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SOP REPORT

Lysine Modifications in sHSPs : Glycation of Lysine in sHSPs

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Abstract

The non-enzymatic process of glycation can have a substantial effect on the composition and capabilities of small heat shock proteins (sHSPs). Advanced glycation end products (AGEs) are produced by the non-enzymatic process of lysine glycation, which is the covalent binding of sugar molecules to proteins. This mechanism may lead to modifications in the stability and structure of proteins, which would modify the sHSPs' chaperone function. Glycation can also interfere with sHSPs' capacity to aid in protein folding and inhibit aggregation by interfering with their interaction with client proteins. These structural alterations may affect cellular proteostasis by impairing sHSPs' overall function.

The mechanisms underlying lysine glycation in sHSPs involve the role of reactive carbonyl species, such as methylglyoxal and glyoxal, in modifying lysine residues. The accumulation of AGEs can result in protein cross-linking, further impairing their function and stability. Understanding the mechanisms of lysine glycation in sHSPs is crucial for developing targeted interventions to mitigate this detrimental process.

Abbreviations used / Keywords

- sHSP/SHSP's : Small Heat Shock Proteins
- Proteostasis
- AGEs : Advanced Glycation End Products
- Chaperone
- Lysine
- Glycation
- Apy: argpyrimidine
- α-crystallin
- Cellular homeostasis

Table of Contents

Glycation of lysine in small heat shock proteins

Introduction to glycation and its implications in small heat shock proteins

Glycation is a non-enzymatic post-translational modification that significantly affects protein's structure and function. [1]. Glycation primarily targets certain amino groups in proteins, which include lysine residues, the N-terminal amino group, and the guanidino groups of arginine residues.[2]. In biological systems, arginine, lysine and protein N-terminal residues are important targets for glycation. [3]. The glycation process is often influenced by the types of amino acids which surround lysine, such as leucine and alanine, which somewhat emphasizes the significant role of the microenvironment in protein modification.[4]. Studies indicate that lysine may play a role in reducing collagen glycation, suggesting its potential to modulate protein glycation processes.[5].

Small heat shock proteins, or SHSPs, are a class of molecular chaperones which are essential for preventing partially denatured proteins from aggregating under adverse conditions such as thermal /chemical / mechanical or any other kind of stress.[6]. These proteins play a vital role in keeping the balance within cells and defending against protein misfolding and clumping by maintaining cellular homeostasis. Lysine residues present in sHSPs are particularly susceptible to glycation which can impact the chaperone role of these proteins.[1]. The glycation of lysine residues in Hsp27, a human small heat shock protein, has been linked to the formation of argpyrimidine, potentially impacting the function of sHSPs in patient-derived tissues.[1]. The importance of lysine glycation in regulating the function of sHSPs has been demonstrated by the fact that their chaperone activity is largely dependent on the specific target proteins they bind with.[1].

Small heat shock proteins have been associated with a wide range of illnesses in a variety of biological conditions, including conditions affecting the retina, including diabetic retinopathy and glaucoma [8]. Besides their chaperone activity, these proteins perform a wide range of roles in cellular processes associated with diabetes and other conditions.[9].

Determining how post-translational changes can impact protein structure and cell processes require an understanding of the impact of lysine glycation in small heat shock proteins. Researchers can uncover a great deal about the processes causing protein malfunction and disease development by studying the glycation of lysine residues within sHSPs. This can pave the way for targeted therapeutic approaches.

Mechanisms of lysine glycation in small heat shock proteins

Glycation is a non-enzymatic modification of proteins that primarily impacts the lysine, arginine, and N-terminal residues of proteins. It is a key step in many biological systems.[3]. Glycation is primarily driven by the interaction of proteins with glucose, leading to the formation of AGEs[2]. This procedure is particularly important when looking at aging and chronic diseases like diabetes, as protein glycation has been associated with the development of these conditions.[4]. Notably, arginine residues' guanidino groups and N-terminal amino group constitute two of the primary sites of glycation in addition to lysine residues.[2].

Glycation has significant effects on the lysine residues present in proteins, which can result in structural changes as well as modifications to the manner in which the affected protein functions.[4]. Research has demonstrated that glycation can lead to localised protein modifications which impact the general structure of proteins.[4]. At least 30% of human proteins are impacted by this modification, suggesting its extensive effect on protein biology.[1]. Moreover, mass spectrometry study has demonstrated that glycation occurs in many different kinds of proteins, including heat shock proteins, highlighting the widespread effects of this posttranslational modification.[10]. Protein stability and biological activity may be significantly altered by glycation-induced modifications to protein structure and function.[2].

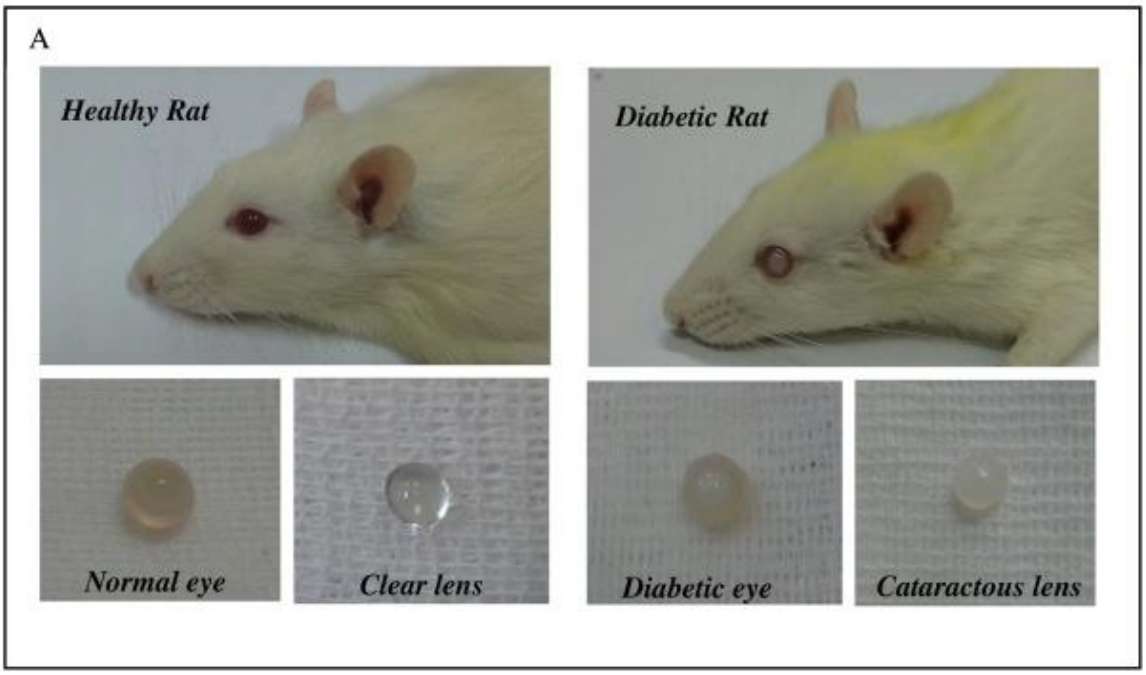
Besides only changing the structure of proteins, glycation also has an impact on the manner in which they function in biological systems.[11]. For example, lysine residues in small heat shock proteins can be glycated to

cause protein cross-linking, which affects the chaperone function and susceptibility of the proteins to any stress.[11]. Additionally, glycation-induced modifications may interfere with protein-protein interactions, enzymatic activities, and overall cellular signalling pathways, highlighting the diverse consequences of protein glycation [12]. Overall, understanding the mechanisms of lysine glycation in small heat shock proteins is essential for revealing the intricate ways in which this posttranslational modification impacts protein structure, function, and cellular physiology.

Consequences of lysine glycation in small heat shock proteins

The glycation of lysine residues in small heat shock proteins can lead to significant structural changes within these proteins [4]. Small heat shock proteins play crucial roles in cellular function, including acting as chaperones and maintaining protein homeostasis [1]. When lysine residues undergo glycation, it may result in local distortions of the protein and alterations in the overall protein structures [4]. For example, in patient-derived tissues, argpyrimidine (Apy), a particular alteration associated with glycation, has been found in human small heat shock protein Hsp27 and closely related proteins. [1]. This alteration emphasizes how glycation affects the structural integrity of sHSP, which may have an influence on their ability to chaperon cells and their general functions. [1].

Beyond the structural changes induced by lysine glycation in small heat shock proteins, there are significant implications for cellular function[1]. Non-enzymatic posttranslational modifications, such as glycation, are known to affect a considerable portion of human proteins, with lysine and arginine residues being common targets[1][14]. Small heat shock proteins are involved in various cellular processes, and their modification through glycation can disrupt these functions. Studies have suggested that glycation, as a non-enzymatic protein modification, is associated with aging and chronic diseases, particularly diabetes[4]. The alteration in small heat shock proteins due to glycation may impact their role in maintaining protein quality control and cellular homeostasis, potentially contributing to disease pathogenesis[9].



α-crystallin, which shields other proteins from damage, becomes diabetic when osmotic stress is brought on by elevated glucose levels. Both in vitro and in vivo, lysine (Lys) helps to prevent α-crystallin glycation. Rats with diabetes produced by streptozotocin that received Lys treatment had a decreased visual cataract score and their biochemical parameters were back to normal. The production of advanced glycation endproducts, protein cross-linking, and α-crystallin's hydrophobicity were all reversed by Lys treatment. Lys treatment's antiglycating and antioxidant properties considerably slowed the progression of diabetic cataracts in rats.[13]

Fig: Effect of Lys therapy on the opacity of the lenses in STZ-diabetic rats. A: The pictures of two normal and diabetic rats, their eyes and lenses at the end of the experimental period.[13]

Camel lens proteins, including as α-crystallin, have a special role in preventing cataract development. The camel α-crystallin carries out a rapid and effective holdase function by effectively preventing ζ-crystallin aggregation up to 89°C. Additionally, it is fully engaged above 40°C and shows 20% chaperone activity between 30 and 40°C. This special function shows how the camel may shield lens proteins from heat stress.[18]

Understanding the consequences of lysine glycation in small heat shock proteins also opens avenues for identifying potential therapeutic targets to prevent or mitigate the effects of this modification[2]. Protein glycation can lead to changes in protein structure and enzymatic activity, which are typically countered by protein degradation and renewal processes within cells[2]. Researchers have explored the use of compounds like betanin and carnosine to mitigate protein glycation and its downstream effects, highlighting the potential for therapeutic interventions to modulate glycation-related damage[15][16]. By elucidating the impact of lysine glycation on small heat shock proteins and exploring strategies to prevent or reverse this modification, researchers aim to uncover novel therapeutic approaches for addressing protein dysfunction in various diseases linked to glycation, such as diabetes[17].

Conclusion

In conclusion, glycation of lysine residues in small heat shock proteins has significant implications for protein structure and function. The process of glycation, which involves the reaction of glucose with lysine residues, can lead to structural changes in small heat shock proteins and impact their cellular function. This highlights the importance of understanding the mechanisms of lysine glycation in small heat shock proteins and identifying potential therapeutic targets for preventing glycation.

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