HLA Class I-Mediated Diseases

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HLA (Human Leucocyte Antigen) class I molecules are pivotal in the immuno-surveillance by presenting peptides to CD8+ T cells. However, some of these molecules are involved in the pathogenesis of several autoimmune/autoinflammatory diseases, but the exact role is still elusive. Genome-Wide Association Studies (GWAS) have highlighted other important susceptibility factors such as Endoplasmic Reticulum Aminopeptidase ERAP1 and ERAP2 whose role is to refine the peptides presented by the HLA class I molecules to $CD8^+$ T cells, pointing to an alteration in the antigen presentation as possible pathogenetic mechanism .

HLA class I molecules | ERAP1 and ERAP2 | Immunopeptidome | CD8+ T cells | autoimmune/autoinflammatory diseases

1. Introduction

The MHC (Major Histocompatibility Complex) class I and II molecules, known as HLA (Human Leucocyte Antigen) in humans, are essential for promoting specific immunity; in particular, HLA class I molecules elicit $CD8^+$ T cell responses directed against epitopes, usually nine residues in length, derived from endogenously synthesized microbial or cellular proteins [1]. These peptides, upon the N-terminal refinement by the Endoplasmic Reticulum Aminopeptidases (ERAP) 1 and 2, are accommodated into the groove of the HLA class I molecules through the so-called “anchor” residues that are embedded into specific pockets [2]. In particular, residues at position 2 (P2) and at the carboxy-terminal (PΩ) are pivotal for the correct placement of the peptides through connections with the B and F pocket, respectively [3][4]. The binding motif is generally conserved for each HLA allele. However, some circumstances, such as an inflammatory environment or the use of specific drugs concomitantly with particular ERAP1 and ERAP2 haplotypes, could allow the binding cleft to assume conformations that can become permissive for unconventional peptides. In this context, it is of interest the case of drug-hypersensitivity induced by abacavir in HLA-B*57:01 positive subjects or by carbamazepine in HLA-B*15:02 carriers [5]. In particular, the non-covalent interaction of the drug with the F pocket of HLA-B*57:01 dramatically alters the self-epitope repertoire displayed by the HLA molecule creating foreign complexes, which induce robust T cell responses in the HLA-B*57:01 carriers taking abacavir [6][7][8]. Moreover, several viruses (i.e., HIV, CMV, EBV) could contribute to the alteration of the peptide repertoire establishing their strategies to escape immune surveillance [9].

Ankylosing Spondylitis (AS), Psoriasis (Ps), Birdshot Chorioretinopathy (BSCR) and Behçet’s disease (BD) are referred as “MHC-I-opathies” as they share an association with HLA-class I genes, in particular HLA-B*27, HLA-

C*06:02, HLA-A*29:02 and HLA-B*51, respectively [10]. Such diseases also share ERAP1 and, in some cases, ERAP2 as susceptibility factors and display as overlapping common targets, tissues undergoing either mechanical (enthesis and bone) or environmental stress such as skin, oral mucosa, gut and eye. In spite of different manifestations, a common basis of these diseases at the crossroads between the innate and adaptive immune system, which culminates in the typical chronic inflammation, has been suggested [10].

Over time, several case-control association analyses and Genome-Wide Association Studies (GWAS) have robustly shown associations of Single Nucleotide Polymorphisms (SNPs) in ERAP1 and/or ERAP2 genes or even of entire haplotypes with the above-mentioned diseases [11][12][13][14][15][16][17][18]. Functional effects of this ERAP1 and 2 variance has also been investigated but little is known about the molecular mechanisms in the critical cells. Moreover, few genetic studies have been focused on ERAP gene promoters and on the mechanisms regulating gene expression [19]. In the case of ERAP1, ten haplotypes (Hap1 to Hap10), derived from a combination of multiple non-synonymous SNPs, account for over 99% of the natural ERAP1 variants; however, the association of these haplotypes with each disease is quite different [20]. The striking association with HLA class I molecules and the involvement of ERAPs would point out a central role for $CD8^+$ T cells or even Natural Killer (NK) cells in tissue-specific damage. Accordingly, an altered antigen presentation could be one of the possible mechanisms behind the autoimmune injury caused by some haplotypes of ERAP1 and ERAP2, which are pivotal in the processing of HLA class I epitopes. In fact, an altered pool of peptides accounting for the ‘mis-immunopeptidome’ that ranges from suboptimal to pathogenetic/harmful peptides could be able to induce non-canonical or autoreactive $CD8^+$ T responses, activation of NK cells and/or garbling the classical functions of the HLA class I molecules [21].

2. HLA-B*27 and Spondyloarthropathies: Beyond the ‘Classical’ Peptidome

The HLA-B*27 is one of the most investigated HLA class I molecule that came to the attention during the early 1970s for its association with AS and other related inflammatory disorders collectively known as seronegative Spondyloarthropathies (SpA), which comprise Psoriatic Arthritis (PsA), Reactive Arthritis (ReA), Anterior Uveitis-associated Arthritis and the Arthritis linked to Inflammatory Bowel Disease (IBD). However, an univocal explanation for this remarkable linking is still lacking [21][22]. Several scenarios take into account not only the canonical function of HLA-B*27 as peptide presenting molecule to cytotoxic $CD8^+$ T lymphocytes (CTLs) or ligand for NK receptors, but also some “aberrant” features such as misfolding and homodimerization [23]. On the other hand, the HLA-B*27 has been described as protective factor against several viral infections (HIV, HCV, EBV and influenza virus), probably due to a better performance of the virus specific HLA-B*27-restricted $CD8^+$ T cells [17][24]. Ideally, the common ground of these two aspects could be the peptidome. In fact, the quality and the quantity of peptides available for the binding to the HLA-B*27 molecules could affect their stability and function. Investigating the immunopeptidome is therefore useful to design more specific therapies.

HLA-B*27 is highly polymorphic with more than 200 subtypes [25] identified so far, but not all associated with AS [26]. Of note, most of the variance is located in the binding groove cleft, substantiating the relevance of the peptide repertoire. Despite the attempts to identify a specific peptidome displayed by the AS-associated molecules (HLA-

B*27:05, -B*27:02, -B*27:04 and -B*27:07) versus the non-AS-associated ones (HLA-B*27:06 and -B*27:09) no definitive answer has emerged as yet [27][28]. However, it is still worth pursuing this goal focusing on a pair of alleles that show a different association with AS such as HLA-B*27:05 and HLA-B*27:09, differing for a single amino acid (Asp116His), or B*27:04 and B*27:06 differing for two amino acids [29][30].

The HLA-B*27 peptidome consists mainly of 9-mers and 10-mers [31] with Arg at P2 and basic, aliphatic or aromatic residues at C-terminus [18]. Although a hallmark of the B27 peptidome is an Arg as main anchor at P2, recent studies have introduced Gln and Lys as alternative P2 residues, albeit much lower represented compared to Arg [32][33]. In this context, Lorente and colleagues have shown that these two amino acids are enriched at P2 in the HLA-B*27:05 ligandome when ERAP2 is absent [34]. The authors also found an increase of basic residues at N-terminal with a concurrent reduction of hydrophobic amino acids at P3, P7 and P9 [34].

Before migrating to the cell surface, the HLA-B*27 molecules load the peptide cargo in the Endoplasmic Reticulum (ER). Interestingly, the tendency of HLA-B*27 molecules to fold slowly and to be retained in the ER in a peptide-receptive state could give to suboptimal peptides the chance to accommodate into the groove at the expense of classical B27 epitopes [35]. The peptide loading efficiency of HLA-B*27 molecules is therefore the result of their receptive state and is strongly influenced by qualitative and quantitative fluctuation of ERAP1 and 2. Notably, there is an epistatic gene-gene interaction between HLA-B*27 and ERAP1, since the association of ERAP1 with AS occurs only in HLA-B*27 positive patients, whereas the association of ERAP2 is independent of HLA-B*27, suggesting for ERAP2 a role distinct from antigen processing [11][12][36][37]. Now we know that the combination of highly active ERAP1 variants (Hap1 to Hap3) and the presence of ERAP2 could promote AS, whereas the opposite seems to be protective [20]. It is not clear whether this could be due to a “disruption” of canonical B27 peptides with consequent generation of new potentially pathogenetic epitopes [38]. In particular, the co-presence of ERAP2 with highly active ERAP1 variants (Hap1 and Hap2) favored an increase of 9-mers with a reduction of basic P1 residues [39]. Moreover, studies from human cells and transgenic rats showed that the depletion of ERAP1 induced the switch of the B27 peptidome towards longer peptides, C-terminally extended, and an alteration on the frequency of P1 residues [40][41]. Notably, longer peptides have been already described as intermediates or accidentally bound peptides with a lower frequency of the Arg in P2 [42]. In addition, the silencing or the inhibition of ERAP1 seemed to promote the reduction of FHC (Free Heavy Chain) homodimers on the surface of C1R and HeLa stably expressing HLA-B*27 as well as on monocytes from AS patients [43], suggesting that lowering the activity of ERAP1 as in the case of protective variants could preserve the stability of HLA-B*27 molecules providing an optimal ligandome.

The nature of the peptidome efficiently bound and presented by HLA-B*27 is highly influenced by the stability of the molecule itself; several studies have described a higher flexibility of HLA-B*27:05, compared to B*27:09, suggesting an intrinsic propensity of this subtype to adopt unconventional conformations, especially in the proximity of the binding groove [44][45][46]. Moreover, a recent work by Loll’s research group has suggested that HLA-B*27:05, but not B*27:09, undergoes metal ion-induced conformational alterations that, in turn, could influence the capability of the AS-associated allele to bind suboptimal peptides [47].

Our group has recently described a polymorphism, SNP rs75862629, located in the intergenic region between ERAP1 and ERAP2 that can affect the expression of both genes and, consequently, of HLA-B*27 molecules [19][48]. In particular, we showed that in the Sardinian population, the G variant, implicating high ERAP1 and low ERAP2 levels, induces a reduction in the surface expression of HLA-B*27:09, but not of HLA-B*27:05 [48]. In this regard, it is known that increased levels of HLA-B*27 expression also promote AS susceptibility [49]. In principle, the "disruption" of the conventional B27 peptidome due to the over-trimming by ERAP1 could cause an increase in suboptimal peptides that are not suitable for the B*27:09 binding but good enough for maintaining B*27:05 stability on the cell surface. As we recently reported, the higher flexibility of the HLA-B*27:05 binding groove and its low dependence on a classical B27 peptidome allow HLA-B*27:05 to present a HLA-B*07 restricted viral peptide (pEBNA3A-RPPIFIRRL) lacking the B27 consensus motif (Arg2) and nevertheless promoting the activation of specific $CD8^+$ T cells. This response is not evoked by the HLA-B*27:09, remarking the lower stringency of the peptide repertoire bound by HLA-B*27:05 [50][51]. At present, we are investigating a possible correlation between this particular $CD8^+$ T response in the context of HLA-B*27:05 and a specific haplotype of ERAP1 and ERAP2 (unpublished data). In this context, Rowntree et al. reported that several peptides derived from viruses causing chronic infections (EBV, CMV and HIV-1), usually displayed by the HLA-A*02, HLA-B*07 or HLA-B*57, could induce alloreactive $CD8^+$ T cell responses towards HLA-B*27 [52]. Consistently, we also showed that the HLA-B*27 molecules can present viral epitopes introduced by chimeric proteins driven by TAT of HIV through a proteasome- and TAP-independent pathway, pointing out again the high flexibility of the HLA-B*27 molecules [53].

Another important aspect is the subclinical gut inflammation occurring in up to 70% of patients with AS as a possible consequence of microbial dysbiosis [54]. The alteration of the gut microbiota could be, at least in part, related to the activation of autoreactive $CD8^+$ T cells towards microbial peptides displayed by HLA-B*27 [55]. Accordingly, the permissive binding of HLA-B*27:05 could enlarge the spectrum of the candidate epitopes.

The complexity of B27 peptidome, especially of B*27:05, is far from an unambiguous definition; matching mass spectrometry analyses with functional studies, could shed light on its double role as a protective factor in viral infections and as a predisposing molecule in the autoimmune diseases.

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