
THE DISTRIBUTION OF IMMUNE CELLS IN THE UVEAL TRACT OF THE NORMAL EYE

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SUMMARY

Inflammatory and immune-mediated diseases of the eye are not purely the consequence of infiltrating inflammatory cells but may be initiated or propagated by immune cells which are resident or trafficking through the normal eye. The uveal tract in particular is the major site of many such cells, including resident tissue macrophages, dendritic cells and mast cells. This review considers the distribution and location of these and other cells in the iris, ciliary body and choroid in the normal eye. The uveal tract contains rich networks of both resident macrophages and MHC class II⁺ dendritic cells. The latter appear strategically located to act as sentinels for capturing and sampling blood-borne and intraocular antigens. Large numbers of mast cells are present in the choroid of most species but are virtually absent from the anterior uvea in many laboratory animals; however, the human iris does contain mast cells. Small numbers of what are presumed to be trafficking lymphocytes are present in the uveal tract of normal eyes. There is little data available on the presence or absence of eosinophils. The role of these various cell types in immune homeostasis and ocular inflammation is briefly considered.

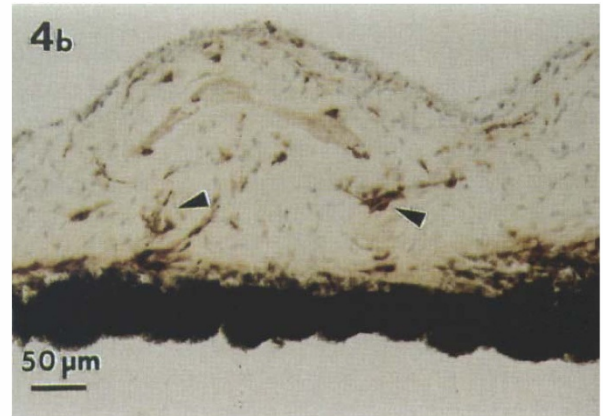
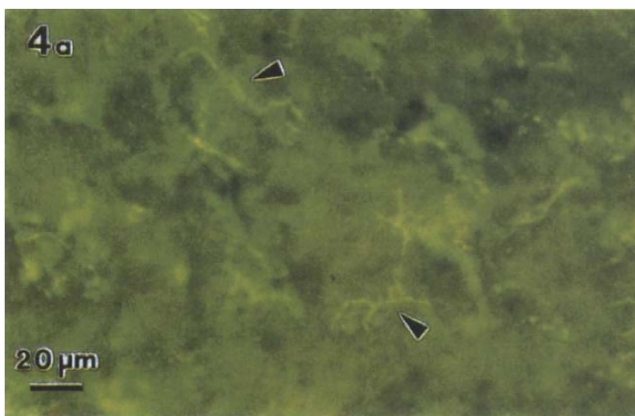
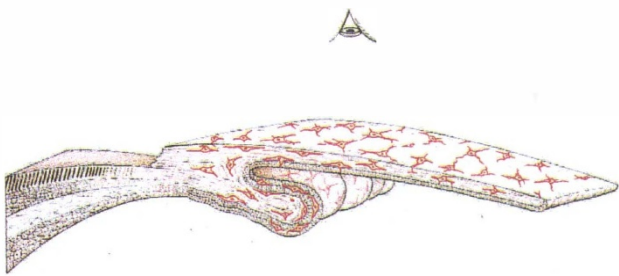
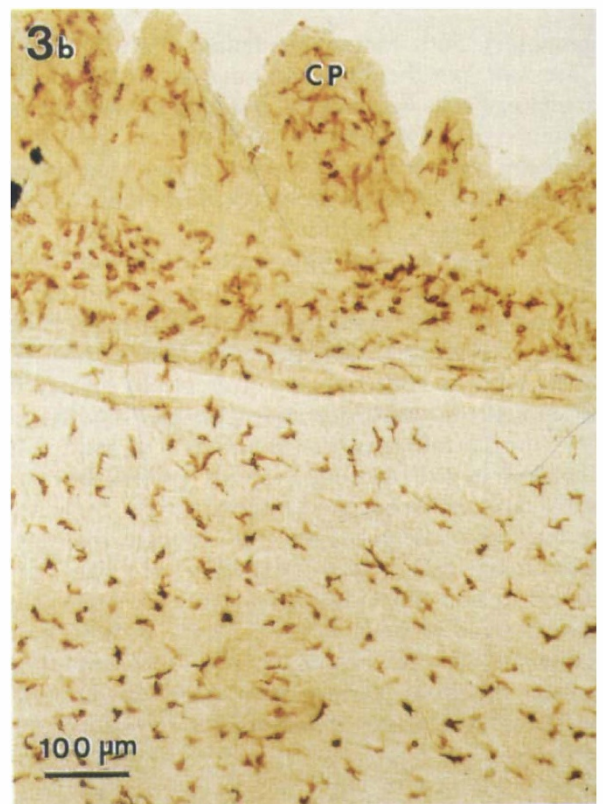
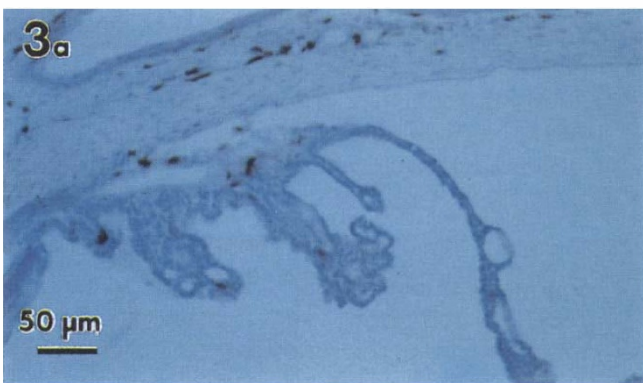
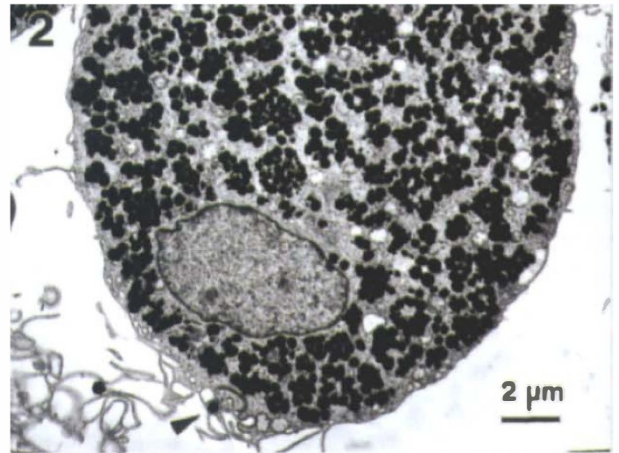
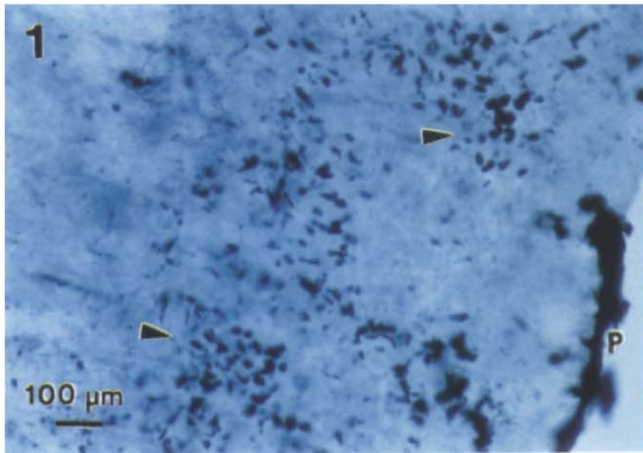
Local and systemic inflammatory and immune-mediated disorders affecting the eye are propagated not only by newly infiltrating inflammatory cells but also by the complement of immune cells normally present in non-inflamed ocular tissues. In addition, immune cells in the normal eye almost certainly play an important role in local immunological homeostasis. Several types of immune cells, such as macrophages, dendritic cells, mast cells, lymphocytes and eosinophils, normally reside for various periods during their life cycle in peripheral tissues. The major aim of this review will be to consider the current state of knowledge on the distribution, phenotype and

function of these cells in the normal iris, ciliary body and choroid. The role of such cell types in ocular inflammation, which will be discussed by other authors in this issue, is not the major focus of this review; however, a few issues will be briefly considered where appropriate.

MACROPHAGES

Mononuclear phagocytes arise from bone marrow precursors and after a brief journey in the blood as monocytes immigrate into tissues to become macrophages. In their mature form they are widely distributed throughout the body. Macrophages are professional phagocytes and play a pivotal role as effector cells in cell-mediated immunity and inflammation.¹ In addition, due to their active secretion of a range of important biologically active molecules such as cytokines, reactive oxygen intermediates and nitric oxide, they play a role in other processes including immune regulation, tissue reorganisation and angiogenesis.¹ The heterogeneous nature, function, morphology and immunophenotype of the monocyte/macrophage series in different tissue microenvironments is well established.² Cells recognised as belonging to the 'mononuclear-phagocyte system' include Kupffer cells (liver), mesangial cells (kidney), alveolar macrophages (lung), microglia (brain parenchyma and retina) and peritoneal macrophages. Macrophages undergo a complex process of activation driven by molecular inductive signals, e.g. interferon-gamma (IFN γ), usually at sites of inflammation. The activation process particularly involves 'young' or newly recruited macrophages (responsive macrophages). Resident tissue macrophages are poorly responsive to such signals.¹ Fully activated macrophages are capable of effecting a range of destructive powers specifically targeted towards certain foreign organisms or tumour cells. An important, although less well understood aspect of macrophage biology is the nature of the signals responsible for suppressing activation. Activated

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macrophages may express low/moderate amounts of major histocompatibility complex (MHC) class II molecule and thus may play a role in antigen presentation in secondary immune responses.³

Macrophages in the Iris

Classical histological and clinical studies described accumulations of large, heavily pigmented cells in the iris stroma close to the pupil margin, and near the iris base (Fig. 1), which were assumed to be of neuroepithelial origin.⁴ Electron microscopic studies⁵ revealed that there were two types of cells: type II clump cells, considered to display the morphological features of neuroepithelial cells, were rare; and type I cells, the predominant type, were considered to be melanin-containing macrophages (Fig. 2). More recently the use of specific anti-macrophage monoclonal antibodies (mAbs: ED1, ED2 and ED3) has revealed that the normal rat iris contains a rich network of resident tissue macrophages whose density and distribution is best appreciated in immunostained iris wholemount preparations (Fig. 3).^{6,7} Prior to the use of wholemounts there had been only a limited amount of data on the presence of macrophages in the iris stroma of the rat⁸ and mouse eye.⁹ Resident tissue macrophages in the normal iris display mixed morphological appearances ranging from pleiomorphic, bipolar to mildly dendriform (Fig. 3b) and are distributed in a largely perivascular and perineural manner similar to many other populations of resident interstitial macrophages. Quantitative studies in rodents^{6,7,10} indicate they are present at densities of 700–800 cells/mm². To the author's knowledge there are no studies of macrophages in human eyes using comparable investigative approaches. Immunostaining studies in humans are complicated by the presence of melanocytes; however, some preliminary immunofluorescence data (Fig. 4a) and conventional immunohistological studies (Fig. 4b) confirm the presence of a similar network of dendriform and pleiomorphic resident macrophages located throughout the iris stroma.

Macrophages in the Ciliary Body

Immunohistochemically stained wholemounts have revealed that macrophages are distributed in the connective tissue stroma of the ciliary body and ciliary processes in the rat and mouse eye (Fig. 3b). Laser scanning confocal microscopy, which provides 'optical sections' of the thick ciliary processes, is a valuable adjunct to conventional light microscopy in these studies. The relationship between macrophages and nerve fibres in dual immunofluorescent stained preparations is currently being investigated in our laboratory (Fig. 5a–c). Specific investigations of the distribution of macrophages in the normal human ciliary body are rare; however, studies by the author support the observations in rodents and suggest the human ciliary body is richly endowed with resident tissue macrophages (Fig. 6).

Macrophages in the Choroid

Like the anterior uveal tract the connective tissue stroma of the normal rodent choroid possesses a rich population of resident tissue macrophages.^{11,12} The choroid in the rat and mouse eye, which is only 20–30 µm thick in places (Fig. 7), can be processed for immunostaining as wholemounts either with the sclera attached (A. Kijlstra, personal communication) or as a separate layer dissected free from the sclera (Fig. 8). Such methods have revealed rich networks (approximately 600 cells/mm²) of largely perivascular resident tissue macrophages throughout the choroid which are ED1⁺, ED2⁺ and ED3⁺ in the rat^{11,12} and SER4⁺ and F4/80⁺ in the mouse (Fig. 8).

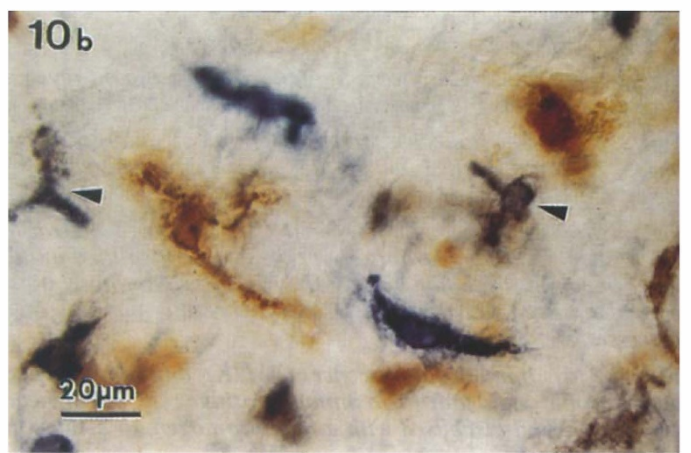
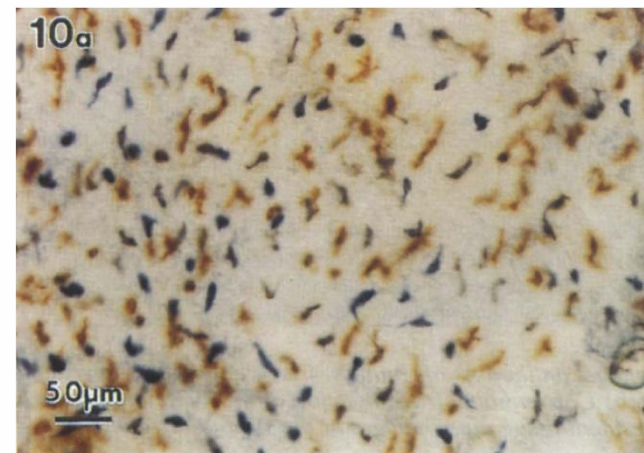
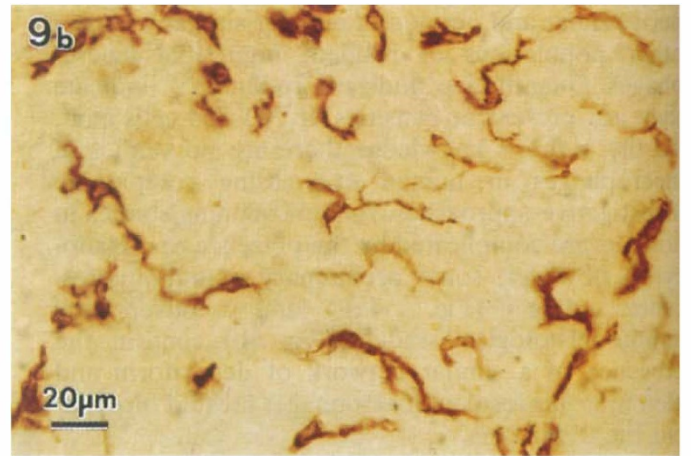
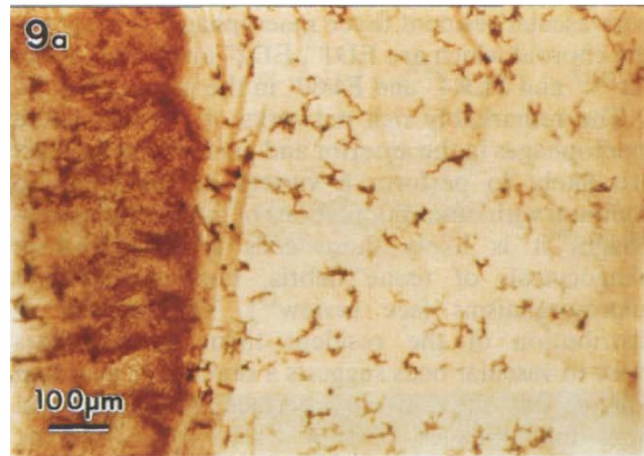
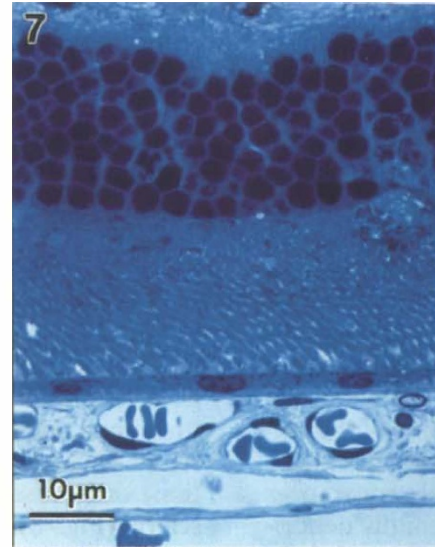
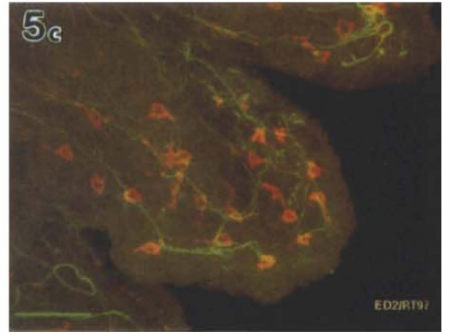
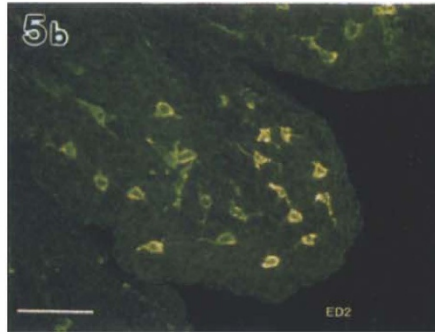
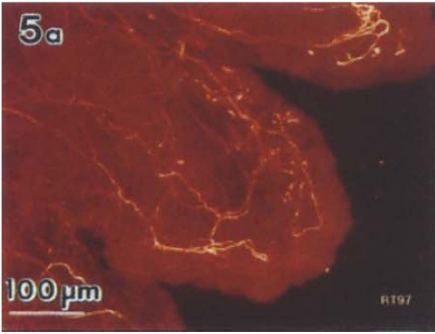
The remarkably rich networks of resident tissue macrophages in the anterior and posterior uveal tract are likely to perform a variety of functions. In common with other populations of interstitial macrophages it is likely these cells are involved in phagocytosis of tissue debris, tumour cells and micro-organisms (see review¹³). The pattern of distribution of the resident tissue macrophages close to vascular beds suggests a sentinel or guardian role at the blood–tissue interface. Whether uveal tract macrophages possess CD14 and thus the

Fig. 1. Light micrograph of a human iris wholemount revealing the 'clump cells' (arrowheads) near the pupil margin (P). Note the posterior iris pigment epithelium has been brushed off.

Fig. 2. Transmission electron micrograph of a large melanin-containing macrophage characterised by large complex phagolysosomes, ruffled cell border and eccentric nucleus. A melanin granule in the process of being phagocytosed is identifiable (arrowhead).

Fig. 3. (a) Upper panel shows a frozen section of the rat anterior segment stained with ED2 mAb (anti-resident-tissue macrophages). Note that only rare cells can be identified in the iris and ciliary body using this method. The diagram in the lower panel illustrates the view of the iris and ciliary body obtained by preparing wholemounts. (b) Iris wholemount from a normal rat eye stained with ED2. Compare the numbers of cells in (b) with those in the upper panel in (a) CP, ciliary processes.

Fig. 4. (a) Immunofluorescence (PM2K, anti-human macrophage antibody) of human iris wholemount revealing pleiomorphic and dendriform immunopositive cells (arrowheads). (b) Conventional frozen section of the human iris stained with PM2K and visualised with a red chromogen, to display the resident tissue macrophages in the stroma (arrowheads).



potential to bind LPS or LPS-binding protein is unknown. If this were the case these macrophages, via subsequent cytokine release, could rapidly initiate the inflammatory cascade in the eye. It is known that uveal tract macrophages produce pro-inflammatory substances such as nitric oxide (personal observation) and cytokines¹⁴ in conditions such as acute anterior uveitis or endogenous posterior uveitis. The possibility that uveal tract macrophages are CD14⁺ offers an attractive explanation for the particular susceptibility of the eye to exposure to systemic endotoxin (see reviews^{15,16}).

Whilst uveal tract macrophages are relatively poor antigen presenting cells (APCs) in comparison with dendritic cells¹⁷ in primary immune responses, they may be efficient local APCs to primed T cells in secondary immune responses. This could be of particular importance in light of their close proximity to the blood–ocular barriers and fenestrated vascular beds of the choroid and ciliary processes. Interestingly, the pattern of distribution and density of resident macrophages does not appear to be particularly affected in the early stages of experimental autoimmune uveitis (EAU) and endotoxin-induced uveitis (EIU) and furthermore they quickly recover to normal density following the massive cellular infiltrate during the peak of disease in these models of uveitis.^{10,12}

DENDRITIC CELLS

Members of the dendritic cell family play a pivotal role in the initiation of antigen-specific adaptive immune responses.^{18,19} Tissue-resident dendritic cells (DC) are characterised by their dendritic morphology, constitutive MHC class II expression and contiguous network arrangement. Whilst resident in peripheral tissue sites DC are specialised for antigen acquisition and processing and possess only a weak immunostimulatory capacity.²⁰ DC are a dynamic population of weakly phagocytic immunoreactive cells whose turnover time seems to vary depending on the tissue, from 3 days in lymphoid organs to up to 7 weeks in skin.²¹ After a defined period of residence or following cytokine-mediated signals DC migrate via lymphatics or blood vessels (as ‘veiled’ cells) to

the T-cell dependent areas of ‘local’ lymphoid tissues. Here they mature, under the influence of cytokines, particularly GM-CSF,²² into potent APC and present antigens/peptides within the groove of the MHC class II molecule on their cell surface to resting T cells.²³ Secondary accessory signals, such as co-expression of B7 and adhesion molecules, are crucial for effective MHC class II/T cell receptor interactions and consequently T cell activation, tolerance and peripheral deletion or apoptosis.²⁴ The specialisation of DC for antigen trapping, processing and presentation, along with their migratory properties, has led to them being regarded as the ‘sentinels’ of the immune system.¹⁸ In addition, they are many times more potent at initiating and perpetuating secondary immune responses than other APC such as B cells and macrophages. DC have attracted considerable attention as important ‘passenger cells’ in transplants able to sensitise host T cells against graft antigens and initiate graft rejection.

Dendritic Cells in the Iris

Following the discovery that MHC class II expression was important to the outcome of transplantation and in the aetiology and pathogenesis of autoimmune disease many groups investigated the pattern of expression of this molecule in normal and diseased ocular tissues. Most of these studies, performed on conventionally sectioned tissue, either failed to reveal any MHC class II⁺ cells or revealed only occasional, scattered cells in the normal eye.^{25,26} More recently the combined use of immunohistochemistry and wholemount methods demonstrated a contiguous network of MHC class DC in the iris (Fig. 9).^{6,7,27} In all species examined iris DC display a variety of forms from pleiomorphic to the characteristic highly dendriform morphology with multiple, often branched cytoplasmic processes and an indented nucleus. The cells do not display such a strong orientation along blood vessel walls as resident tissue macrophages (Fig. 9a). The density of iris DC in rodents (400–500 cells/mm²) is slightly less than in tissue macrophages. Double colour immunohistochemical studies⁷ (Fig. 10a,b) have revealed that DC do not co-localise with anti-

Fig. 5. Confocal microscopic images (Z-series) of a normal rat ciliary process stained for (a) neurofilaments (RT 97, red) and (b) resident tissue macrophages (ED2, green) The two images are combined in (c) but the colours have been reversed.

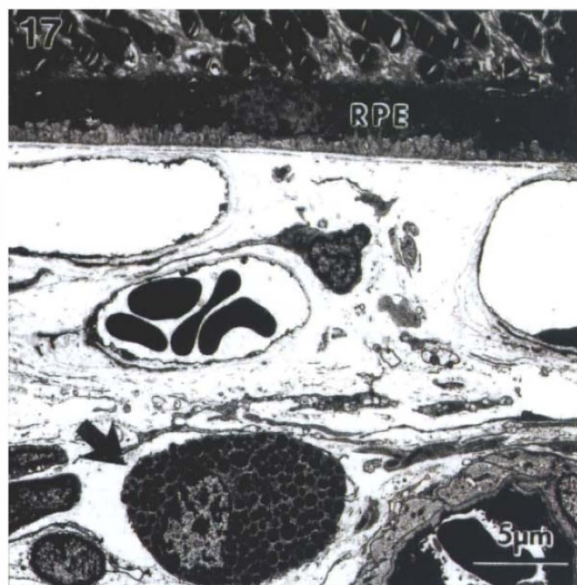
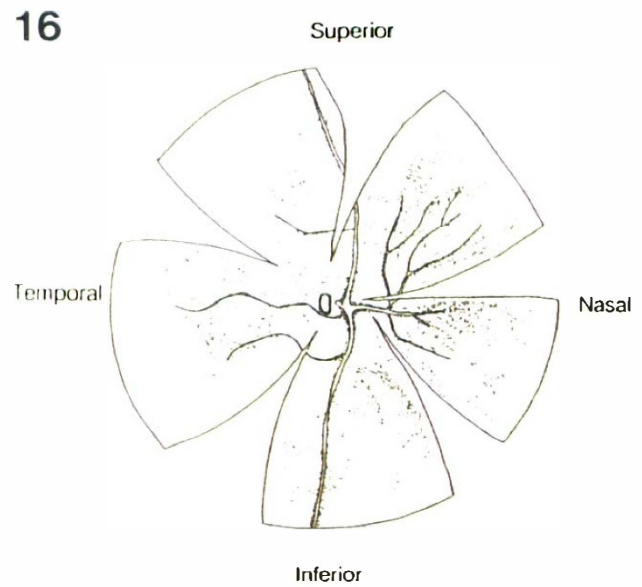
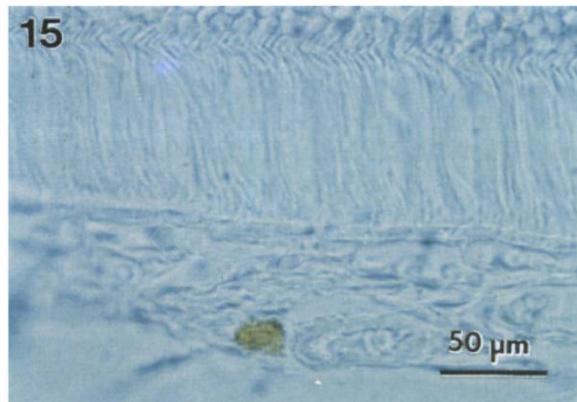
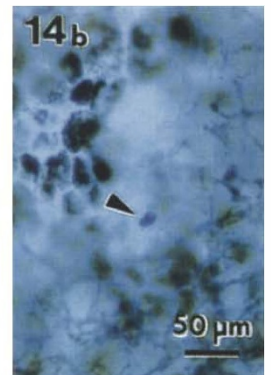
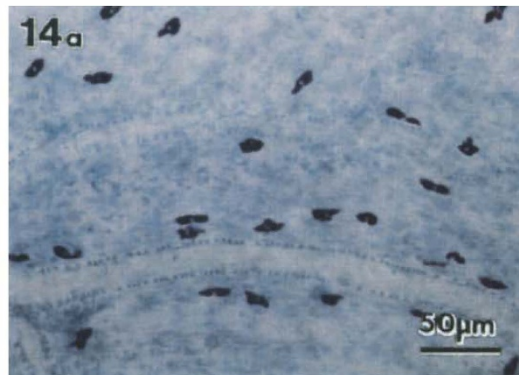
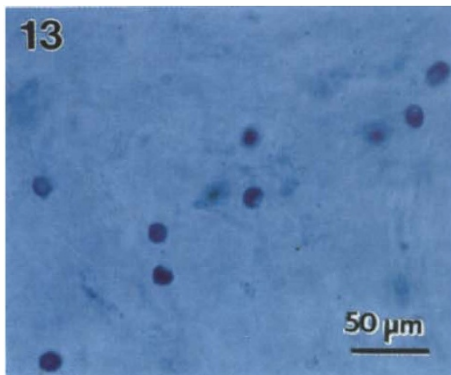
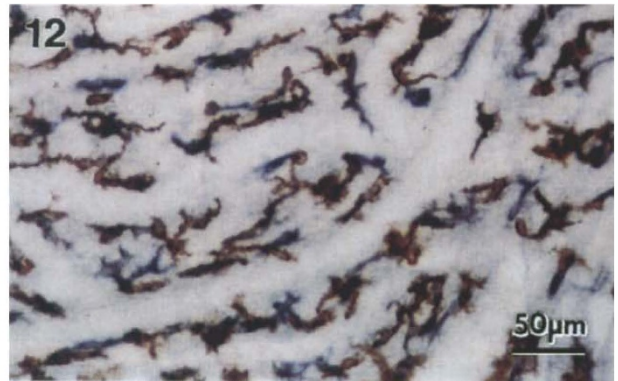
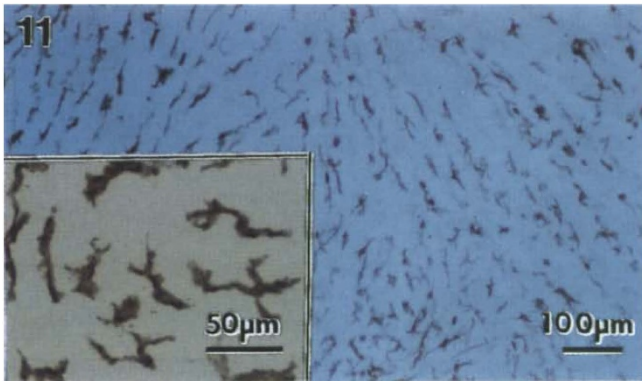
Fig. 6. Light micrograph of human ciliary process immunostained to reveal resident tissue macrophages (PM2K⁺) in the connective tissue stroma (arrowheads).

Fig. 7. Semithin resin section (1 μ m) of the rat outer retina and choroid to demonstrate the thickness of the choroid removed during wholemount preparations.

Fig. 8. Mouse choroidal wholemount stained with an anti-resident-tissue macrophage antibody (SER4).

Fig. 9. (a) Low-power view of mouse iris–ciliary body wholemount stained with anti-MHC class II antibodies (M5/114) to reveal the network of dendritic cells (DC). (b) High-power view of a few DC.

Fig. 10. Low-power (a) and high-power (b) views of double colour immunohistochemical stained rat iris wholemount preparation. Macrophages are ED2⁺ (blue chromogen) and DC are MHC class II⁺ (Ox6, red chromogen). Note that the two populations are distinct and only a few purple cells indicate co-localisation of both markers.



macrophage monoclonal antibodies. This phenotypic characteristic is important in the classification of DC.¹⁸

Recently our group has shown that purified iris DC have the functional capacity to stimulate naive T cells in a mixed lymphocyte response (MLR) similar to conventional DC, such as epidermal Langerhans cells (LC).¹⁷ Iris DC, like other 'immature' DC in peripheral tissues which are weak APC, require appropriate cytokine maturational signals such as GM-CSF in order to display potent stimulatory capacity in an MLR assay.¹⁷ The last piece of conclusive evidence that was required to establish that MHC class II⁺ cells in the iris are equivalent to DC in other non-lymphoid tissue sites was the question of their migratory capacity. DC from all non-lymphoid tissue sites thus far studied regularly traffic to local lymphoid tissues where they present peptides from antigens encountered whilst resident in peripheral tissues.²⁸ The issue of iris DC migration has recently been addressed in our laboratory.²⁹ We have shown, using X-irradiation bone marrow ablation, that iris DC have a half-life of 2–3 days in comparison with 10 days for skin LC in the same experiments and approximately 10 days for ED2⁺ iris macrophages. This rapid turnover of iris DC is comparable to that in DC populations in mucosal surfaces such as the respiratory³⁰ and gastrointestinal tracts.³¹ Until recently it was assumed that due to the absence of lymphatics in the eye antigenic signals, presumably cell-associated, leave the anterior chamber and traffic to the spleen.³² However, there is exciting new experimental evidence³³ that antigens from the anterior chamber reach submandibular lymph nodes. Whether iris DC are the cells responsible for transmitting these signals has yet to be determined, but it would seem highly likely.

Dendritic Cells in the Ciliary Body

A rich network of MHC class II⁺ DC is present in the ciliary body stroma and interposed between the two layers of the ciliary epithelium of the ciliary processes on the vascular side of the blood–aqueous barrier.⁷ At this latter site they are ideally situated to sample antigens arriving via the fenestrated vascular bed and/or those present in the posterior chamber and vitreous. There are no functional studies or migration data specifically pertaining to these cells due to the difficulty in isolating pure populations from such small pieces of tissue in rodent eyes.

Dendritic Cells in the Choroid

It has only recently become apparent that the rat choroid, like the anterior uveal tract, contains a rich population of DC.¹¹ Earlier studies slightly underestimated the densities of these cells in the rat choroid (373 cells/mm²);¹¹ however, more recent studies, in which fixation and wholemount techniques have been modified, demonstrated 746 ± 37 cells/mm² in the normal rat choroid.¹² Subsequent investigations have confirmed that cells of the DC phenotype are present in similar densities in the mouse choroid (Fig. 11) (personal observation). In common with the iris, choroidal DC form a network distinct from choroidal macrophages (Fig. 12). Immunoelectron microscopic studies have shown that DC have fine processes directly adjacent to the basal aspect of the retinal pigment epithelial cells and Bruch's membrane,¹¹ namely where they are in an ideal position to sample retinal proteins. There are to date no immunohistochemical studies of DC in the normal human choroid. Functional studies of rat DC isolated from preparations of the entire posterior segment (retina, choroid and sclera) suggest they are similar to iris DC as assessed by mitogenesis assays and allostimulatory capacity in MLR assays.³⁴ There are no data available on turnover of choroidal DC; however, observations in our laboratory using rat

Fig. 11. Mouse choroidal wholemount stained with anti-MHC class II⁺ monoclonal antibody (M5/114) to reveal the network of DC. Inset: high-power view of a few DC.

Fig. 12. Double colour immunostained choroidal wholemount showing MHC class II⁺ DC (red) and ED2⁺ macrophages (blue).

Fig. 13. Human iris wholemount stained with toluidine blue examined by conventional light microscopy. The iris pigment epithelium has been brushed off the posterior surface to aid light transmission.

Fig. 14. Rat (Lewis) (a) and human (b) choroidal wholemount stained with toluidine blue to reveal mast cells [arrowhead in (b)]. In (b) note the dendriform choroidal melanocytes and ovoid retinal pigment epithelial cells.

Fig. 15. RMCPI⁺ mast cell (connective tissue phenotype) in a histological preparation of the rat choroid and retina. Note the periarteriolar location of the mast cell in the outer choroid.

Fig. 16. Camera lucida drawing of the rat choroid to display the distribution of mast cells in a wholemount preparation. Each dot represents a single mast cell. The large vessels are the long posterior ciliary arteries.

Fig. 17. Transmission electron micrograph of the normal rat choroid containing a mast cell (arrow). Note the periarteriolar location of the mast cell in the outer choroid (compare with Fig. 15).

Fig. 18. Rat choroid wholemount stained with anti-CD8 antibody. Note the occasional cell distributed throughout the choroid.

chimaeras suggest they are replenished by bone-marrow-derived precursors.

MAST CELLS

Besides their well-known role in IgE-mediated hypersensitivity responses, mast cells have been implicated in a range of non-IgE-mediated immunological and pathological processes including responses to parasites and neoplasms, chronic inflammation, fibrosis, angiogenesis and wound healing.^{35,36} In addition to pre-formed stored mediators (e.g. histamine, heparin) mast cells are known to be a potent source of many *de novo* synthesised pro-inflammatory cytokines and chemokines.³⁶ They also appear to regulate blood flow in some tissues and organs.³⁷

Mast Cells in the Iris

There have been a number of studies of the distribution of mast cells in the normal irides of various species (Table I).³⁸⁻⁴⁴ They are absent or extremely rare in rabbits, rats and mice, but are present in some carnivores (e.g. dogs, cats), marsupials and humans, although no true estimates of density are available in the literature. In the human iris they appear more randomly distributed than in the choroid where they are periarteriolar (see below).

Mast cells are best studied by histochemical staining of whole mounts, a fact utilised in the earliest studies of these cells.³⁹ However, in pigmented eyes the quantity of iris melanin makes visualisation difficult, although the iris pigment epithelium can be removed from the posterior surface to aid light transmission through specimens (Fig. 13). Mast cells, due to their low density, are seldom encountered in transmission electron microscopic studies in the iris. The few ultrastructural images available⁴⁵ suggest that human mast cells are of the connective tissue phenotype. No immunohistochemical studies of mast cells in the human iris have been performed to confirm this suggestion.

Mast Cells in the Ciliary Body

The distribution of mast cells in the ciliary body is similar to that described for iris. They are absent or rare in rodent eyes: 0.3 per eye (Brown Norway rat) to 69 per eye (Lewis rat).^{46,47} When present they are distributed in the connective tissue stroma of the

ciliary body and ciliary processes, a pattern also found in humans where they are interspersed among the muscle fibres. They have also been noted during early development in the ciliary body of marsupial eyes.⁴²

Mast Cells in the Choroid

The distribution of mast cells in the choroid has been more intensively investigated in comparison to the iris and ciliary body (see review³⁸). This interest was partly motivated by the hypothesis that the density of choroidal mast cells in various rat strains was correlated with their susceptibility to EAU induction.⁴⁸ Within the choroid, mast cells have a characteristic periarteriolar distribution (Figs. 14a, 15, 16), primarily along the long posterior ciliary arteries (LPCA) and their branches (Fig. 16). In most other tissue sites mast cells display a perivenular location, except in the meninges where they are also periarteriolar.⁴⁹ Histochemical and immunohistochemical studies have revealed rat choroidal mast cells are of the connective tissue phenotype, containing mixed alcian blue/safranin⁺ granules (not illustrated) and Rat Mast Cell Protease I⁺ granules (Fig. 15).⁵⁰ This protease is considered a definitive marker for rat connective tissue mast cells. Transmission electron microscopy confirms these findings by revealing rat choroidal mast cell granules to be of uniform diameter (Fig. 17). Rat mucosal mast cells have granules more heterogeneous in size.⁵¹ Although mast cells are present in the human choroid³⁸ (Fig. 14b) their precise phenotype and density are unknown.

As mentioned above, early investigations described high densities of mast cells in rat strains susceptible to the induction of EAU (e.g. Lewis, 50 cells/mm²) and low densities in resistant strains (Brown Norway, 0.2 cells/mm²). Furthermore, choroidal mast cell degranulation was reported to occur around 7-8 days after immunisation with retinal antigens⁵² and therefore postulated to be an initiating event in the cellular infiltration.⁵² Subsequent studies in our laboratory^{50,53} failed to support this theory since very low densities (1.9 cells/mm²) were found in mildly susceptible rat strains such as PVG and studies of mast cells in EAU revealed a peak in degranulation accompanying disease onset (days 12-14).⁵³

LYMPHOCYTES

Lymphocytes comprise two basic functional subsets: T cells and B cells. Immunophenotypic and functional studies have further revealed that T cells broadly comprise two subpopulations: helper/inducer (CD4⁺) and suppressor/cytotoxic (CD8⁺). Recently, it has become clear that there exist at least two subpopulations of activated CD4⁺ T cells with

Table I. Mast cells in the iris (previous literature)

Taxon	Frequency
Rodentia (mouse, rat)	Rare/absent ^{38,39}
Caviidae (guinea pigs)	Rare/absent ^{38,39}
Lagomorpha (rabbits)	Absent ⁴⁰
Carnivores (cats, dogs)	Common ⁴¹ (130 per section)
Marsupials	Present ⁴²
Primates (humans)	Present ^{43,44}

differing cytokine synthesis profiles (Th1 and Th2). In broad terms, Th1 cells induce cell-mediated immunity, whilst Th2 cells induce humoral immunity. During development, T and B cells acquire antigen specificity but are only activated when specific antigen engages the appropriate receptor on the cell surface, i.e. the T cell receptor and the surface immunoglobulin respectively. T cells expressing CD4 almost invariably recognise foreign antigens/peptides in the context of self-MHC class II molecules, while CD8 T cells recognise foreign antigen presented by self-MHC class I molecules (see review⁵⁴). Presentation of antigen to T cells in the absence of appropriate co-stimulators, e.g. the molecule B7 on the APC interacting with CD28 on T cells, may result in clonal anergy. The cytokine milieu may play a role in T cell activation and differentiation, for example in the selection of the Th1 or Th2 pathway, in that IFN γ selects against Th2 and IL4 against Th1.⁵⁵ T cells are highly dynamic and continually recirculate between blood, lymphoid and non-lymphoid tissues.

Lymphocytes in the Normal Uveal Tract

Originally it was believed T cells were not able to pass through the blood-brain and blood-ocular barrier and enter the parenchyma of the brain or retina; thus lymphocytes in the extravascular space were classically considered a feature of inflammation. However, there is now evidence that small numbers of lymphocytes do indeed penetrate these vascular barriers and actively migrate through the central nervous system parenchyma in non-diseased states.⁵⁶⁻⁵⁸ The incidence of extravasated lymphocytes in these sites would be so low that they may rarely be encountered in histological sections. The extent of T cell trafficking in the uveal tract with its less developed vascular barriers (including a 'leaky' choriocapillaris) would be expected to be greater than in neural tissues; however, lymphocytes were originally reported to be absent or rare in the normal uveal tract of rodents⁹ and in human iris biopsies.⁵⁹ Recent immunohistochemical staining of whole-mounts has revealed the density of lymphocytes to range from 4 cells/mm² (pan T cell, CD5⁺) in the rat iris to 20 cells/mm² in the normal rat choroid.¹² Recent studies have revealed that some of these cells are CD8⁺ (Fig. 18), which may include NK cells although this remains to be clarified. Newly emerging evidence has shown that many cells and tissues in the intraocular environment (retina, cornea) are Fas ligand positive. When Fas⁺ lymphocytes infiltrate the eye and come into contact with the ligand they undergo apoptosis *in situ*.⁶⁰ This may act as a powerful mechanism regulating unwanted T cell infiltration in the intraocular environment.

To our knowledge there have been no specific published studies reporting the presence or absence

of gamma/delta T cells in the uveal tract. This subset of T cells has a predilection for epithelial sites and has the ability to locally down-regulate unwanted immune responses. Immunohistochemical investigations in our laboratory have failed to identify any of these cells in the uveal tract.

B cells are usually absent from the normal eye of most species, although plasma cells are a conspicuous feature of the cellular infiltrate in EAU in guinea pigs, particularly in the late stages.^{61,62}

EOSINOPHILS

Eosinophils, like neutrophils, are motile granulocytes. They are identifiable by virtue of the histochemical (acidophilic) and ultrastructural characteristics of their granules. Eosinophils remain in the blood for 6-12 hours before emigration into the extravascular connective tissues, where they remain for at least few days.⁶³ There are believed to be around 200 times more eosinophils located in tissues than in the circulation.⁶⁴ The characteristic eosinophilic granules contain four highly basic proteins: major basic protein (MBP) (granule core), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN) and eosinophil peroxidase (EPO). These, together with superoxides and hydrogen peroxide, are believed to be the principal effector substances which kill parasites, bacteria and mycobacteria. Human eosinophils possess receptors for complement fragments and the Fc portion of IgG, IgA, IgM and IgE. Upon cross-linkage of secretory IgA, eosinophils become less mobile and secrete ECP and EPO, which may explain their high numbers at mucosal surfaces where secretory IgA is found. Eosinophils also generate lipid mediators *de novo*, particularly leukotriene B4 and C4, lipoxins and platelet aggregating factor.⁶⁵ They also release histaminase and aryl sulphatase which inactivate mast cell products such as histamine and slow-reacting substance of anaphylaxis (SRS-A). This aids in dampening down inflammatory responses and reducing the degree of granulocyte migration to sites of inflammation.⁶⁶

Eosinophils in the Uveal Tract

To the author's knowledge there have been no studies specifically describing the distribution or presence of eosinophils in the normal uveal tract. In some species, e.g. guinea pigs, they constitute a large component of the choroidal infiltrate in EAU.⁶²

In conclusion, the uveal tract of the eye, far from being a unique environment, is, like most vascular connective tissues, rich in a variety of immune cells which normally spend a portion of their life cycle outside the vasculature and lymphoid tissues. An understanding of the distribution, location and

function of such cells in the normal eye and in inflammatory and immune-mediated diseases is crucial to unravelling the immunopathology of the various forms of uveitis and in planning strategies of intervention and immune modulation for diseases affecting the uvea.

The author wishes to thank research staff and students some of whose work is represented in this review, namely Julie Crewe, Sue Morrison, Tanya Butler and Raymond Steptoe.

Key words: Macrophage, Dendritic cell, Mast cell, Lymphocyte, Eosinophil, Iris, Ciliary body, Choroid.

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