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Histone Protein Glycation and Diabetes

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Abstract

Glycation and oxidation are two mechanisms that have been widely attributed with the generation of advanced glycation end products upon proteins in various pathological conditions. Histones being lysine and arginine rich are prone to these reactions and hence they are susceptible to glycoxidation reactions. Post translational modifications in the highly conserved basic core histone proteins are known to induce changes in their structural integrity. Various researchers have documented the structural alterations in histone proteins upon glyoxidation reactions and correlated the same with various disorders. This review aims at presenting the background research in the field of histone glycation and its role in diabetic complications. It tracks the histone modifications under hyperglycaemic conditions and proposes the future avenues of research in the field. This review clearly indicates the lack of research on histone glycation in diabetes. It may be instrumental for future researches on opening new vistas in the field.

Keywords: Histone proteins; Diabetes; Glycation; Advance glycation end products (AGEs)

Histone Glycation in Diabetes

Miescher, in 1869 developed methods for the isolation of "nuclein" [1] and today nuclein is known as deoxyribonucleic acid (DNA), the building block of life. It was Albrecht Kossel, who studied the structure and chemical composition of nuclein and coined the term "histon" [2]. Now, it is well known that eukaryotic cells contain roughly equal mass of histones and DNA [3]. Each nucleosome core particle (NCP) is known to contain 146 base pairs of DNA wrapped around a core histone octamer, comprised of two each of histones H2A, H2B, H3 and H4 [4]. Histones have extended N-terminal tails making up around 28% of the mass of the core histones. They are highly enriched in positively charged residues, lysine and arginine [4,5]. Histones are enzymatically modified by methylation, ADP-ribosylation, phosphorylation, glycosylation, or acetylation [6]. Histone modifications have been attributed with role in various pathological disorders [7].

Besides enzymatic modifications, histone proteins have been reported to suffer various structural changes upon non enzymatic modifications like glycation and oxidation. *In vitro* studies on histone glycation has been reported in 1991 by Jobst et al. who coined the term glycohistone while studying hepatic nuclei of patients dying of decompensated diabetes [8]. Since then, various studies have attempted to understand the pattern of modifications caused by glyoxidation reactions in histones. The role of histone glyoxidation has also been reported in various disease conditions. Our group has earlier reviewed the role of glycoxidation of histone proteins in autoimmune disorders [7].

A latest study has shown various structural changes in histone H1 and the formation of AGEs upon in-vitro glyoxidation that could possibly lead to a compromise in chromatin structure in cases of secondary diabetic complications [9]. Besides H1, glycation induced structural changes have been reported in histone H2A, H2B and H3. Histone H2A has been shown to suffer glycation induced aggregation and lead to the generation of carboxyethylene residues leading to its enhanced melting temperature and heat capacities [10]. Histone H2B has been reported with specific-sites for glycation and oxidation that makes it prone to variety of modifications. It has been shown that increased oxidative damage in the vicinity of the glycated residues is most probable to occur in histone proteins [11]. Histone H3 has been reported to yield Nε-carboxymethyl-lysine and pentosidine like AGEs upon side chain modifications during glycation [12]. Non enzymatic glycation has been shown to induce cross linking of histones in endothelial cells under the effect of reactive oxygen species (ROS) that are increased after hyperglycaemia [13]. ADP-ribose has been shown to glycate almost all the types of histones viz, H1, H2A, H2B, and H4 leading to the formation of protein carboxymethyllysine residues and protein-protein cross-links [14]. These studies clearly indicated the role of hyperglycaemic conditions in histone modification.

Histone glycation has also been attributed with disease conditions. It has been observed that structurally altered glycated histone proteins loose 50% of the alpha helix conformation and lead to the generation of a specific immune response in systemic lupus erythematosus. It has been revealed that SLE patient sera have high specificity for the glycated histones and the same have DNA cross reacting properties as well [15]. Another study has shown 4-Hydroxy-2-nonenal modified histone-H2A as a possible antigenic stimulus for systemic lupus erythematosus autoantibodies wherein HNE-mediated-lipid peroxidation in histone-H2A has been reported to alter histidine, lysine and cystein residues and the modified histone has been associated with role in the initiation/progression of SLE [16].

What needs to be focused is the rationale behind the glyoxidation of histones and this corresponds to the effect of higher concentration of sugars and sugar by-products upon histones. Among disease conditions, diabetes is a major disorder associated with prolonged exposure to hyperglycaemia leading to the gradual build-up of advanced glycation end products (AGEs) in body tissues [17]. It is also well known that protein glycation and AGEs are accompanied by increased free radical activity that contributes towards the biomolecular damage in diabetes [18]. The role of receptors for AGEs (RAGE) in the pathology of diabetic complications is also well established [19]. However, histone glycation has not earned the amount of focus in terms of their studies in diabetes. Besides histones

being lysine and arginine rich and are very prone to glyoxidation reactions under diabetic conditions the field is largely un-explored [20].

Though various researchers have attempted to unfold the role of histone glycation in diabetes but the literature review shows that the work done in this filed is too less and needs detailed efforts. In 1995, it was revealed that histones from diabetic rats contain increased levels of advanced glycation end products. It was found that histones from the liver of diabetic rats contain AGEs levels three-fold higher than those of their age-matched controls [21]. This led to studies on glycated histones in diabetic conditions. The formation of AGEs was then confirmed during studies on liver histones in rats with streptozotocin-induced diabetes, in ethanol (EtOH)-treated rats, and in EtOH-treated diabetic rats [22]. The same idea was re-enforced by the findings showing the liver cell histones of diabetic patients containing glycation end products (AGEs) that possess lipofuscin components [23]. With the various types of details emerging about the histones modified with advanced glycation end products, it was proposed by a group of researchers that glycation of nuclear protein targets may alter chromatin structure and ultimately contribute to chronic changes associated with aging and diseases such as diabetes [24]. It was suggested that teratogenic effects in diabetes may be enhanced by histone glycation with significant implications in the maintenance of nucleosomes and hence DNA integrity [25]. This led to the studies on understanding the pathological importance of histone glycation in diabetes. It was observed that glycated histone H1 derived from rat showed decreased fluorescence emission intensity and reduce alpha-helical content when compared to non-glycated histone samples; this inferred the changes in the folding patterns of histones upon glycation in diabetes. The glycated histone in diabetes patients has been observed with reduced efficiency for binding with DNA and this has been proposed possible mechanisms involved in diabetic complications [26]. Glycated histones have altered structural characteristics than the native histone counterparts and that they are specifically recognized by serum antibodies of type 1 diabetes patients. Methylglyoxal modified histones have been described as potential targets for circulating autoantibodies in patients with type 1 diabetes mellitus [27].

It is clear that the role of glycoxidation of histone proteins in the diabetic complications is yet in the preliminary stages. It needs to be explored as of how the glycaemia introduces glycation in histones *in vivo* and what are its implications in diabetes. It needs to be elucidated whether the glycoxidation modified histones in diabetes generate auto immune response, and in case yes, what about specificity. Whether they can be used for the development of a biomarker for the early detection of diabetes is also a subject worth analysis? Another aspect is the emerging correlation of diabetes and cancer. It has been shown that increased oxidative stress under hyperglycaemic conditions, through the interaction of AGEs with RAGE receptors and via activation of interleukin mediated transcription signalling acts as the molecular link between diabetes and cancer [28]. The oxidative stress in a variety of cells via various metabolic pathways leading to oxidative damage of DNA and proteins are seen as an initial step of carcinogenesis [29]. These modifications probably going to lead to glyoxidation reactions of histone proteins that are known to lie in the vicinity of rapid metabolic processes and eventually contribute to epigenetic modifications. What could be outcome of the research in these directions may possibly throw light on the nexus of AGE-RAGE axis in diabetes and carcinogenesis [30]. It may also lead to the understanding of the correlation between epigenetics and diabetes. It appears a very interesting field of study that could possibly open new vistas of understanding the role of diabetes.

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