Available online at www.sciencedirect.com
SCIENCE DIRECT
ELSEVIER
The International Journal of Biochemistry & Cell Biology 38 (2006) 1662–1677
IJBCB
www.elsevier.com/locate/biocel

Review

Citrullination: A posttranslational modification in health and disease

Bence György [b], Erzsébet Tóth [a], Edit Tarcsa [c], András Falus [b], Edit I. Buzás [b,*]

[a] *Department of Medical Biochemistry, Semmelweis University, Budapest, Hungary*
[b] *Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest, Hungary*
[c] *Abbott Bioresearch Center, Worcester, MA, USA*

Received 22 December 2005; received in revised form 13 March 2006; accepted 14 March 2006
Available online 30 March 2006

Abstract

Posttranslational modifications are chemical changes to proteins that take place after synthesis. One such modification, peptidylarginine to peptidylcitrulline conversion, catalysed by peptidylarginine deiminases, has recently received significant interest in biomedicine. Introduction of citrulline dramatically changes the structure and function of proteins. It has been implicated in several physiological and pathological processes. Physiological processes include epithelial terminal differentiation, gene expression regulation, and apoptosis. Rheumatoid arthritis, multiple sclerosis, and Alzheimer's disease are examples of human diseases where protein citrullination involvement has been demonstrated. In this review, we discuss our current understanding on the importance of protein deimination in these processes. We describe the enzymes catalyzing the reaction, as well as their known protein substrates. We review the citrullinated peptide epitopes that are proposed as disease markers, specifically recognized in certain human autoimmune disorders. The potential autopathogenic role of citrullinated epitopes is also discussed.

Keywords: Biochemistry; Autoimmunity; Clinical; Cell Biology; Apoptosis

Contents

Abbreviations: ACPA, anti-citrullinated protein/peptide antibody; AD, Alzheimer's disease; AKA, anti-keratin antibody; AFA, anti-filaggrin antibody; APF, anti-perinuclear factor; cAMP, cyclic adenosine monophosphate; CIA, collagen induced arthritis; CNS, central nervous system; CARM-1, coactivator associated arginine methyltransferase-1; CIITA, major histocompatibility class II transactivator; DM, dismyelinating; EAE, experimental autoimmune encephalomyelitis; GFAP, glial fibrillary acidic protein; FBG, fibrinogen; H, histone; Hcgp39, human cartilage glycoprotein-39; HGNC, HUGO Gene Nomenclature Committee; HUGO, Human Genome Organisation; K, keratin; MBP, myelin basic protein; NOS, nitrogen monoxide synthase; NO, nitrogen monoxide; PAD, peptidylarginine deiminase (protein); PADI, peptidylarginie deiminase (gene); PRMT-1, protein arginine methyltransferase-1; PTM, posttranslational modification; RA, rheumatoid arthritis; SNP, single nucleotide polymorphism; THH, trichohyalin

* Corresponding author at: Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest, Nagyvarad ter 4, H-1089, Hungary. Tel.: +36 1 2102930/6234; fax: +36 1 3036968.
E-mail address: buzedi@dgci.sote.hu (E.I. Buzás).

1357-2725/$ – see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.biocel.2006.03.008

1. Introduction

Proteins are encoded by a surprisingly limited number of genes in our genome. However, posttranslational modifications (e.g. phosphorylation, glycosylation, citrullination) can tremendously increase both the structural and functional diversity of the proteome. Posttranslational modifications (PTM) are common biological processes that alter specific parts of a protein after synthesis. Nearly all known proteins undergo some form of posttranslational modification, and almost all amino acids can be altered by one or more of these processes. The modified proteins gain rare amino acids that can have critical influence on the structure and function of the molecule. This review will focus on the conversion of arginine to citrulline that was first described by Fearon (Fearon, 1939).

Peptide-bound arginine residues can undergo this modification and the resulting citrulline remains part of the protein as peptidyl citrulline. Citrulline is not a natural amino acid in proteins, therefore may induce immune response. The importance of citrullinated autoantigens in autoimmune inflammatory diseases (e.g. rheumatoid arthritis, multiple sclerosis) has long been suspected.

1.1. The citrullination reaction

The conversion of arginine (Arg) to citrulline (Cit) changes the charge of the amino acid (Fig. 1). Arginine is strongly basic (p$I \sim 10.76$) due to the presence of a guanidino group that could easily be protonated at physiological pH. The removal of the imino moiety (a transformation referred to as deimination) is an enzymatic reaction catalyzed by peptidylarginine deiminases (PAD). The resulting citrulline lacks the strong basic character; it is a neutral amino acid similar to Asn or Gln.

At the protein level, the reaction leads to a 1 Da mass reduction for each Arg modified. Basic charge(s) are lost that will influence the overall charge, charge distribution, isoelectric point, as well as the ionic and hydrogen bond forming abilities of the protein (van Venrooij & Pruijn, 2000; Tarcsa et al., 1996). The interactions of the protein with other proteins might also be altered.

1.2. Enzymes catalysing citrullination: peptidylarginine deiminases

The protein-deimination process is catalysed by a family of calcium-binding enzymes, the peptidylarginine deiminases (EC 3.5.3.15.). To date, five isoenzymes have been identified. Their genomic organisation, subcellular localisation and tissue-specific expression have been more or less determined (for review see Vossenaar, Zendman, van Venrooij, & Pruijn, 2003).

All PADI genes are localized in one cluster at 1p36.13; within a 300 kb region (Chavanas et al., 2004;