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Mini review

Post-translational modifications of integrin ligands as pathogenic mechanisms in disease

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ABSTRACT

Protein post-translational modifications like glycation, carbamylation and citrullination increase the functional diversity of the proteome but in disease situations might do more harm than good. Post-translational modifications of ECM proteins are thus appearing as mechanisms, which contribute to tissue dysfunction in chronic kidney disease, in diabetes and in various inflammatory diseases. In chronic renal failure, carbamylation could lead to kidney fibrosis. In diabetes, high glucose levels lead to non-enzymatic glycation and cross-linking of collagens, which contribute to tissue stiffening with consequences for cardiovascular and renal functions. In inflammatory diseases, citrullination deiminates arginine residues with possible consequences for integrin-mediated cell adhesion to RGD- and GFOGER sequences in ECM proteins. Citrullination of fibronectin was in one study suggested to affect cell adhesion by modifying the heparin-binding site and not the RGD site. In a recent publication citrullination of GFOGER sequences in collagen II was demonstrated to selectively affect α10β1 and α11β1 integrin-mediated cell adhesion to collagen II, with consequences for synovial fibroblast and stem cell adhesion and migration. The implications of citrullination affecting integrin binding in disease open up a new area of study and might have implications for the pathogenesis of inflammatory diseases like rheumatoid arthritis and periodontitis.

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1. Introduction

Glycation, citrullination and carbamylation are three post-translational modifications that can change the interacting properties of proteins containing lysine and arginine in their interactive domains (Fig. 1).

Thinking about these post-translational modifications from a matrix perspective, ECM proteins like fibronectin and collagens represent targets where post-translational changes can potentially affect cell adhesion, physicochemical properties and antigenicity.

A major group of cell surface receptors for the ECM are integrins (Barczyk et al., 2010). Whereas substantial data has been collected on how integrins interact with other signaling receptors to integrate extracellular information (Legate et al., 2009), less is known about how integrins actually interact with their ligands *in vivo*.

Questions that need to be considered include details of how ligand organization, availability and post-translational modifications change the ability of integrins to bind ligand. A recent study suggests that citrullination of collagen II affects integrin binding and implies integrins

Abbreviations: AGE, advanced glycation end-product; ECM, extracellular matrix; CKD, chronic kidney disease; MMP, matrix metalloproteinase; PAD, peptidyl-arginine deiminase; PPAD, *P. gingivalis* peptidyl-arginine deiminase; RA, rheumatoid arthritis.

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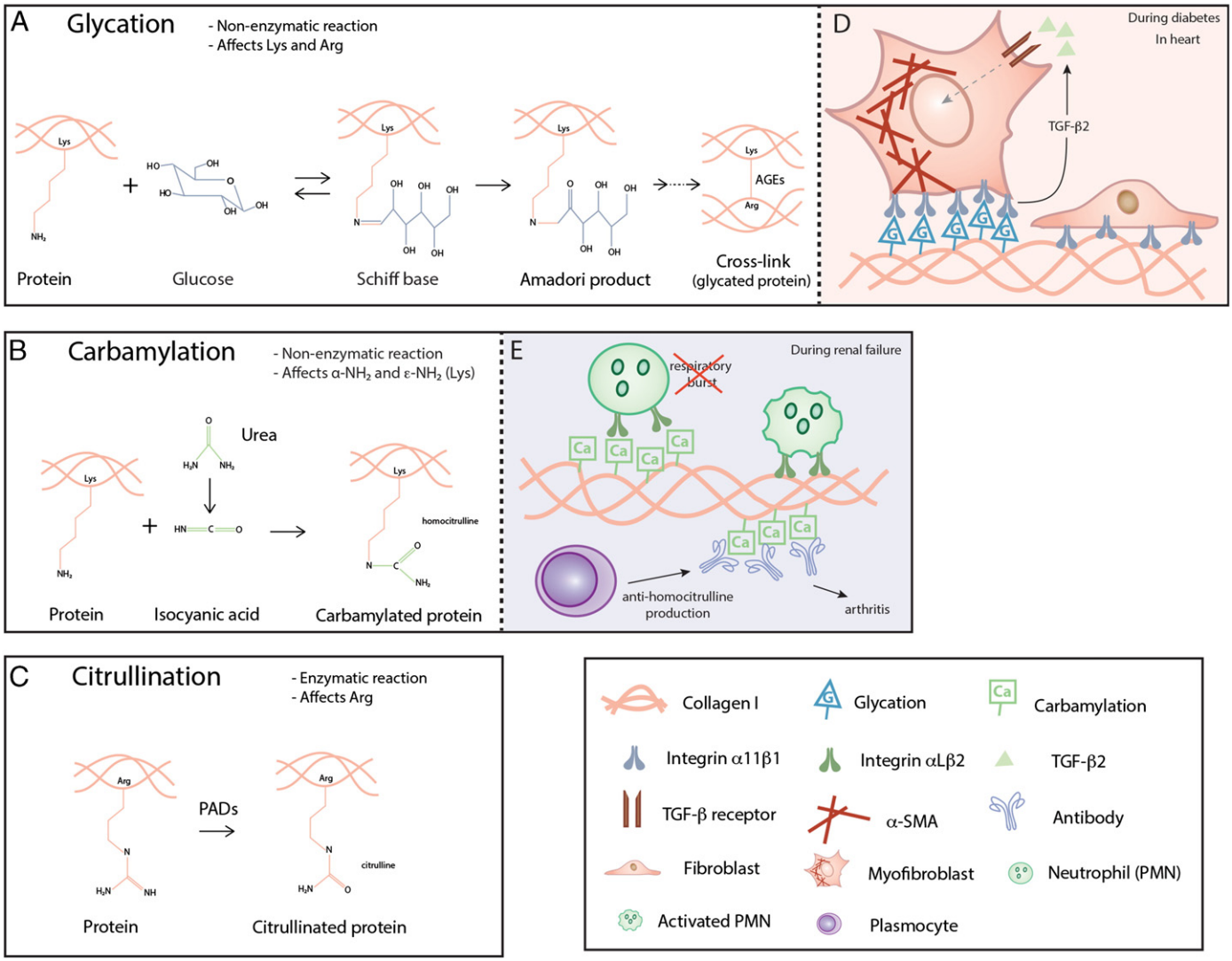

Fig. 1. ECM post-translational modifications and their involvement in disease. Biochemical reactions of glycation (A), carbamylation (B) and citrullination (C) are depicted. PADs: peptidyl-arginine deiminases. D. With an increase of glucose concentration, glycation of collagen I induces differentiation of cardiac fibroblasts into myofibroblasts, via autocrine secretion of TGF-β2 (Talior-Volodarsky et al., 2012). E. Carbamylation of collagen I impaired inflammatory cell functions like respiratory burst (Jaisson et al., 2007). Carbamylation can also promote autoimmune response leading to arthritis (Shi et al., 2014).

to be involved in the pathogenesis of rheumatoid arthritis (Sipila et al., 2014). In relation to this publication we provide a short summary of citrullination with a brief overview on glycation and carbamylation since these are post-translational modifications that affect the same amino acids, and make the link to diseases other than arthritis.

1.1. Mechanisms of extracellular post-translational modifications and their consequences for cell–matrix interactions

Glycation is the non-enzymatically covalent reaction whereby reducing sugars like glucose form bonds to amino groups in amino acids like lysine and arginine (Bucala and Cerami, 1992). Glycated collagen can then form non-enzymatic crosslinks known as advanced glycation end-products (AGEs) (Gautieri et al., 2014). The involvement of integrins in biological effects of glycation and AGEs needs further study, but studies so far indicate that glycation interferes with cell adhesion to collagen I (Avery and Bailey, 2006; McCarthy et al., 2004; Morita et al., 2005).

Carbamylation leads to the non-enzymatic addition of urea-derived isocyanic acid to α-NH_2 (protein N-termini) and ε-NH_2 (lysine residues), and has been shown to affect collagen I triple helix stability and sensitivity to MMP cleavage (Jaisson et al., 2007). Available data suggest that carbamylation does not primarily affect cell adhesion since lysine residues are not present in cell adhesive sequences used by integrins. However, carbamylation could induce the structure modification of ECM proteins that may result in the lack of recognition by integrins (Jaisson et al., 2006).

On the contrary, citrullination is an enzymatic process that thus differs from glycation and carbamylation by physiological roles. Citrullination contributes to distinct functions such as skin protection and gene regulation by affecting keratin and histones, respectively. Hypercitrullination of histones is also involved in immune responses, essential in the formation of highly decondensed chromatin structures (Baka et al., 2012). Citrullination requires enzymes called peptidyl-arginine deiminases (PADs), which act to replace the primary ketimine group (=NH) by a ketone group (=O). PADs are intracellular enzymes and belong to a family of 5 members in humans, PAD 1–4 and PAD-6 (Yoshida et al., 2006). Under some conditions like inflammation, the enzymes can be released into the extracellular space. PAD-4 expressed by neutrophils is considered to be a major enzyme involved in extracellular citrullination in inflammation. Citrullination, leads to deimination of arginine and has the potential to modify cell adhesive properties of proteins containing the RGD sequence (fibronectin, fibrinogen) and GFOGER-like sequences (collagens). Citrullination has been observed