EDITOR'S PICK

In this intriguing article, Margo S. Clarke explores the fascinating topic of disease left–right asymmetry, putting HLA-B27 acute anterior uveitis under the spotlight. She explores the immune system's exquisite selective ability to react to molecular variance and prompts further discussion on how a deeper understanding of lateralisation could impact the medical world at large.

WHY DO DISEASES START ONE SIDED? CLUES FROM HLA-B27 ACUTE ANTERIOR UVEITIS

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ABSTRACT

Uveitis is an inflammatory disease with significant disease burden, as it causes ≤10% of legal blindness in the USA. Patients are usually affected in their prime working years. Even in those with good treatment response, quality of life is substantially compromised. The most common form of uveitis is acute anterior uveitis, and approximately half of these cases are associated with human leukocyte antigen B27 (HLA-B27). The typical clinical presentation is sudden onset of a red sore eye with white cells and protein leaking into the anterior chamber. There is inter-individual variance in clinical signs, with the most severe cell response appearing like a snowstorm in the anterior chamber, causing cells to pile up in a snowbank appearance called a hypopyon. One of the truly curious, yet pathognomonic, features is the tendency for the inflammatory response to have a unilateral presentation. Either the right or left eye can manifest obvious inflammation, yet the other eye is completely unaffected. Also, subsequent attacks may occur on the same or contralateral side. Clearly, the immune system is capable of distinguishing a molecular variance between the two eyes, but what this difference is remains a mystery. This article will review HLA-B27 uveitis plus its associated systemic diseases; additionally, various mechanisms that play a role in determining left–right disease asymmetry will be discussed. Establishing how the immune system makes this left–right decision will have relevance to understanding causes of asymmetry in other inflammatory, degenerative, and malignant disorders.

Keywords: HLA-B27 uveitis, left-right asymmetry, differential protein expression, immunology, genetics, somatic mutation.

INTRODUCTION

Acute anterior uveitis (AAU) presents with the sudden onset of inflammation centred on the iris and ciliary body. At slit lamp exam, there are white cells and flare in the anterior chamber, fine cell precipitates on the corneal endothelium (nongranulomatous keratic precipitates), variable adhesion to lens or spanning trabecular meshwork (synechiae), and variable anterior vitreous cells. Typically, the episode

lasts 6–8 weeks with reoccurrence being common. More than 90% of human leukocyte antigen B27 (HLA-B27) positive AAU are unilateral,[1] and nearly 70% of recurrences involve the same eye.[2] It is the predictable lateralisation that assists in establishing the diagnosis of HLA-B27 uveitis since other forms of uveitis typically present bilaterally.[3] In a busy practice we do not stop to question why one eye is vulnerable while the other is spared. However, understanding the mechanism behind left–right selection could be an important step towards definitive treatment that stops recurrences.

DISEASE ASSOCIATIONS

HLA-B27 uveitis patients have associated spondyloarthritis at a frequency reported to vary from 55–78%.[1,4,5] Ankylosing spondylitis (AS) is the most common, but other forms of spondyloarthritis include reactive arthritis, arthritis associated with inflammatory bowel disease, psoriatic arthritis, undifferentiated spondyloarthropathy, and juvenile spondyloarthritis. Curiously, patients with HLA-B27 co-associated reactive arthritis or inflammatory bowel disease are at greater risk for more severe sudden-onset AAU that can persist to become chronic AAU.[6]

GENETICS AND ACUTE ANTERIOR UVEITIS

The strongest genetic risk factor for AAU remains the associated HLA-B27 genotype.[7,8] Approximately 55% of AAU patients are HLA-B27 positive, with this rising to 70% of patients with recurrent acute iritis episodes.[9] Notably, the prevalence of HLA-B27 varies markedly in the general population and the frequency of AAU and spondyloarthritis corresponds directly.[8] For example, 0.1–0.5% of Japanese, 4% of North Africans, 2–9% of Chinese, 8% of Caucasians,[10] and 50% of Haida Indians[11] are HLA-B27 positive.

The lifetime cumulative incidence of AAU in the general population is about 0.4%.[12] In a Dutch population with 1% HLA-B27 positive individuals, the prevalence of AAU in HLA-B27 positive relatives of HLA-B27 positive AAU patients was 13%.[13] However, the vast majority of those who are HLA-B27 positive do not develop uveitis or ankylosing spondyloarthritis.

Although 90% of AS patients are HLA-B27 positive, as opposed to 55% of patients with AAU, ≤78% of HLA-B27 with AAU have other B27-associated diseases,[1,4,5] while only 20–30% of patients with AS or reactive arthritis develop AAU. Hence, although there is overlap in risk factors there are clearly separate susceptibility modifiers. Having the HLA-B27 genotype starts one down a risky road but additional genetic variances determine which path is more likely.

In the search for both shared and separate genetic risks, association studies for AAU have identified HLA-A*02, HLA-DRB1*08:03, HLA-B*58, *MICA*, *LMP2*, *CYP27B1*, interleukin (IL)-10, complement components CFB, CFH and C22, TNF, the killer immunoglobulin receptor region, and the chromosome 9p region. None of these associations achieved genome-wide significance.[8]

A recent genome-wide study[14] detected that IL-23R, region 2p15, and *ERAP1* were associated with both AAU and AS ($p<5x10^{8}$). At a lower level of significance ($p<5x10^{6}$) IL-6R, EYS, the chromosome 1q32 harbouring KIF21B, IL-18R-IL-1R1, and region IL-10-IL 19 may play a role. Interestingly, IL-10, IL-18R, and IL-23R are shared with inflammatory bowel disease patients. The listed genetic associations relate to receptor polymorphisms that can amplify or diminish response to interleukins. The *ERPA* polymorphisms affect the efficiency of packaging peptides into the HLA-B27 groove.[15] By altering the magnitude or speed of responsiveness, the immune system becomes susceptible to dysregulation. There appear to be both organ and topographic specific differences in the relative importance of messages relayed through different interleukin receptors and their associated downstream signalling system.

ENVIRONMENTAL FACTORS AND PATHOGENESIS

Despite intensive research, the true cause of HLA-B27 diseases remains unclear. The dominant hypothesis is the arthrogenic/uveitogenetic peptides hypothesis.[16] Specifically, HLA-B27 has the unique ability to bind peptides from a microbe that activate CD8 T cells that cross-react with a HLA-B27/self-peptide. The molecular mimicry hypothesis then relates this cross-reactivity as a turning point in breaking tolerance that results in autoimmunity. The microbial culprits identified included yersinia, salmonella,[17] chlamydia,[18] and *Helicobacter pylori*.[19] Finding a clear and direct correlation of exposure to these organisms and causality in AAU is currently awaiting data.

Notably, there are now >105 recognised polymorphisms of HLA-B27.[20] The HLA B*2705 is most common and associated with both AAU and AS. These polymorphisms affect the binding strength of each candidate peptide to subtle variances within the groove which will impact the signal strength received by the T cell. Certain positions along the groove are responsible for the majority of the binding strength and the most significant site in the HLA B*2705 is an arginine at the P2 position.[21,22] Interestingly, if the arginine is switched to a histidine this polymorphism is designated as a HLA B*2709 molecule and is resistant to disease association.[23] This fascinating observation resulted in eluting peptides bound to HLA B*2705 versus HLA B*2709 and comparing their sequences. One study found a more restricted spectrum of peptides[24] in the HLA B*2709 and another group found no quantitative variance but perhaps a quantitative difference.[25] Despite extensive research, the target antigens in AAU and AS remained unknown.

Mear et al.[26] proposed another mechanism after demonstrating that the HLA-B2705 has a unique property to misfold. Misfolded proteins then trigger an internal cell stress response that can lead to increased production of cytokines that are pro-inflammatory, such as TNF-α, IL-1, and IL-6.[27] This may be sufficient to tip the balance toward autoimmunity in tissues responsive to these signals.

A third hypothesis is the homodimer formation hypothesis. HLA-B27 heavy chains tend to pair as homodimers and this can activate the intracellular stress cycle.[28] The dimers can also bind receptors on killer cells and alter their responsiveness leading to a pro-inflammatory state.

ANIMAL MODELS

Rats transgenic for human HLA-B27 develop spontaneous inflammatory arthropathy,[29] supporting that HLA-B27 is a disease associated gene; however, they did not develop AAU. Germ-free environments prevented development of inflammatory joint and gut disease, suggesting the important role for microbes as initiators. Additionally, overexpressing IL-23 in a mouse model[30] resulted in psoriasis, aortitis, and uveitis, confirming the significance of this cytokine in immune regulation for specific locations. Intra-peritoneal β-1,3 glucan, which is present in fungal cell walls, bacteria, and plants, caused arthritis, uveitis, ileitis, and enthesitis.[31] This was associated with elevated IL-12 and IL-23 (which is upstream from IL-17) and reaffirmed the importance of the IL-23 pathway. Currently, there is no ideal animal model that replicates the recurrent, unilateral, 6–8-week duration pattern that is classic for AAU.

ADVANCES IN THERAPY

Over 90% of patients with AAU respond well to topical steroids and cycloplegics. When the disease is particularly severe or poorly responsive, subconjunctival steroids and/or oral steroids are used. Some patients develop high intraocular pressure while on steroids, necessitating glaucoma treatment simultaneous to their uveitis management.

In recalcitrant uveitis, immunosuppressive therapy with methotrexate, cyclosporine, azathioprine, and mycophenolate plus biologics are options.[32] Paradoxical uveitis has been reported with etanercept for treatment of spondyloarthropathies. Hence, guidelines recommend infliximab or adalimumab before etanercept for uveitis management.[33] Fortunately, the majority of AAU patients do not require these more aggressive therapies.

PERSPECTIVES

AAU, like all autoimmune diseases, has significant inter-individual heterogeneity, with each patient following their unique path. This variance should be no surprise, since the 1000 Genomes Project determined a typical genome varies from the reference human genome by 4.1–5 million sites. Although the majority of these polymorphisms do not adversely affect function, the average person has 2,111–2,500 structural variants.[34] Fortunately, by having two parental alleles for each gene and redundant pathways, we often have a workable system. However, epigenomic imprinting affects >80 human genes and silences one allele. Further complexity is added since the allele chosen for inactivation can 'flip flop', in different body sites[35] and be modified based on age, creating mosaic patterns of variability. It was hoped with genome-wide association studies that the genes responsible for AAU and AS would be clearly identified and remediable pathways amenable to new therapies would then be developed. What has emerged however is an increasingly complex puzzle, with each identified gene only increasing the odds ratio to develop the disease by a factor of 1.2–1.5.[36]

Since we each have thousands of at risk variants, it is likely a specific combination of variants may provide a compounding effect. Specific combinations may present at a select body site at disease onset or evolve in a specific sequence, or have unique combinations of phenotypic features. The highest risk in AAU remains the HLA-B27 peptide packaging system, which implies there is one or more antigen and that there will need to be one or more triggering environmental event that sparks clonal expansion and drives the immune cycle sufficiently towards the threshold to precipitate clinical disease. Another intriguing aspect of the genome-wide association studies was that most of the polymorphisms were not in coding parts of the DNA that determine the quality of the protein, but rather in long, short, and micro non-coding segments that determine where, when, and how much of a protein is expressed under different circumstances. Non-coding DNA variances affect large numbers of genes, rather like modules, so to tease out causality necessitates sophisticated bioinformatics and systems biology. The capacity of genetic research to find new answers is strongly dependent on comparing a group of affected individuals that are distinctly homogeneous and consequently diseases are being further subdivided based on clinical features. To date, the topographic site of onset and the initial side of presentation has not been perceived to be a unique phenotype. Perhaps left–right asymmetry is molecularly meaningful (not random) and the side of onset could be useful both as a phenotype for genetic studies and in differential analysis of tissue at the genomic, epigenomic, and at micro, small, and long non-coding RNA levels. Hence, the following section introduces concepts of how lateralisation of lesion site can be determined based on left–right molecular differences.

ASYMMETRICAL PROTEIN EXPRESSION LEFT VERSUS RIGHT: EXPLAINING THE FIRST ATTACK

Autoimmune diseases are initiated by recognition of one or more antigens by T and/or B cells. For AAU to select one eye, there may be quantitative or qualitative left versus right differences in uveal tissue antigen(s), molecular vascular barrier complex, resident tissue signal modifiers, or signalling and receptor pairs that sense, measure, and generate a response detectable to the incoming immune system. Additionally, the immune tolerance and immune suppressive intraocular microenvironment may generate unequal differences in protein expression on each side that differentially impact the immune privilege, resulting in unilateral disease.

Left–right body axis determination[37,38] starts as early as the first cell division after fertilisation and asymmetrical protein expression is consistently present from the single cell zygote throughout development. Co-ordination of sidedness continues with specified proteins (Nodal and Lefty) being more strongly expressed on the left side which co-ordinates proper position of the heart and other internal organs. Protein variances have been identified in left and right sides of the human brain.[39] Curiously, insects exhibit brain lateralisation with hundreds of genes differentially expressed on left versus right sides of bee brains.[40] Additionally, paired organs, such as left and right breast tissue[41] and muscle myotomes[42] have been identified to have left–right protein differences.

From a clinical perspective, pseudoexfoliation syndrome demonstrates clinically visible differential protein production in left versus right eye. Pseudoexfoliation syndrome is a common ocular disease strongly associated with glaucoma. A genetic defect in the enzyme LOXL1[43] leads to defective elastin cross-linkage causing elastin debris to be released into the anterior chamber of the eye, where it settles onto the lens surface. With iris movement, the deposits are pushed like a snowplough, forming a layered ring appearance at slit lamp exam. It is fascinating that, like HLA-B27 uveitis, there is almost always left–right asymmetry. In some patients, the debris is robust in one eye and barely noticeable in the other. It is not known what causes this asymmetry.

A study of 23 post-mortem anterior optic nerve specimens found differences in neurofilament protein expression in each sector, plus surprisingly a consistently higher neurofilament expression in the right optic nerve compared to the left.[44] Jonas et al.[45] found that in 72 normal post-mortem eyes, the number of ganglion nerve fibres ranged from 777,000–1,679,000. When comparing right versus left eyes from the same donor, differences of >300,000 ganglion nerve fibres between left and right eyes were present in 19% of subjects.

An intriguing study of patterns of X-linked inactivation[46] showed that the mosaic pattern generated was individual-specific, but there were select regions, such as the tongue, where essentially

all one side of the tongue expressed the paternal X chromosome, while the opposite side expressed the maternal X chromosome. Hence, a single epigenomic event can induce left–right protein expression difference.

RANDOM SOMATIC MUTATION: AN ALTERNATIVE MECHANISM FOR LOCALISED DISEASE

Although somatic mutations are well known to cause cancer, somatic mutations can arise *de novo* developmentally and the mutation may be restricted to specific tissue. Mutations have been identified in several genes that are associated with enlargement of one hemisphere of the brain that manifest with epilepsy.[47] These mutations are only evident in tissue samples, not in blood. Patients can show dysfunction of essentially an entire half of their cerebral cortex, while only 8–35% of the brain cells carry the mutation. Similarly, somatic mutation has been found to be the cause for Sturge–Weber syndrome, a condition that presents unilaterally with a capillary malformation that follows the distribution of the ophthalmic branch of the trigeminal nerve.[48] Single cell tissue genomics assessing for tissue somatic mutations is relatively new and, to date, tissue somatic mutations have been correlated with diseases associated with structural defects that are often present at birth. However, somatic mutation rates throughout our bodies are incredibly high[49] and it is conceivable that the cell progeny of a somatic uveal mutation could be perceived as aberrant during routine immune surveillance, with the consequence of uveitis being triggered. Curiously, polymorphisms have recently been associated with volumetric differences in select paired right versus left brain regions.[50,51] This may suggest single nucleotide polymorphisms as a mechanism for generating laterality variance.

INNERVATION AND LATERALISATION

When unilateral ocular injury is experimentally induced in one eye in animal models, there is evidence that molecular and cellular changes are induced in the contralateral eye.[52-54] Also, in unilateral ocular infections with herpes simplex[55] or herpes zoster[56] that cause corneal endothelial cell loss or corneal nerve loss, respectively, changes have been detected not only in the previously infected eye but similar less profound changes have been observed in the contralateral eye. It appears that each eye is not working independently and brain sensing of insults are relayed to both eyes. Whether this provides a warning response that may prevent the inflammatory response from being bilateral in HLA-B27 uveitis is currently unknown. Additionally, the right and left brain hemispheres may not provide equivalent responses.[57] The left brain hemisphere may be immunopotentiating while the right is immunosuppressing.[58]

SHIFTING SIDES: BEYOND THE TIME OF INITIAL PRESENTATION

HLA-B27 uveitis may occur repetitively in the same eye in some patients, while in others the attacks can flip flop between left versus right sides. The two eyes are almost never involved synchronously. It is not uncommon with autoimmune diseases where the target antigen is known (such as myasthenia gravis-acetylcholine receptor or NMO-aquaporin 4 water channel) that the quantity of the antigen decreases as the disease progresses.[59,60] Hence, if there is a left–right quantitative variance, the side with more antigens may be initially selected, but with a subsequent attack, when antigen dose has plummeted, then the immune reaction may jump to the opposite side. A somatic tissue mutation is more likely to consistently have one side targeted. As an immune response matures epitope shift often occurs and if the second epitope has preferential left–right lateralisation this may further decide whether the left versus right side is more vulnerable. Hence, both the side of initial attack and whether it remains same sided or flip flops may provide clues regarding causality.

CONCLUSION

When diseases present unilaterally, it strikes us as odd that this should occur. If the disease that occurs is equally commonly on the right side as the left then we are inclined to conclude that the cause is random. However, asymmetry left versus right permeates all structures in our body and multiple molecular variables create that asymmetry. There is no doubt that unplanned environmental events trigger immune activation. Additionally, there will always be a component of chance added since the naïve B and T cell army, with T and B cell receptors generated by random recombination, is changing daily. However, the fact that inflammation can be profound in one eye while the other is remarkably unaffected suggests that the immune system has the exquisite selective capacity to detect

molecular variances that exist in one eye and not in the other. If we could determine how this occurs, we may have an opportunity to understand not only how to better treat uveitis but additionally move closer to directed targeted immunotherapy to one side of the body. Since there are many inflammatory and degenerative diseases that have unilateral presentation, determining this mechanism would have broad implications. This, however, requires a paradigm shift. Perhaps the dogma that sidedness is random needs to be reassessed. Currently, more intensive immunotherapy involves biologicals with associated high costs, variable responsiveness, and risks associated with generalised immunosuppression. Future ideal treatment will be patient-specific and focally directed. Perhaps a deeper understanding of lateralisation may be a key step in that direction.

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