell immunogenicity and potential antigenicity of OVA[148,149]. Characteristic for RAGE is that it recognizes tertiary structures rather than amino acid sequences. This feature endows RAGE with properties of the pattern recognition receptor (PRR), which recognizes repeated antigenic motifs of the type of pathogen-associated molecular patterns (PAMPs)[150]. RAGE can also recruit immune cells in the sites of inflammation. For example, RAGE on endothelial cells can function as an adhesive receptor interacting with the leukocyte β2-integrins[151]. Intriguing findings in recent years suggest that RAGE's actions contribute to perpetuation of AGEs production by sustaining oxidative stress and inflammation, and by suppressing the detoxification of MG as one of the major AGEs precursors[152,153].

Anti-AGEs antibodies

Apart from cellular immune responses, AGEs may elicit a humoral immunity. Excessive accumulation of AGEs with age and in pathology appears to correlate with elevated levels of anti-AGEs antibodies[154]. Glycated proteins [histone H2A[155], HSA[156], poly-*L*-lysine (PLL)[157], IgG[158]], DNA[159,160] and LDL[161,162] have demonstrated higher immunogenicity in experimental animals than the non-glycated counterparts, and sera of diabetic patients were found to exhibit higher binding activity to glycated HSA[163], PLL[157], IgG[158] and DNA[159] than to the unmodified molecules. In addition, patients with renal failure of diabetic or non-diabetic etiology had higher autoantibody activity against CML (an AGE structure) than normal subjects or diabetics without renal failure[164]. The injection of rats with *in vitro* glycated rat skin collagen leads to the formation of anti-collagen Abs, which do not cross-react with non-glycated collagen. The binding of the serum Abs to the glycated collagen is inhibited by 92% when the reaction is conducted in presence of glycated Lys as a competitor. This result indicates that glycated Lys residues on collagen are the most probable epitopes captured by the anti-collagen Abs[165]. Of note, sera from streptozotocin-induced diabetic rats contained Abs that clearly bound glycated collagen.

Vay *et al*[166] have observed 289 diabetic patients and 120 healthy individuals for serum Abs against CML (anti-CML Abs). Although they have found an increased titer of anti-CML Abs (IgG-isotype) in sera of diabetic patients compared to controls ($P < 0.0001$), there was no correlation between the titer of the anti-CML Abs and patients' glycemic status. In a similar study including 58 children with type I diabetes, 19 children have been found to be anti-AGEs Abs positive[167]. In contrast to the previous study, the authors have found that the titer of the anti-AGEs Abs correlates positively with some diabetic markers such as HbA_{1c}, microalbuminuria and retinopathy. While some studies show higher titer of circulating anti-AGEs Abs in diabetic patients than in healthy individuals[164,166], others report on the reverse condition, *i.e.,* lower anti-AGEs Abs titers in diabetics than in normal controls[168,169]. To explain this paradox the authors suggested that circulatory anti-AGEs Abs are either captured by tissue-bound AGEs[168] or entrapped in immune complexes[169] hampering their determination. If real, such events could explain the lack of a correlation between the titer of the serum anti-CML Abs and the patients' glycemic status in the above cited study[166].

It is well known that some patients with rheumatoid arthritis (RA) develop auto-Abs against the IgG constant (Fc) region, which is designated as rheumatoid factor (RF). A pilot study with RA patients has shown that only RF-positive patients have serum IgM Abs binding to *in vitro* glycated IgG (IgG-AGEs), suggesting that the IgM anti-IgG-AGEs together with IgG-AGEs may contribute to the pathogenesis of RA[170]. Further studies have shown that immune complexes isolated from patients' sera indeed contain AGEs (CML and imidazolone) modified IgG. It is very likely that the anti-IgG-AGEs prevent the normal clearance of IgG-AGEs by AGEs receptors[171]. Noteworthy, as with most biologics, some RA patients treated with antagonists of the human tumor necrosis factor (TNF) (infliximab, etanercept and adalimumab) develop anti-drug antibodies[172]. The TNF-antagonists are in fact anti-TNF Abs of IgG isotype[172] and in light of the current review two events could be proposed: (1) if the Fc regions of the therapeutic anti-TNF Abs are also glycated (anti-TNF-AGEs Abs), they could compete with patients' IgG-AGEs for binding RF in human plasma; and (2) if the patients' antibodies against the glycated biologic are specifically directed against the glycated moiety (AGEs) of the anti-TNF-AGEs Abs, apart from binding the drug, they would be also capable of interacting with patients' IgG-AGEs. The net result of this hypothetical and intertwined scenario is difficult to predict, but it should be taken into consideration by pharmacists, pharmacologists and clinicians. Intriguingly, subcutaneous immunization with AGEs modified LDL (AGEs-LDL) significantly inhibited atherosclerosis progression in hyperlipidemic diabetic mice possibly through activation of specific humoral and cell mediated immune responses[173]. The anti-atherogenic effect of the anti-AGEs-LDL Abs, however, is disputable yet[174] in so far as immune complexes containing such Abs are detected in human sera[175] and shown to be important predictors of carotid intima-medial thickening in patients with type 1 diabetes[176].

REASONS FOR THE IMMUNOGENICITY OF PROTEIN THERAPEUTICS

Aggregation of proteins

The most important structural change contributing to protein drugs' immunogenicity is aggregation, which may be both covalent and non-covalent. The non-covalent aggregation results from interaction between non-native transient protein conformers with partially preserved secondary structure called aggregation competent particles. Such particles accumulate progressively in the time course of protein storage due to structural fluctuations and beget intermolecular interactions resulting in protein aggregation. The aggregation process is often accompanied by protein precipitation and loss of biological activity[177]. It is believed that the formation of aggregates proceeds by a cooperative mechanism, *i.e.,* the non-native conformers react with other native molecules to render them aggregation competent. The formation of dimers and higher order multimers in turn accelerates the aggregation process[178,179].

Aggregates in protein drugs substantially contribute to immune response in treated patients[23,180-185]. Studies with interferon-α have shown that the magnitude of the immune response does not depend on the size

of the aggregates but rather on the structure of the protein molecules involved in aggregation. Aggregates, formed by molecules with largely preserved secondary structure (native-like) are more immunogenic compared to aggregates composed of fully denatured molecules[22,186]. This could explain why Purohit *et al*[187] have not observed an immune response against recombinant human factor Ⅷ in model animals. Before injection into animals the authors heated the protein to stimulate aggregation, which perhaps caused its denaturing. The prevalent hypothesis, which explains the immunogenicity of the protein aggregates, is the "array" hypothesis[188-194]. The human immune system is specialized to recognize proteins that are presented in an array format, as is the case with viral capsids and bacterial cell walls. In fact, aggregated proteins are arranged in similar "pathogen-like" structures and thus may be sensed by the immune system as foreign antigens.

Post-translational modifications of proteins

The enzymatic glycosylation is an inborn post-translational modification of many eukaryotic proteins and in most cases is indispensable for their biological activity and stability. Also, the lack of native polysaccharide residues may unmask potentially immunogenic epitopes in proteins. Increasing evidence in the last decade shows that glycoproteins are not a eukaryotic privilege. Competent to enzymatically glycosylate proteins are many prokaryotes including *Escherichia coli* - the "workhorse" of the current biotechnology[195-198]. Prokaryotic glycosylation, however, differs significantly from that in eukaryotes. Therefore, it is preferable that naturally glycosylated human proteins are produced in eukaryotic cell lines. On the other hand, glycosylation in eukaryotes is species and cell specific[199]. Polysaccharides may vary in composition, chain length, binding sites on proteins and points of chain branching. This means that for the production of human proteins with preserved glycosylation pattern appropriate host cells have to be selected performing identical or similar glycosylation to that of the natural proteins[200] .

While native glycosylation of human therapeutic proteins is desirable, other non-enzymatic post-translational modifications should be avoided[201]. Spontaneous oxidation and deamination, sometimes followed by isomerization, are major causes of proteolysis during protein isolation, purification and storage. Deamination affects mainly asparagine residues and leads to their conversion into aspartate or iso-aspartate residues[202,203]. Glutamine in proteins may undergo similar spontaneous deamination to glutamate. Studies with oxidized and non-oxidized forms of IFNβ have shown that oxidized protein species are significantly more immunogenic[204]. The oxidation may lead to covalent aggregation of therapeutic proteins through the formation of cysteine and/or tyrosine covalent cross-links[54,205]. This is the reason why functionally unimportant Cys residues in therapeutic proteins are often replaced by alternative amino acids. To our knowledge, no one has tried so far to reduce covalent cross-linking of therapeutic proteins through replacement of Tyr residues. Last but not least, the leitmotif of the current review, the Maillard reaction, is another non-enzymatic post-translational modification of proteins, which contribution to the immunogenicity of protein drugs will be discussed in detail below.

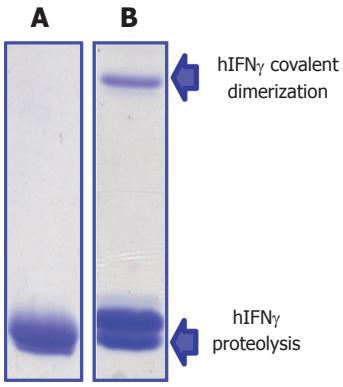

Figure 6 Covalent dimerization and proteolysis of *Escherichia coli*-derived hIFNγ (A) after storage for one month in solution (0.4 mol/L NaCl, Tris-HCl pH 8.2) at 4 ℃ under nitrogen (B). Protein species were separated on 15% denaturing (sodium dodecyl sulfate) polyacrylamide gel.

OUR FOCUS ON THE LINK BETWEEN THE MAILLARD REACTION AND THE IMMUNOGENICITY OF PROTEIN THERAPEUTICS

We entered the Maillard reaction field nearly 15 years ago when searching a reasonable explanation of the unexpected behavior of a cysteine-less variant of human interferon-gamma (hIFNγ) expressed in *E. coli*. Despite the lack of Cys residues, the protein underwent progressive covalent dimerization during storage under anaerobic conditions, which excluded oxidation (*i.e.,* formation of disulfide bridges and tyrosine dimers) as a cause of the observed phenomenon (Figure 6). Brief literature survey led us to suppose that the Maillard reaction may provide a rational explanation of hIFNγ covalent dimerization and proteolysis. At that time, however, it was not yet clear whether the Maillard reaction may occur in prokaryotes because of their short life span and intense protein turnover. We undertook relevant investigations in this direction and found that both endogenous and recombinant proteins[73,206] as well as chromosomal DNA[207] of *E. coli* are involved in glycation under normal physiological conditions. The short life span of *E. coli* does not disagree with these observations. During batch fermentation of *E coli* a generation time of *ca.* 20 min and a few divisions are sufficient for the Maillard reaction to take off through the formation of Schiff bases in proteins. Then, the whole Maillard cascade of chemical

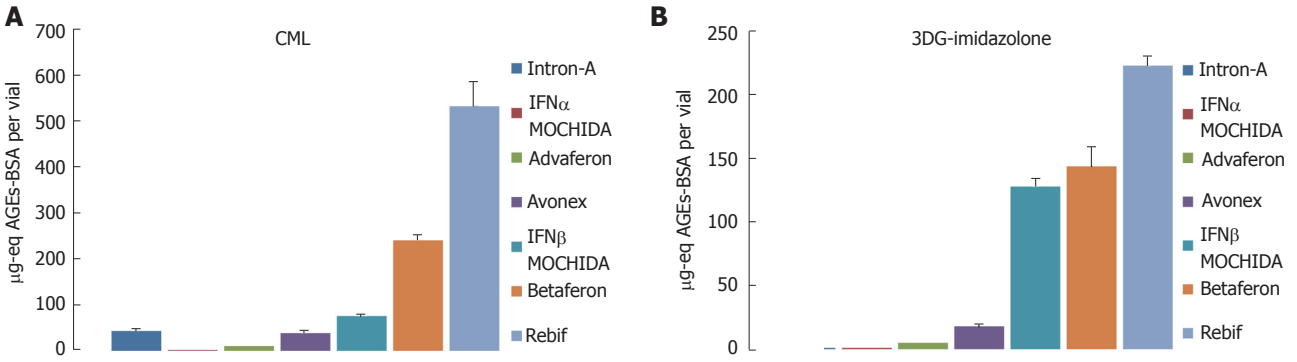

Figure 7 N^{ε}-(carboxymethyl)lysine (A) and 3DG-imidazolone (B) in interferon pharmaceuticals. Three vials of each drug were analyzed by competitive enzyme-linked immunosorbent assay in duplicates, and the pooled results were presented as mean ± SD. One μg-eq AGEs-BSA corresponds to the amount of CML or 3DG-imidazolone present in one microgram of the referent AGEs-BSA. The latter was prepared by incubating 10 mg/mL BSA with 0.5 mol/L glucose for 3 mo at 37 ℃. AGEs: Advanced glycation endproducts; CML: N^{ε}-(carboxymethyl)lysine; BSA: Bovine serum albumin.

transformations resulting in AGEs formation may happen *in vitro* during protein isolation, purification, formulation and storage. We indeed found that freshly isolated hIFNγ contains Amadri products but not AGEs, which accumulated in the protein over time accompanied by covalent aggregation, proteolysis and loss of biological activity[73,208]. Interferons are basic proteins rich in lysine and arginine residues and because of that susceptible to glycation. On the other hand, human interferons Type I (α and β) are the active ingredients of a number of pharmaceuticals used today for treatment of various cancers, autoimmune and viral diseases. For this reason we decided to analyze interferon-based pharmaceuticals for the presence of AGEs.

AGEs in interferon pharmaceuticals

Type I interferon pharmaceuticals manufactured by different companies worldwide were tested: *E. coli*-derived hIFNα-2b (Intron-A, Schering-Plough Corp., Kenilworth, NJ, United States), natural (lymphoblast) nhIFNα (IFNα MOCHIDA1000, Mochida Pharmaceutical Co., Ltd, Tokyo, Japan), *E. coli*-derived hIFNα-con1 (Advaferon-1800, Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan), natural (fibroblast) nhIFNβ (IFNβ MOCHIDA600, Mochida Pharamceutical Co., Ltd, Tokyo, Japan), *E. coli*-derived hIFNβ-1b (Betaferon, Schering AG, Berlin, Germany), CHO-derived IFNβ-1a (Rebif 44 mg, New Formulation, Merck Serono, Bari, Italy), and CHO-derived IFNβ-1a (Avonex 30 mg, Biogen Idec Inc., Weston, MA, United States). All pharmaceuticals except Adaferon and Rebif were powders containing HSA as a stabilizer while Advaferon and Rebif were liquid formulations without protein excipients. We tested all drugs for AGEs by enzyme-linked immunosorbent assay (ELISA) using two monoclonal antibodies specific for CML and 3DG-derived imidazolone (Figure 7). Lymphoblast IFNα MOCHIDA was negative for both CML and 3DG-imidazolone, whereas the content of both AGEs in fibroblast IFNβ MOCHIDA was higher than that in the *E-coli*-derived Intron-A and Advaferon. Also, Rebif produced in Chinese hamster ovary (CHO) cells proved to contain higher levels of AGEs compared to the *E. coli*-derived Betaferon. Based on these observations we concluded that therapeutic proteins are affected by glycation independently of whether they are produced by native or recombinant (either pro- or eukaryotic) cells. This result is not surprising bearing in mind both pro- and eukaryotic cells are glycation-proficient. Whether there are any differences in the glycation power between pro- and eukaryotic cells is a largely unexplored issue and a direction for future investigations. We suggest that the variable AGEs content in the drugs reflects different manufacturing technologies rather than specific characteristics of the cell-producers.

Five of the pharmaceuticals are formulated with HSA at concentrations ten to hundred times higher than that of interferons. Thus the reasonable question emerged whether AGEs, we are measuring, are located in HSA or in interferons. The answer of this question is "in interferons" because of the following reasons: (1) a highly purified pharmaceutical grade HSA is used for drugs' formulation. Own mass-spectral analyses of all five HSA containing drugs confirmed the low glycation status of HSA[209], although 50% of HSA proved to be cysteinylated as shown also by other authors[210]. How HSA-Cys impacts drug stability is not yet clear and should be outlined as another direction for future investigations; (2) we have isolated an IFNβ enriched fraction from Betaferon by size-exclusion HPLC, which demonstrated 15 times higher concentration of CML as compared to Betaferon's HSA[211]; and (3) as seen in Figure 7, the HSA-free drug Rebif demonstrated the highest concentration of CML and 3DG-imidazolone among all seven drugs while the HSA containing IFNα MOCHIDA was deprived of these two AGEs.

AGEs and immunogenicity of IFNβ pharmaceuticals

In most cases AGEs are bulky chemical moieties that may behave like haptens rendering self-proteins immunogenic. As seen in Figure 7, the four IFNβ pharmaceuticals tested proved to contain more CML and 3DG-imidazolone than the three IFNα drugs. Also, a number of studies report on immunogenicity

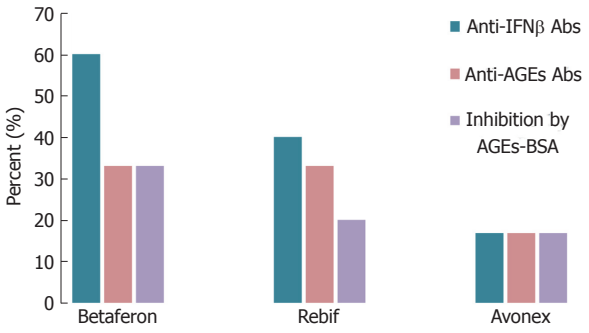

Figure 8 Percent sera of MS patients treated with Betaferon, Avoex and Rebif, containing anti-IFNβ, anti-advanced glycation endproducts Abs, and responding to Advanced glycation endproducts-bovine serum albumin inhibition of binding to IFNβ. For detailed information on the experimental conditions see ref. No. 211. AGEs-BSA: Advanced glycation endproducts-bovine serum albumin.

of IFNβ[2,212-227]. Therefore, to either verify or reject the hypothesis that AGEs contribute to IFNβ immunogenicity, we studied sera from patients suffering from relapsing-remitting multiple sclerosis (MS) treated with Avonex (12 patients), Betaferon (15 patients) or Rebif (15 patients)[211]. Seventy four percent (31/42) of the patients enrolled in our study had flu-like symptoms, injection-site reactions, or both. Sera were tested for binding anti-IFNβ and anti-AGEs Abs of IgG isotype by direct ELISA. The percentage of anti-IFNβ Abs positive (Abs$^+$) patients was highest in the Betaferon group (60%) followed by the Rebif (40%) and Avonex (17%) groups (Figure 8), which is consistent with data about the relative incidence of persistent neutralizing Abs (NAb) in patients treated with the same drugs[228]. Although CML and 3DG-imidazolone levels were higher in Rebif (Figure 7), Betaferon demonstrated higher immunogenicity than Rebif. Note that besides AGEs-modifications, and in contrast to the CHO-derived IFNβ1a (Rebif), the *E. coli*-derived IFNβ1b (Betaferon) lacks glycosylation at Asn-80, has an amino acid substitution (Ser^{17} for Cys^{17}) and is prone to non-covalent aggregation[229], which could explain its higher immunogenicity. Seventeen percent (2/12) of the patients in the Avonex group were anti-AGEs Abs$^+$, whereas for the other two groups (Betafeon and Rebif) the percentage of anti-AGEs Abs$^+$ patients was 20% (3/15). All anti-AGEs Abs$^+$ patients were anti-IFNβ Abs$^+$. This, however, does not necessarily mean that the formation of anti-AGEs Abs in these patients was provoked by the IFNβ therapy. Convincing evidence for the link between the formation of anti-IFNβ and anti-AGEs Abs was obtained by competitive ELISA. The addition of an external AGEs-competitor (AGEs-BSA) to sera inhibited binding to IFNβ of two (Avonex), three (Rebif) and five (Betaferon) sera with inhibition ranging from 9% to 70%. The different degree of inhibition most likely reflects the relative contribution of AGEs to the overall IFNβ immunogenicity in each particular patient. All ten sera responding to inhibition by AGEs-BSA were tested also for response to inhibition by mAbs raised against CML and 3DG-imidazolone. Significant inhibition ($P < 0.05$) of sera reactivity to IFNβ was obtained with one serum from the Avonex group and with two sera from the Rebif group. One can suggest that in the remaining seven anti-AGEs Abs$^+$ sera, which did not respond to inhibition by the two mAbs, the anti-AGEs Abs were raised against other AGEs (not CML and 3-DG-imidazolone) in IFNβ.

Whether the anti-AGEs Abs that cross-react with IFNβ neutralize drug activity and/or contribute to the observed inflammatory side reactions in treated patients are questions to be addressed in the future. Also, besides injection-site reactions and flu-like symptoms, cases of allergy[13-15] and anaphylaxis[11,16] have been reported for MS patients on IFNβ therapy. Therefore, it is worth to conduct case studies with such patients in order to answer the question of whether AGEs in IFNβ have contributed to the observed hypersensitivity reactions.

POSSIBLE SCENARIOS UPON TREATMENT WITH IFNβ-AGEs

AGEs are formed in the human body under normal and pathological conditions, and are consumed with food as well. Because of the negative impact of AGEs on human physiology, elaborate mechanisms do exist for anti-AGEs defense ranging from enzymatic detoxification of AGEs' precursors (*i.e.,* carbonyl compounds[230-234], Schiff bases[235] and Amadori products[236]) going through intracellular proteasome/endosome degradation of protein AGEs, and ending up with renal clearance of free and peptide AGEs. Anti-AGEs antibodies have been detected in sera of healthy individuals as part of a homeostatic mechanism, which clears altered structures *via in situ* destruction or *via* opsonization[237]. The formation of AGEs starts during embryonic development and one can assume that against some stable AGEs in long-lived proteins an immune tolerance might be developed. IFNβ, however, is a short-lived protein (half-life of hours) and it is expected that upon administration in patients IFNβ-AGEs would be recognized as non-self-antigen thus provoking a classical type immune response.

The adaptive immunity against IFNβ may be preceded by activation of the innate immunity. The binding of IFNβ-AGEs to non-specific (for AGEs) cellular receptors, such as the scavenger receptors and AGE-R3 on macrophages can result in IFNβ-AGEs degradation by phagocytosis (Figure 9). On the other hand, it has been shown that the specific receptor for AGEs, RAGE, belongs to the immunoglobulin superfamily and has the properties of a pattern recognition receptor (PRR)[137,238,239], which can sense recurring structures of the type of PAMPs[150]. It is well-known that the interaction of PRR with PAMPs triggers an intracellular signaling cascade, which initiates an innate, inflammatory by nature, immune response[240] resulting in degradation of the pathogen and in enhancement

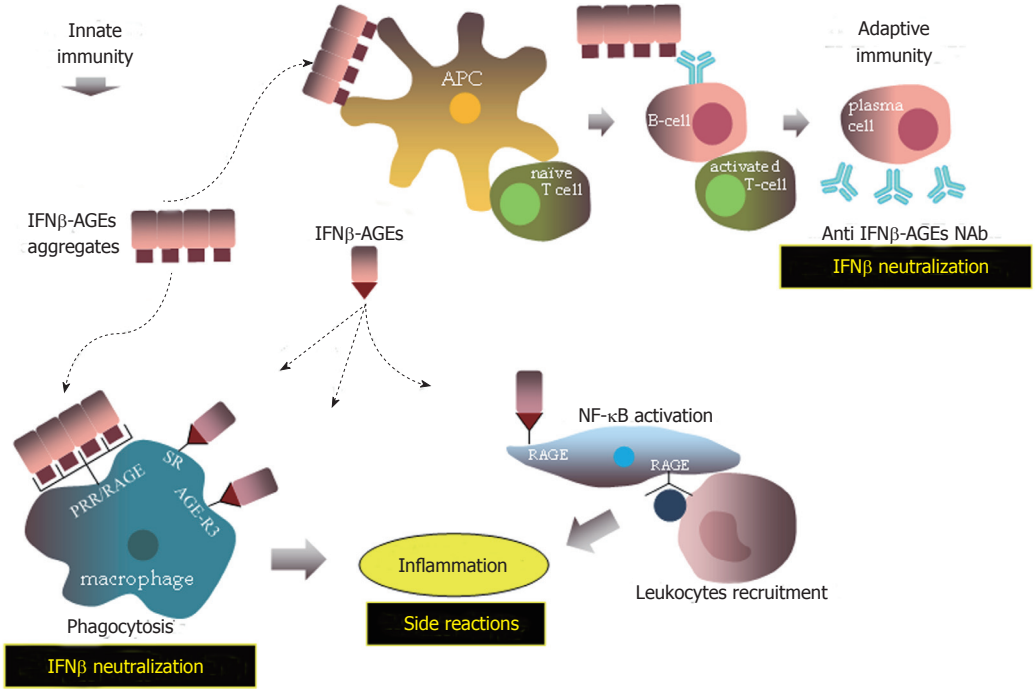

Figure 9 Proposed immune responses against advanced glycation end products modified IFNβ (IFNβ-advanced glycation endproducts). AGEs: Advanced glycation endproducts.

of the adaptive immune response. We have shown that Advaferon, Betaferon and Rebif contain covalent IFNβ aggregates[211,241], which are formed perhaps by glycoxidation *via* the mediator role of crosslinking AGEs like GOLD, MOLD, pentosidine *etc*. Such covalent aggregates may resemble PAMPs thus interacting with RAGE on macrophages, natural killer (NK) cells and other immune cells to elicit an innate immune response.

RAGE may play further role in inflammatory reactions[151,242] during IFNβ-AGEs therapy. It has been reported that CML[243,244] and MG-derived hydroimidazolone[245] are ligands for RAGE. Binding of RAGE with these and other AGEs and non-AGEs ligands such amfoterin does not result in ligands' degradation but rather triggers different signaling pathways, including proinflammatory responses *via* the activation of transcription factor NF-κB[138,246,247]. Also, RAGE on endothelial cells may act as an adhesive receptor interacting with leukocyte β2 integrins[151] to recruit immune cells into sites of inflammation. Taken together the different pathways, in which the immune system may react against IFNβ-AGEs, are expected to result in neutralization of IFNβ activity (inefficient therapy), and in immune-mediated side effects (risky therapy).

CONCLUSION

Many proteins used today in medicine (erythropoietin, insulin, human growth hormone, clotting factors Ⅷ and Ⅸ) have been shown to elicit varying incidence of antibody generation in treated patients[5]. Proteins are susceptible to glycation and it is the protein structure that determines to what extent given protein will accumulate AGEs. Scaling up the studies by including other therapeutic proteins will reveal the magnitude of AGEs as a causal factor of drugs' immunogenicity. On the other side, not only the protein structure but the whole manufacturing process may impact the glycation status of proteins. Therefore, specific anti-glycation strategies have to be applied to prevent protein glycoxidation. The choice and engineering of appropriate host cells are of particular importance. The glycation potential of host cells should be controlled at all stages of the Maillard reaction including its initiation, propagation and progression. Engineering host cells to overexpress enzymes that detoxify carbonyl compounds will block glycation initiation and its propagation. In a similar way, the overexpression of deglycases[235,236] in host cells may interfere with early glycation stages. Also, a number of studies report on synthetic and natural compounds with anti-glycation activity[248]. Such substances can be added to the fermentation media of host cells to inhibit protein glycation. Fermentation parameters such as glucose concentration[249], oxygen supply (when applicable), temperature, and pH-control are also of particular relevance. If despite all these measures there are glycation adducts still left on proteins, additional techniques could be applied such as: (1) boronate affinity chromatography for extraction of protein species modified by early glycation products[250]; and (2) use of AGEs-breakers[251,252] for removal of AGEs. Although costly, isolation, purification, formulation and storage of proteins are best to be conducted under anaerobic conditions, thereby avoiding the use of carbonyl compounds and transition metal ions at each step. Finally, health care authorities

including the American Food and Drug Administration and the European Medical Agency are recommended to undertake relevant initiatives for AGEs assessment of protein drugs.

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