Erap-1 and il-23r as a leading genetic predictors of development of ankylosing spondyloarthritis

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Abstract. A review of the genetic aspects of ankylosing spondylitis (AS), a chronic inflammatory disease of autoimmune origin with a predominant lesion of the axial skeleton is presented. Since the beginning of the era of genome-wide search for associations, more than 150 loci associated with AS have been identified, but this explains no more than 30% of cases of inheritance. The review attempts to understand the role of the ERAP1 genes in the development of AS. Continuation of research in this direction will create the prerequisites for the emergence of new goals for targeted therapy.

Keywords*:* ankylosing spondylitis, ERAP1, IL-23R, single nucleotide polymorphism, genetics.

Ankylosing spondylitis (AS) is a chronic systemic disease characterized by inflammatory lesions of the spine, paravertebral tissues and sacroiliac joints with ankylosing of the intervertebral joints and the development of calcification of the spinal ligaments [1]. AS refers to continuously progressing disabling rheumatic diseases with a polymorphic clinical course, and therefore the diagnosis is established on average after 7-10 years from the onset of the first symptoms. Given this fact, it is not surprising that in recent years, interest in the early diagnosis of AS has sharply increased. In order to study its pathogenetic features, molecular genetic, immunogenetic, population genetic, twin and genealogical research methods are currently being actively pursued. In addition, with AS, organs and systems that are not related to the musculoskeletal system are often affected. Such extraskeletal manifestations primarily include uveitis, aortitis, nephritis, amyloidosis with kidney and intestinal damage, psoriasis. AS is characterized by a polymorphic clinical course, and therefore the diagnosis is made on average 7–10 years after the onset of the first symptoms. Hence, the growth of interest in recent years in the search for methods for the early diagnosis of this disease is understandable [2].

In order to study the pathogenetic features of AS, molecular genetic, immunogenetic, population genetic, twin and genealogical studies are currently being actively carried out. The role of a hereditary factor in the pathogenesis of AS is confirmed by a number of works [3], more than 156 single nucleotide variants associated with AS have been identified, but the significance of each gene in the development of the disease has not yet been determined [1, 3, 4]. similar receptors located on the surface of natural killer cells (NK cells) and CD4 + T cells, which leads to aberrant immunological reactions and the development of autoimmunity;

According to the related gene theory, HLA-B27 is just a marker for the nearby true locus of susceptibility to AS [5].

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HLA-B27

The incidence of AS is closely correlated with the prevalence of HLA-B27 around the world. For example, this antigen is found among Inuit and people of Scandinavian descent. The opposite is true for sub-Saharan African blacks, Australian Aborigines, and Japanese, in whom HLA-B27 is rare. But there are exceptions, for example, in West Africa, its frequency is comparable to that in European populations, but the incidence is lower. Perhaps this is due to the influence of the environment, since HLA-B27 is reliably associated with AS in representatives of the Negroid race [6]. In Sardinia (Italy), a high frequency of HLA-B27 among the population was revealed, but the incidence of AS is low. This paradox can be explained by the prevalence of non-pathogenic or weakly associated HLA-B27 subtypes. According to the European Bioinformatics Database Immuno Polymorphism Database, by 2013, more than 130 subtypes of HLA-B27 have been identified; the strongest association with AC is shown for HLA-B27 [7].

The HLA-B27 subtypes can influence the course of the disease. For example H. Li et al. showed that patients with B-27 have a higher risk of developing uveitis than patients with B-27 in the Chinese population. In 2016, Liye Chen et al. found that a mutation at the P97 position of HLA-B27 is associated with the development of AS [8]. The mechanism of this is not fully understood and may be due to an increase in the expression of free heavy chains (FHC), which requires verification.

The number of known HLA subtypes increases every year; a thorough check is necessary for their possible contribution to the development of the AS.

An unconditional step in understanding the mechanisms of genetic predisposition was the establishment of an association between the development of AS and the antigen of the major histocompatibility complex HLA-B27 [9]. This gene is located on the 6p21.3 chromosome. Its main function is to bind antigenic peptides to the cell surface for presentation to cytotoxic T lymphocytes. The role of the gene in the pathogenesis of AS was confirmed in the populations of Romania, among Arab and Moroccan patients and the population of Tunisia. The role of a number of polymorphisms of the B * 2704, B * 2705 gene in the populations of Wuhan (China) and the population of Hungary was revealed.

The haplotype (HLA-DPA1 and HLA-DPB1) is located on chromosome 6p21.3 and belongs to the group of the major histocompatibility complex [10]. The role of the rs422544 polymorphism of this haplotype has been confirmed in the pathogenesis of AS [11]. HLA-B60 and HLA-DQA1 are distinguished, which also play a role in the occurrence of AS. HLA-B60, class IB, is located on chromosome 6p21.3. Class I molecules play a central role in the immune system, presenting peptides derived from the lumen of the endoplasmic reticulum. They are present in almost all cells [12]. The combination of HLA-B60 and HLA-B27 causes a very high risk of developing AS [13]. HLA-DQA1 (major histocompatibility complex, class II, DQ alpha-1) is located on chromosome 6p21.3 and plays a central role in the regulation of the immune system, presenting peptides derived from extracellular proteins. Class II molecules are expressed in antigen-presenting cells (APC: B-lymphocytes, dendritic cells, macrophages) [14]. It has been found that it can play an important role in increasing susceptibility to AS among the Chinese [15].

An important role in the pathogenesis of AS is played by the gene ERAP1 located on chromosome 5q15 [10]. The ERAP1 gene (also known as ERAP1 and ARTS1) provides the necessary information for the endoplasmic reticulum to make aminopeptidase proteins. Aminopeptidase cleaves some cytokine receptor proteins on the cell surface, reducing their ability to transmit chemical signals into the cell, which affect the inflammation process [16]. The role of a number of polymorphisms in the pathogenesis of AS has been confirmed: rs27044, rs26653, rs2287987, rs27037, rs27434, rs10865331, rs17482078, rs10050860, rs30187 and rs2287987, as well as in the haplotypes 100 rs81760 / , Spaniards, Chinese, Iranians, Turks, Koreans and in the family variant of AC inheritance. Confirmed association of ERAP 1 with HLA-B27 and with its polymorphisms HLA - B * 27: 02 and B * 27: 04 [17]. The role of a number of polymorphisms in the AS rs11209026, rs11465804, rs7517847 has been revealed [24, 49, 13]. Polymorphism

rs11209026 affects the severity of the disease [18], rs17375018 is associated in HLA-B27-positive patients [2]. This gene has been confirmed in Europeans and Asians, in particular the Chinese and French. The authors Chen C., Zhang X., Li J., Wang Y. did not reveal an association of IL-23R polymorphism among the population of East Asia [13].

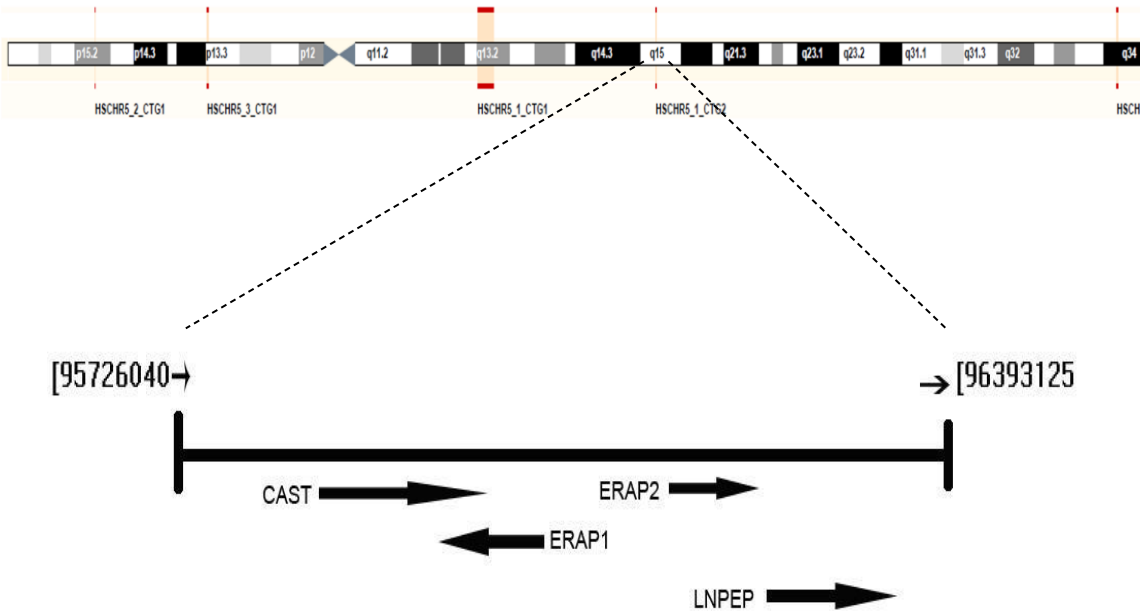
Endoplasmic Reticulum Aminopeptidase 1 (ERAP 1)

Ever since it was realized that HLA-B27 was only one actor in a large dramatis personae, the hunt for other candidate genes started. It was recognized that AS is likely to be an oligogenic disease [14] and several attempts have been made to look for non-major histocompatibility complex (MHC) genes that might contribute to increased susceptibility to the disease [20]. A genome wide association study (GWAS) of nonsynonymous single nucleotide polymorphisms (SNPs) identified a novel association of AS with ERAP1 [1].

The name ERAP1 is approved by the Human Genome Organization (HUGO) Nomenclature Committee. ERAP1 is known by various aliases, such as endoplasmic reticulum aminopeptidase associated with antigen processing (ERAP), adipocytederived leucine aminopeptidase (A-LAP), puromycin-insensitive leucyl aminopeptidase (PILS-AP) and aminopeptidase regulating tumor necrosis factor receptor I (TNFRI) shedding (ARTS-1). ERAP1 consists of 930 amino acids and was identified in mice following solubilization and fractionation of microsomes derived from liver and spleen [21]. At approximately the same time, human ERAP1, which has 941 amino acids and 86% sequence similarity to murine ERAP1 (ERAAP), was isolated from HeLa S cells and found to be the same enzyme as A-LAP and PILS-AP [19]. The human ERAP1 gene spans 54.61 kb of chromosome 5 from 96149849 to 96095244, on the reverse strand. The ERAP1 gene lies between the ERAP2 and Calpastatin (CAST) genes (Figure 1.).

Figure 1.

The Chromosome 5q15 locus with ERAP1 and other surrounding genes



The human ERAP1 mRNA has 2826 nucleotides and the protein has 941 amino acids. The two SNPs that have been reported to be strongly associated with *ERAP1* are rs30187 and rs27044 that lead to R528K and E730Q residue changes respectively.

The discovery of the ERAP1 association has brought new insights and renewed excitement into the field of AS research. After HLA-B27, which has an attributable risk of 50%, ERAP1 has the second strongest association, with an attributable risk of 26% [7]. Thus after 35 years of research since discovering the B27-AS genetic association, for the first time a strong and replicated genetic

association in AS has been identified. The known functions of ERAP1 have further triggered the expectations and imagination of the AS research community.

ERAP1 has two known functions. First, it aids the shedding of the membranebound cytokine receptors TNFRI, IL-1 receptor II (IL-1RII) and IL-6Rα. In fact ERAP1 was independently discovered as a molecule that bound cytokine receptors while searching for receptor shedding enzymes. This function of ERAP1 will be further described and the implications to AS pathogenesis discussed later.

The second known function of ERAP1 is the trimming of peptides within the ER for loading onto MHC-I molecules. ERAP1 has ERAP2, a structurally functionally related ER aminopeptidase, as a close ally in this function. Delineating the functional aspects of the AS-associated ERAP1 and ERAP2 polymorphisms has become a major focus of research. This novel connection could be the long sought bridge between HLA-B27 and AS.

Structure of ERAP1

ERAP1 and ERAP2 belong to the M1 family of zinc metallopeptidase enzymes, which share a HEXXH(X)18E zinc-binding motif [23]. Over the last 3 years there was a rigorous attempt to obtain a 3-dimensional model of ERAP1. Crystallographic structures can aid in predicting the possible functional effects of genetic polymorphisms on molecules.

The first attempt was to develop a molecular homology model of ERAP1 based on the crystallographic structure of a closely related protein, tricorn-interacting factor F3 (TIFF3), with which ERAP1 shares 32% amino acid sequence identity (residues 63– 665) [22]. The sequence similarity increases to 82% when considering the active catalytic site (residues 280–486) of ERAP1, in particular the zinc-binding domain. Based on the crystallographic structure of TIFF3 sequence alignment was performed and a homology model of ERAP1 was generated.

The model of ERAP1 contains a large cavity that could accommodate 9-mer peptides. Based on this structure, none of the SNPs associated with AS are near the catalytic site of the enzyme. There is still an explanation as to how these SNPs can affect the function of ERAP1. ERAP1 has a preference for leucine at the N-terminal end and in fact was characterized first as a Leucine Aminopeptidase [21]. Other hydrophobic residues like methionine, phenylalanine and alanine, when present at the N-terminal end still results in reasonably fast peptide trimming. The enzymatic activity decreases when hydrophilic residues like arginine, lysine, glutamic acid or threonine are present [20]. However, this change in enzymatic activity has been shown with variations in in the C-terminal end with a preference for hydrophobic residues [24]. It is now known that changes in the internal sequence of substrate peptides—and not just in the N- or C-terminal end— affect the enzymatic activity of ERAP1 [4]. Thus for internal sequences to affect the enzymatic activity, a close interaction between the entire peptide substrate and ERAP1 has to be considered. This close association is required for efficient enzymatic activity. Polymorphisms at sites remote from the catalytic sites, and closer to the substrate binding areas, thus can affect this close association.

Two groups have now independently solved the crystal structure of ERAP1. Varying conformations have been identified and clearly ERAP1 appears to take an ‘open’ (Figure 2.) and ‘closed’ (Figure 3) conformation [25].

Figure 2.

ERAP1 Crystal Structure: Open Configuration

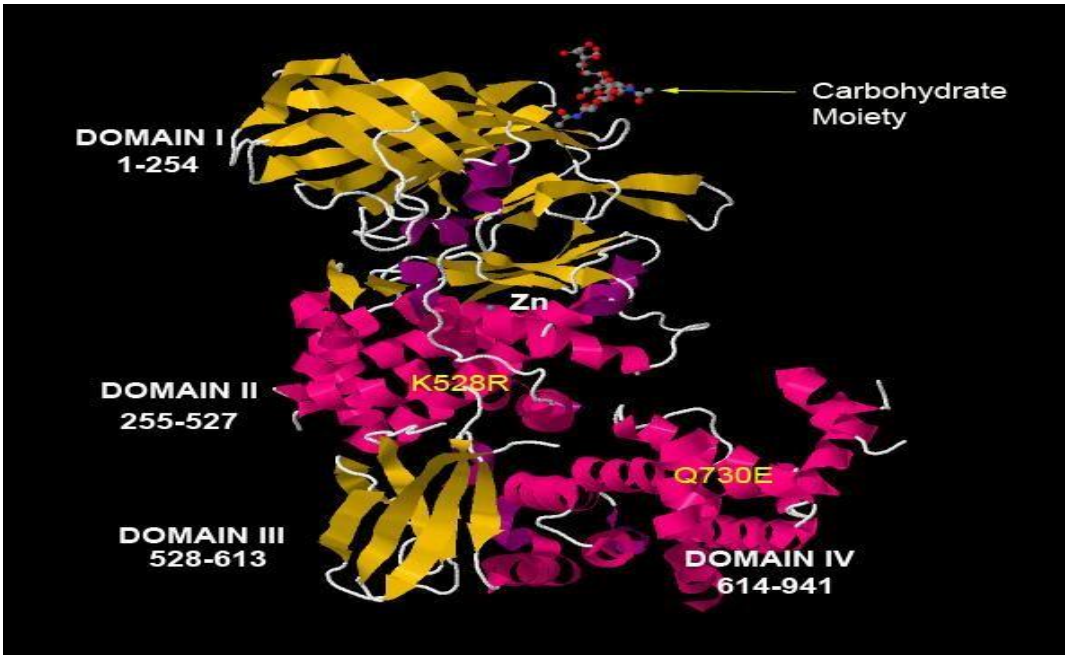
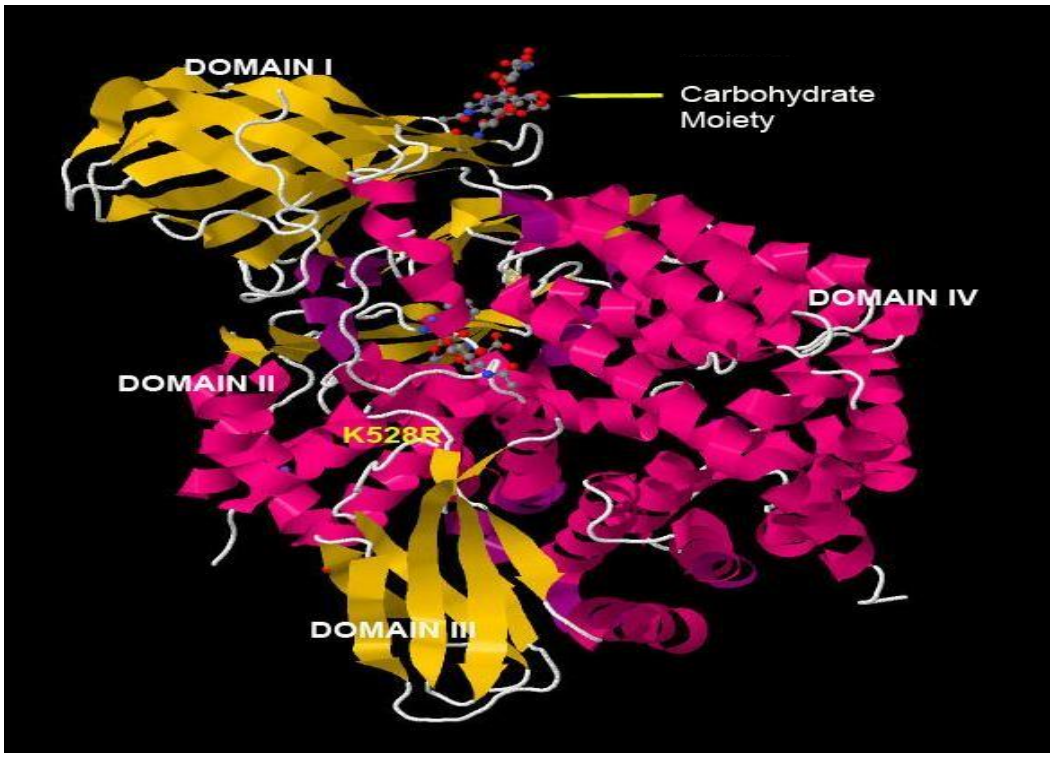


Figure 3.

ERAP1 Crystal Structure: Closed Configuration



The final crystal structure is quite similar to the original computed model with 4 domains. The N terminal end is formed by the first domain extending up to residue 254.

ERAP1 Crystal Structure

Open configuration The N-terminal end is formed by the saddle shaped first domain extending up to residue 254, which forms the binding site for the N-terminal end of the peptide. Domain II (residues 255–527), like all aminopeptidases, houses the catalytic domain, the GAMEN

and the $HEXXHX_{18}E$ motifs. Domain II is connected to the C-terminal Domain IV by a bridging domain III (resides 528-613). In the closed state of ERAP1, domain IV arches over domain II forming a large central cavity enclosing the catalytic site. The zinc ion in the catalytic domain as well as the positions of the ERAP1 SNPs rs30187 (K528R) and rs27044 (Q730E) are depicted here. The surface carbohydrate moiety is composed of Mannose and N-Acetyl Glucosamine. Quite clearly, from the open structure, these polymorphisms are away from the catalytic site. The figure of the crystal structure of ERAP1 [27] was generated using the Jmol software [28].

The closed conformation of ERAP1. In the closed conformation of ERAP1, domain IV closes the catalytic site and forms a large cavity that accommodates large peptides. It is evident that the K528R variation affects the outer surface of domain II and is not near the catalytic site. The K528R variation however could affect the conformational change from open to closed state by altering the interaction with surrounding residues.

In contrast to some other aminopeptidases, domain II is connected to the Cterminal Domain IV by a bridging domain III (resides 528-613). As domain IV forms a cover over the catalytic site on domain II, the presence of domain III increases the size of the cavity. This could be the reason why ERAP1 can accommodate longer peptides for processing. Domain IV (residues 614–941) is made of 16 alpha-helices arranged like a cup. In the closed state of ERAP1, domain IV arches over domain II forming a large central cavity enclosing the catalytic site [24].

Genetic association of ERAP1 with AS

The ERAP1-AS association is well established now and has been replicated in multiple cohorts and ethnicities. The study by the Wellcome Trust Case Control Consortium and the Australo-Anglo-American Spondylitis Consortium (WTCCC-TASC study) was the first to establish this link. Single Nucleotide Polymorphisms (SNPs) are changes in the DNA sequence by one nucleotide and the lowest allele frequency at that particular locus in the population is called minor allele frequency (MAF). When the frequency of this allele is less than 1% it is called a mutation and not as SNP. By looking for overexpression of a particular allele, usually by comparing the MAF, in the disease cohort vs. controls, possibly pathogenic DNA variations can be identified.

In a multicenter study in Canada, which included 992 cases of AS and 1,437 controls, all of Northern European Caucasian ancestry, five genes involved in the antigen-processing pathway were assessed [21]. ERAP1 was found to be significantly associated with AS and the haplotype rs27044/10050860/30187-CCT was strongly associated with an increased risk of AS (odds ratio [OR] 1.8, 95% confidence interval [CI] 1.5–2.2; $P=7x10^{-8}$). The ERAP1 haplotype rs30187/26618/26653-CTG was protective (OR 0.8, 95% CI 0.7–0.9; $P=9x10^{-5}$). The association between ERAP1 and AS has been replicated in Caucasian and non-Caucasian populations, including Han Chinese, Korean and Portuguese individuals [28]**.** In family studies there are no confounding issues of population stratification unlike larger population studies. We studied multiplex AS families in the North American Spondylitis Consortium (NASC) and found a novel haplotype of ERAP1/ERAP2 to be associated with AS [21]. This study was the first to report an association of ERAP2 with AS. This is a particularly interesting finding with implications to the pathogenesis of AS. Unlike ERAP1, the only known function of ERAP2 is peptide trimming for MHC class I molecules. ERAP1 and ERAP2 act in concert for efficient antigen presentation. Hence an association with a haplotype of ERAP1 and ERAP2 would indicate that antigen presentation might be the key abnormality in the pathogenesis of AS. This is corroborated by the recent finding that ERAP1 is associated with AS only in HLA-B27 positive patients [26]. This was not the case for the other well known AS associated genes like IL-23R and IL-12B. Similarly ERAP1 is associated with psoriasis only in patients who are HLA-C positive [27]. Thus a strong genetic interaction between ERAP1 and HLA-B27 could implicate functional interaction as well considering the known functions of the two genes and the fact that the genes are not in linkage.

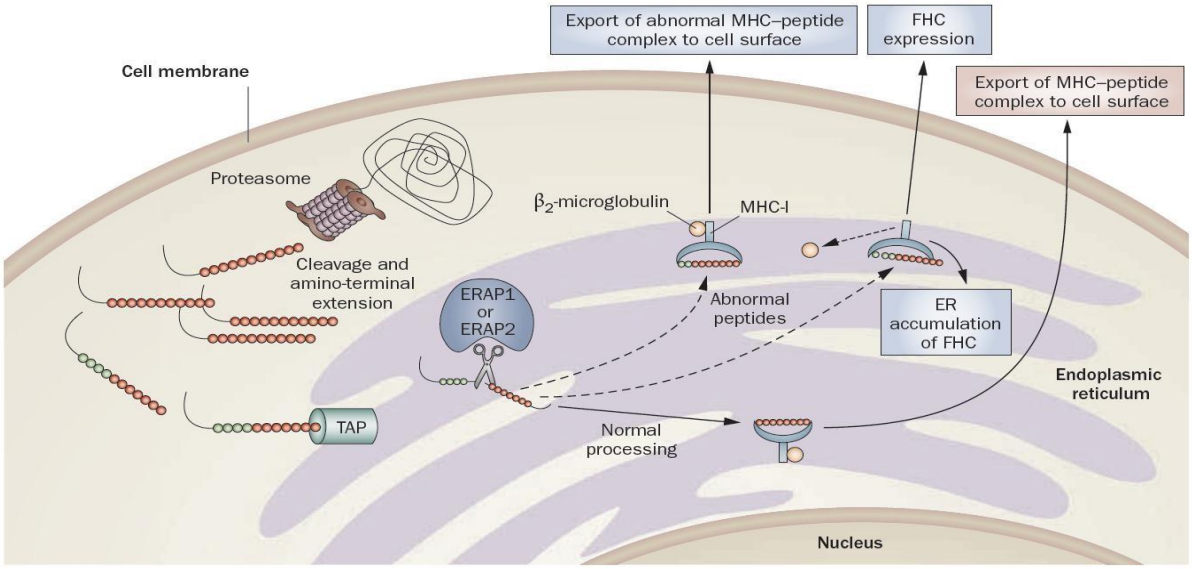
Normal functions of ERAP1

During antigen processing, peptides generated by the proteasome are transported into the ER with the help of the transporter associated with antigen processing (TAP) protein. TAP can

transport peptides up to 16 amino acids in length. Hence these peptides have to be trimmed before presentation on MHC-I. Moreover peptides with proline in any of the first three positions of the peptide are not efficiently transported by TAP. Analysis of MHC–peptide complexes has determined that proline is commonly encountered in these positions [14]. This result suggested that peptides are transported with N-terminal extensions into the ER and then trimmed to appropriate lengths before MHC class I uploading. Following a search for such ER resident enzymes, ERAP1 was discovered [22]. Thus, N-terminally extended peptides generated by the proteasome enter the ER, assisted by TAP. These peptides are, in turn, cleaved by ERAP1 and prepared for loading onto MHC class I molecules (Figure 4). ERAP1 is peculiar among aminopeptidases in its ability to cleave long substrates [6].

Figure 4.

Schematic Diagram to show the role of endoplasmic reticulum aminopeptidases in antigen processing and presentation



Proteins targeted for degradation are processed by the proteasome. The resulting peptides are N-terminally extended, relative to the ideal length of MHC-I binding peptides. They are transported into the Endoplasmic Reticulum (ER) by Transporter Associated with Antigen Processing (TAP). These N-terminally extended peptides have to be trimmed by ER-resident peptidases before they can be finally presented on MHC-I. Abnormal ERAP1 and ERAP2 activity can lead to the generation of abnormal peptides. This can lead to unstable peptide-MHC complexes that can misfold. These can accumulate in the ER or be presented as Free Heavy Chains (FHC) on the surface. Abnormal peptide MHC complexes can also be presented on the surface with resulting altered immune responses.

Functional interaction of ERAP1 and HLA-B27 is subtype specific and could be pathogenic in ankylosing spondylitis

The pathogenesis of AS is not well understood. The significance of genetics is evident from twin and family studies showing an increased risk of recurrence of AS in first degree relatives and twins[28]. The first genetic risk factor identified to be strongly associated with AS was HLA-B27 [1]. Despite thirty-five years of research we still do not know how exactly HLA-B27 contributes to the pathogenesis of AS. As HLA-B27 is a classical MHC-I molecule, an abnormality of antigen presentation has been suspected for some time. Despite arduous efforts to identify ‘arthritogenic peptides’ in AS, they have not met with great success [25].

Recurrence risk modeling studies have hinted at the possibility of AS being an oligogenic disease with contributions from at least 6 important genes[14]. The recent discovery of ERAP1 as an important genetic risk factor in AS invigorates the hope of resolving the pathogenesis of AS.

ERAP1 is an ER resident peptide cleaving enzyme that can functionally interact with HLA-B27 by affecting antigen presentation [26]. Thus variations in ERAP1 can lead to changes in the peptide-B27 repertoire with effects on immune response. Altered peptide-B27 complexes can have reduced stability and lead to the formation of MHC-I free heavy chains (FHC). These FHC can be retained in the ER leading to an ER stress response, or presented on the surface resulting in abnormal immune interactions [29].

Antigens are processed and loaded on MHC-I molecules in the ER and transported to the surface for presentation. Thus the surface expression of MHC-I is a surrogate marker for adequacy of peptide processing. A screening approach to assess the effects of ERAP1 variants on antigen presentation would be to study the level of MHC-I expression on PBMC in AS patients. Considering the potential effects on the pathogenesis of AS, it is important to look for the level of HLA-B27 expression as well as MHC-I FHC.

The ERAP1 SNPs rs30187 and rs27044 lead to a K528R and Q730E change respectively in the ERAP1 protein. These are the most widely replicated and strongest ERAP1 SNPs associated with AS. It is now well established that ERAP1 variants have altered aminopeptidase activity [30]. The rs27044 SNP has less enzyme activity than the ancestral / wild type ERAP1 variant depending on the presence of other substrates in the reaction [26].

As a first step, I compared the surface expression of HLA-B27 and FHC on the peripheral blood mononuclear cells (PBMC) of AS patients with different genotypes of these ERAP1 SNPs. Then I addressed the question whether reducing the level of ERAP1 would have similar results in vitro. I developed an in vitro system with C1R cells and used siRNA for ERAP1 suppression. In addition to FHC and HLA-B27 expression, I studied the effect of ERAP1 suppression on the surface expression of HLA-B27 that reacts with the mAb MARB4 and intracellular FHC (IC-FHC).

Taking this one-step forward, I also addressed if the effects seen with ERAP1 suppression on C1R cells differ with the subtype of HLA-B27 that the cells express. I did this by using different C1R cell lines that have been stably transfected with the HLA-B27 subtypes: B*2704, B*2705, B*2706 and B*2709. As detailed in the introductory chapter, HLA-B*2704 and B*2705 are associated with AS while B*2706 and B*2709 are not.

Hence, if the result of the ERAP1 suppression is different in the AS-associated HLA-B27 subtypes compared to the AS-neutral subtypes, it would further strengthen the hypothesis that ERAP1-B27 interaction is pathogenic in AS.

IL-23R

Interleukins (IL) play a large role in the study of AS. IL-23 (IL-23A) [38], a 23-receptor for interleukin (IL-23R), is located on chromosome 1p31.3. The protein encoded by this gene is a subunit of the IL-23A / IL-23 receptor [39]. The role of a number of polymorphisms in the AS rs11209026, rs11465804, rs7517847 has been revealed [24, 49, 13]. Polymorphism rs11209026 affects the severity of the disease [44], rs17375018 is associated in HLA-B27-positive patients [23]. This gene has been confirmed in Europeans and Asians, in particular the Chinese and French. The authors Chen C., Zhang X., Li J., Wang Y. did not reveal an association of IL-23R polymorphism among the population of East Asia [31].

Participation in the pathogenesis of IL-23R has been proven in various spondyloarthritis - psoriatic, ankylosing and undifferentiated reactive arthritis [32]. Studies have shown an increased level of IL-23 in the blood of patients with AS, as well as a high concentration of IL-23 in the synovial fluid and subchondral bone marrow compared to the values in the control group [33]. IL-23 plays a leading role, as it stabilizes and determines the function and pathogenic ability of T-helpers-17 [23, 24]. The cytokine IL23 is secreted mainly by activated macrophages, dendritic cells and performs a regulatory function during the differentiation of various subsets of secreting IL17 cells [34].

In 2018, Y. Lee and G. Song found that the polymorphisms rs1004819, rs10489629, rs1343151, rs1495965, rs7517847, rs11465804, rs11209032 of the IL23R gene showed a strong association with AS in the European population, but not in the Asian one. In addition, the same

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association with AS was demonstrated by the rs2201841 and rs11209026 polymorphisms of the IL23R gene in the European population in the absence of data for the Asian population, and the association between the rs10889677 polymorphism of the IL23R gene with AS for both the European and Asian populations was rejected. Some polymorphisms can play a protective role in the development of AS, for example, replacement of Arg-Gln rs11209026 of the IL23R gene [24,35].Bin Yang et al. showed the presence of an association of AS with polymorphisms rs6693831, rs1884444 of the IL23R gene and rs2275913 of the IL17A gene for patients belonging to the southwestern Chinese population. Moreover, the first of the 3 listed polymorphisms was associated with a higher level of C-reactive protein [36]. IL23 implicates in the pathogenesis of AS. There is increasing evidence of the involvement of the Th17 pathway in AS pathogenesis. In a study on PBMC from AS and RA patients, IL-23 positive CD4 T cells were increased with higher secretion of IL-23compared with healthy controls [32]. The frequency of IL-23 positive cells was higher in the facet joints of AS patients compared to osteoarthritis patients [33]. There is exciting new evidence which shows that HLAB27 dimer expressing Antigen Presenting Cells (APC) can stimulate the proliferation of KIR3DL2 expressing CD4 T cells. This subset of T cells is enriched for IL-23 production [14]. The unfolded protein response (UPR) resulting from unfolding of HLA-B27 in HLA-B27 transgenic rats induces the production of IL-23 cytokine [37].

A study of serum levels of IL-23 did not differentiate active and inactive AS patients [38]. The serum levels of these cytokines were, however, higher than healthy controls. IL23R polymorphisms are associated with AS and this has been well replicated in genome wide scans [39]. A common association with Crohn's disease again raises the issue of common pathogenic mechanisms in IBD and AS. The level of IL-23R expression in the cecum and distal ileum of AS patients' is comparable to Crohn's disease [4].

Conclusion

Thus, despite numerous studies of genes for susceptibility to AS, the question of their participation in the development of this disease is not completely clear and requires further study. Undoubtedly, information on the primary genetic defects underlying AS will contribute to a better understanding of etiopathogenesis, as well as the development of new effective methods for early diagnosis and therapy. Like ERAP-1, IL-23R also important in AS. The remarkable efficacy of anti-ERAP-1 and IL-23R agents in controlling inflammation but inability to control progression points towards an uncoupling of inflammation and new bone formation. It is not entirely clear if the cytokine defects are the primary event or secondary to other pathogenic events.

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