Journal of Autoimmunity xxx (2018) 1–10

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Expression level of risk genes of MHC class II is a susceptibility factor for autoimmunity: New insights

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ARTICLE INFO

Article history:
Received 31 October 2017
Received in revised form
28 December 2017
Accepted 29 December 2017
Available online xxx

Keywords:
Antigen presenting cells
Autoantigens
MHC polymorphism
RNA processing
Untranslated region

ABSTRACT

To date, the study of the impact of major hystocompatibility complex on autoimmunity has been prevalently focused on structural diversity of MHC molecules in binding and presentation of (auto)antigens to cognate T cells. Recently, a number of experimental evidences suggested new points of view to investigate the complex relationships between MHC gene expression and the individual predisposition to autoimmune diseases. Irrespective of the nature of the antigen, a threshold of MHC-peptide complexes needs to be reached, as well as a threshold of T cell receptors engaged is required, for the activation and proliferation of autoantigen-reactive T cells. Moreover, it is well known that increased expression of MHC class II molecules may alter the T cell receptor repertoire during thymic development, and affect the survival and expansion of mature T cells. Many evidences confirmed that the level of both transcriptional and post-transcriptional regulation are involved in the modulation of the expression of MHC class II genes and that both contribute to the predisposition to autoimmune diseases. Here, we aim to focus some of these regulative aspects to better clarify the role of MHC class II genes in predisposition and development of autoimmunity.

Contents

1. Introduction

The MHC (Human Leukocyte Antigens-HLA in humans) are highly polymorphic surface heterodimeric proteins with a key role in presenting antigens to T cells. The antigen presentation to cognate T cells is a fundamental prerequisite to stimulate a specific

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https://doi.org/10.1016/j.jaut.2017.12.016
0896-8411/

immune response. These molecules are encoded by MHC class I and class II genes that play a central role in the genetic predisposition to autoimmune diseases (AD) [1].

The most accepted mechanism responsible of AD is a breakdown in the immunological tolerance in the central hematopoietic tissues. A developing thymocyte first encounters a highly heterogeneous array of self peptide-MHC complexes on thymic APCs (antigen presenting cells). Based on the affinity/avidity by which the TCRs (T cell receptor) bind peptide-MHC complexes, thymocytes undergo processes of thymic positive or negative selections. As a consequence, the peripheral T cell repertoire is largely composed of $CD4^+$ T cells capable of mounting immune responses against an essentially limitless universe of foreign antigens, but also by some autoreactive cells that, evading negative selection, possess the potentiality to cause autoimmunity [2].

Notwithstanding this alteration of immune tolerance, some MHC genes are strongly associated with AD. The MHC polymorphisms mainly result in a variation of specific amino acid residues within the antigen-binding grooves, with an impact on the repertoire of self-peptides presented to autoimmune T cells. The identification of specific MHC genes associated to AD has remained for a long time difficult due to the great variability, the high gene density and extensive linkage disequilibrium (LD) that exists among genes throughout this locus. In the recent years, GWAS (genome wide association studies) based on SNP (single nucleotide polymorphism) as genetic markers, allowed the univocal association between specific MHC alleles, haplotype and AD [3–5]. Moreover, the reason why only certain MHC alleles predispose to autoimmunity, and why we observed an AD comorbidity so frequently, are still open questions. It is clear that specific MHC alleles may encode for heterodimeric molecules able to bind several self-peptides, either wild-type or modified forms, in a manner capable of eliciting different autoimmune phenotypes. Moreover, as the expression levels of the MHC alleles quantitatively influence the encoded surface heterodimers, the gene transcription and the mRNA processing markedly contribute to the strength of immune response.

In this review, we will focus on MHC class II genes predisposing to the celiac disease (CD) [6] and type 1 diabetes (T1D) [7], in order to discuss the importance of the allele specific expression profile in the establishment of autoimmunity. The role and impact of genetic variability in MHC non-coding regions on the onset of autoimmune diseases will also be deepened.

2. HLA molecules manage self-antigen presentation

HLA class II are heterodimeric molecules composed by an alpha and a beta chain. Each chain is constituted by a highly polymorphic domain (α1 and β1) and by a highly conserved domain (α2 and β2) [8].

The α1 and β1 domains delimited a groove where antigenic peptides allocate. The availability of crystal structure of several HLA class II molecules [9,10] has revealed that the external site of binding groove is open and may harbor peptides with a variable length, approximately of 15–20 amino acids with a core region of 9 residues. Peptides interact with amino acid forming the binding groove through several hydrogen bounds linking different peptide residues, e.g. position 1 and 9 for binding to HLA-DQ8, or position 4, 6, 7 for binding to HLA-DQ2 [10]. The nature of amino acids delimiting the binding groove defines the specificity of antigenic peptides that will be presented by HLA molecules to cognate T cells. As the binding of peptides to HLA molecules is a fundamental prerequisite for the activation of a specific T cell response, the knowledge of peptide amino acid residues involved in the interaction (binding motif) has allowed the identification of pathogenic peptides relevant for several immune diseases. To date, algorithms are available efficaciously predicting HLA class II restricted epitopes trigger of autoimmune, allergic, or infectious diseases, both in human and murine systems. The great majority of these epitope predicting algorithms are public and can be consulted at the Immune Epitope Database and Analysis Resource platform (www.iedb.org) [11]. More recently, the SysteMHC Atlas (https://systemhcatlas.org/), a public database that aims at collecting, organizing, sharing, visualizing and exploring immunopeptidomic data generated by Mass Spectrometry is available. The SysteMHC Atlas mainly contains data of epitopes presented by human MHC class I and class II molecules, that have been collected from laboratories around the world and represents a very powerful platform for the systematic analysis of large immunopeptidomic data [12].

2.1. Central role of HLA-DQ heterodimers in celiac disease and type 1 diabetes pathogenesis

There are many evidences that CD is an immune-mediated disorder in which $CD4^+$ T lymphocytes specific for HLA-DQ2/DQ8 restricted gluten peptides play a fundamental role in the development of small intestinal atrophy, typical of acute disease [13]. Many studies support this finding, in particular the high association with MHC genes encoding for DQ2.5 (DQA1*05 and DQB1*02) and DQ8 (DQA1*03 and DQB1*03) heterodimers, and the isolation from jejunal mucosa of CD patients of gluten-specific T cells exclusively restricted by the disease-predisposing DQ2 and DQ8 molecules [14].

It is known that HLA-DQ2 and -DQ8 heterodimers bind peptides containing negative charged amino acids at the HLA binding sites; however, gluten proteins have few negatively charged residues. Pivotal studies demonstrated that gluten proteins have many glutamine residues substrate for deamidase activity of tissue transglutaminase (tTG), that converts certain glutamine in glutamic acid [15,16]. This deamidating activity by tTG provided the explanation for the strong and exclusive association between CD and HLA-DQ2/-DQ8 genes. The tTG-mediated deamidating reaction occurs specifically within the consensus sequence QXP, that is particularly abundant in gluten proteins [17]. In this way, gluten peptides acquire at the site of mucosal tissue the negative charges allowing their strong binding to HLA-DQ2 and -DQ8 molecules. Thanks to the availability of large peptide libraries, constituted by either overlapping peptides or peptides selected on the base of preferred HLA binding motifs, to date a large number of gluten peptides stimulating $CD4^+$ T cells have been characterized in CD patients [13,18].

Of note, DQ2 and DQ8 genes are susceptibility factors also for T1D and act as restriction molecules for pancreatic β-islet autoreactive $CD4^+$ T cells [19]. CD and T1D share several features, including other than genetic susceptibility genes also environmental factors, as gluten and microbioma changes, and inflammatory pathways [20]. **T1D and CD co-morbidities** are frequently diagnosed in young subjects, and a potential involvement of dietary gluten in T1D aetiology has been hypothesized [21,22]. Interestingly, as for gluten proteins, insulin and GAD65, the main islet autoantigens, are good substrates for deamidase activity of tTG. Similarly to gluten, it has been reported that post translational modification mediated by tTG, that enhances binding affinity for DQ2/DQ8 molecules, are key steps in determining the immunogenicity of insulin peptides [23].

2.2. Genetic variability at MHC class II locus in celiac disease and type 1 diabetes

The complexity of MHC region and the high LD makes too

Please cite this article in press as: C. Gianfran, et al., Expression level of risk genes of MHC class II is a susceptibility factor for autoimmunity: New insights, Journal of Autoimmunity (2018), https://doi.org/10.1016/j.jaut.2017.12.016