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The effects of the Maillard reaction on the physical properties and cell interactions of collagen

Effets de la réaction de Maillard sur les propriétés physiques et les interactions cellulaires du collagène

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Abstract

The non-enzymic glycation of collagen occurs as its turnover decreases during maturation, with complex carbohydrates accumulating slowly and the end-products of these reactions being permanent. The nature of these advanced glycation end-reaction products (AGEs) can be categorised as: 1) cross-linking: intermolecular cross-linking may occur between two adjacent molecules and involve lysine to lysine or lysine to arginine residues. Several compounds have been characterised. They are believed to be located between the triple helical domains of adjacent molecules in the fibre resulting in major changes of the physical properties, primarily, fibre stiffness, thermal denaturation temperature and enzyme resistance, all of which increase slowly with age but the rate is accelerated in diabetes mellitus due to high glucose levels: 2) side-chain modifications: these changes alter the charge profile of the molecule affecting the interactions within the fibre and if they occur at specific sites can affect the cell–collagen interaction. Modification of arginine within the sites RGD and GFOGER recognised by the two specific integrins (α1β2 and α2β1) for collagen reduce cell interactions during turnover and for platelet interactions (α1β2). These changes can ultimately affect repair of, for example, vascular damage and dermal wound healing in diabetes mellitus. Both types of modification are deleterious to the optimal properties of collagen as a supporting framework structure and as a controlling factor in cell matrix interactions. Glycation during ageing and diabetes is therefore responsible for malfunctioning of the diverse collagenous tissues throughout the body.

Résumé

La glysosylation non enzymatique (glycation) du collagène se produit lorsque son renouvellement diminue au cours de la maturation, alors que des sucres complexes s'accumulent lentement et que les « produits terminaux » de leur réaction deviennent permanents. La nature de ces produits avancés de glycation (AGEs) peut être divisée en : 1) pontage : des pontages intramoléculaires peuvent se produire entre deux molécules adjacentes et impliquer des résidus de lysine–lysine ou lysine–arginine. Plusieurs composés ont été caractérisés mais n'ont pas été identifiés dans la fibre de collagène. Ils sont localisés entre les domaines en triple hélice des molécules voisines dans la fibre avec pour résultat des changements majeurs des propriétés physiques, principalement, rigidification de la fibre, dénaturation thermique et résistance aux enzymes, qui augmentent lentement au cours du vieillissement, mais dont la vitesse s'accélère lors du diabète à cause de taux de glucose élevé ; 2) modifications des chaînes latérales : ces changements modifient le profil de la charge de la molécule en affectant les interactions dans la fibre, et si elles surviennent en des sites spécifiques, peuvent affecter les interactions cellule–cellule. Des modifications de l'arginine dans les sites RGD et GFOGER reconnus par les deux intégrines spécifiques pour le collagène (α1β2 et α2β1), réduisent les interactions cellulaires au cours du renouvellement et les interactions plaquettaires (α1β2). Ces changements peuvent affecter la réparation et, par exemple, les lésions vasculaires et la cicatrisation du derme au cours du diabète. Les deux types de modifications sont délétères à cause des propriétés du collagène en tant que réseau structural et facteur de contrôle dans les interactions cellules–matrice. Au cours du vieillissement et du diabète, la glycation est responsable du mauvais fonctionnement des divers tissus collagéniques du corps.

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1. Introduction

Collagen is the most abundant structural protein of vertebrae varying from bone through skin and tendon to thin basement membranes. The collagen family is synthesised by fibroblasts, osteoblasts and chondrocytes, and over the past few years molecular sequence studies have identified a number of genes resulting in 27 genetically distinct types of collagen molecule, which readily accounts for its remarkable diversity of tissue distribution and function from sponge to man. Originally thought to be solely a mechanical support, more recent studies have demonstrated its role as a bioactive surface, playing a role in stimulating and controlling growth and development.

The characteristic feature of all collagens is the triple helical domain, which results from the repeating sequence (Gly-X-Y)n where X is frequently proline and Y hydroxyproline in the amino acid sequence of all three α-chains. These triple helical molecules can spontaneously aggregate to form extracellular assemblies to perform a particular function. The major types of aggregates are the fibrillar collagens, the non-fibrillar basement membrane collagens and the FACIT collagen which are often involved with the surface of fibrillar collagens thereby providing additional functions [1]. The five fibrillar collagens are types I, II, III, V and XI, the latter two being present as minor components in tissues. Recently two additional fibrillar collagens have been identified, types XXIV and XXVII.

Phylogenetic analyses of different invertebrates indicates that the formation of fibrils of variable structure and function arose step by step during invertebrate evolution [2], a finding that rather contradicts the evolutionary molecular incest model previously proposed for fibrillar collagens [3].

It has now become clear that fibrils are generally formed from a mixture of major and minor fibrillar collagens, for example I, III and V are present in most fibrillar tissue and collagens II and IX in the fibres of articular cartilage. The relative composition and concentration of these various types in the fibre determines the ultimate structure and consequently the biomechanical properties primarily due to the specific intermolecular cross-links formed.

The subclass of FACIT collagens are characterised by interruptions in the triple helix and they interact with existing fibrils to produce a further variation in properties. For example, type IX on the surface of type II fibres in cartilage may link type II fibres [4] whilst types XII and XIV are localised at the surface of the collagen type I and III fibres in skin and tendon and may control fibre size. An additional eight members of this FACIT group have been identified but not yet assigned a role.

The major non-fibrous collagen of basement membrane is type IV, the molecules binding head to head to form an open network to support cells and act as a permeable membrane.

Type I collagen is the major supporting structure in skin, tendon and bone, type II in articular cartilage and types I and III in the vascular system. The fibres are strong and virtually inextensible and this is achieved by the formation of intermolecular cross-links between the molecules within the fibre. They are formed by the action of the enzyme lysyl oxidase (LO) which oxidises the single lysines in the amino and carboxy telopeptides. The lysine-aldehyde formed then reacts with a specific hydroxylysine in the triple helix due to the precise quarter-stagger and head to tail end-overlap alignment of the molecules in the fibre. As the tissue matures these divalent cross-links react spontaneously to form stable trivalent cross-links between fibrils [5] thereby increasing the mechanical strength and denaturation temperature of the fibre (Fig. 1).

Non-fibrous basement membrane type IV collagen forms similar aldehyde cross-links in the 7S region of the aggregated non-triple helical carboxy-terminal domain. In contrast the non-helical amino-terminal (NC1) does not form these lysyl-aldehyde cross-links although there is some controversy as to the presence of an alternative cross-link. Than et al. [6] proposed that the NC1 was stabilised by a covalent met-lys cross-link. Although this was initially disputed by Vanacorre et al. [7] these authors subsequently proposed a similar cross-link in the NC1 between met and hydroxylysine [8].

The formation of the trivalent mature cross-links increases in the fibre as the turnover of collagen decreases. The low turnover of the collagen varies between tissues, from about 100 years for type II collagen in articular cartilage, about 10 years for type I in skin and about 1–2 years for bone collagen. Exceptionally, periodontal ligament has a rapid turnover of about 1 day. However the biological half-life for collagen is generally long and it is therefore susceptible to interaction with metabolites, primarily glucose and other aldehydes in what is referred to as the Maillard reaction.

In this short review we will focus on the effect of the Maillard reaction on collagens where its normal functions are well established, that is, the fibrillar and basement membrane collagens.

2. The Maillard reaction and collagen

The Maillard reaction, originally the research field of food chemists, has over the last few decades been extensively investigated primarily because of its relevance to the complications due to ageing and diabetes [9–11]. Since collagen provides the functional properties of the most vulnerable tissues, such as renal basement membrane, the cardiovascular system and retinal capillaries, the effect of the Maillard reaction on fibrous and non-fibrous collagen has been extensively investigated; [12]. Glycated haemoglobin has been used as a marker for the management of diabetic patients, but other markers are needed to evaluate the risk of specific diabetic complications. Fluorescence of skin correlates with retinopathy and arterial stiffness in some individuals, but more specific chemical mar-