Section A -Research paper

The Role of ERAP1 Polymorphism in Autoimmune and Autoinflammatory Diseases

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Abstract

Autoimmune and autoinflammatory diseases significantly impair survival and quality of life, affecting around 10% of the global population. Both the innate and adaptive immune systems' aberrant activation is a feature of several disease types. Interestingly, it has also been demonstrated that autoinflammatory and autoimmune diseases are genetically linked to the endoplasmic reticulum aminopeptidase 1 (ERAP1) protein. This protein is well known for its aminopeptidase function as a "molecular ruler," trimming peptides prior to their loading onto MHC-I molecules for antigen presentation in the ER. It has been discovered that this complex protein performs a wide range of roles that influence the innate and adaptive immune responses. We present a summary of these findings in this review in an effort to pinpoint potential ERAP1-dependent pathways that underlie the etiology of several ERAP1-related illnesses.

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Introduction

While the clinical presentations and etiologies of autoimmune and autoinflammatory disorders differ greatly, there are several genetic and environmental factors in common [1]. More research is showing that the innate immune system is being inappropriately activated in both autoimmune and autoinflammatory illnesses, supporting this theory. While the abnormal activation of the innate immune system in autoimmune diseases is the first step towards pathogenic adaptive immune responses, which are ultimately responsible for end-organ tissue damage, the overactive innate immune system directly causes inflammation and damage in autoinflammatory diseases [2].

It is believed that in the early stages of the onset of autoimmune diseases, pathogen recognition receptors (PRRs) such as toll-like receptors (TLRs) and inflammasomes trigger innate immune responses. These responses subsequently activate both innate immune cells, such as macrophages and

dendritic cells (DCs), and adaptive immune cells, such as B and T cells [2]. Autoantibodies and autoreactive T cell-mediated responses predominate in the later stages of autoimmune disorders, which entail adaptive immune activation [3]. Given their significance for activating not only the innate immune cells but also autoreactive B cells and T cell polarization, it is becoming increasingly clear that inflammasome activation may be the mediator between autoinflammation and autoimmunity [2].

Genome wide association studies (GWAS) have identified multiple genetic loci that are shared by several autoimmune and autoinflammatory diseases, despite the fact that the processes underlying those diseases are still not well understood. One of the strongest genetic relationships is that certain HLA alleles are linked to an increased risk of disease. Interestingly, mutations in the endoplasmic reticulum aminopeptidase 1 (ERAP1) gene have also been linked to a higher risk of developing autoimmune and autoinflammatory disorders [4-7]. Consequently, studying ERAP1 dependent mechanisms in these disorders may contribute to our understanding of the complex relationships that exist between the innate and adaptive immune systems in general as well as the pathogenesis of autoimmune and autoinflammatory diseases in particular. An overview of ERAP1's known functions is given in this review, with an emphasis on how these functions may be related to autoinflammation and autoimmunity, as well as how it operates in innate and adaptive immunity.

ERAP1 background

ERAP1 belongs to the oxytocinase subfamily of M1 zinc metalloproteases [8]. ERAPs are found in a 167Kb region on the short arm chromosome 5q15 [9]. The GAMEN substrate recognition sequences and the HEXXH(X) 18E zinc-binding sequences are two basic sequence motifs that they share and are essential for their enzyme activity[10] [11].

Four domains—Domain I (46–254 residues), Domain II (255–529 residues), Domain III (530–614 residues), and Domain IV (615–940 residues)—that make up the final structure of ERAP1 were identified by the crystallographic configurations of the protein [10]. The catalytic domain is domain II, the hinge that permits the open-close-open transition is domain III, the catalytic site is shielded by domain IV, and domain I stabilizes the closed conformation by means of interactions with both domains II and IV [12]. The four structural domains (I–IV) are arranged in a concave orientation around the active site [13].

The only difference between the two conformations is the overall movement of domains III and IV, with domain III acting as a lever to pull structural domain IV away from the active site, allowing substrate access to structural domain IV. The antigenic peptide is taken in by ERAP1 when it is open, and it then switches to a closed state, cleaving the amino acid off the antigenic peptide's N-terminus. The shift to the open state releases the substrate, and the cycle continues until the peptide's length is insufficient for its N-terminal end to reach

the catalytic site, at which point the cycle stops [14][15]. **Figure 1**

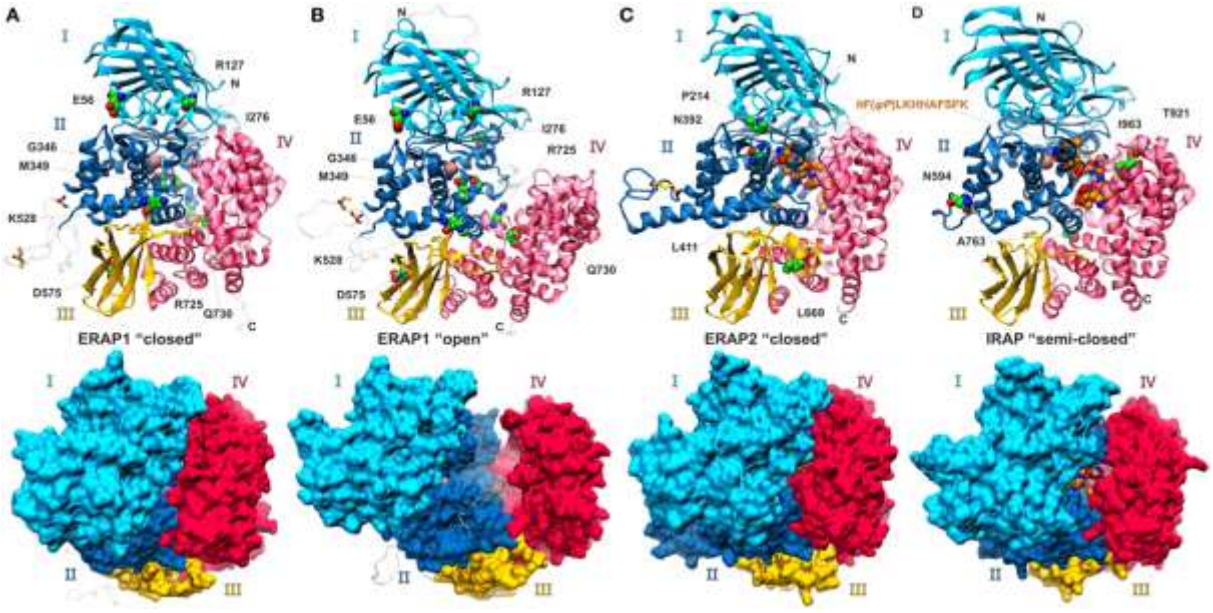

Figure (1) Ribbon and surface representations of ERAP1, ERAP2, and IRAP as revealed from the recent crystallographic studies **[16].**

ERAP1 biological functions:

i) **Biological functions of ERAP1: Antigen processing**

The antigen processing and presentation pathway maintains the cell's peptide repertoire. This process allows for the creation of a wide range of suitable peptides for the major histocompatibility complex (MHC I) molecule **[17].**

A series of steps leads to the presentation process. The initial processing event in antigen presentation occurs in the cytosol, where the proteasome or immunoproteasome operates under inflammatory circumstances. The ubiquitin-proteasome system selects abnormal proteins for breakdown, resulting in the formation of smaller peptide fragments. The proteasome/immunoproteasome cleavage pattern frequently produces a hydrophobic C-terminal residue, which is ideal for loading into the F-pocket of the majority of MHC I peptide-binding grooves **[8].** The resultant peptides are delivered to the ER by the transporter associated with antigen processing (TAP) protein complex **[18].**

How antigenic peptides are selected to bind MHC I molecules in the endoplasmic reticulum ER is a vital stage in MHC I maturation **[19].** MHC I uses the peptide-loading complex to attach their peptide load in the ER. While MHC I typically binds peptides of 8 to 11 amino acids in length

(the majority of which are 9mers), numerous peptides that enter the ER can be significantly longer. ERAP1 and ERAP2 are two ER-resident aminopeptidases that catalyze the processing of these precursor peptides and define the peptide pool that can bind to MHC I **[20].**

The last step in the MHC I antigen processing and presentation pathway involves the use of molecules and chaperones, specifically the peptide loading complex (PLC), tapasin, ERp57, calreticulin, and TAP. These processes produce stable peptide-loaded MHC I molecules that can egress to the cell surface and be expressed by CD8+ T cells and NK**[8].**

Fierabracci, 2023 addressed the theory that autoantigens are cut into modified peptides at the start of the autoimmune process and subsequently loaded on MHC class I molecules to be recognized by the T cell receptor (TCR) on CD8 + T cells. Cell lysis occurs due to T lymphocyte activation. Dendritic cells—also known as antigen-presenting cells, or APC—are attracted to the site of first injury. APC absorbs the modified autoantigenic fragments in the draining lymph nodes and presents them to T and B cells, which triggers the initial attack and the creation of autoantibodies**[21].**

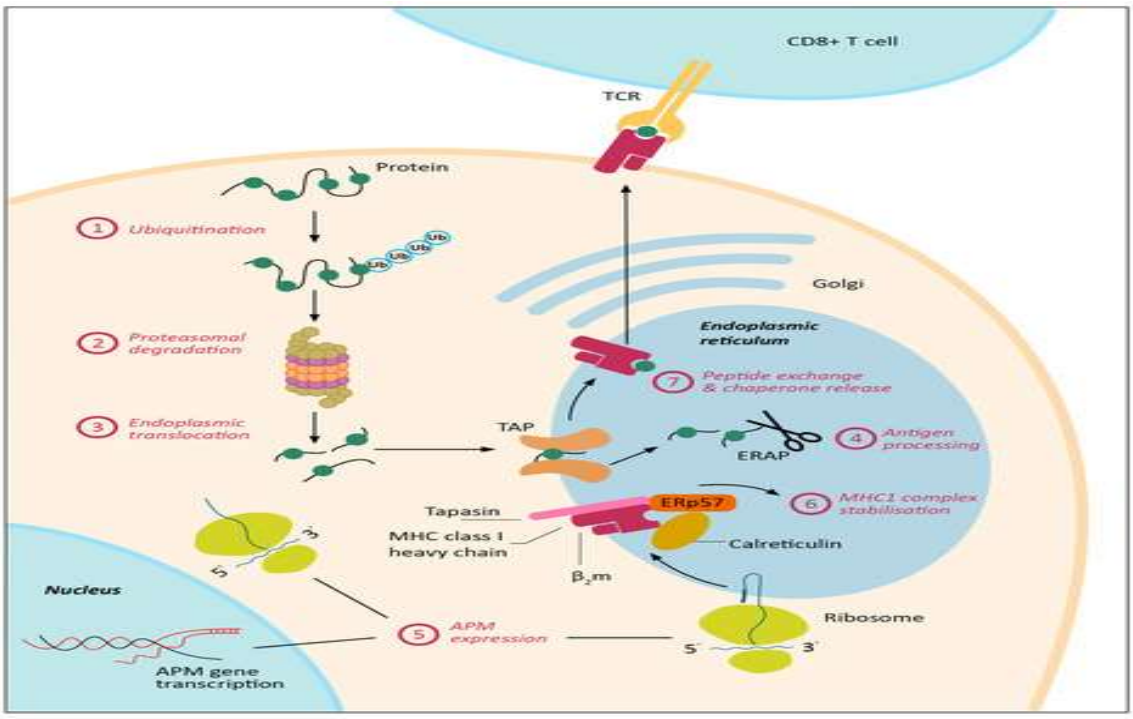

Figure (2): The MHC I antigen processing and presentation pathway **[22].**

Thus, ERAP1 single nucleotide polymorphisms (SNPs) can have significant effects on the repertoire and availability of antigenic peptides that HLA class I molecules can display by

altering ERAP1 activity and/or expression **[23].** and consequently affect the susceptibility to diseases **[24].**

ii) Biological functions of ERAP1: innate immunomodulation

ERAP1 is required to repress a number of pro-inflammatory, innate immune responses in addition to its canonical role in the adaptive immune system as an aminopeptidase processing peptides intended for MHC I presentation to CD8+ T cells in the ER **[25].**

ERAP1 localizes within the ER even in the absence of a clear ER-retention signal. More research, however, indicates that ERAP1 may be found in the cytosol, where it can be found at the cell membrane as a type II integral membrane protein and secreted from the cell. ERAP1 production was dependent on TNF-α and IFN-β activation via toll-like receptor TLR-mediated signaling. Through TLR4 signal transduction, the action of this secreted ERAP1 has been demonstrated to augment/up-regulate macrophage phagocytosis **[8].**

Human ERAP1 polymorphisms induce human immune cells to produce excess IL-1β, a well-known signal of Nod-like receptor protein NLRP3 inflammasome activation. This is attributed to a process that involves K+ efflux. However, it is still unclear what underlying mechanisms underlie these immunological responses that are dependent on ERAP1. The innate immune system produces inflammatory cytokines and chemokines primarily by activation of various germline-encoded pattern-recognition receptors (PRRs), including TLRs, RIG-I-like receptors (RLR), and NOD-like receptors (NLRs). Once these PRRs are activated, intracellular signaling pathways that control the transcription of chemokine genes, inflammatory cytokines, and other innate immune defense responses are also coordinately activated [21].

Furthermore, the lack of ERAP1 also causes a decrease in tolerogenic dendritic cells (tDCs), which are defined as CD11clowCD45RBhigh cells. These cells are distinctive given that they exhibit an immature phenotype and can release high levels of IL-10. They are also crucial for the differentiation and function of Tr1 cells, which are essential for immunological tolerance**[26].**

iii) Biological functions of ERAP1: cytokine receptor shedding

ERAP1 contributes to the proteolytic cleavage of cell surface-expressed cytokine receptors, including tumor necrosis factor receptor 1 (TNFR1), IL6R2, and IL1R2. By altering the availability of receptors on the cell surface, ERAP1's shedding of cell surface receptors can regulate the cellular immune response and reduce pro-inflammatory signals [27].

iv) Biological functions of ERAP1:blood pressure regulation

Subsequent research revealed that ERAP1, which is released extracellularly,

facilitates the trimming of peptides that include N-terminal arginine (Arg) residues. This process produces an abundance of free Arg, which in turn stimulates the creation of nitric oxide (NO). Maximum NO production is necessary for controlling blood pressure through the relaxing of endothelial cells and the modulation of inflammatory responses by certain immune cells like macrophages. Since the greatest synthesis of NO requires supplies of free-Arg, the secretion of ERAP1 in response to inflammatory stimuli may influence blood pressure regulation and inflammation associated with disease both directly and indirectly through NO-mediated pathways **[28].** It's interesting to note that ERAP1 activity has been linked to blood pressure regulation in the past since it cleaves the bioactive peptide hormones angiotensin II and kallidin into angiotensin III and bradykinin, respectively [29].

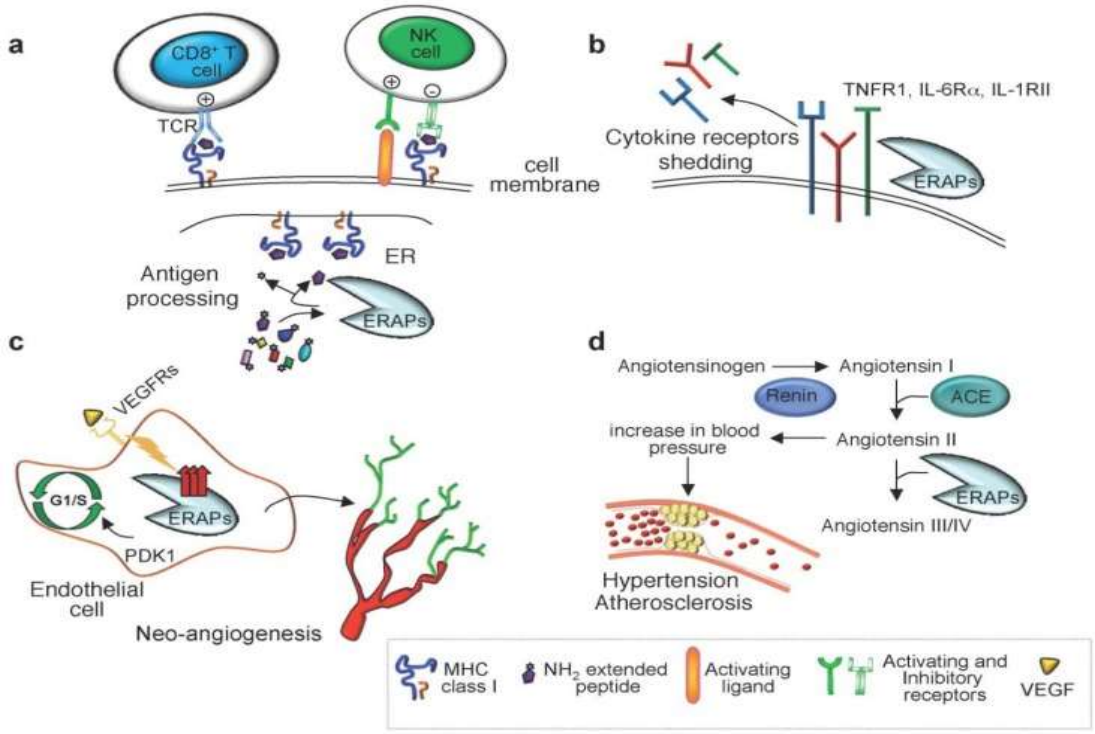

Figure (3): Schematic representation of the multifunctional properties of endoplasmic reticulum (ER) aminopeptidase 1 (ERAP1) and ERAP2 **[30].**

1 ERAP1 Polymorphism

The genetic polymorphism of ERAP1 is very high. Its biochemical properties, immunological response, and pathological function are significantly impacted by ERAP1 polymorphisms. These polymorphisms may impact the relative amounts of ERAP1 isoforms that are co-expressed in all individuals, the catalytic function and activity of ERAP1, the epitopes of endogenous antigenic peptides linked to HLA- I molecules, and the expression

levels of ERAP1**[31].** A significant number of ERAP1 SNPs are linked to autoimmune disorders, including missense, synonymous, and non-coding variants [14].

SNPs in introns alter the structure and composition of intron-transcribed mRNA, which influences mRNA maturation and processing and ultimately impacts the production of the final protein. For instance, AS is highly correlated with the intron SNP rs27037 **[14].**

The polymorphisms in the amino acid sequence of ERAP1, which are primarily represented by missense SNPs, have the greatest direct influence on the protein structure and function of ERAP1, leading to notable variations in ERAP1 trimming antigenic peptide activity and a direct correlation with a number of autoimmune disorders [14].

Natural ERAP1 variants are complex allotypes made up of several haplotypes, or non-synonymous single nucleotide polymorphisms (SNPs). More than 99 percent of the natural ERAP1 variants in human populations can be attributed to ten ERAP1 haplotypes, referred to as Hap1 through Hap10. The catalytic site (residues 346, 349), the peptide binding site (residue 725, 730), interdomain regions, and other locations that may influence conformational rearrangements linked to the acquisition of enzymatic activity are among the locations where polymorphic amino acids are commonly found [32] [33].

Natural ERAP1 variants differ in their precise combinations of polymorphic residues that determine their activity. Because different mutations cause distinct alterations, it is difficult to anticipate a variant's activity based just on the consequences of individual changes. However, R528-containing natural ERAP1 variants (Hap1–Hap3) are less active than K528-containing variants, and the least active haplotype—Hap10—is the one with the greatest accumulation of amino acid alterations that adversely impact ERAP1 activity **[34].**

After analyzing the 1000 Genomes dataset, Tran, T.M. and Colbert, R.A. (2015) [35]. found 10 missense SNPs in ERAP1 that were present in at least one super population at a minor allele frequency of greater than 5%. These missense SNPs are T12I, E56K, R127P, I276, M, G346D, M349V, K528R, D575, N, R725Q, and Q730E, where the first letter indicates the ancestral amino acid, followed by the amino acid position and the non-ancestral amino acid [33] **[20] .**

ERAP1 SNPs rs27044 (Q730E) and rs30187 (K528R) are the most commonly reported and linked to autoimmune disorders. It's interesting to note that these ERAP1 SNPs are distributed across the protein at interdomain junctions or in the regulatory region of domain IV, a place that is thought to bind the peptide's C-terminal residues, rather than within the active site region of ERAP1 (Sui & Guo, 2021). These polymorphisms have a substrate-dependent effect on ERAP1's catalytic activity and substrate selectivity [36].

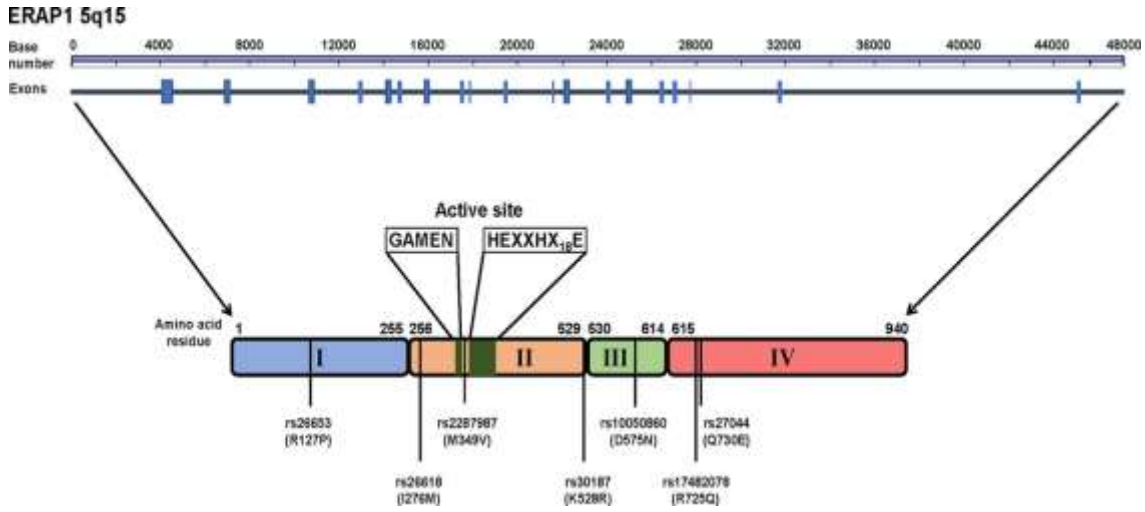

Figure (4) Schematic diagram of ERAP1 gene and ERAP1 SNPs **[1].**

2 ERAP1 association with autoimmune and autoinflammatory diseases:

i. ERAP1 and Ankylosing spondylitis AS

According to genome-wide association studies (GWAS), ERAP1, after HLA-B27, is the second most important non-HLA locus that contributes to 30% of AS-attributed risk in various ethnic groups **[37].**

The heterotrimer HLA-B27 is made up of a heavy chain connected to a β2-microglobulin (β2m). This molecule presents intracellular peptides to CD8 + T lymphocytes by binding to them in the endoplasmic reticulum (ER). HLA-B27 presentation of arthritogenic peptides in AS patients has been linked to ER stress. This can activate autoreactive CD8 + cytotoxic T and/or natural killer (NK) cells, which can produce proinflammatory cytokines [25].

The expression of the conventional forms of HLA-B27 and HLA-B27-free heavy chain (FHC) varies on antigen-presenting cells (APCs), such as macrophages, as a result of disruptions in ERAP1 function (via SNPs). This variation may then influence the activation of NK and T cells. These polymorphisms may also result in changed ERAP1 enzymatic activity when processing cytokines including TNF, IL-1, and IL-6, suggesting that ERAP1 contributes to AS immunopathogenesis by disturbing HLA-B27 function **[38].**

The occurrence of ERAP1 haplotype Q730/K528 and ERAP2 SNP K392N simultaneously, as well as haplotypes K528/D575/R725, K528/D575/E730, and others, has been linked to AS. On the other hand, it has been demonstrated that the ERAP1 haplotype R528/N575 is protective, as the individuals who are homozygous for R528/N575 and HLA-B*27 positive had the lowest risk of AS **[39].**

ii. ERAP1 and Behcet disease

Inflammatory arthritis, recurring mouth ulcers, eye involvement, vaginal ulcers, and skin lesions are the hallmarks of Behcet disease (BD), a chronic inflammatory condition. Being a carrier of the HLA-B*51 allele is the main risk factor for developing BD. As with AS, other risk genes are IL-10 and IL-23R. In contrast to AS, there is a higher risk of BD linked to the ERAP1 SNPs encoding N575 and Q725 **[1].** According to a study on ERAP1's involvement in BD, people homozygous for HLA-B*51 and the ERAP1 allotype *001 (P127/V349/R528/N575/Q725/E730) were around 11 times more likely to develop BD[40].

iii. ERAP1 and Psoriasis

One prevalent autoimmune skin disease mediated by T cells is psoriasis. The primary risk allele that triggers an autoimmune CD8+ T cell response against melanocytes is HLA-C*06:02. By producing the autoantigenic ADAMTS-like protein 5 (ADAMTSL5) peptide, which is normally processed in melanocytes and presented by HLA-C*06:02, ERAP1 induces melanocyte immunogenicity for the psoriatic autoimmune response. This means that due to varying autoantigen yields, distinct ERAP1 haplotypes regulate the degree of an autoimmune response against melanocytes and, thus, likely also the risk of psoriasis in HLA-C*06:02 carriers **[41].**

Wiśniewski et al. (2018) found that rs30187T was protective when the HLA-C*06:02 allele was absent, **[42]** but it raised the risk of psoriasis in patients who tested positive for HLA-C*06:02, most pronouncedly in cases of late-onset psoriasis. HLA-C*06 and rs27044 (E730) were found to interact epistasis, which may contribute to the early development of psoriasis **[43].**

iv. ERAP1 and diabetes mellitus DM

One of the main sources of HLA class I autoantigen epitopes linked to CD8 T cell (CTL)-mediated β-cell death in type 1 diabetes (T1D) is the signal peptide of preproinsulin.It has been shown that inhibition of the IRE1α activity impairs processing of preproinsulin signal peptide antigen and its recognition by specific autoreactive CTLs during inflammation. ER stress regulates ERAP1 gene expression in human β-cells at the posttranscriptional level via the inositol-requiring enzyme 1α IRE1α/micro RNA miR-17-5p axis **[44].**

It was discovered that type 1 diabetes and the ERAP1 SNP, which encodes K528R, are related. Both the ERAP1 (rs26618) and IFN-λ-4 (rs73555604) SNPs showed strong relationships with T1DM in a recent study involving 120 Egyptian patients with the disease **[45].** Additionally, when T1DM patients were compared to the control group, the frequency of the T allele was considerably higher than that of the C allele, suggesting that patients with the CC genotype had a lower risk of developing T1DM than those with the TC and TT genotypes for both genes [46]**.**

v. ERAP1 and multiple sclerosis

Multiple sclerosis (MS) is an autoimmune neurological disease that affects the central nervous system, causing inflammation and nerve demyelination **[1].** The MHC II HLA-DR15 haplotype is the strongest genetic risk factor for MS. The functional ERAP1 mutation rs30187 (K528R) has been linked to an increased risk of developing MS disease, despite the interesting finding that the HLA-C*05 alleles had a protective connection with the disease. The involvement of ERAP1 in MS susceptibility may also be due to its alternate cellular roles, such as mediating cytokine production and shedding cytokine receptors, as ERAP1 is not known to function in the processing of antigens for MHC II presentation. TNFR1 has been identified as a susceptibility locus for MS **[47].**

vi. ERAP1 and Inflammatory bowel disease

Inflammatory bowel disease (IBD) includes ulcerative colitis (UC) and Crohn's disease (CD), among other illnesses characterized by recurrent episodes of chronic inflammation of the small intestine and colon. The ERAP1 functional variation rs30187 (K528R) increases the risk of developing CD and IBD. There have been reports of a correlation between IBD patients' expression of the HLA-C*07 allele and ERAP1 K528R. Due to its decreased enzymatic activity, the K528R linked to CD is probably going to change the peptide repertoire seen on HLA-C*07 alleles [48].

vii. ERAP1 and Rheumatoid arthritis RA

Four exonic and intronic polymorphism areas (rs26653, rs27044, rs27582, and rs30187) were found to be linked to an increased chance of developing RA. For the first time, a haplotype [CGAAT] was linked to an increased risk of RA in Turkey. Polymorphic missense variations have been demonstrated to modify the tertiary structure of proteins, which may have implications for their functional characteristics **[49]**

It is unclear how specifically ERAP1 contributes to the development of RA . It is believed that additional biological structures (genes, ligands, etc.) that interact with peptide products arising from polymorphisms in ERAP1 and its function in cleaving cytokine receptors and mediating the production of cytokines, including TNF, IL6, and IL1, may be involved in the onset of the illness [49]**.**

Table (1): Summary of disease-associated ERAP1 SNPs and imputed ERAP1 haplotypes encoding amino acid changes [1].

Disease	**HLA association**	**ERAP1 SNP association**	**Associated ERAP haplotype**
Ankylosing spondilitis	HLA-B*27	rs26653 (R127P)	Susceptible ERAP1:
	Susceptible alleles: HLA-B*27:02 and	rs2287987 (M349V)	M349/K528/D575/R725/ Q730
	HLA-B*27:05	rs30187 (K528R)	Protective ERAP1: V349/R528/N575/Q725/
		rs10050860 (D575N)	E730
	Protective alleles: HLA-B*27:06 and	rs17482078 (R725Q)	
	HLA-B*27:09	rs27044 (Q730E)	
Behcet's disease	HLA-B*51	rs10050860 (D575N)	ERAP1*001/Hap10:
		rs17482078 (R725Q)	P127/M349/R528/N575/ Q725/E730
Type 1 diabetes	HLA-DR3, HLA-DR4, HLA-DQ2	rs30187 (K528R)	
	HLA-DQ8		
	HLA-A*02:01		
	HLA-A*24:02		
Psoriasis	HLA-C*06:02	rs26653 (R127P)	Susceptible ERAP1:
		rs30187 (K528R)	M349/K528/Q730
		rs27044 (Q730E)	+ERAP2 expression
			Protective ERAP1**:**
			M349/R528/E730
			-ERAP2 expression
Multiple sclerosis	HLA-DR15	rs30187 (K528R)	
	Protective allele: HLA-C*05		
Inflammatory bowel disease	HLA-C*07	rs30187 (K528R)	

3 Drugs designed for ERAP1 SNPs

Due to ERAP1's critical role in immune response regulation, drug development efforts have focused on modifying its activity in order to manage autoimmunity or use it in cancer immunotherapy. According to Giastas et al. (2019a), first-generation ERAP1 active-site inhibitors have been reported and demonstrated to be active in controlling immune response in model systems, providing potential for clinical applications **[50].**

The majority of ERAP1 inhibitor research to date has concentrated on particular pharmacophores that target comparable locations, such as the allosteric site, the N-terminal recognition element, and the active site zinc (II) ion [14]. These inhibitors usually cause ERAP1 to change to the closed conformation because they target the enzyme's active and allosteric sites [12].

An α-hydroxy β-amino dipeptide inhibitor analog, bestatin, for instance, is a broad-spectrum aminopeptidase inhibitor that has an amide and 2-hydroxy oxygen atom attached to the active site of ERAP1. A class of powerful ERAP1 inhibitors that bind close to the catalytic core of ERAP1 and competitively limit its activity is represented by the phosphonic pseudo tripeptide inhibitor DG013 and its family of drugs. Along with small compounds that target the ERAP1 regulatory site, which prevents lengthy peptide hydrolysis by interfering with C-terminal recognition, there are also inhibitors for the ERAP1 allosteric site, such as clerodane acid and Compound 3 **[51].**

Compound 3 and clerodane acid are examples of this type of more selective allosteric inhibitor that has varied potency against ERAP1 polymorphism variations; this difference may be related to K528R. Furthermore, the structure indicates that R725Q and Q730E are both situated within the contact distance of peptide residues that are 10 and 15 mers, which may have an impact on how these inhibitors bind **[12].**

A number of ERAP1 polymorphism sites, including G346D with M349V, K528R, R725Q, and Q730E, may have an impact on how well-known inhibitors attach to their target, causing variations in the effectiveness of inhibitors that contain these polymorphic variants. Targeting proteins with wild-type and various polymorphism mutants would therefore be a useful approach for medication creation**[14].**

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