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The roles of ERAP1 and ERAP2 in autoimmunity and cancer immunity: New insights and perspective

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ABSTRACT

Autoimmunity and cancer affect millions worldwide and both, in principal, result from dysregulated immune responses. There are many well-known molecules involved in immunological process playing as a double-edged sword, by which associating autoimmune diseases and cancer. In this regard, Endoplasmic reticulum aminopeptidases (ERAP) 1, which belongs to the M1 family of aminopeptidases, plays a central role as a "molecular ruler", proteolyzing of N-terminal of the antigenic peptides before their loading onto HLA-I molecules for antigen presentation in the Endoplasmic Reticulum (ER). Several genome-wide association studies (GWAS) highlighted the significance of ERAP1 and ERAP2 in autoimmune diseases, including Ankylosing spondylitis, Psoriasis, Bechet's disease, and Birdshot chorioretinopathy, as well as in cancers. The expression of ERAP1/2 is mostly altered in different cancers compared to normal cells, but how this affects anti-cancer immune responses and cancer growth has been little explored. Recent studies on the immunological outcomes and the catalytic functions of ERAP1 and ERAP2 have provided a better understanding of their potential pathogenetic role in autoimmunity and cancer. In this review, we summarize the role of ERAP1 and ERAP2 in the autoimmune diseases and cancer immunity based on the recent advances in GWAS studies.

1. Introduction

Autoimmune diseases and cancers are a major reason of mortality and morbidity worldwide. So far, large-scale genomic studies have emphasized several disease-associated loci, most notably ERAP1/2 that are associated with predisposition to a growing number of autoimmune diseases and cancer. ERAP1/2 reside in the lumen of the endoplasmic reticulum (ER) and trim antigenic peptides to an optimum size for antigen presentation. ERAP1 and ERAP2 belongs to the oxytocinase subgroup of M1 zinc metallopeptidases, and share 49 percentage sequence similarity and can forms heterodimers (Hattori and Tsujimoto, 2013; Vitulano et al., 2017). The human *ERAP1/2* genes are encoded in the short arm chromosome 5q15 in a 167Kb region in the opposite direction, and probably they have two shared regulatory elements. *ERAP1* contains 20 exons in which exon 6 and 7 encode a HEXXH(X)18 zinc-binding motif, the GAMEN motif crucial for enzymatic activity and essential glutamic acid (E) residue. Alternative splicing of *ERAP1* gene creates two N-glycosylated isoforms namely *ERAP1a* (948 aa) and *ERAP1b* (941 aa), with the active site extending 375 amino acids, which *ERAP1b* is more frequent than the *ERAP1a* and

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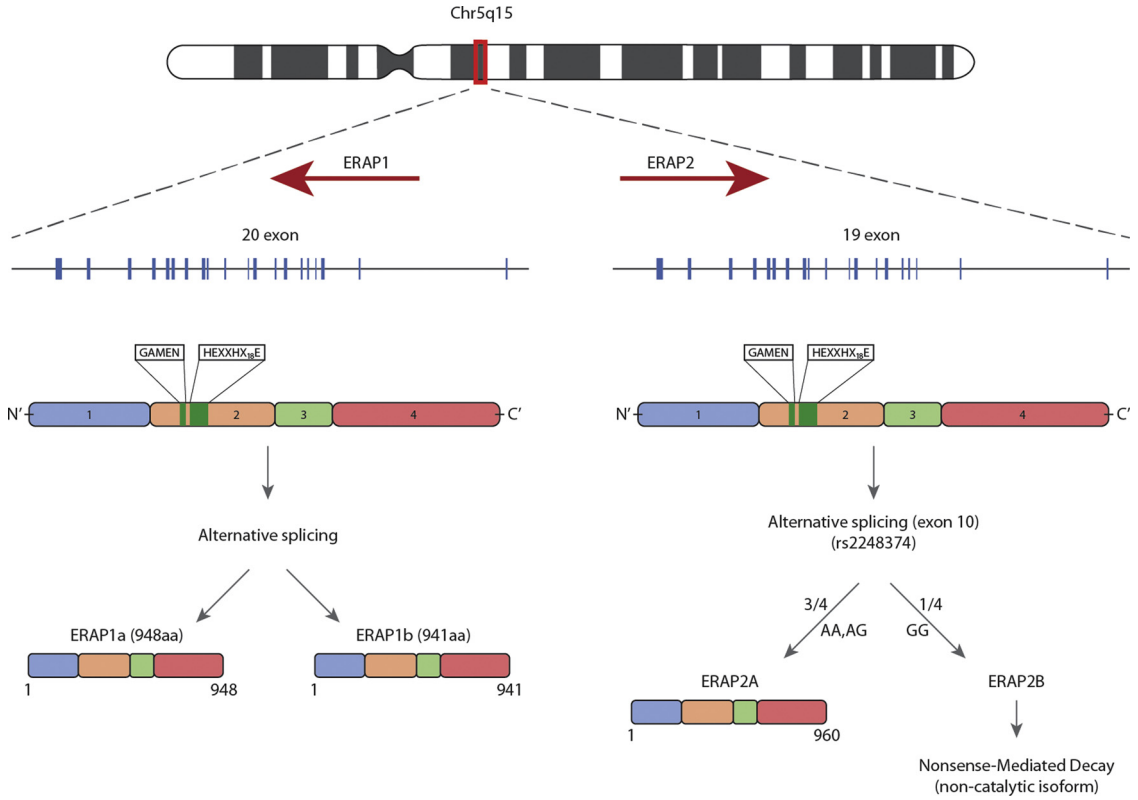

Fig. 1. Schematic model of human endoplasmic reticulum aminopeptidase 1 and 2 (ERAP1/2). Genomic organization of the human chromosome 5q15 containing ERAP1 and ERAP2 in a 167Kb region in the opposite direction. The crystallographic structures of human ERAP1 and ERAP2 consists of four domains: domain 1 in blue, domain 2 in orange, domain 3 in green and domain 4 in red. Alternative splicing of ERAP1 gene gives arise to two isoforms of 948 (ERAP1a) and 941 (ERAP1b) amino acids, while alternative splicing of ERAP2 gene gives arise at least 3 isoforms in correspondence to rs2248374 within exon 10. Only ¾ (with AG and AA genotypes) express a functional ERAP2A isoform, whereas ¼ (with GG genotype) express an undetectable isoform of ERAP2B (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

these two isoforms share the same amino acid sequences except few amino acids at the C-terminal and different 3′-UTR sequence (Hattori et al., 2001; Tanioka et al., 2003). The *ERAP2* gene comprises of 19 exons. Alternative splicing of *ERAP2* gene creates at least three isoforms based on the single nucleotide polymorphism (SNP) rs2248374 (A/G) in the 5′ splice site of exon 10 (Andrés et al., 2010). Only three-fourths of individuals (with AG (50 %) and AA (25 %) genotypes in the rs2248374 SNP) express a functional *ERAP2A* isoform, whereas the remaining individuals (with GG genotype) express an undetectable isoform of *ERAP2B* (Andrés et al., 2010). ERAP1 plays a major function in the antigen processing and trimming of the N-terminal extended peptides to the optimal size for MHC (major histocompatibility complex) class I molecules presentation. Peptides with 8–10 amino acids can be directly presented by MHC class I molecules on the cell surface while peptides longer than ten amino acids are entered to the ER by TAP1/2 (ATP-dependent transporter associated with antigen processing 1/2) and are subjected for peptide trimming by ERAP1 (Chang et al., 2005; Schumacher et al., 1994). (Hammer et al., 2006; Saveanu et al., 2005; York et al., 2002). ERAP1 trims peptides with 9–16 residues, efficiently (Hearn et al., 2009; Kanaseki et al., 2006), whereas ERAP2 exclusively trims peptides with 7–8 amino acids (Abe and Sato, 2006; Cui et al., 2002). Moreover, ERAP1 cleaves peptides with rather large hydrophobic residues (leucine and methionine) (Hattori et al., 1999), while ERAP2 cleaves positively peptides with charged residues (arginine and lysine) (Zervoudi et al., 2011). It has been demonstrated that ERAP1/2 could form a dimeric complex that cuts residues more efficiently (Evnouchidou et al., 2014). The peptides that are presented by MHC molecules could be divided into three different classes based on their association with ERAP1: 1) Peptides that need ERAP1 (Cunningham et al., 2017a) for optimum presention and are not presented in the absence of ERAP1; 2) Peptides that are susceptible to ERAP1 and they can merely be presented if ERAP1 expression is ablolished, proposing ERAP1 role in over-processing and eradicating these peptides 3) and (Cunningham et al., 2017a) peptides that are not affected by the existence or absence of ERAP1, presumably they do not require any additional trimming (Hammer et al., 2007). The tissue distribution of ERAP1/2 is correlated with expression of MHC class I molecules and like another components of the antigen processing and presenting machinery, ERAP1 is up-expressed by TNF-α and IFN-γ stimulation, proposing its major function in antigen presenting machinery (Forloni et al., 2010; Saric et al., 2002; Serwold et al., 2002). In addition to the major enzymatic function of ERAP1 and its contribution to the MHC class I mediated antigen processing pathway, it also has several pivotal functions in the immune system and body haemostasis. ERAP1 serves as a susceptible agent in response to pathogens, and its expression is vital for the immunomodulation of host defences via viral epitopes presentation by MHC class I molecules (Yewdell and Bennink, 1999). ERAP1 and ERAP2 play a significant role in the migration and proliferation of endothelial cells as a vital factor for vessel regeneration (Hattori et al., 2000; Sato, 2004). Also, ERAP1 may contribute to left ventricular mass pathogenesis via the cleavage of angiotensin II to angiotensin III and IV and changing kallidin to bradykinin in the kidney that is important for the adjustment of blood pressure and angiogenesis (Hattori et al., 1999; Hisatsune et al., 2015; Ranjit et al., 2019; Sato, 2004). ERAP1 may occur as a transmembrane and soluble protein in cells. Transmembrane-associated ERAP1 has been categorized as a type II integral transmembrane protein. It is hypothesised that transmembrane-associated ERAP1 may play a role in the cleavage of TNFR1 (Cui et al., 2002), IL-1RII (Cui et al., 2003b) and IL-6R (Cui et al., 2003a) via direct cleavage, which is known as “receptor sheddase”. ERAP1 is well

Table 1
A summary of disease-associated *ERAP1/2* polymorphisms in different populations.

Gene	SNP	Disease	Population	Amino acid change	Reference
ERAP1	rs2287987	AS, Bechet's disease	European/Caucasian	Val349Met (M349 V)	(Roberts et al., 2017; Takeuchi et al., 2016)
	rs27044	AS, HPV-associated cervical carcinoma, Psoriasis	Chinese/Caucasian/Korean	Glu730Gln (Q730E)	(Burton et al., 2007; Zhang et al., 2014)
	rs17482078	AS, Bechet's disease	European/Caucasian	Gln725Arg (R725Q)	(Wang et al., 2017)
	rs26653	AS, HPV-associated cervical carcinoma, Psoriasis	Caucasian	Pro127Arg (R127 P)	(Lee and Song, 2016; Stratikos et al., 2014; Wiśniewski et al., 2018)
	rs30187	AS, MS, Psoriasis, essential hypertension	European/East Asians/ Korean	Arg528Lys (K528R)	(Babaie et al., 2019; Das et al., 2017; Reeves et al., 2013; Roberts et al., 2017)
	rs10050860	AS, Bechet's disease	European/Caucasian	Asn575Asp (D575 N)	(Zee et al., 2018; Zhang et al., 2015)
	rs27524	Psoriasis	European/Caucasian	Intronic	(Strange et al., 2010)
ERAP2	rs2248374	AS, psoriasis vulgaris	European	Intronic	(Robinson et al., 2015a; Vanhille et al., 2013)
	rs2549782	AS, Preeclampsia, Hypertension	Caucasian/Australian/ Norwegian	N392K	(Haroon et al., 2010; Johnson et al., 2009; Zhang et al., 2017)
	rs75862629	AS	Caucasian/Sardinian	Intronic	(Paladini et al., 2019)
	rs10044354	BSCR	Caucasian	Intronic	(Kuiper et al., 2014, 2018)
	rs2548538	Bechet's disease, preeclampsia	African/American/Chilean	Pro435Pro (P435 P)	(Johnson et al., 2009)
	rs2287988	Bechet's disease	African/American/Chilean	Gln563Gln (Q563Q)	(Andrés et al., 2010)
	rs1056893	Bechet's disease	African/American/Chilean	Ser775Ser (S775S)	(Hill et al., 2011)
	rs2910686	Psoriasis	Romanian	Intronic	Popa et al., 2016

AS: Ankylosing Spondylitis, BSCR: Birdshot chorioretinopathy, MS: Multiple sclerosis, HPV: Human papillomavirus.

established to be as an ER-resident which could be upregulated in response to IFN-γ and TNF-α stimulation (Goto et al., 2011). In this review, we will provide an overview of current knowledge on the role of ERAP1/2, and we will discuss the contribution of recent studies to our understanding of their role in the autoimmune diseases and cancer immunity.

2. *ERAP1/2* structure and genetic variants

The crystallographic structures of ERAP1 revealed four domains, Domain 1 (46–254 residues), Domain 2 (255–529 residues), Domain 3 (530–614 residues), and Domain 4 (615–940 residues), which respectively constitute the final structure of ERAP1. ERAP1 shows two different crystalized conformations: open conformation and close conformation, which relates to the mechanism of peptide trimming. Open confirmation provides the possibility for protein binding, which is not any longer available in close conformation. Close conformation supports some critical changes in the active site upon closing, which is critical for the catalytic function (Stamogiannos et al., 2015). The domain and crystal structure of ERAP2 is highly similar to ERAP1 (Fig. 1) (Birtley et al., 2012).

Unlike *ERAP1*, which is extremely polymorphic (with 42,403 SNPs) with powerful linkage disequilibrium (LD) evident across the gene (Reeves and James, 2018), the SNPs in the *ERAP2* gene seem to be highly confined, due to non-synonymous changes affecting the amino acid sequence (Ombrello et al., 2015). Genome-wide association studies (GWAS) have found multiple *ERAP1* SNPs that are powerfully associated with hypertension (Yamamoto et al., 2002) and several human diseases, such as ankylosing spondylitis (AS) (Evans et al., 2011). The location of these SNPs implies their possible impacts on the immunological function of ERAP1 and substrate binding: rs2287987 (M349 V) falls in the active site, rs27044 (Q730E) and rs17482078 (R725Q) are located in the internal surface of the C-terminal cavity, which could influence the length specificity/substrate sequence. Other variants, such as rs10050860 (D575 N), rs30187 (K528R) and rs26653 (R127 P) predicted to be in the junction domains could indirectly influence on either enzymatic activity or specificity by switching between open and close conformations (Evnouchidou et al., 2011; Goto et al., 2006). It has been shown that *ERAP1* is extremely polymorphic and genetic variants within the *ERAP1* gene are associated with the increased risk of AS which is linked to the *ERAP1* catalytic function. The two SNPs namely rs30187 and rs27044 are the most frequently SNPs in almost all population. They both confer a protective role in AS which is due to a notable diminishing in aminopeptidase activity (Kirino et al., 2013; Mehta et al., 2009; Strange et al., 2010). Some SNPs including rs10050860 (D575 N), rs17482078 (R725Q), rs2287987 (M349 V), rs27434, rs27037 were proved by European population studies or Asian population studies to confer powerful pre-disposition to AS disease (Cai et al., 2015; Hemmatzadeh et al., 2019; Lee et al., 2011). Association of ERAP2 with AS was determined in family studies and genome-wide associations (Tsui et al., 2010). There is a frequent polymorphism in the catalytic site of ERAP2, N392 K (rs2549782) which changes the substrate specificity and activity of ERAP2 (Evnouchidou et al., 2012). The gene coding for rs2549782 (N392) is powerful LD with rs1056893 (S775S), rs2287988 (Q563Q), rs2548538 (P435 P), and rs2248374 in the entire world population (Andrés et al., 2010). Promoted activity of ERAP2 in AS disorder might be due to its direct peptide decay and indirectly with basic P1 residues favouring ERAP1-mediated trimming pathway. Although the effect of ERAP2 is important and crucial for some specific peptides, but its effect on *HLA-B27:05* peptidome is fewer than ERAP1 in terms of peptide affinity (Martín-Esteban et al., 2016). Moreover, it has been found that the existence of a G allele instead of an A allele in rs75862629 in the *ERAP2* gene promoter potently impacts on the expression of the *ERAP1/2* with a down-regulation of *ERAP2* coupled with significantly up-regulation of *ERAP1*. Discovery of this SNP pinpoints a quantitative measure of immunoregulation of the *ERAP1/2* genes, which can be helpful for the creation of personalised treatment of autoimmune disease (Paladini et al., 2018). *ERAP1/2* polymorphisms which are associated with several autoimmune diseases and cancer are categorised based on different populations in Table 1.

3. The role of ERAP1/2 in autoimmunity

Self-peptides targeted in autoimmunity usually are present in several tissues. They are subjected for degradation by the proteasomes through poly ubiquitination in the cytoplasm. The generated peptides are either in the optimal size to fit in MHC class I pocket or generated as amino-terminally extended precursors. *TAP* transports peptides into ER for further trimming at the N-terminus by ERAP1/2 before loading into MHC class I molecules (Fierabracci et al., 2012). Peptide- MHC class I complexes reach the cell surface where they can be recognized by T cell receptors (TCR) on CD8 + T cells. Under the non-autoimmune condition, peptide-MHC class I complexes are identified as a self-antigen by TCR and are tolerated. However, under the autoimmune condition, the assembled epitope within MHC class I molecules may be identified by TCR of autoreactive T cells (Zervoudi et al., 2013). Afterwards, this will

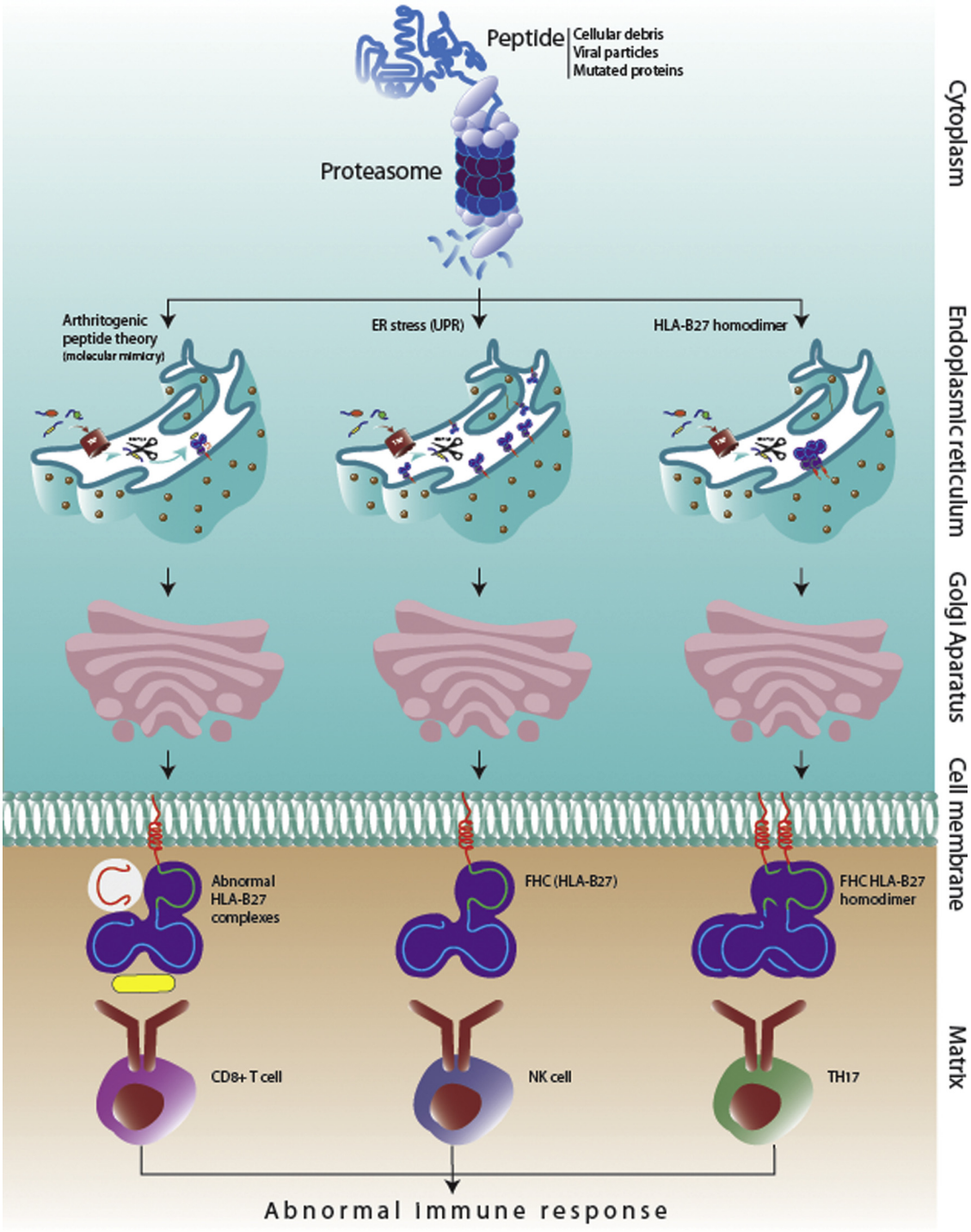

Fig. 2. A pathogenetic model on hypothesized **mechanisms of abnormal immune response induction in ankylosing spondylitis (AS).** As shown above, degraded peptides by the proteasome, being transported by TAP into the endoplasmic reticulum (ER) where they are further trimmed by ERAP1/2. A) Altered or inappropriate self-peptide complexes loading on MHC I molecules. B) Misfolded HLA-B*27 heavy chain leading to ER stress and unfolded protein response (UPR). C) HLA-B27 heavy chains forming homodimers. All three mechanisms lead to the stimulation of specific cells, which induces abnormal immune responses.

activate CD8 + T cells and result in target cell degradation (Fig. 2).

3.1. Ankylosing spondylitis

Autoimmune diseases are a complex class of disorders which involves different systems and/or organs. Epidemiological studies showed a higher risk of immune disorder in people with other autoimmune diseases background, four opathy diseases are powerfully associated with MHC class I molecules including AS, psoriasis, Bechet's disease, and birdshot chorioretinopathy (Table 2) (Gupta et al., 2014; McGonagle et al., 2015; Sieper and Poddubnyy, 2017). AS is a chronic autoimmune inflammatory disease and a member of spondyloarthropathies family (SpA). SpA which comprises a group of immune-mediated inflammatory disorders and occurs in 0.5–1% of the population, while AS accounts for 30–50 % of it. Currently, there is no cure for AS, and the available treatments only suppress the inflammation and reduce pain in a proportion of patients (Mohammadi et al., 2018b, c; Taurog et al., 2016). The chronic inflammation in AS patient is followed

Table 2
A summary of representative studies of HLA susceptibility loci in opathy diseases.

HLA molecule	Alleles	Type	Population	Reference
Ankylosing spondylitis				
HLA-B27	*HLA-B27:02*	Risk allele	European/Mediterranean	(Cortes et al., 2015)
	HLA-B27:04	Risk allele	Asian/Chinese (Han)	(Liu et al., 2010)
	HLA-B27:05	Risk allele	European	(Cortes et al., 2015)
HLA-B47	*HLA-B47:01*	Risk allele	European	(Cortes et al., 2015)
HLA-B40	*HLA-B40:01*	Risk allele	Taiwanese/Dutch	(van Gaalen et al., 2013; Wei et al., 2015)
HLA-B7	*HLA-B7:02*	Protective allele	European	(Chen et al., 2017; Cortes et al., 2015)
HLA-B57	*HLA-B57:01*	Protective allele	European	(Cortes et al., 2015)
Psoriasis				
HLA-C06	*HLA-C06:02*	Risk allele	European	(Gudjónsson et al., 2002)
HLA-Cw6		Risk allele	Caucasians	(Chandra et al., 2016)
Bechet's disease				
HLA-B51	*HLA-B51:01*	Risk allele	various populations	(Sugisaki et al., 2005)
	HLA-B51:02(01)	Risk allele	Turkish	(Arber et al., 1991)
	HLA-B51:08	Risk allele	Turkish/European	(Demirseren et al., 2014)
	HLA-B51:09	Risk allele	Turkish	(Demirseren et al., 2014; Verity et al., 2003)
Birdshot chorioretinopathy				
HLA-A29	*HLA-A29:01*	Risk allele	Caucasians/Asian/African	(Cunningham et al., 2017b; Rodriguez et al., 1996)
	HLA-A29:02	Risk allele	Caucasians/Asian/African	(Brézin et al., 2011)

by bone regeneration, syndesmophyte formation, remodelling and ankylosis. Subclinical gut inflammation (Ciccia et al., 2016) (70 % of AS patients) acute anterior uveitis (Martin and Rosenbaum, 2011) (30–40 % of AS patients) peripheral arthritis are common in AS patients (Exarchou et al., 2015; Montilla et al., 2012). Several GWAS studies have shown a significant association between *Endoplasmic Reticulum Aminopeptidase 1* (*ERAP1*) and AS, conferring 26 % risk (Burton et al., 2007; Reveille et al., 2010). Presumably, the discovered disease-associated single nucleotide polymorphisms do not trigger the disease, but play a role as genetic risk markers, potentially in power of LD with disease-related variants (Babaie et al., 2018a; Mohammadi et al., 2018a; Zikherman and Weiss, 2011). More than 90 % of the variants associated with MHC class I opathy diseases, recognized by GWAS studies are not simply altering the protein structure (i.e. nonsense mutations or nonsynonymous), but identified in noncoding intronic or intergenic sites, and hence play a regulative role. (Ricaño-Ponce and Wijmenga, 2013). Analysis of main GWAS reports revealed *ERAP1* and *ERAP2* variants contribution in several autoimmune conditions. However, further case-control studies are required to prove the relevant SNPs associations (Evans et al., 2011).

3.1.1. The pathogenic role of ERAP1/2 in AS

ERAP1 contribution to the immunopathogenesis of AS remains vague. ERAP1 is associated with AS only in HLA-B27 positive patients; therefore, ERAP1 variants which predispose to AS correlates with the suggested roles for HLA-B27 in AS pathogenesis. There are three classical theories to understand AS pathogenesis and elucidate HLA-B27 contribution to AS: Arthritogenic peptide theory (molecular mimicry), the endoplasmic reticulum stress and the unfolded protein response (UPR) theory and HLA-B27 homodimers theory (Babaie et al., 2018b).

3.1.2. Arthritogenic peptide theory: molecular mimicry

Presentation of particular antigens leads to autoimmunity via cross-reaction or molecular mimicry among self-derived peptides and pathogen-derived peptides (Beukelman and van Leeuwen, 1990). Improper or altered, MHC-self-peptide complexes are presented to the immune cells and identified as dangerous or foreign, which stimulates a self-reactive inflammatory response. A significant objection to this theory is the unknown role of $CD8^+$T-cells in AS pathogenesis (Reveille and Maganti, 2009).

3.1.3. ER stress and the unfolded protein response (UPR) theory

The unfolded protein response (UPR) is another theory of AS pathogenesis, involving misfolding of HLA-B27 heavy chain leading to ER stress and finally activation of unfolded protein response and upregulation of pro-inflammatory cytokines such as IL-23. It is reported that HLA-B27 heavy chains fold slowly and remain longer in the ER in contrast to the other HLA class I molecules (Mear et al., 1999). UPR is a physiologic mechanism operated by the cells in an attempt to return to a healthy condition (Schröder and Kaufman, 2005). HLA-B27 misfolding occurs in the bowel of AS patients and autophagy also seem to stimulate IL-23 upregulation in AS patients with bowel inflammation (Ciccia et al., 2014).

3.1.4. HLA-B27 homodimers theory

Formation of HLA-B27 heavy chain homodimers via cysteine residue at position 67 on the cell surface is the third hypothesis, which can be recognized by immune receptors, including KIR3DL1, KIR3DL2 and LILIRB2 (Shaw et al., 2014). HLA-B27 homodimers recognition can result in an increased number of Th17 cells and consequently upregulated IL-17 among AS patients (Bowness et al., 2011; Ridley et al., 2016; Wong-Baeza et al., 2013). The surface HLA-B27 homodimers formation might be due to the abnormal ERAP1 trimming and the unusual biochemical properties of HLA-B27 molecules.

The two latter theories highlights HLA-B27 might directly play a role as a proinflammatory factor by IL-23/IL-17 axis activation. While all three theories may contribute to AS pathogenesis, the arthritogenic peptide theory is likely the one that lends itself most readily to harmonized effects of HLA-B27 and ERAP1 (Babaie et al., 2018b; Chatzikyriakidou et al., 2011).

ERAP1/2 variants may support all three theories to explain how HLA-B27 involves in AS. Altered rates of peptide trimming by ERAP1/2 could result in the presentation of abnormal peptides on the cell surface by the HLA-B27. Recently, ERAP1 variants have been reported to increase the levels of HLA-B27-free heavy chains (FHC) (Haroon et al., 2012). AS is extremely hereditable and highly associated with HLA-B27 in more than 95 % of the patients in the Caucasian population (Mapstone and Woodrow, 1975; Pedersen et al., 2008). Nevertheless, only 1–5% of HLA-B27-positive carriers develop AS. Implying that other genes and environmental triggers such as bacterial infection along with HLA-B27 predispose to AS disease (Babaie et al., 2018b).

3.1.5. HLA-B27 and ERAP1/2 in AS

Unlike to ERAP1, which is in epistasis with the HLA-B27 in this disease, the association of ERAP2 is not epistatic with the HLA-B27 (Evans et al., 2011). GWAS reported the association of five *ERAP1* variants and AS risks (Burton et al., 2007). Various studies ascribed *ERAP1* haplotypes based on relationships with another SNPs mapping

in the UTR, coding and intronic sites are termed Hap1 to Hap10 (López de Castro et al., 2016; Ombrello et al., 2015; Reeves et al., 2014). These allotypes are categorized in three functional families: efficient allotypes, hypoactive allotypes and hyperactive allotypes. A powerful aminopeptidase activity marks individual *ERAP1* variants or the full haplotypes related with elevated risk of AS (Martín-Esteban et al., 2014; Reeves et al., 2014). Several studies consistently indicated the high-trimming of "*Met349-Lys528-Asp575-Arg725-Gln730*" (*VRNQE* or *Hap10*) haplotype as AS risks, while the low-trimming of "*Val349-Arg528-Asn575-Gln725-Glu730*" haplotype is known as protective haplotype (Roberts et al., 2017).

Lopez et al. showed how HLA-B27 peptidome is affected by ERAP1 allotypes (García-Medel et al., 2012; Sanz-Bravo et al., 2015) which influences mostly the P1 site and, to a lower extend, the antigenic peptide length, the number of specific ligands, the remaining peptide sequence, the affinity of HLA-B27, and thermostability of the entire peptide/HLA-B27 complexes.

Chen et al. reported that patients with AS carrying protective allelic variants of *ERAP1*, rs30187 and rs27044, have diminished monocytic expression of HLA-B27-FHC and inhibition of these variants does not upregulate HLA-B27-FHC expression. They also showed that *ERAP1* silencing or inhibition of peripheral blood mononuclear cells (PBMCs) diminished Th17 cell expansion and IL-17A production. Based on these results, ERAP1 inhibition could potentially be used as a therapeutic approach in AS (Chen et al., 2016). Adrian et al. reported that the AS-promoting activity of ERAP2 may result from both its direct decay of peptides with basic P1 site and from indirectly preferring ERAP1-mediated trimming. Although there is a defined essential and critical role for ERAP2 for some specific peptides, but the effect of ERAP2 on HLA-B27:05 peptidome on peptide characteristics and affinity is smaller than ERAP1 (Martín-Esteban et al., 2017; Sanz-Bravo et al., 2018). Rastall et al. indicated that the expression of specific AS-associated human *ERAP1* variants could have a substantial effect on different aspects of mammalian immune system. They proved that the presence or absence of ERAP1 could significantly affect NK cell killing activity. Moreover, their results show that the existence or absence of specific *ERAP1* variants can change antigen presentation pathway in the *in-vivo* condition (Rastall et al., 2014, 2017). It also has been shown that *ERAP1* silencing declined the level of 9-meric HLA-B27-attachment of antigenic peptides and on the other hand enhanced the rate of longer ligands, mainly with expanded C-terminal (Chen et al., 2014).

One of the areas for future research is the survey of correlation between the aminopeptidase activity of *ERAP1* allelic variants and cell surface expression of HLA-B27. An association between AS-protecting allelic variants of *ERAP1* (such as rs30187 and rs27044) reduced the surface expression of HLA-B27 in monocyte cells of AS patients as well as in HLA-B27$^+$-cell lines. However, with this study, the association of ERAP1 enzymatic activity and HLA-B27 aberrant expression was not conclusive. In another study, dendritic cells (DCs) of AS patients represented ERAP1 overexpression compared to healthy controls, however there were no significant differences in terms of HLA class I dimers between AS patient and healthy group in DCs populations (Campbell et al., 2011).

In another study, executed in HLA-B27$^+$ and HLA-B27$^-$ AS patients, the existence of predisposition or protecting *ERAP1* allelic variants, did not show significant influence on the production of pro-inflammatory cytokines and ER stress markers, refusing the ER stress as an origin of the disease (Kenna et al., 2015).

In contrast, the association of ERAP2 is not epistatic with the HLA-B27, developing in both HLA-B27$^+$ and HLA-B27$^-$ individuals (Cortes et al., 2013; Robinson et al., 2015b). These findings show that ERAP1/2 complex might function differently. Highlighting the fact that, the *ERAP2* null-SNP rs2248374 is powerfully protecting AS (Robinson et al., 2015b), therefore, ERAP2 could be involved in AS disease as coupled and uncoupled with ERAP1. Hence, ERAP2 could affect directly on HLA-B2705 peptidome, and indirectly on the increased rate of monomers via the improvement of ERAP1 enzymatic activity (Martín-Esteban et al., 2016). Recently one study has indicated the impact of ERAP2 on HLA-B27 peptide repertoire and concluded this might change, depending on ERAP1 mediated trimming rate (Martín-Esteban et al., 2017). Altogether, the basic outcome of ERAP2 existence and absence on HLA-B27 structures is not fully understood and the molecular and cellular mechanisms providing the effects of ERAP2 on AS risk are not thoroughly comprehended yet.

3.2. Bechet's disease

Bechet's disease (BD) is a multisystemic and rare disorder, immune-mediated vasculitis of small and large blood vessels which can be triggered by genetic and environmental factors. BD has been seen often in the countries of the 'Silk Road', including Iran, Turkey, China and Japan (Gül et al., 2002; Seyahi and Yazici, 2015). *HLA-B51* allele is the most powerfully associated risk factor for BD, although a weak relation with *HLA-B27:02* was found. BD patients mostly suffer from periodic inflammation often affecting the urogenital mucosa, eyes, and skin (Gül et al., 2002). GWAS study of 779,465 SNPs with attributed genotypes in 1209 Turkish BD patients and 1278 healthy controls showed novel associations of *CCR1, KLRC4, IL-10, IL-23R*, and *STAT4* with BD risk. Morever, two SNPs in *ERAP1* with strong LD, encoding *ERAP1* rs10050860 (D575 N) and rs17482078 (R725Q) variants conferred the BD risk. Inaddition, another study found evidence of *ERAP1* and *HLA-B51* association. Also, two known risk factor variants in inflammatory bowel disease namely *IL-23R* and *IL10* are involved in the AS and BD pathogenesis with the same pathogenic mechanisms (Kirino et al., 2013; Sousa et al., 2015; Talei et al., 2018).Moreover, three SNPs in *ERAP2*, encoding *ERAP2* rs2548538, rs2287988 and rs1056893 variations, recessively conferred the BD risk (Andrés et al., 2010). Guasp et al. recently reported that in the absence of *ERAP1*, *ERAP2* can carry out a significant role in the trimming of the *HLA-B51:01* peptidome, in an *ERAP1*independent manner (Guasp et al., 2019). This study represented *ERAP2* mostly as an independent enzyme, facilitated *ERAP1* processing in shaping the *HLA-B51:01* peptidome (Guasp et al., 2019).

3.3. Psoriasis

Psoriasis is a chronic inflammatory immune-mediated disorder that is developed in the skin and distinguished by differentiation and hyperproliferation of keratinocytes (Chen and Tsai, 2018). Psoriasis is developed in approximately 2–4% of the population across the world (Fan et al., 2008; Gudjónsson et al., 2002). *HLA-C06:02* allele is the most strongly related risk factor predisposing to psoriasis and psoriatic arthritis. There are several genes, which their predisposition in psoriasis incidence have been implicated (Enerbäck et al., 1997; Lysell et al., 2013; Sun et al., 2010). These genes are mainly involved in antigen presentation pathway and immunoregulation (*MICA*, *ERAP1*, *ERAP2* and *HLA-Cw6*), the IL-23/IL-17 immune axis (*IL23Ap19, IL12Bp40, IL23R rs11209026, TYK2, JAK2*), T-cell development and polarization (*RUNX1, RUNX3, TAGAP, STAT3, IL-4, IL-13*), innate immunity (*CARD14, DDX58, TRAF3IP2, IFIH1, c-REL*) and negative regulators of immune responses (*NFKBIA, TNIP1, TNFAIP3, SOCS1, ZC3H12C, IL36RN*). The role of *ERAP1* variations was underlined by the association of rs27524 in *HLA-Cw6* positive individuals (Strange et al., 2010). While future investigation represented the association of rs26653 (R127 P) with the psoriasis risk which is not dependent on *HLA-C06* expression (Lysell et al., 2013). The contribution of some of these genes could develop the psoriatic disease by targeting of vital components such as the IL-17/IL-23 (Harden et al., 2015; Puig et al., 2014). Additionally, Two SNPs in *ERAP1/2*, encoding rs30187 (K528R) and rs2910686 variations, recessively conferred the psoriasis risk (Das et al., 2017; Strange et al., 2010).

3.4. Birdshot chorioretinopathy

Birdshot chorioretinopathy (BSCR) or Birdshot uveitis is a very rare form (almost 1–5 cases/500000) of the ocular-specific inflammatory disorder which is unique among autoimmunity diseases in its organ specificity and its strong association with *HLA-A29:02* allele (Minos et al., 2016; Nussenblatt et al., 1982; Cao et al., 2001). The *HLA-A29.02* which is one of the most common subtypes is powerfully associated with BSCR, being observed in over 95 % of patients and approximately 7% of healthy individuals (Rodriguez et al., 1996; Rosenbaum, 1989). Several large-scale genomic studies revealed a significant association between the *ERAP2* rs10044354 SNP and risk of BSCR (Kuiper et al., 2014). Whereas the association of the haplotype *HLA-A29.02* and BSCR is well known, the precise role of the *HLA-A29* in BSCR immunopathogenesis remains slightly comprehended. The role of *HLA-A29* was emphasised by a GWAS report in the Northern European population (Kuiper et al., 2014). Unlike to the unidentified effect of *ERAP2* polymorphism on the *HLA-A29* peptidome in BSCR, proof for the involvement of *ERAP1* in BSCR has been demonstrated in a recent study (Alvarez-Navarro et al., 2015). Hence further studies for determining the contribution of *ERAP2* to BSCR is required.

4. *ERAP1/2* in cancer

Since the antigen processing and presentation pathway plays a pivotal function in the interplay between tumour cells and human immune system, *ERAP1/2* may be potential targets in reprogramming epigenetic factors and increased the immunogenicity of malignant cells for the purpose of developing anti-cancer immune responses. The efficient MHC class I mediated presentation of tumour peptides, derived from the cytosolic degradation of endogenous peptides via the proteasome complexes and aminopeptidases, is an important step in arising the anti-cancer response. Finally, tumour peptides-MHC class I complexes are expressed on the cell membrane for activating T $CD8^+$ cell and NK cell-mediated immune responses (Cifaldi et al., 2015; James et al., 2013) (Fig. 2). The direct role of *ERAP1/2* in antigen processing and presentation pathway has been represented with studies on mouse models that affect the expression of classical and nonclassical MHC class I molecules (Evnouchidou et al., 2009; Firat et al., 2007; López de Castro, 2018; Yan et al., 2006; York et al., 2006). Besides, imperfections in *ERAP1/2* expression are presumably to be required for the immune escape strategies of tumours via generation and degeneration of peptides with aberrant length and sequence. In endometrial carcinoma, expression of *ERAP1* has been represented in 64 % of the patients correlated with CA-125 levels, thus suggesting a role in endometrial cancer cell development and differentiation (Kazeto et al., 2003; Shibata et al., 2005). Also, polymorphic variation in *ERAP1/2* may play critical roles in the susceptibility to specific tumours, as well as their prognosis and progression. For example in the study of Alvarez et al. it has been demonstrated that allelic variants affecting the aminopeptidase activity of *ERAP1* change the immunopeptidomes presented by HLA class I molecules, resulting in tumour immune escape (Alvarez-Navarro et al., 2015; Joyce, 2015). Several experimental studies demonstrated the deficiencies in the function and expression of *ERAP1/2* genes in different solid tumours and haematological cancers, including leukaemia-lymphomas, melanoma, breast, colon, lung, skin, bladder, chorion, prostate, kidney most especially with the clinical outcome in cervical carcinoma (Kamphausen et al., 2010; Mehta et al., 2009; Stratikos et al., 2014). Mehta *et al.* have investigated the association of *ERAP1* coding SNPs in the cervical carcinoma in Dutch populations and revealed that rs27044 and rs26653 were significantly associated with increased cervical carcinoma risk (the existence of minor alleles G and C, respectively). Furthermore, in this study they have demonstrated that rs30187, rs26653 and rs26618 were significantly associated with the existence of lymph node metastases (Mehta et al., 2007b). Another study by Mehta et al. (2015) in 2015, investigated genetic variations in members of the antigen processing and presenting system, including *TAP1, TAP2, LMP2, LMP7* and *ERAP1* genes in two Indonesian ethnic groups (the Javanese and the Balinese). In this study, it was shown that C allele of rs30187, G allele of rs26653, and C allele of rs27044 were significantly associated with increased cervical carcinoma risk in the Javanese ethnic group, unlike the Balinese ethnic group. Moreover, the genotypes of rs30187, rs27044, rs10050860, and rs26653 were associated with cervical carcinoma incidence in the Javanese, unlike the Balinese ethnic groups (Mehta et al., 2015). In another study, Yao et al. in 2016, analysed genotype and haplotype frequencies of four different SNPs namely, rs26618, rs26653, rs27044, and rs30187, in non-small cell lung carcinoma patients and healthy controls in both Polish populations and Han Chinese. These four SNPs represented an association with non-small cell lung carcinoma in the Han Chinese ethnic group, but not in the Polish ethnic group. Also, the haplotype *rs26653C/rs26618 T/rs30187 T/rs27044G* (*CTTG* protective alleles) represented powerfully protective role against non-small cell lung carcinoma in the Han Chinese ethnic group, unlike the Polish ethnic group (Yao et al., 2016). The variations in *ERAP1* association with lung carcinoma in the different ethnic groups might be due to the variations in MHC allelic distribution between the Polish and Chinese ethnic groups. Moreover, variations in the frequency of the SNP genotypic forms between the Chinese and Polish ethnic groups may also play a role (González-Galarza et al., 2015). MHC genes represents a wide variety in different ethnic groups, and these variations can significantly change the polarity, size, and shape of the peptide-binding groove of MHC molecules. A number of immunopeptidome presented by MHC class I molecules rely on *ERAP1* processing and trimming for optimum size of antigenic peptides in normal and transformed cells and might not be presented without an appropriate *ERAP1* allele (Fruci et al., 2014).

5. Immunomodulation of *ERAP1*/2 in cancer immunotherapy

A huge number of studies have represented another cellular role of *ERAP1/2* in various biological processes such as; migration and proliferation of endothelial cells in solid tumours, tumour neo-vessel formation, inflammation, angiogenesis and activation of the renin-angiotensin system which is involved in blood pressure adjustment and angiogenesis (Fig. 3). Miyashita et al. reported that *ERAP1* is expressed in endothelial cells during differentiation *in-vitro* and *in-vivo*, at the angiogenesis region induced by *vascular endothelial growth factor* (*VEGF*). Inhibition of *ERAP1* expression in endothelial cells suppressed *VEGF*-induced migration, proliferation, and neo-vessel formation *in-vitro,* as well as angiogenesis *in-vivo* (Akada et al., 2002; Miyashita et al., 2002; Suzuki et al., 2007; Yamazaki et al., 2004; Yoshida et al., 2010). In Addition, *ERAP1* regulates the cell cycle progression (G1/S transition) of endothelial cells via VEGF-stimulated activation of the PDK1-S6 kinase pathway and cyclin-dependent kinase (CDK) 4/6 (Yamazaki et al., 2004). In another similar study, it was reported that *ERAP1* regulates the spreading of endothelial cells by activating focal adhesion kinase and endothelial integrins consequently boosting endothelial cells adherence to the extracellular matrix through RhoA activation (Suzuki et al., 2007). In another study it has been demonstrated that *ERAP1* inhibits *VEGF*-induced angiogenesis and endothelial cell migration in human endometrial carcinoma by regulating the renin-angiotensin system in a dose-dependent manner (Watanabe et al., 2003). Bufalieri et al. in 2019, demonstrated that *ERAP1* enhances Hedgehog pathway-dependent tumorigenesis by regulating USP47 and enhancing degradation and ubiquitylation of βTrCP *in-vitro* and *in-vivo* (Bufalieri et al., 2019). A comparison of *ERAP1/2* tissue distribution between human neoplastic and normal counterparts from the same tissue showed *ERAP1* and *ERAP2* are expressed at highly variable levels in all cancer cell lines and independent of each other, likely as part of tumour immunoediting processes. The expression level of *ERAP1/2*, depending on the origin of tumours, ranges from low to high expression: 1(low expression of *ERAP1/2* as the most frequent event observed

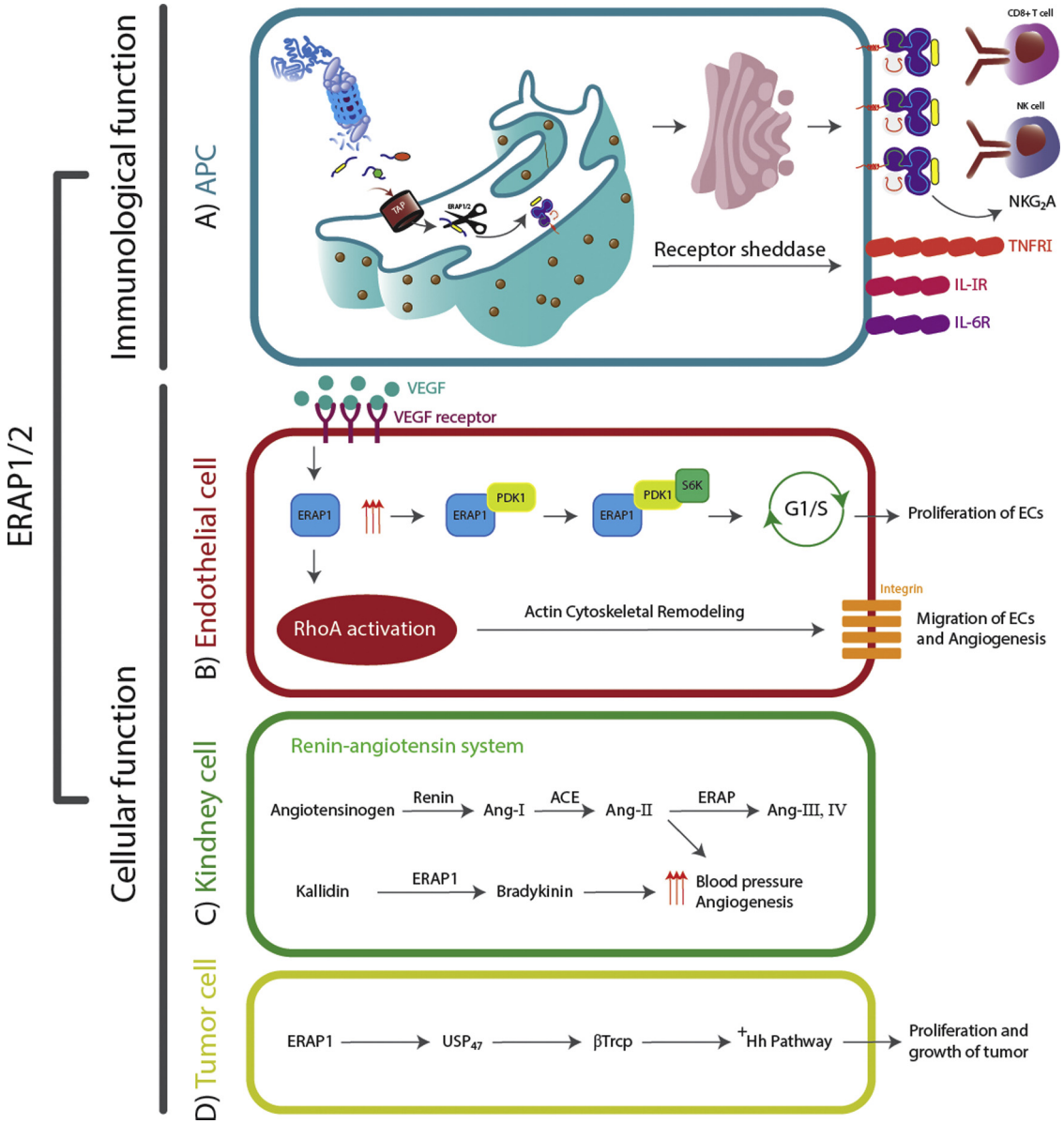

Fig. 3. The immunological and cellular functions of ERAP1/2 in autoimmune disease and cancer. A) ERAP1/2 play a crucial role in processing pathway of peptide antigens for presentation on MHC I molecules at the cells surface, where they are recognized by the CD8 + T cells and by inhibitory receptors such as NKG2A on natural killer (NK) cells. **B)** Another immunological role for ERAP1 in the immune system is shedding of IL-6R, IL-1R and TNFR. Vascular endothelial growth factor (VEGF) stimulation increases ERAP1 expression, which activates PDK1-S6 kinase pathway and resulting in G1/S phase transition and proliferation of endothelial cells (ECs). ERAP1 regulates the spreading of endothelial cells by activating endothelial integrins, boosting endothelial cells adhesion to the extracellular matrix through RhoA activation. This results in VEGF-stimulated migration, proliferation, and neo-vessel formation as well as angiogenesis. **C)** ERAP1 also contribute to the control of left ventricular mass through the cleavage of angiotensin II to angiotensin III/IV and convert kallidin to bradykinin in the kidney that is important for the adjustment of blood pressure and angiogenesis. **D)** In tumor cells, ERAP1 enhances Hedgehog (Hh) pathway-dependent tumor growth and tumorigenesis by regulating USP47 and enhancing proteasomal degradation and ubiquitylation of βTrCP.

in transformed or malignant cells such as an aggressive type of neuroblastoma cells due to a poor fundamental *NF-kβ* nuclear factor activity (Forloni et al., 2010), resulted in low levels of functional trimming of *ERAP1/2* and implying that this phenomenon may promote to tumour escape from immune system responses; 2(downmodulation of one or both *ERAP1/2* as the most frequent condition in ovarian, breast, lung carcinomas and especially down-expression of *ERAP1* as major independent factor in decreasing overall survival and disease free survival in cervical carcinoma (Mehta et al., 2007a) ; 3) upregulation of both *ERAP1/2* in many cancers such as skin cancer, colon, thyroid carcinomas and HPV-induced malignancies (Fruci et al., 2008; Steinbach et al., 2017). MHC class I surface expression is notably correlated with *ERAP1* expression, but not with *ERAP2*, suggesting that *ERAP1* has a key role in the formation of MHC class I epitopes (Fruci et al., 2006). Unbalanced expression of *ERAP1/2* was also discovered in renal cell carcinoma lesions compared with the normal counterparts (Stoehr et al., 2013). However, according to current findings, studies focused on the expression and the function of *ERAP2* have to be re-evaluated according to the involved genotype of *ERAP2* (Andrés et al., 2010). Several studies so far have highlighted that *ERAP1/2* could be a novel and potential target for promoting T cell and NK cell-mediated anti-tumour cytotoxic responses (Cifaldi et al., 2011). For example, Cifaldi et al. in 2011, have demonstrated that in syngeneic animals, inhibition of *ERAP1* induces a conformational alteration in the peptide-MHC class I complexes leading to the stimulation of protective antitumor responses by improving NK cell, and T cell-mediated responses. Also results of this

study demonstrated that *ERAP1* inhibition modifies tumour immunogenicity by altering the balance of activating and inhibitory NK cell receptors such as NKG2A (Cifaldi et al., 2011, 2012). In another study, James et al. (2013) and Keller et al. (2015), showed that *ERAP1* overexpression leads to destruction of tumour-associated immunodominant epitopes (*MART*-1 and *GSW11*) proposing that tumour antigen destruction may establish a novel tumour escape strategy for colorectal carcinoma and melanoma. Moreover, inhibition of *ERAP1* activity has been reported to enhance anti-cancer CD8 + T and NK cells responses. In fact, these two studies confirming the hypothesis of the "bind-trim-release" mechanism for *ERAP1* in cancers. More recently, Reeves et al. studied the relationship between *ERAP1* allotype sequence and the amount of tumour-infiltrating $CD8^+$ T lymphocytes (TIL) with HPV^+ oropharyngeal squamous cell carcinomas and represented that $CD8^+$ T cell tumour infiltration has been associated with improved disease prognosis (Reeves et al., 2019). Also, Koumantou et al. in 2019, have demonstrated the effects of *ERAP1* inhibition, via DG013A on the immunopeptidome of a melanoma cell line, can induce significant alteration on the cellular immunopeptidome of cancer without abolishing antigen presentation pathway (Koumantou et al., 2019). Consequently, these studies prove the possibility of modulating of *ERAP1/2* activity as a novel immunological strategy for cancer immunotherapy. Recently, in addition to the nonspecific pharmacological metallopeptidase inhibitor, such as Leucinethiol, a novel class of more potent inhibitors for *ERAP1* and *ERAP2* with higher potency and selectivity such as DG013A has been developed (Georgiadis et al., 2018; Georgiadis and Dive, 2015; Kanaseki et al., 2006). These new specific inhibitors are effective in targeting *ERAP1* and *ERAP2* at the nM range, suggesting their potential targets for cancer immune surveillance.

6. Conclusions

ERAP1/2 are ER-resident aminopeptidases which are involved in MHC-peptide complex presentation and processing machinery. Despite the fact that there has been a large number of studies exploring these aminopeptidases, but their role in cancer growth and activation of anti-cancer immune responses has not been well comprehended so far. The role of *ERAP1/2* in autoimmunity and cancer are through their effects on the cellular immunopeptidome and consequently activating NK and T cells-mediated cytotoxic responses and proinflammatory cytokine production in which a polymorphic variation plays an important role and make it a pivotal pharmacological target in the personalized treatment of cancer and its prognosis. Hence, the scheme may be more intricate because of the genetic heterogeneity of cancers, and ongoing and further studies are required in order to elucidate further the functional effect of *ERAP1/2* in the tumour microenvironment. There are huge number of researches revealing immune system imbalance and its effect in predisposing to autoimmune or cancerous condition which directly or indirectly might concerns manipulating of *ERAP1/2*. Therefore, a better understanding of *ERAP1/2*' exact physiological role may suggest potential novel approaches for cancer immunotherapy as well as for autoimmune diseases treatment. Further studies regarding the epistatic association between aminopeptidases and HLA genes in different ethnic groups, and their impact on *ERAP1/2* and the process of antigen presentation pathway can have beneficial therapeutic developmental impact. In this review, we have summarised *ERAP1/2* function and its possible association with the autoimmune diseases and cancer immunity. We believe further GWAS will pave the way to understand the pathogenesis of the disease more in detail and will help to find appropriate pathways for anti-tumour therapeutic exploitation.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.molimm.2020.02.020.

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