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Review

The putative role of endoplasmic reticulum aminopeptidases in autoimmunity: Insights from genomic-wide association studies

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ABSTRACT

Autoimmune diseases represent a heterogeneous group of conditions whose incidence is increasing worldwide. This has stimulated studies on their etiopathogenesis, derived from a complex interaction between genetic and environmental factors, aimed at finally improving prevention and treatment of these diseases.
In the autoimmune process, immune responses are generated against self antigens presented by Major Histocompatibility Complex (MHC) class I on the cell surface. These peptide/MHC class I complexes are generated and assembled through MHC class I antigen processing and presentation machinery. In the endoplasmic reticulum (ER), aminopeptidases ERAP1 and ERAP2 display distinct trimming activity before antigenic peptides are loaded onto MHC class I molecules.
The advent of new tools such as genome-wide association studies (GWAS) has provided evidence for new susceptibility loci and candidate genes playing a role in the autoimmune process for the recognized immune function of their transcripts. Genetic linkage has been discovered with MHC antigens and various autoimmune conditions. Recent GWAS showed the importance of ERAP1 and ERAP2 in several autoimmune diseases, including ankylosing spondylitis, insulin-dependent diabetes mellitus, psoriasis, multiple sclerosis, Crohn's disease.
In this review, we first provide a general overview of ERAP1 and ERAP2 genes, their biological functions and their relevancy in autoimmunity. We then discuss the importance of GWAS and the case–control studies that confirm the relevancy of ERAP single-nucleotide polymorphism associations and their linkage with particular MHC class I haplotypes, supporting a putative functional role in the autoimmune process.

Contents

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1. Introduction

Autoimmune diseases are a heterogeneous group of disorders affecting various organs or systems; epidemiological studies demonstrate an increased susceptibility of people with one immune disease to other autoimmune diseases [1] as a result of shared pathophysiological mechanisms. It is recognized that a complex interaction of genetic and environmental factors underlies the etiopathogenesis of autoimmune disorders [2]. As recently shown by genetic mapping studies, multiple genetic loci are responsible for disease susceptibility in insulin-dependent diabetes mellitus (Type 1 diabetes, T1D) [3], systemic lupus erythematosus (SLE) [4,5], multiple sclerosis (MS) [6], inflammatory bowel disease (IBD) [7], rheumatoid arthritis (RA) [8], and psoriasis [9]. Due to this complexity, it has been difficult to investigate the basic molecular mechanisms in the autoimmune process, whose understanding could contribute to the prevention, early diagnosis and timely treatment of these conditions.

Increasing evidence is being produced that autoimmunity derives from a failure to promiscuous thymic expression of peripheral tissue antigens (PTAs) [10,11] causing the escape of antigen-specific autoreactive T cells in the periphery. This suggests that a common and highly regulated mechanism possibly controls the transcription of the organ-specific antigen genes; therefore, possibly, different defects on this mechanism might produce different categories of autoimmune disorders [1].

In the autoimmune process, T helper (Th) cells [12] that escaped mechanisms of self-tolerance produce pro-inflammatory cytokines. These molecules initiate inflammation and provide T cell help to autoreactive B cells [13]. When activated/expanded, mature B cells transform in plasma cells producing autoantibodies, which, in turn, further contribute to the tissue inflammatory process and destruction. By encountering the self- or cross-reactive antigen, T helper cells activate, expand and differentiate into various effector subsets, including Th1, Th2 cells, T regulatory (Treg) and Tr1 cells [1,2]. Th1 and Th2 cells produce mutually inhibitory cytokine profiles: Th1 cells secrete interleukin 2 (IL-2) and interferon gamma (IFN-γ), while Th2 cells secrete interleukin 4 (IL-4), interleukin 5 (IL-5) and interleukin 10 (IL-10). Recent studies demonstrate a novel distinct $CD4^+$ T cell population (Th17) particularly involved in the pathogenesis of RA and MS [3] and producing interleukin 17 (IL-17), tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and granulocyte-macrophage colony-stimulating factor (GM-CSF) [14]. Nowadays, B regulatory cells [15] are also recognized as a distinct entity. They express CD5, a well-established negative regulator of T cell receptor (TCR) [16] and B cell receptor (BCR) signalling [17]. Through the production of IL-10 this population would protect against autoimmunity.

The incidence of autoimmune diseases is increasing worldwide [2]. This has stimulated investigations on their etiopathogenesis, especially with the advent of new tools, such as genome-wide association studies (GWAS) [18]. As a result, evidence was provided for new susceptibility loci and candidate genes in the disease process. Candidate genes have already been investigated as common susceptibility genes involved in immune regulation, in particular the immunological synapse and T cell activation. Among the identified candidates [19], HLA-DR molecules present autoantigens to T cells, cytotoxic T lymphocyte-associated antigen 4 (CTLA4) suppresses T cell activation, protein tyrosine phosphatase non-receptor type 22 (PTPN22) affects the T cell receptor signalling pathway, forkhead box P3 (FOXp3) regulates the differentiation of Tregs, the IL-2Rα/CD25 gene plays a pivotal role in the development and function of Tregs, the TNF-α gene is located on chromosome 6p21.3 and is at the basis of the increased risk for the association of T1D and autoimmune thyroid disease.

During the autoimmune process, immune responses are generated against peptides which are presented in the context of Major Histocompatibility Complex (MHC) class I molecules; these complexes are assembled in endoplasmic reticulum (ER) through MHC antigen processing and presentation machinery. MHC class I binding peptides are generated in the cytoplasm as proteolytic intermediates by degradation of endogenous proteins through the multicatalytic proteasome and other proteases (Fig. 1) [20]. A small fraction of such proteolytic intermediates are then transported into the ER by the transporters associated with antigen processing (TAP1 and TAP2) and further processed by ER aminopeptidases, ERAP1 and ERAP2, before being loaded onto MHC class I molecules [21]. MHC class I antigens are highly polymorphic [22] and are excellent genetic markers for individuality. Furthermore, as they are the primary components of host immune response, the genetic linkage with various immunological disorders have been extensively investigated and close linkages have been found in a number of diseases, including ankylosing spondylitis (AS), MS, T1D, Crohn's disease (CD).

Herein we first provide a general overview of ER aminopeptidases, their biological functions and their relevancy to autoimmune diseases such as AS, T1D, psoriasis, CD and MS, with particular reference to GWAS.

2. ERAP1, ERAP2 and their biological function

The ER aminopeptidase 1 (ERAP1) and the closely related ER aminopeptidase ERAP2, belong to the M1 family of zinc-metallopeptidase enzymes which share the consensus GAMEN and $HEXXH(X)_{18}E$ zinc-binding motifs essential for enzymatic activity [23]. Structural and phylogenetic analysis indicates that ERAP1 and ERAP2 belong to a distinct group of the M1 family of aminopeptidases that has been classified into “the oxytocinase subfamily of M1 aminopeptidases” [24]. Studies on the evolution of ERAP genes have suggested that ERAP1 and ERAP2 arose by gene duplication [25]. Of note, ERAP2 is absent in rodent genome although its phylogeny reveals that it was present in the primate-rodent common ancestor.

The expression of ERAP1 and ERAP2 is enhanced by IFN-γ and TNF-α in human cells [21,26]. These enzymes remove amino acids from unblocked N-termini of peptides or proteins playing important roles in several biological processes. In the ER, ERAP1 and ERAP2 have the potential to trim peptide antigens to optimal length for binding to MHC class I molecules [21]. Moreover, ERAP1 has been shown to bind directly to cytokine receptors such as TNF receptor 1 (TNFR1), IL-6α receptor and IL-1 type II receptor and promote IL-1β-mediated ectodomain cleavage to generate soluble receptors [27–29]. They are also involved in the regulation of blood pressure and angiogenesis [30,31]. Based on their multifunctional properties, these enzymes are known with many alias: ERAP1 is also designated endoplasmic reticulum aminopeptidase associated with antigen processing (ERAAP), adipocyte-derived leucine aminopeptidase (A-LAP), aminopeptidase regulating TNFR1 shedding (ARTS-1) and puromycin-insensitive leucine-specific aminopeptidase (PILS-AP), whereas ERAP2 is known as leukocyte-derived arginine aminopeptidase (LRAP). The Human Genome Organization (HUGO) Nomenclature Committee has approved ERAP1 and ERAP2 nomenclature, respectively, and for uniformity we will use these names throughout this article.

2.1. ERAP1 structure and their variants

The *ERAP1* human gene is located on the long arm of chromosome 5 (5q15) and consists of 20 exons spanning about 47 kilobases [32]. The zinc-binding motif HEXXH is encoded in exon 6, while the essential glutamic acid (E) residue is encoded in exon 7. The GAMEN motif, which was shown to be important for the enzymatic action of gluzincin aminopeptidases, is also encoded in exon 6. Two major ERAP1 protein isoforms are generated depending on the differences in exon 20: the longer isoform a (ERAP1-a) and the shorter isoform b (ERAP1-b). Recently, Kim et al. found that the isoform ERAP1-b is more abundant than that of the isoform ERAP1-a mRNA in various cell lines, and that the amount of the isoform ERAP1-b accounts for most of the cellular content of ERAP1 [33].