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Review

Molecular and pathogenic effects of endoplasmic reticulum aminopeptidases ERAP1 and ERAP2 in MHC-I-associated inflammatory disorders: Towards a unifying view

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ABSTRACT

The inflammatory diseases that are most strongly associated with major histocompatibility Complex class I (MHC-I) alleles are also influenced by endoplasmic reticulum aminopeptidase (ERAP) 1 and/or 2, often in epistasis with the susceptibility MHC-I allele. This review will focus on the four major MHC-I-associated inflammatory disorders: ankylosing spondylitis, birdshot chorioretinopathy, Behçet's disease and psoriasis. The genetics of ERAP1/ERAP2 association and the alterations induced by polymorphism of these enzymes on the risk MHC-I allotypes will be examined. A pattern emerges of analogous effects on peptide length, sequence and affinity of disparate peptidomes, suggesting that similar peptide-mediated mechanisms underlie the pathogenesis and the joint contribution of ERAP1/ERAP2 and MHC-I to distinct inflammatory diseases. Processing of specific antigens, peptide-dependent changes in global properties of the MHC-I molecules, such as folding and stability, or both may be pathogenic.

Contents

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1. Introduction

Various inflammatory diseases are strongly associated with MHC-I genes (Table 1). Birdshot chorioretinopathy (BSCR), a rare ocular disorder involving inflammation of the posterior eye segment (Shah et al., 2005), occurs among HLA-A*29-positive individuals in >95% of cases (Nussenblatt et al., 1982; Shah et al., 2005); patients with ankylosing spondylitis (AS), a relatively frequent disease characterized by enthesitis, bone remodeling and ankylosis, have HLA-B*27 with 90–95% frequency (Brewerton et al., 1973). Behçet's disease (BD), a systemic vasculitis showing ocular, skin and mucosal lesions (Sakane et al., 1999), is conspicuously associated with HLA-B*51:01 (Ohno et al., 1982; de Menthon et al., 2009; Gul and Ohno, 2012). Psoriasis, a phenotypically complex and common disease showing epidermal hyper-proliferation, vascular remodeling and skin inflammation (Nestle et al., 2009), is associated with HLA-C*06:02 (Henseler and Christophers, 1985; Gudjonsson et al., 2006).

All these diseases are polygenic and of unknown etiology. In particular, the pathogenetic role of the MHC remains elusive. Genome-wide association studies (GWAS) established that the endoplasmic reticulum aminopeptidases ERAP1 and/or 2, which are involved in the final processing of MHC-I ligands (Saric et al., 2002; Saveanu et al., 2005) are risk factors for these diseases. ERAP1 is associated with AS (WTCC Consortium, 2007; The TASK and WTCCC2 Consortia 2011), BD (Kirino et al., 2013; Takeuchi et al., 2016), and psoriasis (Strange et al., 2010) in epistasis with B*27:05, B*51:01 and C*06:02, respectively, although the epistatic association in psoriasis was disputed in one study (Lysell et al., 2013). ERAP1 may also be a risk factor for BSCR, since the current analyses lacked power to unambiguously distinguish this association from that of ERAP2. The expression of this enzyme is a risk factor for BSCR (Kuiper et al., 2014b), AS (Agrawal and Brown, 2014; Robinson et al., 2015) and probably psoriasis (Tsoi et al., 2012; Yin et al., 2015) (Table 1). This review will focus on the functional interaction of ERAP1 and ERAP2 with the main susceptibility MHC-I allotypes in the four major MHC-I associated diseases, aiming to define common features of this interaction. Although not addressed here, the function of ERAP1 may not be limited to antigen processing (Alvarez-Navarro and Lopez de Castro, 2014). Particularly relevant might be its capacity to modulate innate immunity (Aldhamen et al., 2015).

2. ERAP1 and ERAP2: enzymatic features and polymorphism

These enzymes trim peptides reaching the ER for MHC-I binding (Fig. 1). Both are Zn-metallopeptidases sharing about 50% amino acid identity (Tsujimoto and Hattori, 2005). ERAP1 adopts two conformations: one closed and active and another open and with low activity (Nguyen et al., 2011; Kochan et al., 2011; Stamogiannos et al., 2015). The transition between both states is mediated by substrate binding to a regulatory site distinct from the catalytic site, in a way that short peptides cannot reach the latter. This explains the seemingly unique *molecular ruler* mechanism of ERAP1 (Chang et al., 2005), consisting in that peptides of 9–16 residues, but not shorter, are efficiently trimmed. It cleaves virtually all peptide bonds, except those involving Pro, albeit with different efficiency, showing preference for hydrophobic residues and poor cleavage of acidic and basic ones (Hearn et al., 2009).

ERAP2 shows significant differences in specificity and substrate handling, relative to ERAP1 (Tanioka et al., 2003; Saveanu et al., 2005; Evnouchidou et al., 2008; Zervoudi et al., 2011; Evnouchidou et al., 2011; Birtley et al., 2012; Evnouchidou et al., 2012; Mpakali et al., 2015; Stamogiannos et al., 2015): 1) ERAP2 preferentially cleaves N-terminal, basic, specially Arg, residues, 2) it efficiently digests octamers and its activity quickly decreases with longer substrates, 3) ERAP2 and ERAP1 bind substrates, and are affected by their sequence downstream the N-terminus, in distinct ways, 4) ERAP1, but not ERAP2, is allosterically activated by peptides. Their residue and length preferences confer complementarity to both enzymes in antigen processing (Fig. 1). Both enzymes form heterodimers (Saveanu et al., 2005), which allosterically activates ERAP1, and digest substrates with a faster rate than the uncoupled proteins *in vitro* (Evnouchidou et al., 2014). Yet, heterodimers account only for about 30% of the pool of ERAP1 and ERAP2 in live cells, and their significance *in vivo* is still unclear.

ERAP1 is remarkably polymorphic. Natural variants are complex allotypes, including various missense single nucleotide polymorphisms (SNPs), referred to as ERAP1 haplotypes, whose protein products differ among each other in multiple amino acid changes, which can affect the enzymatic activity (Goto et al., 2006; Evnouchidou et al., 2011; Kochan et al., 2011; The TASK and WTCCC2 Consortia 2011; Martin-Esteban et al., 2014; Stamogiannos et al., 2015) and substrate binding (Evnouchidou et al., 2011). Among these, Lys528Arg drastically reduces ERAP1 activity. Asp575Asn and Arg725Gln confer higher and lower activity, respectively (Martin-Esteban et al., 2014; The TASK and WTCCC2 Consortia 2011). These two mutations are in high linkage disequilibrium (LD), and the Asp575/Arg725 combination shows higher activity than Asn575/Gln725 (Reeves et al., 2013). The Gln730Glu change influences length preferences by ERAP1 (Stamogiannos et al., 2015).

In addition to its direct effect on ERAP1 activity, the Lys528Arg polymorphism goes along differences in the expression level of ERAP1. The Lys528 allotype is associated with higher ERAP1 transcript (Harvey et al., 2009) and protein expression (Costantino et al., 2015). This interesting observation reveals a mechanism by which the influence of a polymorphism that significantly alters ERAP1 activity is further potentiated by its association with increased expression levels of the more active variant.

ERAP2 shows limited polymorphism. Of two alleles coding for an amino acid change, Lys392Asn, which affects the enzymatic activity (Evnouchidou et al., 2012), the Asn392 variant is almost never expressed due to high LD with another polymorphism that impairs the expression of the protein (Andres et al., 2010). Due to the high frequency of this allele, and the existence of at least another polymorphism impairing ERAP2 expression (Kuiper et al., 2014b), only about 75% of individuals express ERAP2, generally the Lys392 variant, but exceptions are known (Vanhille et al., 2013).

3. Ankylosing spondylitis

This is a chronic form of arthritis typically affecting the entheses of the sacroiliac and intervertebral joints. Inflammation is followed by bone erosion and remodeling, syndesmophyte formation and ankylosis. Gut inflammation, frequently subclinical, occurs in about