Ocular immunopathology

Immunopathology Lecture 7 Lindsay Nicholson

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Summary of lecture

♦Goals of the lecture ...

- Overview of inflammation in the eye
- Understanding autoimmune disease progression
- Identifying autoantigens
- Special aspects of eye immunology



Ocular immunopathology is caused by inflammation within the eye



Pathology can often be localised to the front or back of the eye



Normal Retina





Uveitis in the mouse





Abnormal Retina -Histology

Experimental autoimmune uveoretinitis (EAU)





Carly Guyver

Optical coherence tomography









NORMAL RETINA

CYSTOID MACULAR OEDEMA IN UVEITIS



Multifocal choroiditis/posterior ueveitis



Retinochoroidal Granulomata



What causes inflammation?

Infection
Trauma
Tumours
Autoimmunity



Associated with systemic disease . . .

- Immunosuppression: AIDS, organ transplant
- Congenital infections: Toxoplasmosis
- Diabetes
- Sarcoidosis
- Thyroid eye disease
- Multiple sclerosis
- Seronegative arthropathies
- Juvenile idiopathic arthritis



...and "Idiopathic"

Birdshot retinochoroidopathy
Vogt-Koyanagi-Harada disease
Fuch's heterochromic cyclitis
Serpiginous Choroiditis

- Incidence of uveitis 70/100 000
- ♦35% become blind
- 2nd commonest cause of blindness in the working age population



Summary 1

- Inflammation can rapidly destroy eye function
- There are several ways of classifying eye pathology
- Eye disease can be the presenting manifestation of many systemic conditions



Cell populations in uveitis



EAU Immunisation protocol



Waves of inflammation



BRISTOL

Large numbers of infiltrating cells

Days Post- immunisation	CD4+		CD11b ⁺	
	n	Mean	n	Mean
Normal	46	24 ± 5	42	660 ± 54
5	20	120 ± 14	19	$\textbf{1,050} \pm \textbf{110}$
13	7	$23{,}520\pm 5{,}700$	7	$103,390 \pm 26,770$
16 - 28	47	$12,150 \pm 2,140$	45	$24,160 \pm 4,630$
34 - 44	20	3,870 ± 1,230	20	$4,980\pm2,110$



Cell populations in EAU





Kerr et al. Progress in Retinal and Eye Research 27, 527-535 (2008)

Th17 cells and neutrophils peak together





Kerr et al. J. Autoimmun. 31:354 (2008)

Summary 2

- The normal eye contains low numbers of T cells and APCs
- Inflammation leads to an influx of large numbers of cells
- Patterns of cytokine secretion change during the course of disease
- The tissue does not return to its basal state



Autoimmunity and Identifying Autoantigens



Squashed Eyeball

 1974: 56 year old male in accident on squash court. Severe retinal detachment and blindness.

Should he have his eye removed? Why?



Sympathetic Ophthalmia

- In 1583 George Bartisch wrote that after injury the eye may shrink and become painful, "in this case the other eye is in great danger"
- 80% of cases develop within 3 months; can occur up to 50 years after initial injury



Normal activation



Bystander activation



Identifying autoantigens

- Choose a candidate protein
- Analyse immune response to whole protein
- Screen overlapping peptides to find epitopes
- Induce disease in a model
- Identify and characterise the inciting cells
- Correlate with responses in humans
- Caution the presence of autoreactive cells does not equal disease

Retinal Autoantigens

Protein	MW	Location
S-Antigen (Arrestin)	48 kDa	Rod outer segments
Retinol Binding Protein-3 (IRBP)	140 kDa	Interphotoreceptor space
Rhodopsin	40kDa	Rod photoreceptors
Recoverin	23 kDa	Rod photoreceptors
Phosducin	33 kDa	Photoreceptors



Criteria for identifying autoantigens

- Epitopes that bind MHC
- Naturally processed
- Induce disease





Development of sympathetic ophthalmia



Injury and release of autoantigens

Traffic to target organ and activation



Presentation by activated DCs to





Progression in autoimmune disease

Why relapses and remissions?

- Eliminating autoantigens may be very difficult
- 'New' immune responses to previously untargeted antigens



Epitope Spreading



Intramolecular Epitope spreading

100 60 1 week 50 80 ∎ 40 60 □ ▲ ▽ V 30 40 20 20 ₽ X 10 8 ¢2 0 0 nedium nedium PCV.IN N.25 30.23 14.96 3547 81.100 21.140 120 35 1 month 30 100 . 25 80 20 60 15 40 10 20 5 ¥ . 0 0 medium nedium 87.700 121.140 30,23 ACTIN 14.96 10,20 35-47 mouse MBP peptides Hen egg lysozyme peptides

University of BRISTOL

Nature 358:155 (1992)

Autoimmune eye disease shares features with other organ specific autoimmune disease

- Antigen specific response directed at specific components of the eye or surrounding tissue
- Genetic and environmental factors control the development of disease e.g. HLA DRB1*0405
- Mediated in animal models by CD4⁺ autoantigen specific T cells
- Responds to immunosuppression



Summary 3

- Sympathetic ophthalmia is an autoimmune disease
- Initiation is through injury in the context of a permissive set of genes
- Antigen release provokes an immune response targeted to antigens found in both eyes
- Disease can progress by intra- and intermolecular epitope spreading



Special Aspects of Eye Immunology



The eye is an unusual environment

No lymphatic drainage: As brain.

- Blood ocular barrier: As brain.
- Functional immune privilege: TGF-β, IL-10, MIF, VIP. FasL expression.





Tumour growth limited by histoincompatibility





Anterior chamber-associated immune deviation



Streilein et al. JEM 152:1121 1980



Anterior chamber-associated immune deviation



Summary 4

- Special mechanisms modulate immune responses in the eye
- Antigens injected into the eye can induce tolerance
- Autoimmune disease directed at the eye shares many common features with other organ specific autoimmune diseases



Summary of lecture

- Autoimmune disease that arises in the eye it shares many features with other organ specific autoimmune conditions
- Different tissues are attacked because specific proteins are targeted by the immune response
- Disease progression correlates with epitope spreading
- The eye has specific mechanisms to reduce the likelihood of sight threatening inflammation
- The impact of an inflammatory response is modified by its context



Further Reading

- Vanderlugt and Miller. Nat. Rev. Immunol. 2:85-95 (2002)
- Kerr et al. J. Autoimmun. 31:354 (2008)
- Kerr et al. Progress in Retinal and Eye Research 27, 527-535 (2008)

