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# EULAR study group on 'MHC-I-opathy': identifying disease-overarching mechanisms across disciplines and borders

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## ABSTRACT

The 'MHC-I (major histocompatibility complex class I)-opathy' concept describes a family of inflammatory conditions with overlapping clinical manifestations and a strong genetic link to the MHC-I antigen presentation pathway. Classical MHC-I-opathies such as spondyloarthritis, Behçet's disease, psoriasis and birdshot uveitis are widely recognised for their strong association with certain MHC-I alleles and gene variants of the antigen processing aminopeptidases ERAP1 and ERAP2 that implicates altered MHC-I peptide presentation to CD8+T cells in the pathogenesis. Progress in understanding the cause and treatment of these disorders is hampered by patient phenotypic heterogeneity and lack of systematic investigation of the MHC-I pathway.

Here, we discuss new insights into the biology of MHC-I-opathies that strongly advocate for disease-overarching and integrated molecular and clinical investigation to decipher underlying disease mechanisms. Because this requires transformative multidisciplinary collaboration, we introduce the EULAR study group on MHC-I-opathies to unite clinical expertise in rheumatology, dermatology and ophthalmology, with fundamental and translational researchers from multiple disciplines such as immunology, genomics and proteomics, alongside patient partners. We prioritise standardisation of disease phenotypes and scientific nomenclature and propose interdisciplinary genetic and translational studies to exploit emerging therapeutic strategies to understand MHC-I-mediated disease mechanisms. These collaborative efforts are required to address outstanding questions in the etiopathogenesis of MHC-I-opathies towards improving patient treatment and prognostication.

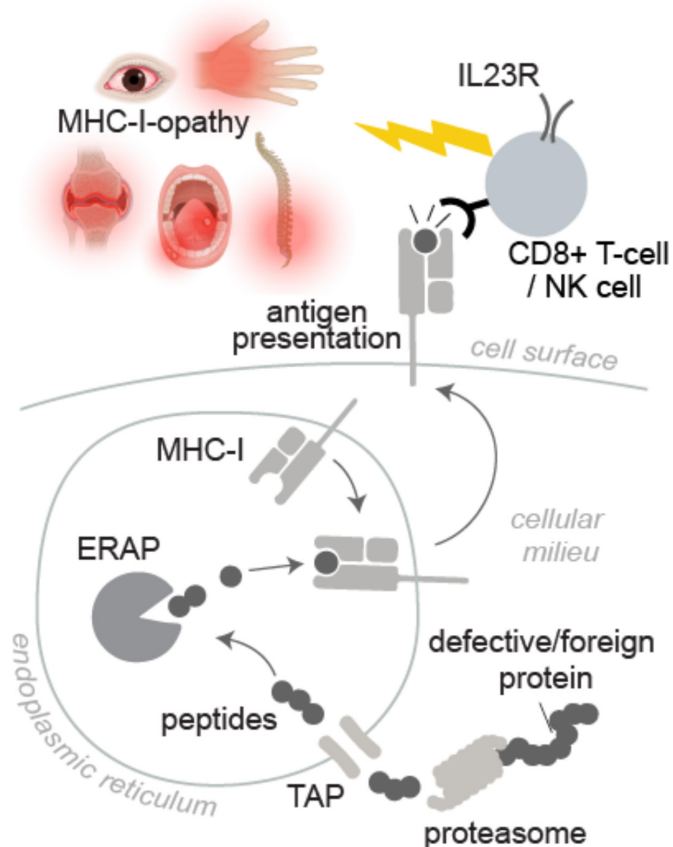
## THE INCEPTION OF THE MHC-I-OPATHY FAMILY

Inflammation against self is orchestrated by a continuum of incompletely understood innate and adaptive immune mechanisms. The term 'autoinflammatory' refers to inflammation against self, caused by abnormal innate immunity, whereas

'autoimmunity' is caused by aberrant adaptive immunity.<sup>1–2</sup> Since this dichotomous definition overlooked conditions such as psoriasis (PsO) and Behçet's disease (BD), the concept of 'mixed-pattern' or 'intermediate' diseases was proposed.<sup>3</sup>

Genome-wide association studies (GWAS) of MHC-I-associated diseases, such as BD (associated with *HLA-B\*51*),<sup>4–5</sup> PsO (associated with *HLA-C\*06:02*),<sup>6–8</sup> *HLA-B\*27-associated* spondyloarthritis (SpA)<sup>9–11</sup> *HLA-B\*27-associated* anterior uveitis (AU)<sup>12</sup> and *HLA-A\*29-associated* birdshot uveitis (BU),<sup>13–14</sup> revealed that these 'intermediate diseases' share a distinguishable genetic background defined by MHC-I genes, the antigen processing genes *ERAP1* and *ERAP2*, and the IL-17 pathway gene *IL23R*. Such genetic overlap implicates MHC-I peptide presentation as the key mechanistic commonality. Furthermore, it substantiates the idea that BD, PsO, SpA and BU belong to a distinct disease cluster known as 'MHC-I-opathies'.<sup>15</sup>

There is ongoing debate and incomplete evidence regarding underlying mechanisms of MHC-I-opathies.<sup>16–18</sup> MHC-I proteins (also called HLA-A, HLA-B and HLA-C) bind short peptides from degraded or pathogenic proteins, which have been proteolysed inside the cell by the proteasome.<sup>19–21</sup> Most MHC-I peptides are derived from proteins from the host. ERAP1 and ERAP2 are endoplasmic reticulum aminopeptidases associated with antigen processing that trim a certain fraction of these peptides if they are not short enough before loading them onto MHC-I molecules.<sup>22</sup> This process enables MHC-I to present tens of thousands of peptides on the cell surface, collectively referred to as the 'immunopeptidome'.<sup>23</sup> CD8+T cells read out the immunopeptidome by binding to the peptide-MHC-I complexes with their T cell receptors (TCR) (figure 1). MHC-I molecules can



**Figure 1** An overview of the role of the MHC-I pathway in MHC-I-opathies. The proteasome produces peptide fragments that are transported into the endoplasmic reticulum by the transporter associated with antigen processing (TAP) and trimmed by ERAP1 and ERAP2 (ERAP) to a length of 8-11 amino acids before binding to MHC-I molecules. After trafficking to the cell surface the MHC-I-peptide complex is “read out” by surveying immune cells, triggering antigen-specific CD8+ T cell responses or natural killer (NK) cell activation. MHC-I-opathies are genetically associated with functionally distinct variants of MHC-I and ERAP which alter the peptide repertoire presented by MHC-I. Autoreactive T cells in the periphery that escape tolerance mechanisms and promote inflammation against self-peptide epitopes. Biorender software was used to create elements from this figure under an academic license.

also bind to killer-cell immunoglobulin-like receptors (KIRs) and other receptors on natural killer (NK) cells.<sup>24</sup>

There is much conjecture about the cause(s) of MHC-I-opathies<sup>15 25 26</sup> and several popular hypotheses have been proposed which are not necessarily mutually exclusive. The primary hypothesis for the cause of MHC-I-opathies is that disease-associated MHC-I alleles present specific immunogenic peptides that trigger ‘autoimmune’ reactions (ie, the arthritogenic peptide theory).<sup>27</sup> The genetic association with ERAP genes also supports this hypothesis since the activity of these enzymes can modify the immunopeptidome.<sup>28</sup> Proof of concept has been shown in PsO and recently in SpA and HLA-B\*27+AU.<sup>29</sup> The identification of CD8+T cells in PsO react against melanocytes in the context of HLA-C06:02 as skin-specific target cells of the psoriatic autoimmune response,<sup>30-32</sup> while CD8+T cells from synovial and eye fluid of SpA and AU patients recognise both self and microbial peptides presented by HLA-B\*27.<sup>29</sup>

There is still no conclusive evidence that this mechanism underlies other MHC-I-opathies since mechanistic studies are

technically challenging to conduct, owing to multiorgan involvement having complex tissues, which requires labour-intensive technology to screen for many epitopes. Consequently, several alternative theories for MHC-I-opathies have been proposed, one of which suggests that MHC-I protein misfolding directly leads to inflammation. According to this theory, predisposing MHC-I molecules may exhibit properties which could cause excessive misfolding and accumulation in the ER, promoting the ‘unfolded protein response’.<sup>33-38</sup> Studies of (HLA-B\*27) transgenic animals and cellular models support this hypothesis, but there is a paucity of translational evidence.<sup>39-43</sup> A third popular hypothesis suggests that the predisposing MHC-I alleles are recognised by KIRs or leucocyte immunoglobulin-like receptors (LILRs) on the cell surface of NK cells.<sup>44 45</sup>

In our opinion, the first hypothesis applies to the majority of MHC-I-opathies (with the most robust evidence for PsO and SpA), but definitive proof for CD8+T cell-mediated pathologies is lacking for several other conditions. Hypotheses 2 and 3 may also apply to certain conditions. For example, in BD, ERAP1 may mediate HLA-B51 recognition via NK cells,<sup>17 46 47</sup> and pathogens that can cause reactive arthritis induce unfolded protein responses in HLA-B\*27-positive individuals.<sup>48</sup> While these other pathways and mechanisms are implicated, including the very interesting interactions of altered microbiomes in patients,<sup>49</sup> we focus our discussion on the MHC-I pathway as the key determinant for this family of complex conditions.

#### THE MANY FACES AND CHALLENGES OF MHC-I-OPATHIES

Several conditions are considered to be ‘classical’ MHC-I-opathies (PsO, psoriatic arthritis (PsA), SpA, B\*27-AU, BD and BU) and share strikingly similar clinical symptoms (table 1).

BU is a rare and severe type of uveitis, leading to retinal damage and vision loss that exclusively affects HLA-A\*29-positive individuals.<sup>50 51</sup> Although it is unclear which other clinical features are shared between BU and other MHC-I-opathies, 1 study of 118 cases revealed that many patients also suffer from arthralgia and PsO.<sup>52</sup> We also discuss PsA because it shares many characteristics with PsO, including strong association with MHC-I alleles and IL23R.<sup>7 8 53-55</sup> While some patients with inflammatory bowel disease may have similar symptoms,<sup>56</sup> we will only discuss classical MHC-I-opathies here.

MHC-I-opathies overlap in their pattern of organ involvement (table 1). Uveitis, for instance, is a disease feature reported in every classical MHC-I-opathy, although with different prevalence and anatomical location (anterior/posterior).<sup>57 58</sup> Sacroiliitis is present in patients with SpA, PsA as well as BD.<sup>59-61</sup> Cutaneous involvement is also a shared feature of MHC-I-opathies (table 1).

However, not every patient exhibits the symptomatic hallmarks of every clinical entity. For example, arterial, venous and neurological complications are common in BD, but infrequent in other MHC-I-opathies.<sup>18 62</sup> For several MHC-I-opathies, patients with the associated risk MHC-I alleles are more likely to manifest early-onset disease and a worse prognosis.<sup>63-66</sup> Furthermore, substantial clinical and geographical variation in disease phenotypes exists, for example, the prevalence of gastrointestinal involvement in BD in Asian versus European populations.<sup>67 68</sup>

#### WHAT YOU (DO NOT) SEE IS WHAT YOU (DO NOT) GET!

The clinical management of MHC-I-opathy patients is complicated by heterogeneity in age of onset, symptoms and disease course. Unlike cases with commonly recognised symptoms (e.g.,

**Table 1** Summary of tissue involvement per MHC-I-opathy, organised per clinical specialty (references underlying the summarised data and scores can be found in online supplemental table 1)

	Disease	PsO*	PsA†	SpA	B*27 AU	BD	BU
Medical specialty	Primary risk MHC-I-allele(s)	C*06	C*06/B*27	B*27	B*27	B*51	A*29
	Prognosis worse when primary MHC-I allele present	3	0	3	n.a	3	0
Ophthalmology	Uveitis‡	1	1	3	3	3	3
Dermatology	Oral ulcerations	0	1	1	0	3	0
Dermatology	Genital ulcerations	0	0	0	0	3	0
Dermatology	Psoriasiform dermatitis§	3	3	2	2	1	1
Dermatology	Pustular lesions¶	2	2	1	0	3	0
Dermatology	Erythema nodosum-like lesions	0	0	0	0	3	0
Rheumatology	Spondylitis	1	3	3	3	1	0
Rheumatology	Arthritis	2	3	3	2	3	0
Rheumatology	Enthesitis	2	3	3	3	1	0
Rheumatol/immunol	Vasculitis**	1	1	1	0	3	0
Gastroenterology	Inflammatory bowel disease	1	1	2	1	2	0
Internal medicine	Comorbid hypertension	1	2	2	0	0	2
Neurol/Int Med/cardiol	Comorbid cardiovasc disease	2	2	2	0	1	0
	Legend:	3	part of the disease spectrum				
		2	regularly reported				
		1	infrequently reported				
		0					

3 part of the disease spectrum.  
2 regularly report.  
1 infrequently reported.  
0 either unknown / no reports / not present.  
\*Psoriasis: besides plaque psoriasis. This encompasses other forms of psoriatic disease like psoriasis guttate and (several types of) pustular psoriasis.  
†PsA: both axial and peripheral disease.  
‡Uveitis anterior is the main subtype reported in PsO, PsA, SpA, whereas in Behçet's multiple anatomical subtypes of uveitis are reported. BU manifests as posterior uveitis.  
§Psoriasiform lesions: refers to the several types of psoriasis; classical plaque psoriasis, guttate, nail lesions and erythematous as well as pustular lesions.  
¶Pustular lesions: covers acneiform, papulopustular and non-follicular pustules.  
\*\*Vasculitis in PsO as well as in PsA and SpA vasculitis is in the large vessels (aortitis); in B27-AU and BU not reported outside the eye; in Behçet's vasculitis is in all types of vessels, arteries and veins.  
BU, birdshot uveitis; PsA, psoriatic arthritis; PsO, psoriasis; SpA, spondyloarthritis.

uveitis in SpA patients), asymptomatic or atypical involvement of the skin, bowel or other comorbidities in patients may be overlooked (table 1). For example, reexamination of SpA patients revealed that up to one-third may have comorbid PsO.<sup>69</sup> In the DUET study, over 40% of patients with B\*27-AU were diagnosed with SpA or PsA on re-evaluation by a rheumatologist,<sup>70</sup> which was confirmed by other studies.<sup>71</sup> Large population-level data also correlate disease manifestations of MHC-I-opathies such as uveitis, PsO, PsA and BD.<sup>58 72 73</sup> Observations from well-powered cohort studies substantiate that oral disease, which is a hallmark of BD, is also linked to SpA.<sup>74–76</sup> Despite considerable phenotypic heterogeneity, these studies support that MHC-I-opathies are interconnected conditions that cannot be understood in isolation and require a multidisciplinary approach.

The human phenotype ontology (HPO) provides a framework for standardised nomenclature of disease symptoms, which can facilitate improved classification of disease phenotypes.<sup>77</sup> Although originally designed to systematically capture the clinical manifestations of rare, monogenic conditions, HPO has more recently been used to successfully infer several rare phenotypes of the UK Biobank.<sup>78</sup> In its current form, the HPO may not be optimal for the annotation of the clinical spectrum of patients with MHC-I-opathies. As a result, the EULAR study group aims to evaluate the HPO and adapt it to fit the symptoms of MHC-I-opathies. The spectrum of MHC-I-opathies will benefit from standardisation of disease manifestations, allowing existing cohorts to be merged into a well-powered study. The precise delineation of clinical phenotypes will allow us to relate them to molecular endotypes. We expect that this process will facilitate the discovery (and validation) of better diagnostic, prognostic and therapeutic biomarkers.

## A COMMON GENETIC ARCHITECTURE

### MHC-I, the tip of the iceberg

Strong genetic association with certain MHC-I alleles is the hallmark of the MHC-I-opathy cluster: MHC-I association studies date back to 1973 with the discovery of the association of *HLA-B\*27* and SpA as well as *HLA-B\*51* and BD (formerly 'HL-A5'),<sup>79–81</sup> followed by reports on *HLA-C\*06:02* (previously known as 'HLA-Cw6') and PsO in 1977,<sup>82 83</sup> and the association between *HLA-A\*29* and BU in 1982<sup>84</sup> (table 2). In comparison to genes associated with complex inflammatory conditions, the effect size of MHC-I alleles accounts for a disproportionate amount of genetic risk. For almost 50 years, researchers have struggled to understand the role these class I alleles play in their disease biology.

Interestingly, recent fine-mapping studies showed that statistical adjustment for *HLA-B\*27* in SpA revealed independent associations for other MHC-I alleles, including *HLA-A\*02:01*, *HLA-B\*07*, *HLA-B\*57* and *HLA-B\*40*<sup>85 86</sup> (table 2). This is significant because it also implicates the MHC-I pathway for cases lacking the primary MHC-I risk allele and strongly incriminates peptide presentation rather than alternative mechanisms.

Association with several of these alleles was also found after correcting for the primary risk MHC-I allele in PsO (*HLA-A\*02:01*, *HLA-B\*27* and *HLA-B\*07*), BD (eg, *HLA-B\*27* and *HLA-B\*57*), PsA (eg, *HLA-B\*07* and *HLA-A\*02*) and AU.<sup>7 12 87–90</sup> To date, small GWAS in the rare BU had limited power to detect *HLA-A\*29*-independent loci in detail, but also reported independent risk MHC-I alleles.<sup>13 14</sup> These findings raise the possibility that an ensemble of disease-overarching MHC-I alleles contribute to MHC-I-opathy susceptibility.

**Table 2** Reported HLA class I associations in four MHC-I-opathies

MHC-I-opathy	Prevalence	Primary HLA class I association	% cases negative for primary HLA class I allele	Independent* HLA class I associations
Birdshot uveitis	1.5/500 000	HLA-A*29:02	0	HLA-A*30 <sup>13 14</sup> HLA-A*33 <sup>14</sup>
Spondyloarthritis†	0.5%	HLA-B*27	~ <30	HLA-B*40 <sup>85 86</sup> HLA-A*02 <sup>85</sup> HLA-B*07 <sup>85</sup> HLA-B*57 <sup>85</sup> HLA-C*15 <sup>86</sup>
Behçet's Disease	0.19-120/100 000 <sup>9</sup>	HLA-B*51	~30-70	HLA-A*02 <sup>87</sup> HLA-B*27 <sup>87</sup> HLA-B*57 <sup>87</sup> HLA-A*03 <sup>87</sup> HLA-B*15 <sup>87</sup> HLA-B*49 <sup>87</sup> HLA-A*26 <sup>87 89</sup> HLA-C*07 <sup>89</sup>
Psoriasis	2-4%	HLA-C*06:02	~30-70	HLA-A*02 <sup>122</sup> HLA-B*27 <sup>122</sup> HLA-B*07 <sup>122</sup> HLA-C*07 <sup>176</sup>

\*Identified by statistical adjusting for primary associated HLA class I allele.

†Majority of data are from genetic studies in ankylosing spondylitis. Includes both risk and protective alleles.

Therefore, functional studies that consider only one MHC-I allele may not capture the complexity of the MHC-I pathway in patients. This emphasises the need to use primary patient tissues to investigate disease mechanisms. It remains to be determined whether the full MHC haplotype (including 'secondary' risk MHC-I alleles) improves patient stratification. Large population-based studies (ie, UK Biobank) support that MHC-I alleles are associated with a variety of health biomarkers.<sup>91</sup> A first step into this direction could be the conduction of a multiethnic MHC-I-opathy GWAS analysis by combining several available large-scale genome-wide datasets and interrogating the *MHC* for different phenotypic states.

### The devil is in the ERAP1 and ERAP2 details

Perhaps one of the major accomplishments for the progress in the understanding of MHC-I-opathies was the discovery of the association with the *ERAP1* and/or *ERAP2* genes.<sup>4 6 7 9 12-14 92-95</sup> These genes encode two ER-resident enzymes specialised in trimming peptides to facilitate or prevent their binding in the groove of MHC-I.<sup>96 97</sup> By generating and destroying peptide epitopes, ERAPs can affect CD8+T cell and NK cell responses.<sup>98-101</sup> Genetic variants in *ERAP1* and *ERAP2* affect the enzymatic activity and expression levels of these enzymes.<sup>93 102</sup> Consequently, a change in ERAP activity may expose CD8+T cells to altered peptide repertoires (self or non-self) via MHC-I risk alleles, which can be harmful.<sup>28</sup>

Genetic association between *ERAP1* and MHC-I-opathies is typically observed in individuals carrying the primary risk MHC-I.<sup>4 6 11 13 85 93</sup> Coding variants in *ERAP1* organise into several common haplotypes often referred to as ERAP1 'allotypes'<sup>103 104</sup> that exhibit a wide range of enzymatic activities towards peptide substrates and differentially shape the immunopeptidome of MHC-I.<sup>28 105</sup> Risk polymorphisms in *ERAP1* (and *ERAP2*) are also strongly associated with mRNA and protein expression levels of these aminopeptidases.<sup>50 102 106</sup> Haplotype-based analyses have singled out specific ERAP1 allotypes as risk factors for MHC-I-opathies. While several terms have been proposed for ERAP1 allotypes, standardised nomenclature has yet to be widely adopted. One functionally distinct ERAP1 allotype (often referred to as *Haplotype 10* (*hap10*)) is a risk factor for BD and BU,<sup>93 107</sup> but protective for SpA, AU and PsO.<sup>28 108</sup> Interestingly, in PsO, the protective *hap10* was less effective in generating the autoantigenic epitope than the risk haplotypes of ERAP1,

leading to lower HLA-C expression and immunogenicity of melanocytes.<sup>31</sup>

ERAP1 may also influence NK cell responses via inhibitory receptors NKG2A/CD94 (also expressed by CD8+T cells<sup>109</sup>) to non-classical MHC-I molecule HLA-E.<sup>46</sup> The inhibitory activity of HLA-E requires the presentation of a signal sequence from MHC-I molecules, which are also present in HLA-A29, HLA-B27 and HLA-B51.<sup>110-112</sup> Therefore, ERAPs may also affect NK cells and CD8+T cells via MHC-I-related molecules, as was previously shown in cancer models.<sup>46 113</sup> Although KIR receptors can recognise immunopeptidome changes caused by ERAP1, KIR genes do not influence *HLA-B\*27* and *ERAP1*-mediated ankylosing spondylitis risk.<sup>114 115</sup> This suggests that the disease mechanisms mediated by ERAP1 and MHC-I are less dependent on KIRs.

In contrast to *ERAP1*, *ERAP2* genetic variants are not associated with all MHC-I-opathies (eg, BD). Also, ERAP2 is associated with SpA regardless of *HLA-B\*27* status. Because there is also epistasis between *ERAP1* and *HLA-B\*40* in SpA (independent of *HLA-B\*27*),<sup>85</sup> it is possible that ERAP2 modifies disease in SpA via alternative risk MHC-I alleles. Functional studies support that ERAP2 significantly affects the immunopeptidome of many MHC-I alleles, including *HLA-B\*40*.<sup>115 116</sup>

Note that *ERAP2* allotypes co-occur non-randomly with *ERAP1* allotypes.<sup>93 105</sup> Furthermore, although *HLA-A\*29* is common in many regions, *HLA-A\*29*-positive individuals who carry both *ERAP1* and *ERAP2* risk alleles are only observed in countries where BU is prevalent.<sup>93</sup> Therefore, an individual's ERAP1 and ERAP2 allotypes along with their MHC-I profile (and T cell repertoire) are most likely to determine their susceptibility to MHC-I-opathies.<sup>117</sup>

Studies linking ERAP genotypes with clinical end points may have potential,<sup>118 119</sup> but we would like to emphasise that these studies should be carefully controlled and well powered. Both ERAP1 and ERAP2 are common denominators of MHC-I-opathies, which place antigenic peptide presentation at the heart of their pathogenesis.

### IL23R and T cells

There are many other genes associated with conditions within the MHC-I-opathy spectrum that have been discovered through GWAS. While they are important to disease biology, we only briefly discuss *IL23R*, a receptor for IL-23 expressed by T cells (and

### Box 1 The aims of the EULAR study group on "MHC-I-opathy"

1. Multidisciplinary collaboration between rheumatologists, dermatologists and ophthalmologists for consensus and standardised annotation of disease symptoms.
2. Detailed phenotypic evaluation by patient-reported symptoms/outcomes.
3. Integration of GWAS data of MHC-I-opathy-related diseases, across a larger number of existing cohorts, to facilitate fine mapping of the genetic basis.
4. Harmonisation of the nomenclature (eg, ERAP allotypes) and provide expert synthesis of current best practice for the study of key aspects of the biology in MHC-I-opathies.
5. Establishment of a pan-European consortium with standardised clinicopathological disease phenotypes from aim 1 and 2, (complemented by molecular data on ERAP and MHC-I haplotypes and possibly other biological data such as metagenomics to assess microbiome involvement and TCR-repertoire data) for improved disease classification, diagnostic criteria and prognostic biomarkers for prediction of disease progression and efficacy of (type of) therapy.
6. Evaluation of MHC-I-opathies in different ethnic backgrounds, given the massive heterogeneity within class-I antigens.
7. Patient participation: involvement of patient research partners.

innate lymphocytes), because it is common to MHC-I-opathies and is associated with disease severity and phenotypes.<sup>8 118 120-122</sup>

Fascinatingly, despite IL23R expression by CD4+T cells, epigenetic analyses implicate CD8+T cells as major perpetrators of MHC-I-opathies.<sup>88</sup> Interleukin-17-producing CD8+T cells (termed 'Tc17') infiltrating skin and synovial lesions in PsO, BD, SpA and PsA patients express IL23R.<sup>123-125</sup> Tc17 cells are also more abundant in patients with BU.<sup>126 127</sup> IL23R's role in the pathophysiology of MHC-I-opathies is incompletely understood, but likely to be tissue-dependent.<sup>128</sup> This may explain why patients with PsO<sup>129</sup> and PsA<sup>130</sup> exhibit clinical response to therapy that disrupts T cell IL-23 signalling, while initial trials were less successful in SpA.<sup>131 132</sup> A better understanding of clinical and molecular features will help overcome challenges posed by patient heterogeneity as well as identify therapeutic biomarkers which will guide the selection of candidates eligible for treatment with IL-23 inhibitors.<sup>21 128 131-134</sup>

### UNMET NEEDS IN MHC-I-OPATHY PATHOPHYSIOLOGY UNDERSTANDING

#### Evidence for autoreactive CD8+ T cell involvement

A number of immunopeptidome studies in cell models have shown that polymorphisms in ERAP cause change in the peptides presented by HLA-B27, HLA-B51, HLA-A29 and other MHC-I alleles.<sup>28 115 116</sup> Circumstantial evidence suggests that these enzymes introduce or remove peptides that bind to risk MHC-I alleles and signal CD8+T cells to attack healthy tissues. The fact that CD8+T cells are clonotypically expanded in patients with SpA, PsO and PsA supports this concept.<sup>135-138</sup> In BD, carriers of the disease-associated ERAP1 allotype<sup>107</sup> show enrichment for circulating antigen-experienced effector CD8+T cells and ERAP1 modulation influenced CD8+T cell responses.<sup>107</sup> The lack of identification of causative autoantigens or indeed alloantigens has resulted in discussion about whether CD8+T cells drive pathology in MHC-I-opathies.<sup>17</sup> Regardless,

autoantigen-derived peptide recognition by CD8+T cells in patients has previously been reported, including an HLA-B51-presented peptide derived from a stress-inducible autoantigen in BD,<sup>139</sup> HLA-C06:02 presented peptide from innate host defence protein LL-37 in PsO,<sup>140</sup> and HLA-B27-restricted epitope from a peptide hormone receptor and cartilage-derived peptides in SpA.<sup>141 142</sup>

To date, the most compelling conceptual proof that CD8+T cells mediate autoimmune inflammation is based on studies of PsO, and very recently in HLA-B\*27-positive SpA and AU patients.<sup>29 30</sup> Skin lesional CD8+T cells in PsO can recognise an HLA-C06:02-restricted autoantigen epitope from ADAMTSL5 highly expressed in skin melanocytes.<sup>30 31</sup> ADAMTSL5-specific CD8+T cells secrete PsO-promoting cytokines (eg, IL-17) specifically after recognising melanocyte-peptide processed by ERAP1 and presented by the disease-associated MHC-I HLA-C06:02.<sup>30-32</sup> Here, the immunogenicity of melanocytes for self-reactive CD8+T cell responses was increased by disease-associated ERAP1 haplotypes through greater supply of the peptide autoantigen.<sup>30</sup> It has, therefore, been suggested that pharmacological modulation of ERAP activity towards precursor peptides specifically presented by MHC-I alleles could reverse inflammation in MHC-I-associated diseases.<sup>143 144</sup>

Researchers recently found that tissue-infiltrating CD8+T cells shared TCRs in eye liquid as well as synovial fluid of HLA-B\*27-positive patients with AS and AU.<sup>29</sup> These CD8+T cells specifically recognise microbial (eg, YEIH protein from reactive arthritis-triggering pathogens) and self-antigens (eg, peptides from GPER1 or PRPF3 proteins) specifically within the context of HLA-B27. According to these findings, environmental pathogens may trigger autoimmunity via CD8+T cell activation in MHC-I-opathies, thus supporting the primary hypothesis of the MHC-I-opathy pathogenesis. Future research might explore whether HLA-B27 presentations of these peptides are affected by risk allotypes of ERAP1 and whether pharmacological targeting of ERAPs interferes with these responses.

It remains unclear why of the thousands of self-peptides in the immunopeptidome only a minority become immunogenic, while the majority remain tolerable. However, T cell autoantigens often have post-translational modifications or show altered binding conformation.<sup>145-147</sup>

What triggers CD8+T cell self-reactivity in MHC-I-opathies remains unknown. The classical view is that negative selection in the thymus eliminates autoreactive T cells. Some self-reactive CD8+T cells manage to escape this filtering process and are reintroduced into the circulation (sometimes at high frequencies) but kept in check by tolerance mechanisms.<sup>148-150</sup>

Interestingly, recent work suggests that thymic regulatory T-cells, rather than negative selection of autoreactive T cells, enforce protection against autoimmunity.<sup>148 151</sup> Here, the cytokine IL-23 eliminates thymic regulatory T cells in an IL23R-dependent manner,<sup>152</sup> while selectively enriching IL23R-expressing CD8+T cells.<sup>153</sup> Moreover, there is no sharp affinity threshold for the recognition of MHC-peptide complex by TCRs, and CD8+T cells with otherwise low affinity TCRs can be activated by a large increase in presented autoantigen.<sup>154 155</sup> This also fits with the recently proposed 'autoimmune surveillance of hypersecreting mutants' theory that links high autoantigen levels to T-cell autoimmunity.<sup>156</sup> Cross-presentation of extracellular antigens in dendritic cells can also lead to the entry of extracellular antigens into the MHC class I pathway, thereby greatly expanding the potential pool of immunogenic peptides. Conceptually, this integrates the possibility of microbial agents causing disease, as demonstrated for SpA, and AU.<sup>29</sup> Virus-triggered

clonal CD8+T cell responses are processed through MHC class I, and some of these responses are controlled by ERAP1.<sup>157</sup>

Recent technological advancements which have increased the sensitivity and scale of analysing immunopeptidomes of primary patient tissues (ideally sampled at the affected organs) as well as high-throughput profiling of (auto)antigen-specific T-cell repertoires (ie, single-cell TCR sequencing) may help identify CD8+T cell-mediated disease mechanisms in MHC-I-opathies in greater detail.<sup>158–161</sup>

### Towards MHC-I pathway therapy

This study group's ultimate goal is to improve disease outcome of MHC-I-opathies. Although definite disease mechanisms need to be established, available clinical and molecular evidence allow us to outline several potential strategies. Given that MHC-I is considered a root cause for MHC-I-opathies, therapeutic targeting of antigen processing and presentation seems self-evident. This may be achieved by interventions aimed at disrupting cytokine signalling (see section *IL23R and T cells*) or strategies that facilitate restoration of the microbiome.<sup>48</sup> Patients with MHC-I-opathies may have an altered microbiota,<sup>162–164</sup> but healthy individuals may also show microbiota compositions that cluster according to their HLA alleles (eg, *HLA-B\*27*, *HLA-A\*29*).<sup>165</sup> Emerging T cell-antigen discovery approaches within the microbiome may provide an exciting field for upcoming studies.<sup>166</sup> In case of autoantigen-mediated pathology, it may be possible to specifically negate T cell interaction by antibodies or small compounds that specifically block access to MHC-I-peptide complexes. T-cell engagement may also be blocked by preventing or changing the abundance of target peptide presentation by manipulation upstream of MHC-I, including the cellular proteome (eg, chemotherapy), or pharmacological inhibition or modulation of the proteasome, TAP or the antigen loading complex,<sup>167–171</sup> although with limitations in specificity at the cost of potential adverse effects.

Inhibiting or, depending on the disease, enhancing the action of ERAP1 and ERAP2 may be a promising approach, since these enzymes are highly specialised for antigen presentation, and much is known about their structure and function to allow the development of inhibitors or enhancers.<sup>143 144 172</sup> The fact that their impact on antigen presentation may be limited to a part of the immunopeptidome,<sup>173</sup> may constitute a middle ground between single antigen strategies (antibodies for MHC/peptide complex) and general suppression of the MHC-I pathway. Most of these therapeutic 'options' are still in their infancy and require translational studies in suitable preclinical models. Although the *HLA-B\*27*-transgenic rodent models,<sup>174</sup> have provided valuable insights into the disease mechanisms of MHC-I-opathies, there remains an unmet need for additional transgenic MHC-I models. To determine if it is possible to target the MHC-I pathway therapeutically in patients, these models should be 'fully' humanised and capture a broader spectrum of clinical and molecular characteristics.

### Mission of the EULAR study group on MHC-I-opathies

As a result of the complexity of the clinical phenotypes and the lack of knowledge about the underlying mechanisms of MHC-I-opathies, international cross-disciplinary collaborations and complementary scientific expertise are urgently needed. The EULAR study group on MHC-I-opathies provides an international network that brings medical specialists, translational and fundamental scientists under one umbrella with the aim of cooperatively overcoming long-standing unmet needs in the disease management and understanding of the biology of MHC-I-opathies.

The study group (currently >50 participants: dermatologists, ophthalmologists, rheumatologist, scientists and patient representatives from >15 countries) was founded in 2020 amidst the COVID-19 pandemic. The global pandemic restricted initial discussion to online meetings. An inaugural meeting took place in May 2022, in Amsterdam, followed by a meeting during EULAR in June 2022 in Copenhagen. Study group research and collaborations will focus on the pathophysiology of MHC-I pathway in these conditions. Briefly, the study group aims are summarised in **box 1** and the objective is to harmonise, facilitate and improve research methodology and terminology, study disease mechanisms more collectively; foster basic and translational knowledge exchange in an interdisciplinary fashion through meetings via symposia during EULAR meetings ([https://www.eular.ch/myUploadData/files/study\\_group\\_aims\\_mhc\\_i\\_opathy\\_for\\_web.pdf](https://www.eular.ch/myUploadData/files/study_group_aims_mhc_i_opathy_for_web.pdf)) and disseminate progress via social media (eg, an open Linked-in page for interested colleagues, <https://www.linkedin.com/groups/12722534/>). To accomplish these objectives, the Study Group formed several multidisciplinary task forces composed of clinicians, biologists and patient representatives to prioritise unmet research needs that would require cross-European collaboration. For example, one of the task forces aims to conduct meta-analysis of GWAS data of the MHC-I-opathies to fine map the *MHC* and identify novel risk loci in relation to clinical features. Another task force currently works on evaluation of a patient-reported symptom infrastructure, which has already been successfully employed in COVID-19 studies.<sup>175</sup> Although currently all work within the study group is contributed in kind by its members, the rapidly growing study group aims to apply for external funding for research. This will also be required to achieve more ambitious goals, such as the collection of biomaterials to foster innovative research by deep immunoprofiling (eg, T-cell repertoires, MHC-I immunopeptidomes) and translational studies (eg, ERAP modulation in patient tissues). The EULAR study group will complement their scientific objectives with the organisation of interactive workshops and symposia connected to EULAR to exchange basic, translational and clinical knowledge in an interdisciplinary fashion and further facilitate the growth of the study group by inclusion of physicians and scientists active in this field.

In conclusion, the EULAR study group on MHC-I-opathies bridges a variety of medical scientific disciplines with the ambitious joint objective to conduct an integrated investigation of MHC-I-opathies to discover the cause and cure for a variety of complex inflammatory conditions.

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