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Intraocular Health and the many faces of Inflammation

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Abstract

Dogma for reasons of immune privilege including *sequestration* (sic) of ocular antigen, lack of lymphatic and immune competent cells in the vital tissues of the eye has long evaporated. Maintaining tissue and cellular health to preserve vision requires active immune responses to prevent damage and respond to danger. *A priori* the eye must contain immune competent cells, undergo immune surveillance to ensure homeostasis as well as an ability to promote inflammation. By interrogating immune responses in non-infectious uveitis and compare with age-related macular degeneration (AMD), new concepts of intraocular immune health emerge. The role of macrophage polarisation in the two disorders is a tractable start. TNF–alpha regulation of macrophage responses in uveitis plays a pivotal role, supported via experimental evidence and validated by recent trial data. Contrast this with the slow; insidious degeneration in atrophic AMD or in neovasular AMD, with the compelling genetic association with innate immunity and complement, highlights an ability to attenuate pathogenic immune responses and despite known inflammasome activation. Yolk sac derived microglia maintain tissue immune health. The result of immune cell activation is environmentally dependent, for example on retinal cell bioenergetics status, autophagy and oxidative stress, alterations in which skew interaction between macrophages and retinal pigment epithelium (RPE). For example, dead RPE eliciting macrophage VEGF secretion but exogenous IL-4 liberates an anti-angiogenic macrophage sFLT-1 response. Impaired autophagy or oxidative stress drives inflammasome activation, increases cytotoxicity and accentuation of neovascular responses, yet exogenous inflammasome derived cytokines such as IL-18 and IL-33 attenuate responses.

Introduction

Keeping the peace.

To maintain the viability of both a clear media and a functional neuroretina and vision requires an ability to maintain cellular health under stress and to various extents require an orchestration of an immune response (1-3).

The eye and in particular the retina and the choroid, is furnished with a contiguous network of myeloid cells – namely microglia and macrophages (4, 5). These cells alongside the ascribed non-immune cells (such as RPE and Muller Glia in the retina) establish an immune tissue tone that maintains homeostasis. Myeloid cell activation in the retina is regulated by a *tonic break* functioning to prevent overt activation but maintain a scavenger function for daily housekeeping. The argument as to whether microglia contribute to onset of ocular inflammation (6)is balanced against their homeostatic role in maintaining a healthy retina, and where data is supportive (2). Microglia from a network throughout the retina, and display regulatory phenotypes and functions consistent with other tissue-resident macrophages elsewhere in the body (4). Furthermore, although we are still awaiting the advent of live *in vivo* imaging of immune cell trafficking to understand the dynamics and kinetics of cell trafficking and/or turnover, the results experimentally demonstrate a persistence of macrophages throughout disease (7, 8) and where myeloid, macrophage, and T cell accumulations are noted in later disease (9). The activity and extent of immune surveillance and cell traffic is yet to be determined in man.

So one paradigm is that the retina possesses an *activation threshold* to subvert damage. One example of a *tonic break* that supports homeostasis is the regulation of macrophage activation via the cognate-receptor interplay of CD200R and its ligand, CD200. CD200 is ubiquitously expressed on macrophages, neurons and endothelium (10-13) and perturbing their interaction results in an aggressive disease phenotype (14, 15). If we attempt to reconstitute and de-activate macrophage function (by direct ligation of CD200R with anti-CD200R monoclonal antibodies or by a CD200Fc), attenuation of retinal or CNS inflammation can be achieved (14, 16) as well as regulation of other myeloid cells including mast cells in the lung (17-20).

How do we keep the peace? A premise lies that there is continual immunosurveillance, akin to CNS, and that alongside the immune cell inhabitants of the retina and choroid, together achieve constant sensing to respond to danger signals. In support, we observe that tissue damage in experimental retinal inflammation is significantly attenuated when macrophages are removed (21, 22)or macrophage/monocyte activation is blocked (16, 23-25). Experimentally, we observe that the tissue is protected when TNF-alpha activity is neutralised (and indeed show the requisite requirement of TNF for macrophage activation in ocular inflammation (26-28)), or by reprogramming macrophage activation threshold with CD200R treatment. These consistent observations have led to a pipeline for therapeutic opportunities to redress activation thresholds of immune cells.

A tail of two conditions

Understanding Uveitis.

Uveitis is defined as an "orphan disease", yet in 2010 uveitis accounted for 10% of the estimates of 285 million people visually impaired and 39 million blind (29). Non-infectious uveitis comprises a heterogeneous group of disorders diagnosed based on their clinical characteristics and whether associated with systemic disorders (30, 31).

The healthcare burden is significant, where non-infectious uveitis accounts for substantial medical, social and workload costs in the USA and aligns with data that persistent disease gives rise to considerable ocular and systemic morbidity (24, 32-34).

The clinical phenotype of non-infectious intraocular inflammation is replicated in experimental animal models that are driven by immune responses to self-antigen (35). The animal models, such as experimental autoimmune uveoretinitis (EAU) support a role for autoimmunity with clinical-pathological features bearing remarkable similarity to man (7, 8, 36, 37). The currently held notion is that of a $CD4^+$ T helper cell-driven process and supported in man by the association of sympathetic ophthalmia and Vogt–Koyanagi–Harada disease with specific HLA class II alleles as well as the identification of ocular antigen-responsive T cells in both the peripheral blood and eyes of patients (38-40). When T cells are activated they assume different functional phenotypes directed through canonical transcription factors (41, 42) and characterised by the secretion of signature cytokines (43, 44). In EAU, both Th1 and Th17 T helper cells are important inducers of autoimmune disease [(35, 45)]. It is the cytokines (especially IFN-γ produced by Th1 cells) produced by these cells that activate the non-specific mononuclear tissue infiltration (principally macrophages) and recruit neutrophils as seen in EAU (e.g., through IL-17 produced from Th17 cells; (7, 8, 23, 24, 26-28)).

However, some of the uveitic conditions are likely to be driven through both autoinflammatory and autoimmune disease processes. Advances defining the molecular pathology of autoinflammatory conditions have illuminated how many inflammatory diseases are driven by genetic mutations affecting elements of the innate immune system (46). For example, in Blau syndrome, there is a gain-of-function mutations in the NOD2 gene driving nuclear factor κB (NFκB) transcriptional activation (47) and gives rise to early onset inflammatory disease and in the skin there is an abundance of $CD4^+$ T cells, $CD68^+$ macrophages and extensive expression of IFN-γ, IL-17, and IL-6 (48). Uveitic conditions express changes in inflammasome activation, including Behcet's and spondyloarthropathies. Also the complex interplay between changes in innate immunity, autoinflammation and autoimmunity implicates an infectious aetio-pathogenesis. The inflammasome is a multiprotein complex comprising a sensor protein, the adaptor protein ASC (apoptosis-associated speck-like domain containing caspase recruitment domain), and the inflammatory protease caspase-1. The eye has many inflammasome-forming sensors (49), including

NLRP receptor molecules (nucleotide binding domain and leucine-rich repeat containing pyrin domain family). Inflammasome-dependent biological effects may be mediated not only by IL-1b and IL-18, but also by the multifaceted activities of caspase-1. Secondary effects of protecting against inflammasome activation, such as when autophagy is increased is observed and has relevance to degenerative disease or remodeling during persistent inflammatory diseases, such as uveitis (50, 51). The implications of which will be discussed later. It is clear, however that uveitis we observe as a result of autoimmune responses or through activation of cellular pathways linked to autoinflammatory disorders, namely activation of inflammasome, is an appropriate response to the signals received. That is, it is a sequel to an overwhelming adaptive T cell or innate PAMP-derived response to danger signals. This results in further recruitment of immune cells to the target tissue and these cells inflict the subsequent damage we observe clinically. However, control of responses of both innate and adaptive immunity are likely more intertwined. Adaptive responses and T cell polarization rely on both close interplay between intracellular complement regulation and NLRP3 assembly (52).

The knowledge accrued from animal models of uveitis and in particular how to subvert tissue damage, has illuminated pivotal role for many targets. The most successful to date is TNF-alpha (1, 53). Controlling the macrophage response is a principal effect of anti-TNF-a agents. The ability of macrophages to respond to environmental, cytokine, and receptor signals provides adaptability in controlling inflammation and in restoring structure and function (54). Translation will remain challenging (given the plasticity of myeloid cells and how rapidly they adapt) when considering timing of treatment. In EAU there are other compounding influences to consider for therapy and in particular whether such mechanisms exist for translation for AMD therapeutics. For example, complement is activated during disease; whilst arguably not critical to development of inflammation and suppressing or regulating complement diminishes EAU expression (55-57). A convergant mechanism of action is at the level of suppressing macrophage activation. Similarly, chemokine gradient support or perturbation can suppress or exacerbate EAU disease, where the myeloid compartments are being manipulated (58-62).

For targeting TNF-alpha, we now have substantial evidence through randomised clinical trials exhibiting successful outcomes. The Abbvie sponsored VISUAL trials in adults have shown adalimumab (a humanized anti-TNFalpha monoclonal antibody) significantly lowered the risk for uveitic flare or vision loss in patients with non-infectious, intermediate, posterior or panuveitis upon complete prednisone taper in both active (uncontrolled despite 10-60 mg prednisone, VISUAL I) and inactive (corticosteroid-dependent on ≥10 mg prednisone, VISUAL II) uveitis. The enpoints were statistically significant in favour of adamimumab reducing the time to treatment failure (HR= 0.56 (0.40-0.76, P<0.001) for VISUAL I and HR=0.52 (0.37-0.74, P<0.001) for VISUAL II)(63). The safety profile was consistent with the known safety profile across the approved ADA indications and the patient population. In children, the SYCAMORE randomised placebo-controlled trial looking at effectivity and safety of adalimumab therapy in methrotrexate-resistent JIA-Uveitis provides evidence

of efficacy of adalimumab treatment used in addition to methotrexate. The final analysis of the primary outcome of time to treatment failure was showed a positive treatment effect in favour of adalimumab: hazard ratio (HR) 0.27 (95% CI 0.13-0.52); p<0.0001 (64).

Age-related macular degeneration (AMD) and altered immunity

AMD, as the leading cause of central visual loss affects the choriocapillaris, Bruch's membrane and the retinal pigment epithelium, with dysfunction and death of overlying photoreceptors. If we compare patients with ocular inflammatory disorders such as a uveitis that show alterations in the circulating immune system with AMD, we observe similar. Complement and innate immune gene polymorphisms have been clearly implicated in the development of AMD (65-67). While differences in complement regulation between those with the variant and the wild type alleles have been reported as well as the impact of rare variants in the rapidity of disease onset (68), functional immune mechanism remain elusive, particularly with respect to CFH. We have shown that CFH binds mCRP to dampen its proinflammatory activity. CFH from AMD patients carrying the "risk" His402 polymorphism display impaired binding to mCRP, and therefore proinflammatory effects of mCRP remain unrestrained, at least in vitro (69). Whether this translates to disease or not requires validation but even so alone does not account for all the immune related changes we observe in AMD.

It is clear immune dysregulation exists and data continues to further illuminate the original notion (70). Drusen are immunologically active deposits containing oxidative lipids, lipofuscin, complement and other immune activating components that develop as the consequence of RPE stress and altered tissue homeostasis(70, 71). Degenerating RPE is also a major source for drusen components, indicating that age-related changes in RPE may be a causal factor and drive disease progession as we will discuss further(72). For example, cells from eyes with AMD exhibit upregulated expression of immune receptors and molecules (73, 74), including expression of IL-17RC, a receptor for a dimer of IL-17A and IL-17F and activation of NLRP-3 inflammasome that promotes cleavage of pro-IL-1beta and IL-18 (75-77). Furthermore, both macrophages and multinucleated giant cells, mainly associated with vascular channels and breaks in Bruch's membrane are evident (78-83). Macrophage subtype changes have been noted in the eyes of patients with AMD, including a change in the M1/M2 ratio in AMD eyes compared to that in control eyes of the same age (83). With all the data demonstrating immune activation we need to reconcile these findings with the knowledge that the development of AMD is slow. Firstly, given that AMD is insidious, altered immune responses within the tissue likely occur as a result of persistent lifetime oxidative stress and changes to cell health in the retina. In such conditions, a concept of para-inflammation emerges (3, 84), where evidence of activated immunity (complement, antibody deposition, macrophage and microglia activation) serves to protect the tissue and prevent overt inflammation and tissue destruction. Does this demonstrate the success of active immune regulation in the eye? Secondly, the inflection to a more rapid progression (if indeed that occurs) may be co-incident to the heightened inflammasome

activation. The consequence is a switch to a more 'classical' chronic inflammatory responses propagating tissue destruction and angiogenesis and as 'frame-shots' of evidence in man supports (3, 85-87). The cause of change from para-inflammation to chronic inflammation remains unknown. We can however make in roads and unwrap possible mechanisms for AMD by comparing with immune mediated uveitis and the role of innate immunity and in particular macrophages.

The altered faces of Macrophage activation

Persistent 'inflammation', altered immunosurveillance and aberrant healing responses?

Increasing evidence suggests there is persistent dysregulation of immunosurveillance of the retina following the induction of disease (7, 9, 37). If we take the notion that para-inflammation or any evidence of immune responses reflects active immune regulation, then it is possible that following the original insult or danger signal in inflammatory disease the tissue modifies or heightens immunosurveillance. The result may be predicted (not exclusively) to result in: (i) persistence of inflammatory cells and continued immune targeted destruction; (ii) persistent tissue remodelling and thus potential altered function as a result of for example, aberrant wound healing, and (iii) maintained architecture but residual increased numbers of inflammatory cells as a consequence of heightened thresholds (both activation threshold (see above) as well as 'patrolling' cell numbers) to maintain tissue integrity and health.

Talking this further and in support of points (ii) and (iii) above, a principal observation in inflammatory disease such as murine EAU is the persistence of inflammation, implying that the threshold of myeloid activation is not reset. It is in this context that para-inflammation' is operative or as said above, another way of describing this phenomenon are immune responses to protect tissue – heightened immunosurveillance with or without tissue remodelling. In the presence of persistent T cell responses, the tissue remains vulnerable. A constant macrophage infiltrate remains, although in nearly all models the macrophages exhibit an alternative activation phenotype in later stages (as opposed to the early disease classical activation phenotype) and this again supports concept of tissue remodelling. Taken together, a consequence of a chronic immune cell infiltrate is persistent tissue remodelling contemporaneous with macrophage/monocyte activation, of which one hallmark result is angiogenesis. The angiogenic response during persistent tissue immune, cell infiltrate requires an operative CCL2-CCR2 axis, but is also influenced by multifunctional matrix proteins, such as thrombospondin-1 (TSP-1) (9). Subverting the angiogenic response (but without altering the initial inflammation and antigen-specific targeting of tissue) by knocking out matricellular proteins such as TSP-1 results as expected persistent disease (as observed in wild-type mice (88)) but notably results in increased angiogenesis (a detriment to retinal function as observed in neovascular diseases AMD). The results infer that there is matricellular control (e.g.TSP) of macrophage activation in terms of remodelling and angiogenesis

during T cell mediated responses and whilst initial disease severity is not altered with loss of TSP, regulating tissue remodelling, (as determined by extent of angiogenesis) is perturbed.

Macrophage conditioning, angiogenesis and tissue viability.

As introduced above, the function and phenotype of macrophage subtypes is conditioned by signals encountered within the tissue microenvironment. The paradigm of M1 and M2 macrophages has been studied with respect to angiogenesis (89-92). Classical activation generates M1 macrophages, which have pro-inflammatory functions as we have discussed, operative during inflammation in EAU and impart tissue destruction that is effectively neutralized via blocking TNF-alpha activity. Alternatively activated M2 macrophages confer responses related to wound healing, and are capable of generating VEGF and promoting angiogenesis. However, pathological angiogenesis is observed most commonly in the presence of M2 macrophages (93). The role of macrophages in driving a VEGF-dependent angiogenic response remains debatable. Data supported by recent evidence from studies using the laser-induced CNV model show that early initiation of choroidal angiogenesis is dependent upon macrophage phagocytosis of damaged RPE components. This in turn elicits an Arg-1$^+$, VEGF$^+$ M2 phenotype that is only seen early in the genesis of the angiogenic bed (94). Contrary, in an attempt to understand VEGF and upstream players using the mouse CNV models with various conditional inactivation of Vegfa, Hif1a, or Epas1, macrophages were not the source of VEGF (95).

But yet on the other hand, macrophage subtypes are plastic, and functional outcomes may not be straightforward. For example, IFN-γ and TLR4 ligation (with LPS) can generate VEGF$^+$ M1 macrophages, but PGE_2 remains a potent stimulus for the generation VEGF$^+$ M2 macrophages as well, *in vitro*. So when macrophages are alternatively activated via IL-4 they result in a sFlt-1-secreting M2 cell and this is seen in both mouse and man (96). In man, macrophages associated with CNV or in specimens of AMD retina that are assessed using immunohistochemistry confirm the nature of VEGF-expressing CD68$^+$ cells (97). Finally, perturbing macrophage function can attenuate neovascularization in experimental models (98).

What causes an inflection in immune responses that may drive conversion from early AMD to late stage of AMD? One switch as we discussed above is that of the change from a homeostatic para-inflammatory response, which may become increasingly operative with age, to an unchecked persistent low grade inflammatory response resulting in loss of RPE and/or pathological angiogenesis(3). We have recently demonstrated that RPE destruction in the model of laser-induced CNV polarizes infiltrating myeloid cells toward a pro-angiogenic phenotype. The latter can be perturbed through the augmentation of inhibitory CD200R signaling or through the administration of Th2 cytokines to either tonically suppress macrophage activation or drive anti-angiogenic

function respectively(94, 96, 98). Thus our data and those from others(99, 100) support the concept that interplay between macrophage and RPE within the subretinal space likely contributes to disease progression.

Autophagy is the central cellular housekeeping function that facilitates the disposal of long-lived, defective organelles (eg. mitochondria) and protein aggregates through "self-eating" via autophagosomes and lysosomes(101). Increasing evidence indicates impaired autophagy is associated with age-related degenerative disorders, highlighted by studies in which pharmacological or genetic manipulation of autophagy pathways can induce cellular and tissue degeneration *in vitro* and *in vivo*(102-104). In the eye, autophagy is highly active in RPE and photoreceptor cells, and impaired autophagy in RPE leads to RPE transcytosis and exocytosis and early signs of RPE degeneration(104-106). Impaired autophagy generates dysfunctional RPE that modulates macrophage responses, driving further cell death and promotes angiogenesis in the eye(107). There is therefore a growing body of evidence to support interaction between RPE degeneration and subsequent macrophage activation that may simulate earlier events occurring in AMD leading to progression of disease and neovascularisation.

Moreover, the activation of the NLRP3 inflammasome (that is almost certainly a protective response initially), provides a rapid response to danger in order to preserve tissue function and integrity. The corollary is that inflammasome activation may also cause tissue damage. NLRP3-inflammasome can 'sense' drusen isolated from human AMD donor eyes that liberates active IL-1β and Interleukin (IL)-18 production. IL-18 however has been shown to protect against the development of choroidal neovascularization (108). Another family member, and in a similar vain is IL-33. IL-33 is unique as it is active without caspase-1 cleavage and does not require inflammasome activation for secretion and bioactivity (109). IL-33 triggers an inflammatory response, recruiting monocytes, contributing to photoreceptor loss in a photoxic retinal model of degeneration (110) and infers a pathogenic role of endogenous IL-33 and an *a priori* for neutralizing IL-33 to reduce myeloid cell accumulation as a possible intervention. However, as with IL-18, and in consideration of the emerging role of IL-33 in inflammatory disorders (111, 112) and in the absence of progressive cell death, IL-33 regulates tissue responses. IL-33 subverts angiogenesis, via direct inhibition of fibroblasts and endothelial cells that express high levels of ST2, and recombinant IL-33 protects against CNV development (113).

Ageing, Senescence and bioenergetic sources

O'Neill highlighted the prominence to the 'Warburg effect' in context to immune responses and the role in the pathogenesis of immune mediated disorders, such as diabetes and atherosclerosis (114-116). Extrapolating from Warburg's original observations that tumour cells undergo a bioenergetic switch (permissive for survival and proliferation), to aerobic glycolysis, we now appreciate that such bioenergetic switch occurs in the ageing and early AMD RPE. The Warburg effect rapidly provides ATP and enhances metabolic pathways

to support immune cell function. With age, there is increasing strain on mitochondrial function, autophagy and mitophagy to maintain cellular and tissue health. A response for the good is to divert energy sources – Warburg effect - to maintain function against the stress, allow an ability to proliferate if required, and respond to the oxygen drain by upregulating transcription factor HIF-1α. However, with that also comes a price; inflammasome activation.

Any cell with mitotic potential may undergo senescence (often associated with ageing), resulting in cell cycle arrest but also a cell with a high metabolic demand and with respect to inflammation a distinct secretory phenotype that promotes inflammation (117). The senescent associated secretory phenotype provokes further immune mediated deleterious effects on the local tissue microenvironment. Senescence also evokes an anti-Warburg effect. All told, senescence may be a drive of immune-mediated degenerative disorders, such as AMD.

In degenerative disease the Warburg effect may be beneficial. The upregulation of the inflammasome may act to protect cells and subvert angiogenesis as shown with IL-18 and IL-33. Such a response, and where we observe inflammation is one of the constituents of the para-inflammatory response we discussed earlier. Parainflammation works to enable and reset immune thresholds to protect the tissue.

The Immune response work group at the annual Beckman Initiative for Macular Research conference concluded in 2014 with a provocation and notion that AMD is an inflammatory disease, more permissive with age due to an interaction of an aged systemic immune system with an aged or senescent eye. Immune activation that protects and any dysegulation that promotes damage is orchestrated through a playlist of many of the same players, and not exhaustively, altered intracellular lipid handling, Warburg effect, inflammasome activation and macrophage activation. However, as discussed here, the outcome is dependent on other interactions and external forces, such as the many associations we appreciate with complement protein polymorphisms that will dictate altered cell responses as well as the insidious and persistent influence of oxidative stress and senescence.

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