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HLA and Citrullinated Peptides in Rheumatoid Arthritis

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1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that mostly attacks synovial joints, although other tissues and organs can be affected. The final effect is usually the destruction of articular cartilage and ankylosis of the joints, with a prevalence of the wrist and small joints of the hand. Diagnostic criteria have recently been revised (Aletaha et al., 2010; Neogi et al., 2010). The prevalence of RA is about 1% in the total population, being women more affected than men in a ratio of approximately 2-3:1 (Alamanos & Drosos, 2005).

RA is considered an autoimmune disorder, although the etiology and pathogenesis of the disease remain unclear. A complex set of factors are involved in the onset of the disease, including genetic and environmental. The strongest genetic association is with the genes encoding major histocompatibility complex (MHC, HLA in human) class II molecules (Gregersen et al., 1987; Stastny, 1978), although other genes have been associated with RA, including *PTPN22*, *STAT4*, *TRAF1/C5*, and others.

Antibodies against the Fc fraction of IgG are found in the serum of about 80% of patients with RA. These autoantibodies are called rheumatoid factor (RF), and the consideration of RA as an autoimmune disease has largely been based on the presence of RF in the serum of patients. Nevertheless, the presence of RF is not exclusive of RA and that, together with the absence of definitive data demonstrating an arthritogenic effect of RF, suggest that these antibodies are produced as a consequence of the immune response rather than being the cause of it (Nemazee, 1985; Tarkowski et al., 1985). However, the adaptive immune response seems to play an important role in the disease as suggested by the strong association of RA with the presence of some HLA class II alleles. Autoantibodies against citrullinated proteins (ACPAs) have been described in the serum of about 50-70% of RA patients in comparison with about 2% of the healthy population (Avouac et al., 2006; Kroot et al., 2000; Nishimura et al., 2007; Schellekens et al., 2000; van Gaalen et al., 2004; Vincent et al., 2002). The presence of ACPAs is very stable during the course of the disease and is quite specific for RA. These antibodies can be detected several years before of symptomatic disease, making the presence of ACPAs a good clinical marker for RA. Patients containing ACPAs in the serum usually have a more severe disease. The presence of these antibodies correlates very well with the

presence of some of the HLA-DR alleles containing the “shared epitope” (see below). All of these data have led to the postulation that there actually are two different disorders (Klareskog et al., 2008). However, the cause of the specificity of the generation of ACPAs in RA and whether the antibodies are pathogenic or secondary to the joint inflammation remain unanswered.

Many reports have been published in the last years describing some of the features of the antibodies that recognize citrullinated proteins and showing some of the proteins that are target of these autoantibodies. The generation of an effective B cell response requires the recognition by specific CD4⁺ T cells of peptides derived of the antigen in the context of MHC class II molecules. In this chapter some of the data indicating the importance of anti-citrulline responses will be reviewed and concretely emphasize on reviewing the last reports dealing with MHC presentation and T cell responses to citrullinated peptides will be done.

2. HLA and rheumatoid arthritis

The strongest genetic association of RA susceptibility is with some specific HLA class II alleles. In Northern Europe, the strongest association is with the serotype HLA-DR4 (Jaraquemada et al., 1986; Stastny, 1978). The association is with some allelic variants of HLA-DR4, including DRB1*0401, *0404, *0405 and *0408. However, other HLA-DR4 subtypes do not confer predisposition to RA. In Southern Europe and other populations the susceptibility to RA is associated to alleles other than DR4. Thus, DRB1*0101, *0102, *1402 and *1001 have been reported with predisposition to RA (Cutbush et al., 1993; de Juan et al., 1994; Gonzalez-Escribano et al., 1999; Hameed et al., 1997; Lacki et al., 2000; Mody & Hammond, 1994; Poor et al., 2007; Salvarani et al., 1999; Sanchez et al., 1990; Yelamos et al., 1993). A major feature shared by the alleles that confer susceptibility to RA is the presence of some residues at position 67 and 70-74 of the third hypervariable region of DRB1 (Table 1). Thus, the presence of specific residues in these positions (L...(Q/R)(K/R)RAA) led to the proposal of the “shared epitope” hypothesis (Gregersen et al., 1987), in which the molecular basis for the association of some alleles with RA was restricted to this critical region in the β chain of HLA-DR molecules. The P4 residue of the peptide core directly interacts with some of the residues that are part of the shared epitope (SE). Other residues are exposed to outside the binding groove. Thus, the side chains of these amino acids could be involved in the pathogenesis of the disease by defining the peptide preference or directly interacting with the T cell receptor (TCR), influencing the T cell repertoire selection, and specific T cell activation. Alternatively, molecular mimicry of this HLA-DR region and proteins from pathogenic agents might contribute to the disease process. Other mechanisms have been proposed to explain the role that the SE plays in the disease, including direct triggering by the five-amino acid SE sequence leading to NO production (Ling et al., 2007), ability to bind to heat shock proteins (Auger et al., 1996), and the ability to present citrullinated peptides (Hill et al., 2003). A putative “protective epitope” has also been defined for the same region, with the sequence DERAA, corresponding to DRB1*0402, *1102, *1301, *1302, and *1304, and is associated with a less severe disease (van der Helm-van Mil et al., 2005).

HLA genes show strong linkage disequilibrium, so they segregate as haplotypes with a low recombination rate, specially between HLA-DR and HLA-DQ. Different data indicate that some HLA-DQ alleles that segregate with given HLA-DR alleles play an important role in RA, although these data are not totally understood. The combination of the presence of the SE-containing HLA-DR alleles and specific HLA-DQ alleles opened the possibility that

peptides containing the SE can be presented to T cells in the context of specific HLA-DQ, shaping the T-cell repertoire (Salvat et al., 1994).

HLA-DRB1 allele	Amino acid residue					
	67	70	71	72	73	74
High risk						
*04:01	L	Q	K	R	A	A
*01:01	-	-	R	-	-	-
*01:02	-	-	R	-	-	-
*04:04	-	-	R	-	-	-
*04:05	-	-	R	-	-	-
*04:08	-	-	R	-	-	-
*10:01	-	R	R	-	-	-
Protection or low risk						
*04:02	I	D	E	-	-	-
*07:01	I	D	R	-	G	Q
*11:02	I	D	E	-	-	-
*13:01	I	D	E	-	-	-
*13:02	I	D	E	-	-	-
*13:04	I	D	E	-	-	-
*15:01	I	-	A	-	-	-

Table 1. Residues in the shared epitope positions in HLA-DR molecules differentially associated to RA

3. Citrullination

Citrullination is a post-translational protein modification that consists in the deimination of the positive charged amino acid arginine, generating the neutral amino acid citrulline (Figure 1). The process requires high concentrations of Ca^{2+} and is produced in inflammatory environments (Baeten et al., 2001; Chavanas et al., 2004; Vossenaar et al., 2003). Other mechanism that triggers arginine deimination is apoptosis (Baeten et al., 2001). Environmental insults such as smoking increases the expression of PAD2 and induces citrullination in the mouse (Makrygiannakis et al., 2008).

The conversion of arginine to citrulline is carried out by a family of enzymes known as peptidyl arginine deiminases (PADs) (Vossenaar et al., 2003). Five members of this family of enzymes have been described in human (PAD1, PAD2, PAD3, PAD4 and PAD6). The members of this family are differentially expressed in many cell types (including neutrophils, monocytes, and macrophages) and tissues (Migliorini et al., 2005; Nijenhuis et al., 2004; van Venrooij & Pruijn, 2000; Vossenaar et al., 2003; Wysocka et al., 2006). Thus, PAD2 and PAD4 are expressed in the synovium of patients with RA, but PAD1, PAD3 and PAD6 are not (Foulquier et al., 2007). At least some functional haplotypes of PAD4 are associated with RA (Suzuki et al., 2003). Interestingly, PAD4 is capable of self-citrullination, which can regulate its activity and control the citrullination of other proteins (Andrade et al., 2010).

Citrullinated proteins have been detected in several inflamed tissues: arthritic joints (Vossenaar et al., 2004a), brain (Nicholas & Whitaker, 2002), muscle and lymphoid organs (Makrygiannakis et al., 2006) and lungs (Bongartz et al., 2007; Klareskog et al., 2006). In addition, some proteins from the epidermis and central nervous system are constitutively citrullinated (Kubilus et al., 1979; Nicholas et al., 2003).

The function of citrullination is not totally understood, although it is important in some physiological processes such as apoptosis (Asaga et al., 1998) and cell differentiation (Senshu et al., 1996). The loss of a positive charge can produce changes in some relevant protein features. Thus, electrostatic interactions are usually important in generating and maintaining protein structures. A citrullinated protein modifies some of the interactions that stabilize the native conformation, and decreases its isoelectric point, affecting the secondary and tertiary structure, which can result in a different protein folding that may modify the function of the protein (Gyorgy et al., 2006). Regarding the specific protein functions affected by citrullination it has been reported that arginine deimination influences protein-protein interaction (Tarcza et al., 1996), and can modulate signalling potency (Proost et al., 2008). In addition, citrullinated proteins often change their sensitivity to degradation by proteolytic enzymes (Pritzker et al., 2000).

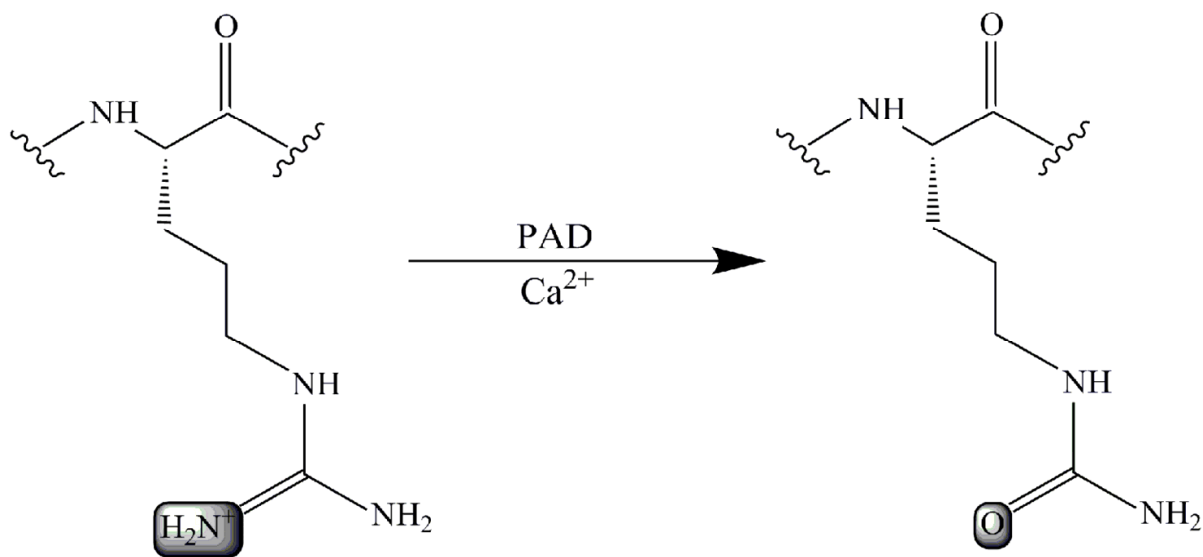


Fig. 1. **Conversion of arginine to citrulline.** The protein posttranslational modification known as citrullination consists in a deimination of arginine to citrulline. The reaction is carried out by an enzyme of the family of peptidyl arginine deiminases (PAD), and requires high concentration of Ca^{2+} . This reaction results in the loss of a positive charge in the protein.

4. Citrulline and rheumatoid arthritis

As mentioned above, the presence of citrullinated proteins is detected in the joints of patients with RA (Baeten et al., 2001), although it is not exclusive for rheumatoid synovial tissue (Vossenaar et al., 2004a). The specificity of citrullination has not been solved and several proteins have been found to be citrullinated in the synovium, including vimentin (Bang et al., 2007; Vossenaar et al., 2004b), fibrinogen (Masson-Bessiere et al., 2001), and collagen type II (Klareskog et al., 2008). The role of these modified proteins in the joints remains unknown, although some of these proteins are known targets of the autoimmune response. Thus, specific antibodies have been detected in RA patients that recognize citrullinated filaggrin (Nijenhuis et al., 2004; Schellekens et al., 1998; Sebbag et al., 1995; Simon et al., 1993), fibrinogen (Bang et al., 2007), vimentin (Burkhardt et al., 2005; Despres et al., 1994; Hayem et al., 1999; Hueber et al., 1999) and collagen type II (Burkhardt et al., 2005).

A relevant feature of ACPAs is that their presence is RA specific. Thus, in contrast with RF, patients with inflammatory diseases other than RA rarely carry ACPAs in serum. It still remains unclear why ACPAs are present in the serum of most RA patients but absent in the serum of other systemic autoinflammatory diseases.

As with RF, the generation of ACPAs in the serum of RA patients can occur several years before the onset of the disease (Aho et al., 2000; Kurki et al., 1992; Nielen et al., 2004; Rantapaa-Dahlqvist et al., 2003). The detection of these ACPAs can be used as clinical tests to predict the clinical course of the disease (Kastbom et al., 2004; Ronnelid et al., 2005). There are some clinical and genetic differences between ACPA⁺ and ACPA⁻ RA patients. Clinically, ACPA⁺ RA patients have a more severe disease course than patients without detectable ACPAs (Forslind et al., 2004; Kastbom et al., 2004; Kroot et al., 2000; Ronnelid et al., 2005). Genetically, the detection of ACPAs in the serum of RA patients correlates very well with the presence of HLA-DR alleles containing the SE, which does not happen with RF. Some reports have shown that the presence of HLA-DRB1 alleles containing the SE is directly related and restricted to the ACPA⁺ subset of RA (Huizinga et al., 2005; van der Helm-van Mil et al., 2006) and SE alleles influence both the magnitude and the specificity of this RA-specific antibody response (Verpoort et al., 2007). Other HLA-DRB1-independent genetic associations in the HLA region to ACPA positivity have been reported (Okada et al., 2009). In contrast, ACPA⁻ RA is not related with the SE-carrying HLA-DRB1 alleles and it has been associated with HLA-DRB1*03 (Irigoyen et al., 2005), an DRB1 allele that does not contain the SE. Taking together, it seems clear that ACPA⁺ and ACPA⁻ RA do not present the same genetic background or clinical course and evidence strongly suggest that these are two different RA subsets, so they should be considered as different entities when treated.

Since ACPAs are developed before the onset of the disease and their presence predicts a more severe clinical course, this seems to indicate that the immune response against citrullinated proteins contribute to the pathogenesis of this form of RA.

5. Citrullinated peptides and HLA

The SE contains residues 70-74 of the DR β chain, and is located in one α -helix of the binding groove. These residues are located in a position such that some of them can interact with the peptide bound to the HLA-DR molecule. Concretely, the crystal structures of HLA-DR1 and HLA-DR4 with different peptides have shown that the residues Lys71 in DRB1*0401 and Arg71 in DRB1*0101 directly interact with the amino acid located in position 4 (P4) of the peptide core bound to the binding groove of HLA-DR molecules (Dessen et al., 1997; Rosloniec et al., 2006). The binding motifs of the peptides associated to HLA-DR1 and HLA-DR4 were described years ago. More recently, our group reported an exhaustive analysis of the peptide pool associated to HLA-DR10 by mass spectrometry and identified the anchor motif of the peptide repertoire bound to this RA-associated allele (Alvarez et al., 2008). This motif was consistent with a more recent report by Kwok's group using an approach based on binding assays (James et al., 2010). An important structural information extracted from these data is that HLA-DR molecules containing the SE do not bind peptides with basic residues in P4 position. This is due to the presence of basic residues at position 71 of the HLA-DR β chain (table 1).

Conversion of the basic amino acid arginine to the neutral citrulline produces the loss of a net positive charge on the protein or peptide that suffer this post-translational modification. Thus, citrulline is a neutral, polar, large amino acid with structural features similar to

glutamine. Interestingly, peptides with arginine in P4 are poorly tolerated for the HLA-DR molecules that comprise the SE alleles (Fremont et al., 1996; Friede et al., 1996), while peptides with glutamine in P4 of the binding core have been described for DRB1*0101, DRB1*0401 and DRB1*1001 (Alvarez et al., 2008; Dengjel et al., 2005; Muntasell et al., 2004; Stern et al., 1994; Verreck et al., 1996). Basic residues, such as arginine or lysine, in P4 position of the peptide core produce electrostatic repulsion with the basic residues in position 71 of the β chain in the HLA-DR molecules that contain the SE. However, glutamine can accommodate well in the pocket and can be stabilized by hydrogen bonds with Arg71 or Lys71 in the HLA-DR β chain. Thus, positively charged amino acids (e.g., arginine) in P4 inhibit peptide binding to RA-related HLA-DR molecules containing the SE, whereas peptides with uncharged polarity (e.g., glutamine) are bound to these molecules with high affinity (Hammer et al., 1994; Hammer et al., 1995). Peptides with citrullin in P4 would interact favourably at the P4 anchoring pocket of SE-containing HLA-DR molecules. This was confirmed both for DRB1*0101, DRB1*0401 (Hill et al., 2003) and DRB1*1001 (James et al., 2010). Concretely, modified peptides derived from joint associated proteins were able to bind to RA-associated MHC molecules: the peptide spanning residues 65-77 from vimentin, vimentin (65-77) to DRB1*0101 and DRB1*0401 (Hill et al., 2003), and peptides vimentin (58-72), Fib A (737-751), Fib B (68-82) and cartilage intermediate layer protein CILP (982-996) to DRB1*1001 (James et al., 2010). These data open the possibility that in the inflamed joint, some arginines may be deiminated by activated PAD2 or PAD4 and, after protein catabolism, citrulline-containing peptides would be bound to SE HLA-DR molecules.

The peptide repertoires associated to many MHC molecules have been described, both for MHC class I and for MHC class II. However, up to now, no peptide with citrulline in P4 has been reported to be a natural ligand of any HLA-DR molecule. Some reasons make the identification of citrullinated peptides from the peptide repertoire bound to HLA-DR molecules very difficult. First, the conditions to obtain high level of protein citrullination are not totally controlled, although some protocols have been reported, as increasing intracellular calcium by the addition of ionomycin to the cell culture (Vossenaar et al., 2004c). Second and more important, after deimination induction, most of the peptides will remain containing arginine instead of citrulline, and probably, the amount of citrullinated peptides in the peptide pool will be low. Mass spectrometry analysis give information of the most abundant peptides in the MHC-associated peptide pools making complicated to find a low-abundance citrullinated peptide. An approach that could be used to solve these problems would be to enrich citrullinated peptides in the sample. Antibodies specific for citrullinated peptides can not be used because they can recognize some peptides but not others. A technique for the specific enrichment of citrulline-containing peptides has been described, based on the immobilization of a glyoxal derivative that reacts exclusively with the ureido group of the citrulline residue at low pH (Tutturen et al., 2010). The ureido group can be chemically modified by diacetyl monoxime and antipyrine (Senshu et al., 1992). The chemically modified citrulline can be detected, using a specific antibody, by Western blotting and immunohistochemistry (Makrygiannakis et al., 2008). Peptides or proteins containing the modified citrulline can also be detected by mass spectrometry (Stensland et al., 2009).

6. T cell responses to HLA-restricted citrullinated peptides

The induction of a typical humoral response that results in a production of classes of antibodies others than IgM requires the help of CD4 T cells. T cells recognize complexes

formed by MHC molecules and peptides derived from antigenic proteins. In the case of ACPAs, the targets of the immune response are modified self proteins, as vimentin, fibrinogen and collagen type II. CD4 T cells that help in the generation of an anti-citrullinated proteins B cell response do not necessarily recognize citrullinated peptides. However, a role of T cell responses in RA is well known, which makes the identification of T cell responses against citrullinated peptides presented in the context of RA-related HLA-DR of great interest. These peptides could be citrullinated outside the binding core, in the core positions other than P4, or in P4, as discussed above.

In the last years, T cell responses to citrulline-containing peptides have been studied. First, using DR4-IE transgenic mice (expressing the chimeric molecule DR4-IE, that contains the DR4 binding groove and part of the murine class II molecule), Hill and collaborators demonstrated that deimination of arginine to citrulline significantly increased the peptide-MHC affinity when arginine was in P4 position. In addition, activated CD4⁺ T cells were detected in these transgenic mice against a peptide spanning residues 65 to 77 of vimentin, vimentin (65-77), which had a citrulline in position 70 instead of the arginine of the unmodified protein. These results revealed that HLA-DRB1 alleles with the SE could initiate an specific autoimmune response to citrullinated self-antigens in DR4-transgenic mice (Hill et al., 2003). In this animal model, citrullinated fibrinogen induced arthritis. The disease induced in these mice was characterized by synovial hyperplasia followed by ankylosis, but lacked a large leukocyte infiltrate. Specific humoral and cellular responses to citrullinated components were observed, which were absent in wild-type mice immunized with citrullinated or unmodified fibrinogen and in transgenic mice immunized with unmodified fibrinogen (Hill et al., 2008). HLA-DRB1*0401-restricted T cell reactivity to fibrinogen (371-383) was clearly seen in transgenic mice after immunization with either citrullinated fibrinogen or unmodified fibrinogen, whereas no specific response to this peptide was detected in wild-type mice. Ten peptides derived from α , β or γ chains of human fibrinogen containing an aliphatic or aromatic residue in P1 position of the binding core and arginine or citrulline at P4 were tested to generate T cell responses. Only one citrullinated peptide, Fib α_{R84Cit} , induced a consistent T cell response, whereas no response was seen against the corresponding arginine-containing peptide Fib α_{79-91} . Therefore, these data confirm that a citrullinated protein can be arthritogenic when RA-associated alleles are expressed, and specific T cell responses to citrullinated peptides are part of the immune response. Citrullinated peptides-specific T cell activation plays an important role in the development and progression of arthritis in this animal model. Thus, when given prior to disease onset, treatment with CTLA-4Ig, an agent that blocks T cell costimulation, prevented T cell activation induced by citrullinated human fibrinogen. This effect was not seen with non-specific IgG1 (Yue et al.).

Other approach using the mouse model detected that a response against citrullinated peptides could be generated even when the antigen was administered in unmodified form. Concretely, HEL was used as a model antigen, and T cells specifically reactive to citrullinated epitopes were detected among the responding repertoire to immunization with an unmodified HEL protein. In addition, antigen presenting cells (APCs), including dendritic cells and peritoneal macrophages, were able to present citrullinated peptides when provided an intact, unmodified HEL *ex vivo* (Ireland et al., 2006). Therefore, APCs were capable to capture and process the antigen, to deiminate some specific arginine residues and to present some citrullin-containing peptides to T cells in a correct way to induce an specific response against citrullinated peptides.

More than 90% of patients positive for citrullinated vimentin-specific ACPAs carry SE-containing HLA-DRB1 alleles. In a DR4-transgenic mouse model, animals were immunized with 33 citrulline-containing peptides (all possible citrullinated peptides of human vimentin) and tested for T cell reactivity. T cell responses were generated against some of these peptides restricted by HLA-DRB1*0401 (vimentin (26-44) and vimentin (415-433)). Antigen presenting cells were able to generate these peptides from entire vimentin. In addition, T cell reactivity against these citrullinated peptides derived from vimentin were observed when PBMCs from ACPAs-positive, HLA-DR4-positive patients with RA were used (Feitsma et al.). These data strongly suggest the presence of HLA-DRB1*0401-restricted T cell responses against citrullinated vimentin-derived peptides in RA patients. The data do not exclude T cell responses against non-citrullinated peptides restricted by this or other HLA-DRB1 alleles, that also could facilitate a humoral response against citrullinated epitopes.

The generation of T cell responses against citrullinated peptides has also been confirmed for other autoantigens. Thus, a proliferative response was observed in more than 60% RA patients after stimulation with citrullinated aggrecan-derived peptide, aggrecan (84-103) (von Delwig et al., 2010). This response was absent in PBMCs from healthy controls, and there was no response to the unmodified aggrecan analog peptide, indicating that citrulline residue is required for T cell recognition. In addition, cytokine production was analyzed by ELISA and intracellular cytokine analysis. High levels of the proinflammatory cytokine interleukin-17 (IL-17) was produced by PBMCs from RA patients in response to stimulation with citrullinated aggrecan. This IL-17 production was absent when PBMCs from RA patients and healthy controls were stimulated with the unmodified aggrecan-derived peptide. Therefore, citrullinated aggrecan-specific T cells may play a role in the pathogenesis of RA and in the inflammatory process.

Most of the T cell responses to citrullinated peptides have been generated in models that express HLA-DRB1*0401. In addition, responses against citrullinated peptides restricted by the RA-associated, SE-containing HLA-DRB1*1001 molecule have been obtained (James et al., 2010). Authors demonstrated that HLA-DRB1*1001 can accommodate citrulline in three anchor positions, and three of the modified peptides that were evaluated developed specific CD4⁺ T cell responses. These peptides derived from fibrinogen α , fibrinogen β and cartilage intermediate-layer protein, and these data suggest a role for these three proteins as relevant antigens in RA in HLA-DRB1*1001⁺ patients. In addition, T cell clones specific for these sequences proliferated only in response to citrullinated peptides. One more time, these data suggest that deimination of arginine can have as a consequence the generation of new HLA-DR ligands that can be recognized by T cells as neoepitopes, and may play an important role in the initiation or progression of RA. As described recently, T cell responses to other post-translational modifications may play a similar role in generating inflammatory responses. One of this could be carbamylation of lysine to homocitrulline. Thus, mice were immunized with carbamylated peptides, which induced chemotaxis, and T and B cell responses. Mice immunized with carbamylated peptides developed erosive arthritis when citrullinated peptides were injected intra-articularly. In addition, T and B cells induced arthritis after adoptive transfer into normal recipients (Mydel et al., 2010). Therefore, the T cell response to homocitrulline-derived peptides, as well as the subsequent production of anti-homocitrulline Abs, was critical for the induction of autoimmune responses against citrulline-derived peptides which may provide a novel mechanism for the pathogenesis of arthritis.

Constitutive protein citrullination occurs in some tissues in absence of inflammation, which imply the existence of tolerance against these modified proteins. The thymus is the organ where the immunocompetent T cell repertoire is generated. During selection processes to generate central T cell tolerance, about 95-97% of the thymocytes die by apoptosis, which is an inductor of citrullination. Thus, PAD activity and arginine deimination may be active in this organ. Citrullinated peptides that bind to HLA-DR molecules in the thymus should not be able to induce an immune response in periphery. Differences in the machinery of antigen processing have been reported between thymic cells and other presenting cells. Thus, the identification and analysis of HLA-DR-associated citrullinated peptides in the thymus could reveal which peptides can generate central tolerance.

7. Conclusions

The finding that the sera of most RA patients contain antibodies specific for citrullinated proteins opened the possibility of a new mechanism in the etiology of the disease. These antibodies are specific for RA, can be detected years before the development of the disease, and correlate with the presence of SE-containing alleles. In the last years, relevant advances on the identification of the citrullination process in the inflamed joints by PADs' activity, the presentation by RA-associated HLA-DR molecules that contain the SE, and T cell responses against citrullinated proteins have been made. Nevertheless, it remains to be defined which citrullinated peptides are really involved in the development of the disease in humans and if any of them can efficiently be presented in the context of various SE-containing HLA-DR molecules.

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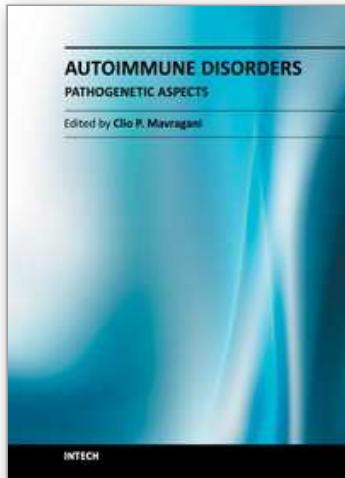
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