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Review

Citrullination and autoimmunity

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ABSTRACT

Autoimmune diseases are characterized by the body's own immune system attack to the self-tissues, a condition enabled, in predisposed subjects, by the reduction of self-tolerance. A central role has been recently recognized to post-translational modifications, since they can promote generation of neo-(auto)antigens and in turn an autoimmune response. During the last years great attention has been paid to citrullination, because of its role in inducing anti-citrullinated proteins/peptide antibodies (ACPA), a class of autoantibodies with diagnostic, predictive and prognostic value for Rheumatoid Arthritis (RA). Nonetheless, citrullination has been reported to be a process present in a wide range of inflammatory tissues. Indeed, citrullinated proteins have been detected also in other inflammatory arthritides and in inflammatory conditions other than arthritides (polymyositis, inflammatory bowel disease and chronic tonsillitis). Moreover, environmental exposure to cigarette smoke and nanomaterials of air pollution may be able to induce citrullination in lung cells prior to any detectable onset of inflammatory responses, suggesting that protein citrullination could be considered as a sign of early cellular damage. Accordingly, citrullination seems to be implicated in all those para-physiological processes, such as cells death pathways, in which intracellular calcium concentration raises to higher levels than in physiologic conditions: hence, peptidylarginine deiminases enzymes are activated during apoptosis, autophagy and NETosis, processes which are well-known to be implicated in autoimmunity. Taken together, these data support the hypothesis that rather than being a disease-dependent process, citrullination is an inflammatory-dependent condition that plays a central role in autoimmune diseases.

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1. Introduction

Autoimmune diseases are characterized by the body's own immune system attack to the self-tissues. Normally, the immune system does not react against self-antigens, because of the processes of central and peripheral immune tolerance. In predisposed subjects the abnormality in self-tolerance might be enabled by post-translational modifications, since these processes might promote generation of neo-(auto)antigens. During the last ten years great attention has been paid to citrullination, because of its role in inducing anti-citrullinated proteins/peptide antibodies (ACPA), a class of autoantibodies with diagnostic, predictive and prognostic value for Rheumatoid Arthritis (RA).

Citrullination is the post-translational modification of protein-bound arginine into the nonstandard amino acid citrulline, catalyzed by Ca^{2+} dependent peptidylarginine deiminases (PAD) enzymes. Each converted molecule (arginine to citrulline) leads to a 0.984 Da mass increase and the loss of one positive charge [1]. This latter change determines a substantial effect on the acidity of the amino acid side chain, changing the iso-electric point (pI) from 11.41 for arginine to 5.91 for citrulline [2]. Moreover, it can influence the hydrogen bond forming ability and the interaction with other amino acidic residues of the same protein or of another one. Thus, a conformational alteration may occur, and consequently a possible functional alteration and change in the protein half-life, so that a new protein is finally created. Noteworthy, the modifications of proteins can generate new epitopes, thus causing the formation of new autoantigens, different from that to which the self has apprehended to be tolerant. Indeed, it is well established that small modifications can enhance the immunogenicity of the proteins, due to an enhanced protein unfolding and subsequent processing and exposure of the immunogenic epitopes [3]; to an increased uptake of the modified antigen by the antigen presenting cells (APC) [4]; and to an improved presentation through enhanced recognition by the APC [5]. Interestingly, it seems that citrullinated peptides, but not Epstein Barr Virus-derived citrullinated peptides, fit better in the HLA-DRB1 (DRB1*0401 or *0404) antigen binding grooves – the so-called shared epitope (SE) – than the corresponding arginine containing peptides [6]. This observation is confirmed by studies in rats immunizated with citrullinated collagen type II which develop a more frequent and a more severe form of arthritis than do those immunized with unmodified collagen type II [7].

1.1. Peptidylarginine deiminase enzymes (PAD)

The conversion of peptidylarginine into peptidylcitrulline is catalyzed by PAD [7]. To date, five isoforms of this enzyme have been identified with different tissue expression and consequently different functions [9]. PAD1 is predominantly expressed in the epidermis and the uterus. PAD2 has been found in muscle tissues, central nervous system (CNS), and hematopoietic cells, including mast cells and macrophages. PAD3 is localized in the hair follicles, while PAD4, formerly known as PAD5, has been found in neutrophils and eosinophils, spleen and secretory glands. Finally, PAD6 expression has been detected in eggs, ovaries, testis tissues, small intestine, spleen, lung, liver, skeletal muscle cells and in early embryos [10,11].

PAD induced citrullination has been studied in different physiological and pathological conditions. PAD1, physiologically implicated in the keratinization of the skin, has been demonstrated to be hypofunctional in psoriasis; on the other hand, PAD2, essential for myelin sheath stability and the plasticity of the brain, is hyperfunctional in multiple sclerosis. PAD4 reciprocally influences the expression of estrogen and p53 target genes, so it seems to play a role in tumorigenesis. Of note, citrullination catalyzed by PAD4, which physiologically alters the functions of chemokines and participates in antibacterial neutrophil extracellular traps (NETs) formation, is pathologically implicated in the generation of new autoantigens in RA. Moreover, because PAD is not expressed in the thymus [12], the likelihood that citrullination occurs in the thymus is low and T cells reactive to citrullinated antigens could be not eliminated, generating a possible immune reaction against citrullinated antigens. Citrullination could be triggered by smoking or infections and lead to ACPA production in susceptible individuals with SE containing HLA molecules and/or general autoimmunity marker protein tyrosine phosphatase non-receptor type 22 (PTPN22) [13].

Besides eukaryotes, PADs have been found only in one prokaryote, *Porphyromonas Gingivalis* (PPAD), a major pathogen bacterium in periodontitis (PD). PPAD differs from human PADs in that it is not dependent on Ca^{2+}; further, it is active at higher pH and preferentially citrullinates C-terminal arginines, both the peptide-bound and the free ones [14,15]. The citrullinated peptides generated by *P. Gingivalis* are produced by the combined action of arginine gingipains cleaving polypeptides in short peptides with C-terminal arginines followed by rapid citrullination by PPAD. It is plausible that this may trigger an immunological response to citrullinated proteins in a subset of RA patients with PD, who have the SE.

It has been recently demonstrated that PAD4 may undergo to autocitrullination, a process that in one hand might inactivate the same enzyme, as a mechanism of control, but in the other one modifies the structure of the enzyme, increasing its recognition by human autoantibodies [16]. In addition, anti-PAD4 antibodies have been reported to have predictive and prognostic value in RA patients [17]. Interestingly, also PPAD autocitrullinates and is a common antigenic target; so antibodies generated against autocitrullinated PPAD could perpetuate the immune response through epitope spreading and cross-reactivity with citrullinated human proteins [14]. Nonetheless, Konig and colleagues have recently reported data disproving this hypothesis, since anti-PPAD antibodies do not correlate with ACPA levels and disease activity in RA and seem even to have a protective role for the development of PD in patients with RA [18].

1.2. Anti-citrullinated proteins/peptide antibodies (ACPA)

ACPA are a collection of partly cross-reactive antibodies recognizing citrulline-containing proteins and peptides. The ACPA response, often detected in assays capturing the vast majority of ACPA such as the cyclic citrullinated peptide (CCP) assay, can be divided into several partly cross-reactive fine specificities. Overall, ACPA binding to citrullinated proteins (i.e., citrullinated fibrinogen) cross-reacts with other citrullinated proteins (i.e., citrullinated vimentin) [19]. Presumably, these proteins contain multiple citrullinated residues [19]. Reactivity to a specific citrullinated peptide shows a more private recognition pattern, although these reactivities can also be partly cross-reactive. At present, it is not known whether the immune-reactivity against CCP peptides or peptides with sequences derived from citrullinated proteins reflect the ability of these ACPA to recognize citrullinated proteins present in the inflamed joint, although often otherwise speculated.

During the last years, the autoantibodies directed against cyclic citrullinated proteins (anti-CCP) have been object of different studies aiming to find a serological marker able to early confirm clinical diagnosis of RA and to predict disease evolution. History of ACPA starts in 1964 when fluorescence of perinuclear keratohyalin granules of human buccal cells, defined as anti-perinuclear factor antibodies (APF), was described. After, anti-keratin antibodies (AKA) were identified [20,21], showing, accordingly to APF, a high specificity for RA. Over the years, other candidate citrullinated autoantigens have been identified, such as fibrinogen, vimentin, fibronectin and α-enolase [22–25]. More recently, van Beers and coworkers coined the term 'citrullinome' referring to the whole citrullinated proteins, 53 in all, identified in sera and synovial fluid of RA patients [26].

ACPA are detectable in about 70% of RA patients [27]. First-generation CCP test (anti-CCP1) showed 68% sensitivity with 97–98% specificity [28]; a higher sensitivity (80%) and superior specificity (98%) was next obtained with the second-generation CCP test (CCP2), developed through several citrulline-containing peptide libraries

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