Progress in Retinal and Eye Research xxx (2014) 1–12

Contents lists available at ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/prer

The immunopathogenesis of birdshot chorioretinopathy; a bird of many feathers

Jonas Kuiper [a, b, *, 1], Aniki Rothova [c, 1], Joke de Boer [a, 1], Timothy Radstake [b, 1]

[a] Department of Ophthalmology, University Medical Centre Utrecht, Heidelberglaan 100, 3584CX, Utrecht, The Netherlands
[b] Laboratory of Translational Immunology, University Medical Centre Utrecht, Lundlaan 6, 3584 EA, Utrecht, The Netherlands
[c] Department of Ophthalmology, Erasmus University Medical Centre, s-Gravendijkwal 230, 3015 CE, Rotterdam, The Netherlands

ARTICLE INFO

Article history:
Received 5 August 2014
Received in revised form
22 October 2014
Accepted 18 November 2014
Available online xxx

Keywords:
Birdshot
Chorioretinopathy
BSCR
HLA-A29
ERAP2
Uveitis
Autoimmunity
T cell
IL-17
Tc17
Th17
Peptide
Choroid
Retina

ABSTRACT

Birdshot chorioretinopathy (BSCR) is a bilateral chronic intraocular inflammation or posterior uveitis that preferentially affects middle-aged Caucasians. BSCR is characterized by distinctive multiple choroidal hypopigmented lesions in combination with retinal vasculitis and vitritis, and the extraordinary feature that virtually all patients are HLA-A29 positive. Its pathophysiology is still poorly understood. BSCR is the strongest documented association between HLA and disease in humans, which makes it an excellent model for studying the underlying immuno-genetic mechanisms of HLA class I-associated diseases. Although the association with HLA-A29 suggests that it is directly involved in the presentation of peptide antigens to T cells, the exact contribution of HLA-A29 to the pathophysiology of BSCR remains enigmatic. This article revisits the HLA-A29 peptidome using insights from recent studies and discusses why HLA-A29 can be considered a canonical antigen presenting molecule. The first genome-wide association study facilitated novel concepts into a disease mechanism beyond HLA-A29 that includes strong genetic predisposition for the *ERAP2* gene that affects antigen processing for HLA class I. Furthermore, patients manifest with pro-inflammatory cytokine profiles and pathogenic T cell subsets that are associated with IL-17-linked inflammation. We are beginning to understand that the underlying biology of BSCR comprises various pathologic aspects branched into multiple molecular pathways. We propose to employ *Systems Medicine* to reveal their dynamic interplay for a holistic view of the immunopathology of this intriguing archetypal HLA class I-associated disease.

Contents

* Corresponding author. Department of Ophthalmology, University Medical Centre Utrecht, Heidelberglaan 100, 3584CX, Utrecht, The Netherlands. Tel.: +31 8 755 1683.
E-mail address: J.J.W.Kuiper@umcutrecht.nl (J. Kuiper).

[1] Percentage of work contributed by each author in the production of the manuscript is as follows: Jonas Kuiper: 40%, Aniki Rothova: 25%, Joke de Boer: 15%, Timothy Radstake: 20%.

http://dx.doi.org/10.1016/j.preteyeres.2014.11.003
1350-9462/

1. Introduction

Birdshot chorioretinopathy (BSCR) is an organ-specific, presumably auto-immune disorder of the eye typically affecting middle aged and elderly individuals of European descent (Shah et al., 2005). BSCR manifests as a severe progressive intraocular inflammation of the posterior eye segment, typically leading to extensive retinal atrophy resulting in visual field loss, and is potentially blinding. Patients frequently complain of blurred vision especially in low light conditions, difficulties in distinguishing colors, floaters and poor contrast sensitivity and present with various symptoms including fluctuating vision, glare, decreased peripheral vision, metamorphopsia, and decreased depth perception (Shah et al., 2005). The most characteristic disease hallmarks are the numerous distinct white-creamy light spots scattered throughout the fundus that appear like birdshot from a shotgun (Fig. 1) (Howe et al., 1997; Kiss et al., 2006; Shah et al., 2005). Hence, the term *birdshot chorioretinopathy* was introduced by Ryan and Maumenee in 1981 (Ryan and Maumenee, 1980).

BSCR is clinically well-distinguishable from other posterior uveitis entities, but its underlying cause is still unknown. Evidence for any distinctive mode of inheritance is lacking, however, BSCR has been observed in monozygotic twins and has been reported in members of the same family (Fich and Rosenberg, 1992; Trinh et al., 2009). It was hypothesized that BSCR may be associated with infectious agents, including *Borrelia burgdorferi* or *Coxiella burnetii* (Kuhne et al., 1992; Suttorp-Schulten et al., 1993). Scarce extra-ocular manifestations including hearing loss, cutaneous vitiligo, psoriasis and presence of systemic sarcoidosis have only incidentally been reported (Gass, 1981; Heaton and Mills, 1993; Hesse et al., 1993; Yoshioka et al., 1983). Systemic hypertension, frequently seen in middle-aged Caucasians, is the most commonly reported non-ocular event in BSCR (Gasch et al., 1999; Priem, 1989; Rothova et al., 2004). However, no systemic disease or specific extra-ocular manifestations have been convincingly associated with BSCR (Gasch et al., 1999; Pagnoux et al., 2010).

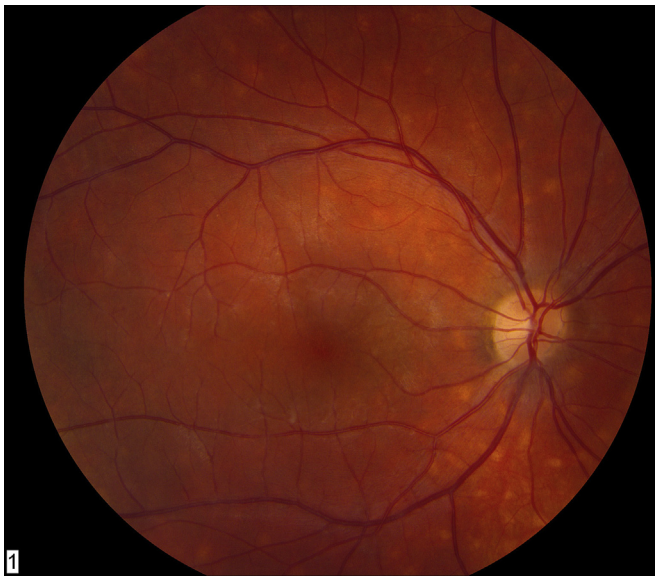

Fig. 1. Fundus photography of a patient with birdshot chorioretinopathy showing hallmark creamy yellow-orange chorioretinal lesions along the main retinal vessels.

The aim of this review is to provide an update on recent novel insights and emerging concepts of immuno-genetics that underlie the pathophysiology of BSCR.

2. The role of HLA-A29

A unique feature to BSCR is the extraordinary link with the human leukocyte antigen (HLA)-A29. Essentially all patients carry a particular variant of the HLA-A29 allele which represents one of the strongest associations between an HLA class I allele and human disease (Nussenblatt et al., 1982; Priem et al., 1988). Although the link with HLA-A29 has been well-known for over three decades, the association is both intriguing and puzzling, since its role in the pathophysiology of BSCR is not conclusive (Nussenblatt et al., 1982). Consequently, HLA-A29, present in about 7–10% of Caucasian population, is currently not essential for diagnosis (Levinson et al., 2006). Curiously, HLA-A29 has also been associated with non-classical forms of iron overload and incidentally to chromoblastomycosis (Porto et al., 1998; Tsuneto et al., 1989). The HLA-A29 serotype can be subdivided in at least 17 distinct subtypes (Holdsworth et al., 2009), but the predominant subtypes in Caucasians and patients are HLA-A*29:02 and HLA-A*29:01. Accordingly, these two subtypes have both been associated with BSCR (Lehoang et al., 1992; Levinson et al., 2004). The much rarer allele HLA-A29*10 has only been incidentally reported in patients (Donvito et al., 2010). The very similar HLA-A*29:02 and HLA-A*29:01 have only a minor amino acid difference which does not seem to affect interaction with the presented peptides. In fact, the amino acid sequence of HLA-A29 in BSCR patients is not different from unaffected HLA-A29-positive individuals (Donvito et al., 2005). Since HLA-A29 itself did not seem to bear pathogenic alternations, it was hypothesized that the HLA-A29 association merely represented a bystander marker in linkage disequilibrium with pathogenic polymorphisms in the MHC region (Levinson, 2007). However, previous reports on the investigation of short tandem repeats near *HLA-A* in small patient cohorts revealed highly various haplotypes for A*29:01, A*29:02, and A*29:10, suggesting that HLA-A29 itself confers risk to developing to BSCR (Donvito et al., 2005, 2010).

In depth genetic profiling of the entire MHC region could provide an answer to questions on the role of HLA-A29 in BSCR. With this in mind, Kuiper et al. recently investigated the entire *MHC* region of 117 Dutch and Spanish patients using genotyping and subsequent high-

Please cite this article in press as: Kuiper, J., et al., The immunopathogenesis of birdshot chorioretinopathy; a bird of many feathers, Progress in Retinal and Eye Research (2014), http://dx.doi.org/10.1016/j.preteyeres.2014.11.003

resolution imputation of classical HLA alleles and >3000 additional amino acid polymorphisms near these loci (Kuiper et al., 2014b). The extreme association with HLA-A29 was ascertained and, as expected, the classical A29 effect could be primarily attributed to the A*29:02 allele, which is the reflection of its greater prevalence amongst Caucasians. Using conditional analysis on HLA-A29:02 no other additional loci in this region were found to be associated with BSCR that could not be explained by linkage disequilibrium with HLA-A29:02, including frequently associated alleles such as HLA-B44 (Priem et al., 1988). Interestingly, in contrast to common autoimmune diseases, no association with any HLA class II was observed (Kuiper et al., 2014b). Hence the hypothesis that HLA-A29 may indirectly mark ambiguous genetic variants at the MHC (Levinson, 2007) seems unlikely. Therefore, it is reasonable to assume that HLA-A29 functions as a canonical antigen presenting molecule for yet to be determined uveitogenic peptides.

Observations from studies in other HLA class I-associated diseases may provide additional insights into the role of HLA-A29 in BSCR. HLA-B27 is the most profoundly studied HLA class I antigen due to its association with ocular inflammation and spondyloarthropathies (Schlosstein et al., 1973; Brewerton et al., 1973). Despite being designated a risk factor and related to hyperactivation of the immune system in chronic inflammatory diseases such as ankylosing spondylitis (AS) and anterior uveitis, HLA-B27 has also been designated beneficial for protection against various viral infections (Sorrentino et al., 2014). The HLA-B27 antigen was shown to present immunodominant peptide epitopes to virus-specific CD8+ T cells that enhances the intrinsic capacity to control viral infections (Brooks et al., 1993; Neumann-Haefelin et al., 2006). Therefore, it is hypothesized that carriers of the HLA-B27 allele may have superior anti-viral immunity at the price of enhanced risk for developing chronic inflammatory diseases such as AS (in combination with other environmental factors and additional genetic predisposition) (Sorrentino et al., 2014). Related opposing mechanisms might also underlie to the development of BSCR in HLA-A29 positive individuals. Interestingly, HLA-A29 has been associated with specific anti-viral responses and there are numerous virus-specific $CD8^+$ T cell epitopes identified that are presented in the context of HLA-A29 (Koziel et al., 1993; Fleischer and Kreth, 1983; Frahm et al., 2007; Khanna et al., 1997; Jones et al., 2004; Lohman et al., 2005; Wilson et al., 1997; Masemola et al., 2004; Jing et al., 2005; Bollard et al., 2004).

The HLA-A29 antigen was even suggested to out compete some other HLA alleles in overlapping binding epitopes for presenting viral epitopes to $CD8^+$ T cells, by direct binding competition in the endoplasmic reticulum or mechanisms that favor processing of HLA-A29 epitopes over other HLA class I motifs (Wilson et al., 1997). It is not known whether HLA-A29 has a favorable influence on the control of specific viral infections in BSCR. Curiously, however, in contrast to HLA-B27, the HLA-A29 was linked to rapid progression to AIDS in HIV positive patients (Hendel et al., 1999). Further research is necessary to clarify the potential relationship of HLA-A29 in viral clearance and susceptibility towards autoimmunity in the HLA-A29 positive unaffected individuals and patients that suffer from BSCR. Still, the HLA-A29 allele is common in the Caucasian population (Levinson et al., 2006) and the evidence for its role in viral-specific $CD8^+$ T cells activation might suggest that the cause of BSCR is somehow related to previous concealed viral infection.

2.1. HLA-A29 transgenic mouse

Most of our understanding of uveitis comes from various transgenic or antigen-induced experimental animal models that greatly improved our understanding of the complex underlying signaling pathways (Caspi et al., 2008; Caspi, 2010; Horai and Caspi, 2011). Szpak et al. previously generated an HLA-A29 transgenic mouse with a construct derived from cDNA of HLA-A29 obtained from a BSCR patient (Szpak et al., 2001). Strikingly, the aging HLA-A29 transgenic mice developed spontaneous mild chronic posterior uveitis, very similar to human autoimmune uveitis and shared several characteristics with BSCR. This model implied an explicit role for HLA-A29 in the development of BSCR, but by a differential and unknown mechanism since the presence of HLA-A29 itself is not sufficient to cause the disease in humans. However, a more recent study by Mattapallil et al. revealed that the ocular phenotype of the HLA-A29 transgenic mice appeared to be degenerative instead of inflammatory and could best be explained by the unfortunate contamination of a retinal degenerative *Rd8* mutation in the *Crb1* gene of C57BL/6 mice, independently of the HLA-A29 construct (Mattapallil et al., 2012). The original strain of Szpak et al. had been lost making exclusion of the degenerative contamination in these mice not possible, however the mutation was observed in most substrains from vendors of the United States and Japan (Mattapallil et al., 2012). Therefore, novel generation of HLA-A29 transgenic mice that do not harbor *rd8*, perhaps on several genetic backgrounds, are necessary to conclusively study the contributing role of HLA-A29 to the ocular phenotypes seen in this model.

2.2. The HLA-A29 binding motif

Since HLA molecules orchestrate immune responses by presenting peptide antigens to T cells, it is plausible that HLA-A29 presents ocular peptides to circulating ocular-specific T cells that results in tissue damage of the eye. Evidently, better insights in the characteristics of these peptides may enhance our understanding of their source and contribution to the initiation or disease progression of BSCR.

In 1996 Biósgerault et al. conducted a series of bindings studies and reported the natural motif of HLA-A29 to be defined by a glutmate (E) at anchoring position 2 (P2) and tyrosine (Y) at anchoring position 9 of the peptide (P9) (Boisgerault et al., 1996; Lund et al., 2004). This was partly supported by other binding studies that showed that peptide motifs only need to fulfill the requirement of the aminoacid tyrosine at P9 to be able to sufficiently bind HLA-A29 (Table 1) (De Backer et al., 1999; Luescher et al., 1996). For example, a more recent in-depth analysis of endogenous ligands eluted from HLA-A29:02 molecules reported >100 peptides derived from a great variety of intracellular proteins that contained highly variable aminoacids at each of the anchors, but all contained the tyrosinase at P9 (Granados et al., 2012). Consistent with these data, viral and tumor-associated peptides that are recognized by cytotoxic T cells in the context of HLA-A29, also only require the tyrosinase at P9 (Table 1) (Bollard et al., 2004; De Backer et al., 1999; Jing et al., 2005; Lundegaard et al., 2008; Masemola et al., 2004; Terakura et al., 2007; Slyker et al., 2011; Warren et al., 2010). In addition, loss of tyrosinase at P9 within the aminoacid sequences of HLA-A29-binding peptides can reduce the ability of the peptide to sensitize target cells for lysis by cytotoxic T cells (Jones et al., 2004).

Considering that there is a great number of eye related proteins that by immunization are able to cause uveitis in animal models (Caspi et al., 2008) and that the only most likely prerequisite for HLA-A29 seems to be the amino acid tyrosinase at P9, the number of possible peptide motifs derived from these proteins is immense and studying the specific role of each will be labor-intensive. Nevertheless, BSCR manifests exclusively in the eye so the nature of these antigens must be related to proteins that are present in ocular tissues.

Please cite this article in press as: Kuiper, J., et al., The immunopathogenesis of birdshot chorioretinopathy; a bird of many feathers, Progress in Retinal and Eye Research (2014), http://dx.doi.org/10.1016/j.preteyeres.2014.11.003

Table 1
HLA-A29 restricted epitopes recognized by cytotoxic T cells and HLA-A29 binding peptide motifs reported in literature. All peptides are denoted with the corresponding binding affinity predicted using NetMHC version 3.4[a], which is the best-performing MHC-binding predictor (Lundegaard et al., 2008).

Antigen	Peptide										Binding affinity (nM)[a]	Reference
		P2								P9		
HLA-A29 restricted T cell epitopes												
Latent membrane antigens (LMP) 1 and 2		I	L	L	A	R	L	F	L	Y	3	Bollard et al., 2004
UDP-glucuronosyltransferase 2B17	A	E	L	L	N	I	P	F	L	Y	127	Terakura et al., 2007
GAGE-1 protein		Y	Y	W	P	R	P	R	R	Y	9	De Backer et al., 1999
P2RX7 protein		W	F	H	H	C	H	P	K	Y		Warren et al., 2010
HIV gag protein		L	Y	N	T	V	A	T	L	Y	24	Masemola et al., 2004
HIV gp120 protein		F	N	C	G	G	E	F	F	Y	7	Slyker et al., 2011
Vaccinia virus C12L protein		V	Y	I	N	H	P	F	M	Y	4	Jing et al., 2005
HIV gp120 protein		S	F	E	P	I	P	I	H	Y	65	Jones et al., 2004
HLA-A29 binding epitopes												
S-arrestin		G	E	L	T	S	S	E	V	A	30977	Boisgerault et al., 1996
S-arrestin		S	E	V	A	T	E	V	P	F	17522	Boisgerault et al., 1996
Endogenous ligand HLA-A29		K	E	F	Q	E	H	Y	E	Y	109	Boisgerault et al., 1996
Endogenous ligand HLA-A29		K	E	I	E	L	I	L	E	Y	410	Boisgerault et al., 1996
MAGE-2		E	V	V	P	I	S	H	L	Y	8	Luescher et al., 1996
MAGE-3		E	V	D	P	I	G	H	L	Y	138	Luescher et al., 1996
MAGE-6		E	V	D	P	I	G	H	V	Y	984	Luescher et al., 1996
MAGE-12		E	V	V	R	I	G	H	L	Y	28	Luescher et al., 1996
Actinin alpha 4[b]		A	I	D	Q	L	H	L	E	Y	28	Granados et al., 2012
Baculoviral IAP repeat-containing protein 6[b]		A	K	I	P	L	G	F	Y	Y	91	Granados et al., 2012
Regulator of G-protein signaling 22[b]		E	V	L	K	P	L	L	L	Y	34	Granados et al., 2012
Tyrosinase[b]	F	F	I	S	S	K	D	L	G	Y	15	Granados et al., 2012

[a] 9-10mer binding predictions for HLA-A29:02 using Artificial Neural Networks NetMHC version 3.4. Prediction values are given in nM IC50 values. Strong binder threshold 50 nM. Weak binder threshold score 500 nM.
[b] 4 randomly selected peptides of >100 peptides eluted from HLA-A29 reported by Granados et al., 2012.

2.3. Potential ocular antigens presented by HLA-A29

Classical candidates for protein antigens that are targeted by T cells in BSCR are thought to be the retinal specific *S-antigen (S-ag)* and *interphotoreceptor retinoid-binding protein* (IRBP) that are located in the outer retina. BSCR patients demonstrate increased proliferation of peripheral blood mononuclear cells to these antigens (de Smet et al., 1990; Nussenblatt et al., 1982). Furthermore, BSCR resembles S-ag-induced experimental autoimmune uveitis (EAU) and peptides derived from amino acid sequence of the S-ag can bind to HLA-A29 in vitro (Boisgerault et al., 1996; Nussenblatt et al., 1981a, 1981b). Although the S-ag is a highly uveitogenic protein competent to cause uveitis in several species, this is thought to be a predominantly $CD4^+$ T (helper) cell-mediated (via HLA class II) autoimmune disease of the retina (Adamus and Chan, 2002; Mattapallil et al., 2011). Besides, immune responsiveness to the S-ag is a phenomenon seen throughout non-infectious uveitis, most of which are not associated with HLA class I locus, and can be even detected in non-affected individuals (de Smet et al., 1990; de Smet et al., 2001; Doekes et al., 1987; Hirose et al., 1988; Morgan et al., 2002; Nussenblatt et al., 1980). Like the S-ag, immunization of susceptible animal models with other retinal antigens (rhodopsin, recoverin, phosducin) results in very similar forms of autoimmune uveitis (Caspi et al., 2008). Thus, retinal autoimmunity may be an important epiphenomenon that drives inflammation, but perhaps develops after retinal damage is caused by other (yet to be determined) factors probably associated with HLA-A29 (Gasch et al., 1999).

The origin of the typical birdshot-lesions remains controversial. The demographic distribution of the creamy lesions in color fundus photographs differs from the retinal pigment epithelium atrophy visualized by fundus autofluorescense, indicating independent choroidal and retinal damage (Giuliari et al., 2009). Some suggest that the lesions appear to arise in the choroid (Gaudio et al., 2002; Pulido et al., 2012; Herbort et al., 2004; Levinson and Monnet, 2012). The choroid comprises a network of bloodvessels, fibroblasts, resident immune cells and melanocyte-rich tissue that supports the outer retina (Nickla and Wallman, 2010).

Enhanced depth imaging using spectral optical coherence tomography (EDI-OCT) can be used to visually evaluate the pathologically changes of the choroid during ocular inflammation (Imamura et al., 2009). Keane et al. examined the choroid in BSCR patients using extramacular EDI-OCT and revealed, in addition to extensive pathological retinal changes, choroidal hyperreflective foci indicating lymphocytic aggregates (Keane et al., 2013). The choroidal lesions were generally located near larger-sized choroidal vessels and choroidal abnormalities were seen as deep as the suprachoroid, the melanocyte-, collagen- and fibroblast-rich tissue of the choroid, that would suggest inflammatory activity even at deeper levels of the choroid (Keane et al., 2013; Nickla and Wallman, 2010). In addition, two histology studies on enucleated eye tissues of HLA-A29 positive birdshot patients revealed non-granulomatous focal nodular T cell infiltrates primarily throughout the choroid (Gaudio et al., 2002; Pulido et al., 2012). Interestingly, Rothova et al reported up to 19% of BSCR patients with previous skin malignancy including melanoma and basal cell carcinoma or malignancies of the prostate, bladder, lung and breast (Rothova et al., 2004). Curiously, the patients described in the two histopathology studies both had a past medical history of melanoma (Gaudio et al., 2002; Pulido et al., 2012). Moreover, there have been several reports on the association of melanoma with uveitis and BSCR in both animal and man (Arevalo et al., 2003; Feeney-Burns et al., 1985; Gaudio et al., 2002; Yeh et al., 2009a). This implies a potential role for T cells directed to melanoma-associated antigens. In T cell responses to melanoma it is, however, important to differentiate between tumor-associated antigens (TAAs) and melanocyte differentiation antigens (MDAs). The *MAGE* and *GAGE* family of genes are TAAs widely expressed in epithelial malignancies, including melanoma (De Backer et al., 1999; Luescher et al., 1996). MDAs include the proteins Tyrosinase and gp100 that are expressed by normal melanocytes, but overexpressed in melanoma. MAGE-reactive T cells are specifically reactive against a range

Please cite this article in press as: Kuiper, J., et al., The immunopathogenesis of birdshot chorioretinopathy; a bird of many feathers, Progress in Retinal and Eye Research (2014), http://dx.doi.org/10.1016/j.preteyeres.2014.11.003

of melanoma and non-melanoma tumor cells, but anti-MAGE immune responses also result in destruction of healthy melanocytic tissue and exposure of MDAs (Chinnasamy et al., 2011; Johnson et al., 2009a). Note, an endogenous HLA-A29:02 strong binding peptide derived from Tyrosinase was eluted from B cells by Granados et al. (Granados et al., 2012) (see also Table 1). Therefore, the typical hypopigmented lesions in the choroid make it tempting to speculate that BSCR may, at least in part, be related to pigment-destruction diseases such as cutaneous vitiligo and Vogt-Koyanagi-Harada disease, which are both considered autoimmune diseases caused by melanocyte-specific T cells (Bordaberry, 2010; Le Poole and Luiten, 2008).

3. Pathogenesis beyond HLA-A29

HLA-A29 is relatively common in European populations (7–9%) whereas BSCR is a rare disease, which indicates that over 99% of HLA-A29 positive Caucasians do not develop BSCR (Shah et al., 2005; Wee and Papaliodis, 2008). Consequently, HLA-A29 can be considered a necessity, but not the only and conclusive factor for developing BSCR. This warrants additive (epi)genetic or exogenous factors that confer risk for developing BSCR in HLA-A29 positive Caucasians (Donvito et al., 2010; Shah et al., 2005; Wee and Papaliodis, 2008). This concept is strengthened by the observation that despite the common prevalence of HLA-A29 in the Hispanic, Afro-american and Asian populations, BSCR is not or very sporadically reported in these populations (Baddar and Goldstein, 2014; Brezin et al., 2011; Shah et al., 2005; Wee and Papaliodis, 2008). Moreover, the differential prevalence of HLA-A29 in these ethnic groups inadequately explains the near exclusive occurrence of BSCR in Caucasians (Brezin et al., 2011). This led to the curious hypothesis that other possible genetic requirements involved could have a differential ethnic distribution and predispose Caucasians to BSCR (Donvito et al., 2005). An example of a gene that is highly variably distributed between ethnic groups is the *UDP glycosyltransferase 2 family, polypeptide B17* (UGT2B17) gene. Individuals of Asian ancestry have a homozygous gene deletion in 73% of individuals and absent expression of UGT2B17 compared with 27% in Caucasians (McCarroll et al., 2006). Anecdotally, a peptide antigen derived from UGT2B17 can be presented by HLA-A*2902 and was recognized by $CD8^+$ T cells isolated from a patient with graft-versus-host-disease (Terakura et al., 2007).

3.1. The role of KIR genes

A first glimpse of other potential genes that, in addition to HLA-A29, contribute to disease susceptibility came from previous observations by Levinson et al. who demonstrated that specific combinations of *Killer immunoglobulin-like receptor* (KIR) gene haplotypes are more frequent in BSCR patients (Levinson et al., 2008). The findings of this study have previously been extensively reviewed (Levinson, 2007, 2011). Accordingly, only a brief description on the association of KIR in BSCR will be provided here: KIR genes encode inhibitory and activation receptors that are expressed on immune cells such as natural killer (NK) cells and T cells, and regulate self-non-self recognition by binding to its ligands (Single et al., 2007). Levinson et al. reported on the strong association of the KIR genes *3DL1* and *3DS1* with HLA-B44 in BSCR patients possibly resulting in loss of self-tolerance during inflammatory conditions and, thus, suggested a role for HLA-B44 in BSCR, beyond the strong linkage disequilibrium with HLA-A29 (Levinson et al., 2008). Note, KIR3DL1 that specifically recognizes an epitope in HLA-B and HLA-A, was shown to interact partly with the presented peptide that affect the binding of KIR to HLA molecules (Peruzzi et al., 1996).

The underlying mechanisms of HLA class I interacting molecules (f.e. KIRs that interact with HLA-B44) and their contribution to BSCR pathology are not well understood yet and may include several others, such as the macrophage MHC receptor I (MMRI) that is expressed on human monocytes and specifically targets the HLA-B44 antigen (Tashiro-Yamaji et al., 2012).

3.2. Recent genome-wide association study findings in birdshot chorioretinopathy

Similar to BSCR, other HLA class I associated diseases such as psoriasis, ankylosing spondylitis, and Behçet's disease are currently considered to have a multifactorial etiology, including environmental (stress) factors and multiple genetic risk loci (Evans et al., 2011; Johnson et al., 2009b; Kirino et al., 2013; Strange et al., 2010). In the last decade, the method of choice for the identification of novel genetic risk loci in such complex traits has been the use of *genome-wide association studies*, or GWAS. A GWAS is a hypothesis-free case-control approach that studies the genome of a population (of patients) by genotyping and subsequent imputation of millions of genetic variants, or single-nucleotide polymorphisms (SNPs) (Evangelou and Ioannidis, 2013). The main outcomes of a GWAS provides an answer to the question of whether certain SNPs are found more often than expected in a particular disease, compared to non-affected individuals that derive from the same population. Therefore, the use of GWAS to identify novel genetic risk loci associated with BSCR would be evidently suitable.

Thus, Kuiper et al. recently performed a GWAS in three BSCR populations (Dutch, Spanish, and UK) and identified *Endoplasmic reticulum aminopeptidase* (*ERAP*)*2* as a novel susceptibility locus associated with BSCR.

3.2.1. The role of ERAP2

The results of the GWAS in BSCR revealed a novel strong association for a variant near the *ERAP2* gene that results in high mRNA and protein expression of *ERAP2* (Kuiper et al., 2014b). The *ERAP2* gene is located on chromosome 5 and is positioned between the closely related *ERAP1* and the *leucyl/cystinyl aminopeptidase* (*LNPEP*) gene, that all belong to the M1 family of aminopeptidases, also known as the oxytocinase sub-family, and function in peptide trimming for antigen-presentation (Evnouchidou et al., 2009; Saveanu et al., 2005, 2009). Peptides presented by HLA class I molecules are generated by proteolysis of intracellular polypeptides by the proteasome in the cytoplasm (Kloetzel and Ossendorp, 2004). In the endoplasmic reticulum, ERAP1 (previously known as ARTS-1 or A-LAP) and ERAP2 (previously known as L-RAP) shape the cellular peptidome; the composition of peptides normally presented by HLA class I molecules to T cells (Saveanu et al., 2005). To orchestrate this final step in antigen processing, ERAP1 and ERAP2 form a unique complex, thus joining their unique sequence specificities to generate mature 8-10-mer peptide-motifs by removing several N-terminal amino acids from 15-mer precursor peptides, and shape the peptide cargo of HLA class I (Fruci et al., 2001; Haroon and Inman, 2010; Saveanu et al., 2005). ERAP2 has different substrate preferences compared to ERAP1 and is required mainly for the removal of positively charged (arginine) and basic residues, (Saveanu et al., 2005). Consequently, some peptide antigens, such as the immunodominant nonameric peptide derived from the HIV gag protein are fully dependent on trimming by ERAP2 (Fruci et al., 2001).

Importantly, recent advances in genome-wide association studies substantiate the emerging concept of a critical role for the interaction of the *ERAP1-ERAP2* locus with HLA class I as a common pathogenic mechanism in HLA class I-associated immune disorders including psoriasis (Strange et al., 2010), ankylosing spondylitis (AS) (Cortes et al., 2013; Evans et al., 2011), preeclampsia (Johnson

Please cite this article in press as: Kuiper, J., et al., The immunopathogenesis of birdshot chorioretinopathy; a bird of many feathers, Progress in Retinal and Eye Research (2014), http://dx.doi.org/10.1016/j.preteyeres.2014.11.003

et al., 2009b), and Behçet's disease (Kirino et al., 2013). Furthermore, *ERAP2* has also been linked to Crohn's disease (Franke et al., 2010) and even resistance to HIV-1 infection (Cagliani et al., 2010). Curiously, BSCR is specifically associated with *ERAP2* whereas most of these HLA class I associated diseases have a particular interaction with the *ERAP1* gene or combined *ERAP1/ERAP2* association. More importantly, in AS the association with *ERAP1* is only observed in HLA-B27-positive patients, while the association with *ERAP2* is particularly associated with HLA-B27-negative cases (Cortes et al., 2013). The functional implications of the association of *ERAP1* and *ERAP2* in AS are currently unknown, but it was suggested to be directly involved in the generation of arthritogenic peptides (Tsui et al., 2014).

In order to better understand the role of *ERAP2* in BSCR it needs to be emphasized that this gene undergoes a "balancing selection". Balancing selection maintains high genetic diversity in the major histocompatibility (MHC) locus to ensure high diversity in the antigenic repertoire. Genes involved in *MHC* function are generally in co-evolution with the *MHC* and substantially undergo balancing selection such as the KIR genes (also associated with BSCR, see *The role of KIR genes*) (Single et al., 2007). Since ERAP2 functions in close interaction with the MHC (or *HLA* in humans), it is not surprising that the *ERAP2* gene also undergoes balancing selection. The balancing selection of *ERAP2* maintains two main haplotypes with highly differential protein expression due to alternative mRNA splicing (Andres et al., 2010). Due to balancing selection the haplotype distribution of *ERAP2* in the Caucasian population is 25% for homozygotes that have two functional ERAP2 protein expressing alleles, 50% have at least one coding allele and express ERAP2, and 25% fail to express ERAP2 and are, thus, ERAP2-deficient. The strong association with *ERAP2* illustrates the clinical relevance of this functional dichotomy as the SNP (and SNPs in linkage disequilibrium) associated with BSCR at chromosome 5 also serve as tags for these haplotypes; with high expression levels of ERAP2 in BSCR patients and no or low expression in healthy individuals that do not carry the allele. We hypothesize that the established HLA-A29 association in BSCR represents a conventional peptide presenting HLA molecule and that ERAP2 controls the generation or destruction of selected peptide epitopes that are preferentially or exclusively presented by HLA-A29. This means that having the coding *ERAP2* allele may for example be beneficial for immune-homeostasis (f.e. clearance of pathogens), but perhaps disadvantageous in HLA-A29 positive individuals that are susceptible to autoimmune inflammation as observed in BSCR(Andres et al., 2010). In other words this implies that potentially uveitogenic epitopes presented by HLA-A29 are dependent on trimming by ERAP2. One such hypothetical epitope could be the 9-mer VTLGILVSY peptide derived from the highly uveitogenic S-ag that is predicted to strongly bind to HLA-A29 (IC50: 20 nM) by the peptide-binding prediction software netMHC(Lundegaard et al., 2008). Like the epitope derived from the HIV gag protein, this particular peptide motif derived from the S-ag protein contains an arginine (R) at the N-terminus that is likely dependent on ERAP2 for trimming of the mature epitope (Fruci et al., 2008; Haroon and Inman, 2010). Of course, the exact role of ERAP2 in antigen generation and peptide loading of HLA-A29 in BSCR needs to be clarified using appropriate models. Studying the antigen processing pathway using HLA-A29 transgenic mice may not be sufficient since there is no murine homolog of the *ERAP2* gene. Instead the murine *ER aminopeptidase associated with antigen processing (ERAAP)* gene represents a single aminopeptidase that functions similar to *ERAP1* (Saveanu et al., 2005; Serwold et al., 2002). Regardless, therapeutic targeting of ERAP2 using novel selective inhibitors may potentially be of interest since no clear adverse effects on health are associated with the loss of ERAP2 function, given that 25% of Caucasians are in fact ERAP2-deficient (Andres et al., 2010; Papakyriakou et al., 2013; Zervoudi et al., 2013).

4. T cells in birdshot chorioretinopathy

In general, non-infectious uveitis represents a highly sophisticated interplay of innate and adaptive immunity targeting the eye and is characterized by the accumulation of intraocular leukocytes (Deschenes et al., 1988; Forrester et al., 2013; Kaplan et al., 1984; Keino et al., 2001). These leukocytes include mostly ocular-specific T cells, but also neutrophils, macrophages, dendritic cells and polyclonal T cells that synergistically contribute to local inflammation and tissue damage (Caspi, 2010; Kerr et al., 2008). The conventional view is that environmental (stress) factors activate (the poorly understood) auto-inflammatory pathways that trigger ocular-specific T cells activation in patients that are genetically prone to autoimmunity and/or auto-inflammation (Willermain et al., 2012). The best understood perpetrators of uveitis, retinal-specific T lymphocytes, are directed to multiple retinal antigens (Caspi, 2010). Exposure of the highly immunogenic ocular antigens to T cells is normally prevented by blood-ocular barriers and the 'immune privileged' environment of the eye. However, when these barriers function inadequately, ocular-specific T cells may breach and induce tissue damage, vigorously (Kaplan et al., 1984; Keino et al., 2001). A role for T cells in the pathophysiology of BSCR is obviously implicated by its extreme HLA association (Nussenblatt et al., 1982) and the observation that the typical choroidal lesions contain predominantly infiltrated T cells (Gaudio et al., 2002; Pulido et al., 2012). Also, vitreous fluid samples from BSCR patients obtained during intraocular surgery (pars plana vitrectomy) contain almost exclusively $CD4^+$ and $CD8^+$ T lymphocytes (Kuiper et al., 2014a). Some of these intraocular T cells demonstrate reactivity to retinal and choroidal lysates, however, the exact nature of the antigens is currently still unknown (Kuiper et al., 2014a). All together, these observations delineate a central role for T cells directed to ocular resident antigens in the pathophysiology of BSCR.

4.1. The role of Th17 and Tc17 cells in birdshot chorioretinopathy

T cells that survived the clonal selection process in the thymus enter the peripheral circulation as immature naive T cells. Upon activation via their unique T cell receptor and under distinct cytokine conditions, these naive cells differentiate into specific effector and helper phenotypes (McKinstry et al., 2010; Zuniga et al., 2013). $CD4^+$ T helper cells play a central role in guiding immune responses to adequately fit the encountered antigen and the distressed tissue environment. T helper cells accomplished this by differentiating into so called polarization states with distinct phenotype, function and downstream immune pathways. The three most studied T helper polarization states are the T helper (Th)1, Th2 and Th17 triad that are promoted by distinct cytokines (Goriely and Goldman, 2008; Muranski and Restifo, 2013). In the last decade, clinical and experimental observations have put forward a prominent role for Th17 cells that drive chronic inflammation in T cell-associated immune disorders (Brown, 2010; Holtta et al., 2008; McInnes and Schett, 2007) including non-infectious uveitis (Amadi-Obi et al., 2007). Th17 cells are the subset of T helper cells that derived their name from the production of their hallmark cytokine IL-17 and characteristic expression of retinoic acid receptor-related orphan receptor γ-t (RORγt) (Bettelli et al., 2007). IL-23 is a heterodimeric cytokine that belongs to the IL-12 family and is among the key cytokines that induces the proliferation and maintains the function of Th17 cells (Kastelein et al., 2007; Maloy, 2008; Maloy and Kullberg, 2008). Other cytokines, such as IL-1β, IL-6 and transforming growth factor-β (TGF-β) also contribute to the differentiation of Th17 cells from naive precursors, cytokines that were found to be elevated in ocular

Please cite this article in press as: Kuiper, J., et al., The immunopathogenesis of birdshot chorioretinopathy; a bird of many feathers, Progress in Retinal and Eye Research (2014), http://dx.doi.org/10.1016/j.preteyeres.2014.11.003

fluids and serum of BSCR patients by multiple research groups (Amadi-Obi et al., 2007; Bettelli et al., 2007; Kuiper et al., 2011; Yang and Foster, 2013). The levels of IL-17 were specifically elevated in the eyes of BSCR patients, indicating that Th17 cells may also play a role in BSCR (Kuiper et al., 2011). This hypothesis particularly gained strength by the later observations of Yang and associates who reported on elevated immune mediators that can promote Th17 responses in the serum of patients with active disease naïve to immunomodulatory therapy (Yang and Foster, 2013). In addition, peripheral blood mononuclear cell cultures from BSCR patients with active disease demonstrated a specific production of IL-17 in response to retinal antigens that is accompanied by a modest enrichment of Th17 cells (Kuiper et al., 2013).

Although IL-17 is a hallmark cytokine for Th17 cells it can be produced by various cell types that include, but is not limited to, NK cells and neutrophils (Cua and Tato, 2010; Li et al., 2010; Passos et al., 2010). Strikingly, a subset of $CD8^+$ T cells that express the endothelial adhesion molecule 'MCAM' (CD146), also secrete IL-17 (so called Tc17 cells) and were recently found to be more abundant in peripheral blood of BSCR patients (Dagur et al., 2014). This suggests that in addition to Th17 cells, also Tc17 cells may contribute to the IL-17-flavored inflammation. In fact, this is in line with the presence of both $CD4^+$ and $CD8^+$ T cells in ocular tissues of BSCR patients and reflects observations from the related disease model experimental autoimmune encephalomyelitis, in which Tc17 were found to be critical for induction of Th17-mediated inflammation (Huber et al., 2013; Kuiper et al., 2014a; Pulido et al., 2012). In addition, retinal specific IL-17 producing $CD8^+$ T cells have been shown to be uveitogenic in experimental autoimmune uveitis (Peng et al., 2007). Similar mechanisms could also underlie the pathophysiology of BSCR, but are currently unknown. Although vitreous fluid and ocular tissues derived from BSCR patients are rare, it would be highly informative to evaluate the IL-17 production of intraocular T cells in BSCR to support this hypothesis. Perhaps Tc17 are able to target HLA-A29 molecules that present epitopes that are dependent on ERAP2 trimming, linking the HLA class I association with IL-17 associated immunity in BSCR. Currently, the role of IL-17 in BSCR is not clarified. Although IL-17 is generally associated with pathogenic inflammation, it was also linked to protective mechanisms during inflammation (Li et al., 2014; Nishikawa et al., 2014; Liu et al., 2012). Th17 cells and elevated IL-17 in affected tissues are common in chronic inflammatory diseases and could very well be an epiphenomenon that overhauls the underlying distinct causal molecular pathways.

Regardless, current evaluation of agents that specifically dampen Th17/Tc17 immunity would still be of particular interest as a novel treatment modality for BSCR. Although therapeutic targeting of IL-17 by the monoclonal human antibody *secukinumab* has not been evaluated in patients with BSCR, it proved to be rather disappointing for controlling inflammation in other types of noninfectious uveitis (Hueber et al., 2010; Dick et al., 2013). Since IL-17 itself does not drive IL-17 mediated inflammation, it might be better to target more upstream cytokines that play a role in the differentiation of Th17 and Tc17 cells. This is particularly attractive given that Tc17 cells are induced under similar circumstances as Th17 cells in that they also require conditional cytokines such as IL-23 and IL-6 (Ciric et al., 2009; Satoh et al., 2012). This warrants the evaluation of the efficacy of human monoclonal antibodies that specifically target IL-23 and IL-6 signaling for treatment of BSCR. *Ustekinumab* is a monoclonal antibody that targets the p40 subunit of the IL-12 and IL-23 cytokines (Benson et al., 2011). The effectiveness of ustekinumab for reducing inflammation in BSCR remains to be determined, but there is an upcoming phase 1 and 2 study for the use of ustekinumab in uveitis that is expected to be completed in June 2015 (ClinicalTrials.gov Identifier: NCT01647152). Recently, targeting IL-6 signaling, by the human monoclonal antibody tocilizumab was effective for treatment of cystoid macula edema in otherwise treatment-refractory cases of BSCR (Adan et al., 2013).

4.2. T regulatory cells in birdshot chorioretinopathy

Uveitis is currently considered to be the result of an imbalance between regulatory mechanisms that inhibit the immune system and active pro-inflammatory mechanisms (Forrester et al., 2013). This balance is normally regulated by a dynamic interplay of effector and regulatory cells of which T regulatory cells (Tregs) are a prominent subgroup of immune cells that regulate inflammation. Hallmark for autoimmunity is the loss of self-tolerance and escape of auto-aggressive T cells due loss of control by Tregs (Workman et al., 2009). Tregs are generated in the thymus or induced in the periphery from $CD4^+$ T cells and control auto-aggressive T cells by not yet completely understood mechanisms that include the use of several anti-inflammatory mediators such as IL-10, TGF-β and IL-35 (Collison et al., 2007; Wing and Sakaguchi, 2010). As mentioned, TGF-β induces the differentiation of Th17 cells under pro-inflammatory conditions together with cytokines such as IL-6. Interestingly, when T cells are only exposed to TGF-β, they upregulate the transcription factor fork head box P (FOXP)-3 and can develop into Tregs (Bettelli et al., 2006). It is becoming clear that Tregs comprise a family of regulatory T cell subsets that differ in their stability of FOXP3 expression and suppressive capacity (Fantini et al., 2004; Roncarolo et al., 2006; van Loosdregt et al., 2010; Workman et al., 2009). Diminished frequency and suppressive function of Tregs have been associated with non-infectious uveitis (Chen et al., 2008; Yeh et al., 2009b). Although the characteristics of Tregs have not been investigated in detail in BSCR patients, Foster et al. reported lower percentage of $CD4^+$ $CD25^+$ $Foxp3^+$ Tregs in a small pilot study of 5 BSCR patients compared with controls (Foster et al., 2013). This indicates that immune regulation by these regulatory cell subsets may be altered in BSCR and favor escape of auto-aggressive T cells that target the eye.

As described in the introduction, BSCR generally affects middle-aged Caucasians (Shah et al., 2005). Models of aging in mice reveal specific alterations that may give a clue on the relative age of onset of BSCR; Although the absolute numbers and overall suppressive capacity of Tregs does not decline, Tregs of aged mice demonstrate a specific diminished capability to suppress IL-17-producing T cells during chronic inflammation (Sun et al., 2012). As described, IL-17 is intrinsic to many autoimmune disorders and BSCR. This implicates that Tregs of middle-aged and elderly individuals may have reduced capacity to also control ocular-specific T cells that produce IL-17 which may favor this subset during chronic inflammatory conditions in BSCR (Jagger et al., 2014; Kuiper et al., 2013).

Besides Tregs, emerging evidence reveals regulatory counterparts in several other leukocyte lineages (La Cava, 2011). In B cells, these B regulatory cells or *Bregs*, are induced by IL-35 and strongly suppress experimental autoimmune uveitis by inhibiting pathogenic Th17 cells while promoting the expansion of Tregs (Tedder and Leonard, 2014; Wang et al., 2014). The contribution of Bregs in the inflammation of BSCR remains to be investigated, but the potential use of IL-35 to induce such regulatory B cells for controlling inflammation in BSCR could be an exciting upcoming field of research.

5. Conclusion and future directions

5.1. An immune mediated conceptual framework for birdshot chorioretinopathy

BSCR is a prototype HLA class I-associated disease that manifests as an intraocular inflammation of choroid and retina primarily. Patients exhibit increased levels of IL-17 related cytokines and

Please cite this article in press as: Kuiper, J., et al., The immunopathogenesis of birdshot chorioretinopathy; a bird of many feathers, Progress in Retinal and Eye Research (2014), http://dx.doi.org/10.1016/j.preteyeres.2014.11.003

pathogenic T cells are considered to play a central role in its immune pathogenesis. More recently, BSCR occurrence was strongly associated with the presence of HLA-A29 & *ERAP2* suggesting that these two genes represent a major cause of its pathology. In fact, the *ERAP1-ERAP2* risk locus can be considered a master-switch for HLA-associated autoimmune diseases. Given the genetic similarity, BSCR may share more susceptibility loci (which are as yet undetectable due to lack of power resulting from small cohorts and the rarity of the disease) with related HLA class I diseases (Cortes et al., 2013; Kirino et al., 2013). This is consistent with the finding that BSCR shares Th17 signatures that also play a central role in Behçet's disease and ankylosing spondylitis (Brown, 2010; Holtta et al., 2008; Kuiper et al., 2011). Follow-up genetic studies in larger independent panels of cases and controls are needed to establish the contribution of additional susceptibility factors associated with BSCR.

Based upon the described previous and recent insights summarized in this review, we propose the following underlying disease mechanism for BSCR that involves two steps: 1) The BSCR specific initiation of the inflammation via HLA-A29 and ERAP2. 2) The strong secondary autoimmune response towards retinal antigens that are exposed upon the loss of the integrity of the blood-retinal barrier, the mechanism possibly more common to various types of ocular inflammation.

1) Given the strong association with HLA-A29 we consider the HLA-A29 antigen central to the initiation of the pathogenesis of BSCR. If HLA-A29 is predominantly recognized by $CD8^+$ T cells through their T cell receptor or by natural killer cells through their killer immunoglobulin receptor, or in parallel remains to be elucidated. However, since $CD8^+$ T lymphocytes are present in ocular tissues of BSCR patients (Pulido et al., 2012; Kuiper et al., 2014a), we consider HLA-A29 as a canonical antigen presenting molecule that orchestrates particular immune responses by presenting microbial and self-peptides for immune surveillance by $CD8^+$ T cells. HLA-A29 has been implicated in controlling specific viral infections by presenting viral peptides to cytotoxic $CD8^+$ T cells (see *the role of HLA-A29*) and we speculate that, like the HLA-B27 antigen, having the HLA-A29 antigen presentation may be beneficial for eradication of a specific viruses. Here, HLA-A29 presents viral peptides to circulating virus-specific $CD8^+$ T cells, leading to adequate clearance of the virus. The potent virus-derived HLA-A29-binding motifs may closely resemble peptides derived from ocular resident proteins that are presented by HLA-A29 in ocular tissues, shifting the favorable anti-viral responses to unwanted targeting of the choroid and retina. Although this may apply to several other forms of ocular inflammation, unique for BSCR is the combination of the genetic predisposition of *HLA-A29* and *ERAP2*; HLA-A29 separates itself from other HLA alleles by its distinct binding motif and ERAP2 contributes to the generation of a specific subset of peptide antigens for presentation by HLA class I. Therefore, we suggest that the HLA-A29 presented peptides that favor adequate anti-viral response, but also activate unwanted auto-aggressive $CD8^+$ T cells, are heavily dependent on ERAP2 trimming; Ocular resident proteins are degraded by the intracellular proteasomal machinery. Most of the peptide fragments then enter the endoplasmic reticulum and are subjected to trimming by the aminopeptidase ERAP1, but few (that bear positive residues such as the amino acid arginine) are specifically dependent on trimming by ERAP2. These peptides are than loaded on the HLA-A29 antigen. HLA-peptide complexes are presented on the cell surface and recognized by the T cell-receptor or KIR of ocular specific $CD8^+$ T cells that attack the cells and subsequently produce pro-inflammatory cytokines (Fig. 2).

2) The second step of the mechanism points towards more common inflammatory mechanisms: The pro-inflammatory conditions lead to tissue damage in the eye, thus promoting the exposure of multiple highly immunogenic antigens such as the S-ag and IRBP leading to extensive retinal autoimmunity. Here, the peptide fragments that are derived from retinal antigens after the initial damage of the choroid and retina are now also presented in the context of other HLA antigens, including HLA class II. These are recognized by circulating ocular specific $CD4^+$ T cells, such as the Th17 cells. The specific loss of Treg function in elderly regarding the control of IL-17 producing cells during chronic inflammation supports flourishing of this cell subset and could explain the IL-17 signatures that have been reported in BSCR (see *T regulatory cells in birdshot chorioretinopathy*). The chronic inflammatory conditions in the choroid might further deteriorate the retinal-blood barrier and lead to increased exposure of immunogenic retinal antigens and further amplification of autoimmune responses towards the eye with subsequent tissue damage. Alternatively, $CD8^+$ IL-17-producing T cells (Tc17) in peripheral blood of BSCR patients (see *The role of Th17 and Tc17 cells in birdshot chorioretinopathy*) perhaps directly target HLA-A29 molecules that present uveitogenic epitopes that are dependent on trimming by ERAP2, directly connecting the well-known HLA class I association (HLA-A29) with recent genetic insights (ERAP2) and accumulating evidence for IL-17 signatures in BSCR pathophysiology.

5.2. New treatment opportunities derived from novel insights into the pathogenesis

The best treatment approach for patients with BSCR is not clear. Current treatment of BSCR patients involves local or systemic

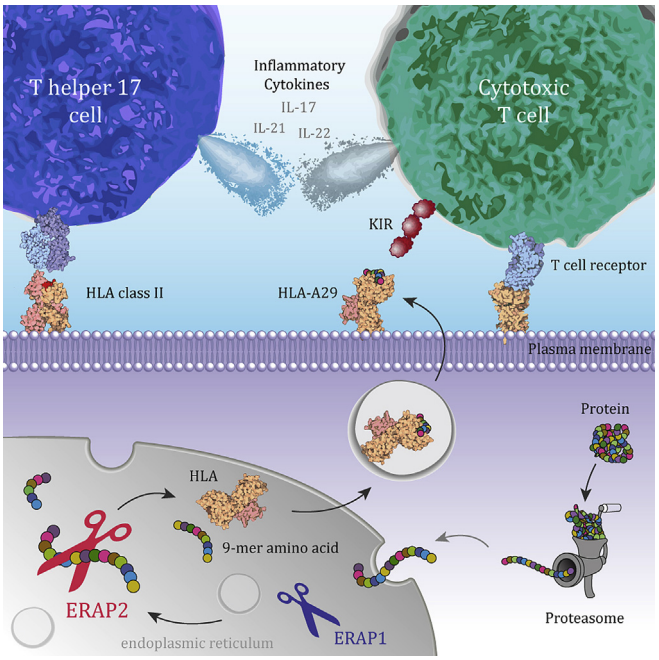

Fig. 2. Overarching model of the immunopathogenesis of birdshot chorioretinopathy (BSCR). Proteins present in cells of the tissue of the retina and choroid are subject to canonical proteasomal degradation. The consecutive approximate 15 amino acid-long peptide motifs are transported to the endoplasmic reticulum for trimming and loading on HLA-class I molecules (presumably HLA-A29, given the strong association with BSCR) by ERAP1 and particularly ERAP2. The HLA-A29 antigen presents uveitogenic peptides to $CD8^+$ T cells that recognize ocular antigens that mimic viral or bacterial epitopes. These $CD8^+$ T cells include IL-17 producing Tc17 cells. KIR antigens are expressed on subsets of T cells and specific KIR-HLA interactions contribute to the perpetuation of the inflammation in susceptible BSCR individuals. The subsequent ocular tissue damage reveals multiple highly immunogenic antigens in the context of HLA class II that are recognized by circulating ocular specific $CD4^+$ T cells, including Th17 cells. Th17 cells augment the chronic inflammation in the eye during clinical manifestation and secrete cytokines such as IL-17 and IL-21.

Please cite this article in press as: Kuiper, J., et al., The immunopathogenesis of birdshot chorioretinopathy; a bird of many feathers, Progress in Retinal and Eye Research (2014), http://dx.doi.org/10.1016/j.preteyeres.2014.11.003

corticosteroids and immunosuppressive agents, each with different adverse events and success rate (Menezo and Taylor, 2014; Pavesio et al., 2010). The emerging use of fully humanized monoclonal antibodies directed to cytokines in inflammatory disorders, provides new treatment opportunities for otherwise immunosuppressive therapy-resistant patients (Saadoun et al., 2013). TNF-α neutralizing antibodies (infliximab and adalimumab) for treatment of uveitis are currently the best studied biologicals due to their wide availability and can be effective in controlling inflammation in BSCR patients (Artornsombudh et al., 2013; Lindstedt et al., 2005; Suhler et al., 2005; Theodossiadis et al., 2007). Emerging data on IL-17 and Tc17/Th17 cells supports the idea of targeting interleukins such as IL-6 and IL-23 for treatment of BSCR using several available humanized monoclonal antibodies (Yoshimura et al., 2009). Alternatively, in contrast to biologicals that target interleukins, the administration of recombinant interleukins themselves, such as IL-35 and IL-33 that attenuate Th1/Th17 mediated inflammation in experimental uveitis models, may provide another potential new treatment strategy for BSCR (Tedder and Leonard, 2014; Wang et al., 2014; Barbour et al., 2014).

In addition, specific manipulation of the antigen processing pathway, using advanced chemical inhibitors, by targeting ERAP2 may be a promising new strategy for reducing ocular inflammation in BSCR. Especially since targeting ERAP2 seems to be relatively safe (Andres et al., 2010; Papakyriakou et al., 2013). Novel selective chemical inhibitors for endoplasmic aminopeptidases are currently been developed (Papakyriakou et al., 2013; Zervoudi et al., 2013). Alternatively, *ERAP2* is among the few human genes that would be suitable for therapeutic targeted genomic editing by the rapidly emerging *clustered, regularly interspaced, short palindromic repeat* (CRISPR) technology, an important new approach for generating RNA-guided genome editing that exploits nucleases such as the *CRISPR-associated protein 9* (Cas9) nuclease from *Streptococcus pyogenes* (Sander and Joung, 2014). These bacterial derived adapted CRISPR-Cas9 complexes can be directed to any DNA sequence for the specific and highly efficient incorporation or deletion of genomic information. The principle of this technology is based around a nuclease that is guided by an engineered RNA sequence that binds to complementary DNA, leading to various, but highly controllable adjustments of the targeted genomic sequence. Exploiting the fast evolving field of CRISPR technology for targeting *ERAP2* will greatly enhance our understanding of this mysterious aminopeptidase in antigen processing and could have therapeutic potential for treatment of BSCR.

Above all, the exact role of ERAP2 in the pathophysiology and the effect of selective inhibition of ERAP2 should be an active field of investigation in the upcoming years (Zervoudi et al., 2013).

5.3. A systems medicine approach for birdshot chorioretinopathy

Altogether, the emerging pathophysiologic concepts described in this review cannot sufficiently clarify why BSCR manifests exclusively in the eye or, for example, explain the heterogeneity in treatment response in patients. Interestingly, previous pilot studies indicated few restricted signatures of molecular pathways in peripheral blood that are involved in the pathogenesis of noninfectious uveitis, but these pathways and their relation to clinical phenotypes are, however, still poorly understood (Li et al., 2008). Due to the complexity to elucidate multiple downstream molecular pathways that exclusively manifest in the eye, further unraveling of the causative pathways in BSCR justifies an integrated and State-of-the-Art approach. Future in-depth unbiased modeling of multiple informative biological layers (epigenome, methylome, metabolome, transcriptome and proteome) of the immune system will revolutionize our understanding of disease biology and provide a holistic and dynamic overview of the underlying immune-dysregulation (Pulendran et al., 2010). Accumulating evidence rapidly reveals that chronic inflammatory diseases constitute dysregulation of multiple cell subsets, various cytokines, chemokines and growth factors, and regulatory elements such as gene methylation status and microRNAs that expose the complex and dynamic interactions of all these different components and layers of the immune system (Bielekova, et al., 2014). Many of these facets of the immune system of patients with BSCR have not yet been studied, but given related pathogenic signatures with other autoimmune diseases are also likely to play a role in the pathophysiology of BSCR. Thus, delineating the need for better understanding of the dynamic relation of all these underlying molecular pathways for which we propose to employ *Systems Medicine*.

Systems Medicine is the new discipline that emerges as a translational extension of systems biology, an interdisciplinary approach that systematically describes the complex interactions between all parts of a biological system, with a view to elucidating new biological rules capable of predicting the behavior of the biological system. To this aim, data are collected from all the components of the immune system, analyzed and integrated in order to generate a mathematical model that describes or predicts the response of the system to individual perturbations. To delineate these networks acquisition of high throughput analyses of distinct layers (e.g. mRNA, microRNA, methylation status, proteome) and various cellular subsets (e.g. T cells, dendritic cells, B cells, NK cells) that constitute the network is obligatory. Systems biology capitalizes on several so-called “omic” technologies, which are used to define and monitor all the components of the systems and has been shown to be highly successful in the identification of the central processes responsible for successful vaccination (Pulendran et al., 2010). Omics technologies generate massive datasets that can be mined for correlations with patient outcomes, drug responses, toxicity and other parameters of interest. This will provide a unique opportunity to merge therapeutic development with improvement of the fundamental understanding of the disease. This approach is presently being adopted in oncology, but has yet to penetrate the immunology field. By employing this approach we revealed important molecular pathways that lead to some paradigm shifting results in scleroderma (van Bon et al., 2013). This validated the use of this approach in the field of immunology on the basis of which we can now start to unravel the molecular pathways in BSCR.

In the upcoming years, the emerging Systems Medicine approach will form the frontier for improving clinical management of inflammatory disorders, including BSCR, towards patient specific therapeutic regimes or so called *personalized medicine* (Bielekova et al., 2014). We are at the dawn of overcoming the current challenges to setup appropriate bioinformatic tools for the integration and subsequent analysis of these high-throughput data that will guide us in an era of holistic biology with unprecedented improvement of our understanding of the underlying molecular pathways, and hopefully accelerating future tailor-made treatment for patients with BSCR.

Acknowledgments

The here described research conducted by the authors was supported by the combined grants from the Dr F.P. Fischer Stichting, Amersfoort; the Algemene Nederlandse Vereniging Ter Voorkoming Van Blindheid, Doorn; the Landelijke Stichting Voor Blinden en Slechtzienden, Utrecht, the Stichting Nederlands Oogheelkundig Onderzoek (SNOO), Rotterdam and the Blindenpenning Stichting (Grant number: 2009-2), Amsterdam, the Netherlands. We also would like to thank all participants involved in the research, including the Birdshot Uveitis Society (http://birdshot.org.uk/), The Moorfield Biobank (UK) and Spanish Birdshot Group (GENUVE).

Please cite this article in press as: Kuiper, J., et al., The immunopathogenesis of birdshot chorioretinopathy; a bird of many feathers, Progress in Retinal and Eye Research (2014), http://dx.doi.org/10.1016/j.preteyeres.2014.11.003

References

Adamus, G., Chan, C.C., 2002. Experimental autoimmune uveitides: multiple antigens, diverse diseases. Int. Rev. Immunol. 21, 209–229.
Adan, A., et al., 2013. Tocilizumab treatment for refractory uveitis-related cystoid macular edema. Graefes Arch. Clin. Exp. Ophthalmol. (9).
Amadi-Obi, A., et al., 2007. TH17 cells contribute to uveitis and scleritis and are expanded by IL-2 and inhibited by IL-27/STAT1. Nat. Med. 13, 711–718.
Andres, A.M., et al., 2010. Balancing selection maintains a form of ERAP2 that undergoes nonsense-mediated decay and affects antigen presentation. PLoS. Genet. 6, e1001157.
Arevalo, J.F., et al., 2003. Giant nodular posterior scleritis simulating choroidal melanoma and birdshot retinochoroidopathy. Ophthalmic Surg. Lasers Imaging 34, 403–405.
Artornsombudh, P., et al., 2013. Infliximab treatment of patients with birdshot retinochoroidopathy. Ophthalmology (3).
Baddar, D., Goldstein, D.A., 2014. HLA-A29-positive birdshot chorioretinopathy in a hispanic patient. Ocul. Immunol. Inflamm. 1–3.
Barbour, M., et al., 2014. IL-33 attenuates the development of experimental autoimmune uveitis. Eur. J. Immunol. (11) [Epub ahead of print] PubMed PMID: 25116404.
Benson, J.M., et al., 2011. Discovery and mechanism of ustekinumab: a human monoclonal antibody targeting interleukin-12 and interleukin-23 for treatment of immune-mediated disorders. MAbs 3, 535–545.
Bettelli, E., et al., 2006. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature 441, 235–238.
Bettelli, E., et al., 2007. T(H)-17 cells in the circle of immunity and autoimmunity. Nat. Immunol. 8, 345–350.
Bielekova, B., et al., 2014. How implementation of systems biology into clinical trials accelerates understanding of diseases. Front. Neurol. 5, 102.
Boisgerault, F., et al., 1996. Definition of the HLA-A29 peptide ligand motif allows prediction of potential T-cell epitopes from the retinal soluble antigen, a candidate autoantigen in birdshot retinopathy. Proc. Natl. Acad. Sci. U. S. A. 93, 3466–3470.
Bollard, C.M., et al., 2004. The generation and characterization of LMP2-specific CTLs for use as adoptive transfer from patients with relapsed EBV-positive Hodgkin disease. J. Immunother. 27, 317–327.
Bordaberry, M.F., 2010. Vogt-Koyanagi-Harada disease: diagnosis and treatments update. Curr. Opin. Ophthalmol. 21, 430–435.
Brewerton, D.A., et al., 1973. Acute anterior uveitis and HL-A 27. Lancet 302, 994–996.
Brezin, A.P., et al., 2011. HLA-A29 and birdshot chorioretinopathy. Ocul. Immunol. Inflamm. 19, 397–400.
Brooks, J.M., et al., 1993. Different HLA-B27 subtypes present the same immunodominant Epstein-Barr virus peptide. J. Exp. Med. 178, 879–887.
Brown, M.A., 2010. Genetics of ankylosing spondylitis. Curr. Opin. Rheumatol. 22, 126–132.
Cagliani, R., et al., 2010. Genetic diversity at endoplasmic reticulum aminopeptidases is maintained by balancing selection and is associated with natural resistance to HIV-1 infection. Hum. Mol. Genet. 19, 4705–4714.
Caspi, R.R., et al., 2008. Mouse models of experimental autoimmune uveitis. Ophthalmic Res. 40, 169–174.
Caspi, R.R., 2010. A look at autoimmunity and inflammation in the eye. J. Clin. Investig. 120, 3073–3083.
Chen, L., et al., 2008. Diminished frequency and function of CD4+CD25high regulatory T cells associated with active uveitis in Vogt-Koyanagi-Harada syndrome. Investig. Ophthalmol. Vis. Sci. 49, 3475–3482.
Chinnasamy, N., et al., 2011. A TCR targeting the HLA-A*0201-restricted epitope of MAGE-A3 recognizes multiple epitopes of the MAGE-A antigen superfamily in several types of cancer. J. Immunol. 186, 685–696.
Ciric, B., et al., 2009. IL-23 drives pathogenic IL-17-producing CD8+ T cells. J. Immunol. 182, 5296–5305.
Collison, L.W., et al., 2007. The inhibitory cytokine IL-35 contributes to regulatory T-cell function. Nature 450, 566–569.
Cortes, A., et al., 2013. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. Nat. Genet. 45, 730–738.
Cua, D.J., Tato, C.M., 2010. Innate IL-17-producing cells: the sentinels of the immune system. Nat. Rev. Immunol. 10, 479–489.
Dagur, P.K., et al., 2014. Secretion of interleukin-17 by CD8+ T cells expressing CD146 (MCAM). Clin. Immunol. 152, 36–47.
De Backer, O., et al., 1999. Characterization of the GAGE genes that are expressed in various human cancers and in normal testis. Cancer Res. 59, 3157–3165.
de Smet, M.D., et al., 1990. Cellular immune responses of patients with uveitis to retinal antigens and their fragments. Am. J. Ophthalmol. 110, 135–142.
de Smet, M.D., et al., 2001. Human S-antigen determinant recognition in uveitis. Investig. Ophthalmol. Vis. Sci. 42, 3233–3238.
Deschenes, J., et al., 1988. Activated T lymphocytes in uveitis. Br. J. Ophthalmol. 72, 83–87.
Dick, A.D., et al., 2013. Secukinumab in the treatment of noninfectious uveitis: results of three randomized, controlled clinical trials. Ophthalmology 120, 777–787.
Doekes, G., et al., 1987. Humoral and cellular immune responsiveness to human S-antigen in uveitis. Curr. Eye Res. 6, 909–919.
Donvito, B., et al., 2005. Different HLA class IA region complotypes for HLA-A29.2 and -A29.1 antigens, identical in birdshot retinochoroidopathy patients or healthy individuals. Investig. Ophthalmol. Vis. Sci. 46, 3227–3232.
Donvito, B., et al., 2010. A new HLA extended haplotype containing the A*2910 allele in birdshot retinochoroidopathy: susceptibility narrowed to the HLA molecule itself. Investig. Ophthalmol. Vis. Sci. 51, 2525–2528.
Evangelou, E., Ioannidis, J.P., 2013. Meta-analysis methods for genome-wide association studies and beyond. Nat. Rev. Genet. 14, 379–389.
Evans, D.M., et al., 2011. Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility. Nat. Genet. 43, 761–767.
Evnouchidou, I., et al., 2009. A new role for Zn(II) aminopeptidases: antigenic peptide generation and destruction. Curr. Pharm. Des. 15, 3656–3670.
Fantini, M.C., et al., 2004. Cutting edge: TGF-beta induces a regulatory phenotype in CD4+. J. Immunol. 172, 5149–5153.
Feeney-Burns, L., et al., 1985. Uveitis in melanomatous swine: lack of evidence for humoral immune melanocyte destruction. Investig. Ophthalmol. Vis. Sci. 26, 551–560.
Fich, M., Rosenberg, T., 1992. Birdshot retinochoroidopathy in monozygotic twins. Acta Ophthalmol. (Copenh) 70, 693–697.
Fleischer, B., Kreth, H.W., 1983. Clonal analysis of HLA-restricted virus-specific cytotoxic T lymphocytes from cerebrospinal fluid in mumps meningitis. J. Immunol. 130, 2187–2190.
Forrester, J.V., et al., 2013. Uveitis in mouse and man. Int. Rev. Immunol. 32, 76–96.
Foster, C.S., et al., 2013. Regulatory T cells in blood of patients with birdshot retinochoroidopathy. Ophthalmology 120, 430–430.
Frahm, N., et al., 2007. Extensive HLA class I allele promiscuity among viral CTL epitopes. Eur. J. Immunol. 37, 2419–2433.
Franke, A., et al., 2010. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nat. Genet. 42, 1118–1125.
Fruci, D., et al., 2001. Efficient MHC class I-independent amino-terminal trimming of epitope precursor peptides in the endoplasmic reticulum. Immunity 15, 467–476.
Fruci, D., et al., 2008. Altered expression of endoplasmic reticulum aminopeptidases ERAP1 and ERAP2 in transformed non-lymphoid human tissues. J. Cell Physiol. 216, 742–749.
Gasch, A.T., et al., 1999. Birdshot retinochoroidopathy. Br. J. Ophthalmol. 83, 241–249.
Gass, J.D., 1981. Vitiliginous chorioretinitis. Arch. Ophthalmol. 99, 1778–1787.
Gaudio, P.A., et al., 2002. Histopathology of birdshot retinochoroidopathy 1 574. Br. J. Ophthalmol. 86, 1439–1441.
Giuliari, G., et al., 2009. The spectrum of fundus autofluorescence findings in birdshot chorioretinopathy. J. Ophthalmol. 2009, 567693.
Goriely, S., Goldman, M., 2008. Interleukin-12 family members and the balance between rejection and tolerance. Curr. Opin. Organ Transpl. 13, 4–9.
Granados, D.P., et al., 2012. MHC I-associated peptides preferentially derive from transcripts bearing miRNA response elements. Blood 119, e181–e191.
Haroon, N., Inman, R.D., 2010. Endoplasmic reticulum aminopeptidases: biology and pathogenic potential. Nat. Rev. Rheumatol. 6, 461–467.
Heaton, J.M., Mills, R.P., 1993. Sensorineural hearing loss associated with birdshot retinochoroidopathy. Arch. Otolaryngol. Head Neck Surg. 119, 680–681.
Hendel, H., et al., 1999. New class I and II HLA alleles strongly associated with opposite patterns of progression to AIDS. J. Immunol. 162, 6942–6946.
Herbort, C.P., et al., 2004. Differential inflammatory involvement in retina and choroid in birdshot chorioretinopathy. Klin. Monbl. Augenheilkd. 221, 351–356.
Hesse, S., et al., 1993. Psoriasis and birdshot chorioretinopathy: response to aromatic retinoids. Dermatology 187, 137–139.
Hirose, S., et al., 1988. Lymphocyte responses to retinal-specific antigens in uveitis patients and healthy subjects. Curr. Eye Res. 7, 393–402.
Holdsworth, R., et al., 2009. The HLA dictionary 2008: a summary of HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1 alleles and their association with serologically defined HLA-A, -B, -C, -DR, and -DQ antigens. Tissue Antigens 73, 95–170.
Holtta, V., et al., 2008. IL-23/IL-17 immunity as a hallmark of Crohn's disease. Inflamm. Bowel Dis. 14, 1175–1184.
Horai, R., Caspi, R.R., 2011. Cytokines in autoimmune uveitis. J. Interferon Cytokine Res. 31, 733–744.
Howe, L.J., et al., 1997. Choroidal abnormalities in birdshot chorioretinopathy: an indocyanine green angiography study. Eye (Lond) 11 (Pt 4), 554–559.
Huber, M., et al., 2013. IL-17A secretion by CD8+ T cells supports Th17-mediated autoimmune encephalomyelitis. J. Clin. Investig. 123, 247–260.
Hueber, W., et al., 2010. Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. Sci. Transl. Med. 2, 52ra72.
Imamura, Y., et al., 2009. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. Retina 29, 1469–1473.
Jagger, A., et al., 2014. Regulatory T cells and the immune aging process: a mini-review. Gerontology 60, 130–137.
Jing, L., et al., 2005. Diversity in the acute CD8 T cell response to vaccinia virus in humans. J. Immunol. 175, 7550–7559.
Johnson, L.A., et al., 2009a. Gene therapy with human and mouse T-cell receptors mediates cancer regression and targets normal tissues expressing cognate antigen. Blood 114, 535–546.
Johnson, M.P., et al., 2009b. The ERAP2 gene is associated with preeclampsia in Australian and Norwegian populations. Hum. Genet. 126, 655–666.
Jones, N.A., et al., 2004. Determinants of human immunodeficiency virus type 1 escape from the primary CD8+ cytotoxic T lymphocyte response. J. Exp. Med. 200, 1243–1256.

Please cite this article in press as: Kuiper, J., et al., The immunopathogenesis of birdshot chorioretinopathy; a bird of many feathers, Progress in Retinal and Eye Research (2014), http://dx.doi.org/10.1016/j.preteyeres.2014.11.003

Kaplan, H.J., et al., 1984. Immunologic analysis of intraocular mononuclear cell infiltrates in uveitis. Arch. Ophthalmol. 102, 572–575.
Kastelein, R.A., et al., 2007. Discovery and biology of IL-23 and IL-27: related but functionally distinct regulators of inflammation. Annu. Rev. Immunol. 25, 221–242.
Keane, P.A., et al., 2013. Characterization of birdshot chorioretinopathy using extramacular enhanced depth optical coherence tomography. JAMA Ophthalmol. 131, 341–350.
Keino, H., et al., 2001. Identification of Th2-type suppressor T cells among in vivo expanded ocular T cells in mice with experimental autoimmune uveoretinitis. Clin. Exp. Immunol. 124, 1–8.
Kerr, E.C., et al., 2008. The dynamics of leukocyte infiltration in experimental autoimmune uveoretinitis. Prog. Retin. Eye Res. 27, 527–535.
Khanna, R., et al., 1997. Evolutionary dynamics of genetic variation in Epstein-Barr virus isolates of diverse geographical origins: evidence for immune pressure-independent genetic drift. J. Virol. 71, 8340–8346.
Kirino, Y., et al., 2013. Genome-wide association analysis identifies new susceptibility loci for Behcet's disease and epistasis between HLA-B*51 and ERAP1 4. Nat. Genet. 45, 202–207.
Kiss, S., et al., 2006. Birdshot retinochoroidopathy. Int. Ophthalmol. Clin. 46, 39–55.
Kloetzel, P.M., Ossendorp, F., 2004. Proteasome and peptidase function in MHC-class-I-mediated antigen presentation. Curr. Opin. Immunol. 16, 76–81.
Koziel, M.J., et al., 1993. Intrahepatic cytotoxic T lymphocytes specific for hepatitis C virus in persons with chronic hepatitis. J. Immunol. 149, 3339–3344.
Kuhne, F., et al., 1992. Is A29, B12 vasculitis caused by the Q fever agent? (Coxiella burnetii). J. Fr. Ophtalmol. 15, 315–321.
Kuiper, J.J.W., et al., 2011. Intraocular interleukin-17 and proinflammatory cytokines in HLA-A29-associated birdshot chorioretinopathy. Am. J. Ophthalmol. 152, 177–182.
Kuiper, J.J.W., et al., 2013. Interleukin-17 production and T helper 17 cells in peripheral blood mononuclear cells in response to ocular lysate in patients with birdshot chorioretinopathy. Mol. Vis. 19, 2606–2614.
Kuiper, J.J.W., et al., 2014a. Detection of choroid- and retina-antigen reactive CD8(+) and CD4(+) T lymphocytes in the vitreous fluid of patients with birdshot chorioretinopathy. Hum. Immunol. 75, 570–577.
Kuiper, J.J.W., et al., 2014b. A genome-wide association study identifies a functional ERAP2 haplotype associated with birdshot chorioretinopathy. Hum. Mol. Genet. (22).
La Cava, A., 2011. Regulatory immune cell subsets in autoimmunity. Autoimmunity 44, 1–2.
Le Poole, I., Luiten, R.M., 2008. Autoimmune etiology of generalized vitiligo. Curr. Dir. Autoimmun. 10, 227–243.
Lehoang, P., et al., 1992. HLA-A29.2 subtype associated with birdshot retinochoroidopathy. Am. J. Ophthalmol. 113, 33–35.
Levinson, R.D., et al., 2004. Human leukocyte antigen A29 subtypes associated with birdshot retinochoroidopathy. Am. J. Ophthalmol. 138, 631–634.
Levinson, R.D., et al., 2006. Research criteria for the diagnosis of birdshot chorioretinopathy: results of an international consensus conference. Am. J. Ophthalmol. 141, 185–187.
Levinson, R.D., et al., 2008. Combination of KIR and HLA gene variants augments the risk of developing birdshot chorioretinopathy in HLA-A*29-positive individuals. Genes Immun. 9, 249–258.
Levinson, R.D., 2007. Immunogenetics of ocular inflammatory disease. Tissue Antigens 69, 105–112.
Levinson, R.D., 2011. Killer immunoglobulin-like receptor genes in uveitis. Ocul. Immunol. Inflamm. 19, 192–201.
Levinson, R.D., Monnet, D., 2012. Imaging in birdshot chorioretinopathy. Int. Ophthalmol. Clin. 52, 191–198.
Li, L., et al., 2010. IL-17 produced by neutrophils regulates IFN-gamma-mediated neutrophil migration in mouse kidney ischemia-reperfusion injury. J. Clin. Investig. 120, 331–342.
Li, Q., et al., 2014. Interleukin-17 indirectly promotes M2 macrophage differentiation through stimulation of COX-2/PGE2 pathway in the Cancer cells. Cancer Res. Treat. 46, 297–306.
Li, Z., et al., 2008. Gene expression profiling in autoimmune noninfectious uveitis disease. J. Immunol. 181, 5147–5157.
Lindstedt, E.W., et al., 2005. Anti-TNF-alpha therapy for sight threatening uveitis. Br. J. Ophthalmol. 89, 533–536.
Liu, L., et al., 2012. Interleukin-17 and prostaglandin E2 are involved in formation of an M2 macrophage-dominant microenvironment in lung cancer. J. Thorac. Oncol. 7, 1091–1100.
Lohman, B.L., et al., 2005. Longitudinal assessment of human immunodeficiency virus type 1 (HIV-1)-specific gamma interferon responses during the first year of life in HIV-1-infected infants. J. Virol. 79, 8121–8130.
Luescher, I.F., et al., 1996. HLA photoaffinity labeling reveals overlapping binding of homologous melanoma-associated gene peptides by HLA-A1, HLA-A29, and HLA-B44. J. Biol. Chem. 271, 12463–12471.
Lund, O., et al., 2004. Definition of supertypes for HLA molecules using clustering of specificity matrices. Immunogenetics 55, 797–810.
Lundegaard, C., et al., 2008. NetMHC-3.0: accurate web accessible predictions of human, mouse and monkey MHC class I affinities for peptides of length 8-11. Nucleic Acids Res. 36, W509–W512.
Maloy, K.J., Kullberg, M.C., 2008. IL-23 and Th17 cytokines in intestinal homeostasis. Mucosal. Immunol. 1, 339–349.
Maloy, K.J., 2008. The Interleukin-23/Interleukin-17 axis in intestinal inflammation. J. Intern. Med. 263, 584–590.
Masemola, A.M., et al., 2004. Novel and promiscuous CTL epitopes in conserved regions of Gag targeted by individuals with early subtype C HIV type 1 infection from southern Africa. J. Immunol. 173, 4607–4617.
Mattapallil, M.J., et al., 2011. Uveitis-associated epitopes of retinal antigens are pathogenic in the humanized mouse model of uveitis and identify autoaggressive T cells. J. Immunol. 187, 1977–1985.
Mattapallil, M.J., et al., 2012. The Rd8 mutation of the Crb1 gene is present in vendor lines of C57BL/6N mice and embryonic stem cells, and confounds ocular induced mutant phenotypes 1. Investig. Ophthalmol. Vis. Sci. 53, 2921–2927.
McCarroll, S.A., et al., 2006. Common deletion polymorphisms in the human genome. Nat. Genet. 38, 86–92.
McInnes, I.B., Schett, G., 2007. Cytokines in the pathogenesis of rheumatoid arthritis. Nat. Rev. Immunol. 7, 429–442.
McKinstry, K.K., et al., 2010. The potential of CD4 T-cell memory. Immunology 130, 1–9.
Menezo, V., Taylor, S.R., 2014. Birdshot uveitis: current and emerging treatment options. Clin. Ophthalmol. 8, 73–81.
Morgan, J.P., et al., 2002. S antigen specific effector T cell activation detected by cytokine flow cytometry. Br. J. Ophthalmol. 86, 517–520.
Muranski, P., Restifo, N.P., 2013. Essentials of Th17 cell commitment and plasticity. Blood 121, 2402–2414.
Neumann-Haefelin, C., et al., 2006. Dominant influence of an HLA-B27 restricted CD8+ T cell response in mediating HCV clearance and evolution. Hepatology 43, 563–572.
Nickla, D.L., Wallman, J., 2010. The multifunctional choroid. Prog. Retin. Eye Res. 29, 144–168.
Nishikawa, K., et al., 2014. Interleukin-17 induces an atypical m2-like macrophage subpopulation that regulates intestinal inflammation. PLoS One 25, e108494.
Nussenblatt, R.B., et al., 1980. Cellular immune responsiveness of uveitis patients to retinal S-antigen. Am. J. Ophthalmol. 89, 173–179.
Nussenblatt, R.B., et al., 1981a. S-antigen uveitis in primates. A new model for human disease. Arch. Ophthalmol. 99, 1090–1092.
Nussenblatt, R.B., et al., 1981b. Resemblance between rhodopsin kinase and S-antigen induced uveitis. Br. J. Ophthalmol. 65, 778–782.
Nussenblatt, R.B., et al., 1982. Birdshot retinochoroidopathy associated with HLA-A29 antigen and immune responsiveness to retinal S-antigen. Am. J. Ophthalmol. 94, 147–158.
Pagnoux, C., et al., 2010. Extraocular manifestations of birdshot chorioretinopathy in 118 French patients. Presse Med. 39, e97–e102.
Papakyriakou, A., et al., 2013. Novel selective inhibitors of aminopeptidases that generate antigenic peptides. Bioorg. Med. Chem. Lett. 23, 4832–4836.
Passos, S.T., et al., 2010. IL-6 promotes NK cell production of IL-17 during toxoplasmosis. J. Immunol. 184, 1776–1783.
Pavesio, C., et al., 2010. Evaluation of an intravitreal fluocinolone acetonide implant versus standard systemic therapy in noninfectious posterior uveitis. Ophthalmology 117, 567–575.
Peng, Y., et al., 2007. Characterization of IL-17+ interphotoreceptor retinoid-binding protein-specific T cells in experimental autoimmune uveitis. Investig. Ophthalmol. Vis. Sci. 48, 4153–4161.
Peruzzi, M., et al., 1996. A p70 killer cell inhibitory receptor specific for several HLA-B allotypes discriminates among peptides bound to HLA-B*2705. J. Exp. Med. 184, 1585–1590.
Porto, G., et al., 1998. Major histocompatibility complex class I associations in iron overload: evidence for a new link between the HFE H63D mutation, HLA-A29, and non-classical forms of hemochromatosis. Immunogenetics 47, 404–410.
Priem, H., 1989. Vascular manifestations in birdshot chorioretinopathy. Bull. Soc. Belge. Ophtalmol. 230, 41–48.
Priem, H.A., et al., 1988. HLA typing in birdshot chorioretinopathy. Am. J. Ophthalmol. 105, 182–185.
Pulendran, B., et al., 2010. Systems vaccinology. Immunity 33, 516–529.
Pulido, J.S., et al., 2012. Histological findings of birdshot chorioretinopathy in an eye with ciliochoroidal melanoma. Eye (Lond) 26, 862–865.
Roncarolo, M.G., et al., 2006. Interleukin-10-secreting type 1 regulatory T cells in rodents and humans. Immunol. Rev. 212, 28–50.
Rothova, A., et al., 2004. Birdshot chorioretinopathy: long-term manifestations and visual prognosis. Ophthalmology 111, 954–959.
Ryan, S.J., Maumenee, A.E., 1980. Birdshot retinochoroidopathy. Am. J. Ophthalmol. 89, 31–45.
Saadoun, D., et al., 2013. Biotherapies in inflammatory ocular disorders: interferons, immunoglobulins, monoclonal antibodies 8. Autoimmun. Rev. 12, 774–783.
Sander, J.D., Joung, J.K., 2014. CRISPR-Cas systems for editing, regulating and targeting genomes. Nat. Biotechnol. 32, 347–355.
Satoh, T., et al., 2012. The development of IL-17/IFN-gamma-double producing CTLs from Tc17 cells is driven by epigenetic suppression of Socs3 gene promoter. Eur. J. Immunol. 42, 2329–2342.
Saveanu, L., et al., 2005. Concerted peptide trimming by human ERAP1 and ERAP2 aminopeptidase complexes in the endoplasmic reticulum. Nat. Immunol. 6, 689–697.
Saveanu, L., et al., 2009. IRAP identifies an endosomal compartment required for MHC class I cross-presentation. Science 325, 213–217.
Schlosstein, L., et al., 1973. High association of an HL-A antigen, W27, with ankylosing spondylitis. N. Engl. J. Med. 288 (14), 704–706.

Please cite this article in press as: Kuiper, J., et al., The immunopathogenesis of birdshot chorioretinopathy; a bird of many feathers, Progress in Retinal and Eye Research (2014), http://dx.doi.org/10.1016/j.preteyeres.2014.11.003

Serwold, T., et al., 2002. ERAAP customizes peptides for MHC class I molecules in the endoplasmic reticulum. Nature 419, 480–483.
Shah, K.H., et al., 2005. Birdshot chorioretinopathy. Surv. Ophthalmol. 50, 519–541.
Single, R.M., et al., 2007. Global diversity and evidence for coevolution of KIR and HLA. Nat. Genet. 39, 1114–1119.
Slyker, J.A., et al., 2011. Phenotypic characterization of HIV-specific CD8+ t cells during early and chronic infant HIV-1 infection. PLoS ONE 6, e20375.
Sorrentino, R., et al., 2014. HLA-B27 and antigen presentation: at the crossroads between immune defense and autoimmunity. Mol. Immunol. 57, 22–27.
Strange, A., et al., 2010. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nat. Genet. 42, 985–990.
Suhler, E.B., et al., 2005. A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. Arch. Ophthalmol. 123, 903–912.
Sun, L., et al., 2012. Aged regulatory T cells protect from autoimmune inflammation despite reduced STAT3 activation and decreased constraint of IL-17 producing T cells. Aging Cell. 11, 509–519.
Suttorp-Schulten, M.S., et al., 1993. Birdshot chorioretinopathy and Lyme borreliosis. Am. J. Ophthalmol. 115, 149–153.
Szpak, Y., et al., 2001. Spontaneous retinopathy in HLA-A29 transgenic mice. Proc. Natl. Acad. Sci. U. S. A. 98, 2572–2576.
Tashiro-Yamaji, J., et al., 2012. Specific binding of HLA-B44 to human macrophage MHC receptor 1 on monocytes. Gene 501, 127–134.
Tedder, T.F., Leonard, W.J., 2014. Autoimmunity: regulatory B cells-IL-35 and IL-21 regulate the regulators. Nat. Rev. Rheumatol. (11).
Terakura, S., et al., 2007. A single minor histocompatibility antigen encoded by UGT2B17 and presented by human leukocyte antigen-A*2902 and -B*4403. Transplantation 83, 1242–1248.
Theodossiadis, P.G., et al., 2007. Tumor necrosis factor antagonists: preliminary evidence for an emerging approach in the treatment of ocular inflammation. Retina 27, 399–413.
Trinh, L., et al., 2009. Clinical features, treatment methods, and evolution of birdshot chorioretinopathy in 5 different families. Am. J. Ophthalmol. 147, 1042–1047, 1047.
Tsui, F.W., et al., 2014. The genetic basis of ankylosing spondylitis: new insights into disease pathogenesis. Appl. Clin. Genet. 7, 105–115.
Tsuneto, L.T., et al., 1989. HLA-A29 and genetic susceptibility to chromoblastomycosis. J. Med. Vet. Mycol. 27, 181–185.
van Bon, L., et al., 2013. Proteome-wide analysis and CXCL4 as a biomarker in systemic sclerosis. N. Engl. J. Med. 370, 433–443.
van Loosdregt, J., et al., 2010. Regulation of Treg functionality by acetylation-mediated Foxp3 protein stabilization. Blood 115, 965–974.
Wang, R.X., et al., 2014. Interleukin-35 induces regulatory B cells that suppress autoimmune disease. Nat. Med. 20, 633–641.
Warren, E.H., et al., 2010. Therapy of relapsed leukemia after allogeneic hematopoietic cell transplantation with T cells specific for minor histocompatibility antigens. Blood 115, 3869–3878.
Wee, R., Papaliodis, G., 2008. Genetics of birdshot chorioretinopathy. Semin. Ophthalmol. 23, 53–57.
Willermain, F., et al., 2012. Interplay between innate and adaptive immunity in the development of non-infectious uveitis. Prog. Retin. Eye Res. 31, 182–194.
Wilson, C.C., et al., 1997. Overlapping epitopes in human immunodeficiency virus type 1 gp120 presented by HLA A, B, and C molecules: effects of viral variation on cytotoxic T-lymphocyte recognition. J. Virol. 71, 1256–1264.
Wing, K., Sakaguchi, S., 2010. Regulatory T cells exert checks and balances on self tolerance and autoimmunity. Nat. Immunol. 11, 7–13.
Workman, C.J., et al., 2009. The development and function of regulatory T cells. Cell. Mol. Life Sci. 66, 2603–2622.
Yang, P., Foster, C.S., 2013. Interleukin 21, interleukin 23, and transforming growth factor beta1 in HLA-A29-associated birdshot retinochoroidopathy. Am. J. Ophthalmol. 156, 400–406.
Yeh, S., et al., 2009a. Ocular and systemic autoimmunity after successful tumor-infiltrating lymphocyte immunotherapy for recurrent, metastatic melanoma. Ophthalmology 116, 981–989.
Yeh, S., et al., 2009b. CD4+Foxp3+ T-regulatory cells in noninfectious uveitis. Arch. Ophthalmol. 127, 407–413.
Yoshimura, T., et al., 2009. Involvement of Th17 cells and the effect of anti-IL-6 therapy in autoimmune uveitis. Rheumatology(Oxford) 48, 347–354.
Yoshioka, T., et al., 1983. Birdshot retinochoroidopathy as a new ocular sign of the sarcoidosis. Nihon Ganka Gakkai Zasshi 87, 283–288.
Zervoudi, E., et al., 2013. Rationally designed inhibitor targeting antigen-trimming aminopeptidases enhances antigen presentation and cytotoxic T-cell responses. Proc. Natl. Acad. Sci. U. S. A. 110, 19890–19895.
Zuniga, L.A., et al., 2013. Th17 cell development: from the cradle to the grave. Immunol. Rev. 252, 78–88.

Please cite this article in press as: Kuiper, J., et al., The immunopathogenesis of birdshot chorioretinopathy; a bird of many feathers, Progress in Retinal and Eye Research (2014), http://dx.doi.org/10.1016/j.preteyeres.2014.11.003