Paravascular Pathways in the Eye: Is There an ‘Ocular Glymphatic System’?

In 2012, Iliff and colleagues\(^1\) proposed the existence of a paravascular transport system, which they termed the ‘glymphatic system’. We propose that a similar system is present in the eye, the ‘Ocular Glymphatic System’, and that this may be a key player in retinal diseases ranging from AMD to retinal vasculitis.

Healthy brain function is dependent on the regulation of the volume and composition of the fluids that support it, namely cerebrospinal fluid (CSF) and interstitial fluid (ISF) of the brain parenchyma.\(^2\) Although a number of investigators had invoked the possibility that transport into and out of brain parenchyma might occur partly via perivascular spaces,\(^2\) it was the paper by Iliff et al.\(^1\) in 2012 who first proposed a complete paravascular transport system, which they termed the ‘glymphatic system.’ This was based on in vivo two-photon and ex vivo fluorescence imaging in a mouse model using intracisternally infused CSF tracers. Their findings suggested a brain-wide paravascular system in which CSF enters the brain along para-arterial channels to exchange with ISF, and ISF is cleared from the brain along paravenous pathways, from which it travels to the lymphatic vessels of the neck and eventually to the systemic circulation. They argued that this system was critical to the efficient clearance of solutes and waste from the brain. Subsequently, they used dynamic intrathecal gadolinium-enhanced magnetic resonance imaging (MRI) in rats to demonstrate key areas of flow and to map the proposed glymphatic system in a time-sequenced three-dimensional (3D) manner.\(^3\) The same group have since gone on to provide data on scenarios where the glymphatic system appears to be deranged and the possible implications for human disease. A key example is that age adversely affects clearance of interstitial solutes such as amyloid-\(\beta\); they speculate that the failure to clear misfolded proteins may be a factor in the pathogenesis of Alzheimer's disease.\(^4\) The investigators have undertaken a programme of work to develop their techniques for use in humans\(^5;\) however, this is extremely challenging and all published findings so far are based on animal studies. The glymphatic system in humans remains a hypothesis only.

But maybe ophthalmologists can visualize it, and indeed have been recording signs of its existence for years? We propose that the glymphatic system, or at least a paravascular system capable of sending transport of substances and probably cells in a manner that is independent of retinal intravascular flow, does indeed exist in the eye and may be relevant to a large number of ocular diseases. Our hypothesis was originally based on biological extrapolation, but the greater resolution provided by adaptive optics (AO) devices is now providing more substantial evidence for this theory. The excellent work by Paques and colleagues using the rtx1 AO camera (ImagEye, Orsay, France) has provided, for the first time, ultrahigh resolution images of the retinal vasculature in patients with retinal vasculitis.\(^6\) In the original paper from this group, Errera et al.\(^6\) demonstrate images of patients with retinal vasculitis in the context of Lyme disease (\(n = 2\)) and presumed ocular TB (\(n = 1\)). In all three cases, it is striking how the perivascular infiltrate (seen as high signal or ‘loss of transparency’) arises approximately 30 to 50 \(\mu\)m from the lumen of the vessel, revealing a potential space (of homogeneous medium signal) external to the vessel wall. The images also demonstrate that after clinical resolution of the disease this potential space greatly reduces and even disappears. Even more dramatic is their report presented at this year’s ARVO Annual Congress in which they provided further high resolution images of additional patients with retinal vasculitis (Errera M-H, et al. IOVS 2015;56:ARVO E-Abstract 5303). Images of active disease were again consistent in showing a visualisable paravascular space. Of particular interest was one case in which the authors noted a ‘paravascular band’ running parallel to the vessel wall, containing within it a number of ‘white dots.’ It is fascinating to speculate as to whether these are immune cells and whether we are seeing, for the first time in human, their migration through (or along) the retinal paravascular space. The images contained in both reports are generally of vessels with only mild levels of inflammation. It would be interesting to undertake AO images of more severely affected vessels, and to know whether the striking delineated patterns seen in forms of retinal vasculitis such as frosted branch angiitis reflects the distribution of infiltrate and exudation within the glymphatic system.

If further work confirms the presence of an ocular glymphatic system, the implications would be wide-ranging. We know from the work of Iliff and colleagues that the brain glymphatic system is delicate and can be adversely affected by a number of insults including age,\(^4\) trauma,\(^7\) sleep deprivation, and other factors. Extrapolating to the eye, it is possible that the reduced clearance of waste products by an ageing glymphatic system is contributory to the pathogenesis of AMD. Similarly injury to the glymphatic system from blunt ocular trauma might also affect the recovery of retinal manifestations, notably retinae commotio. And what if it is the glymphatic system that explains (or at least contributes to) the striking vulnerability of some eyes to modest elevations of intraocular pressure, resulting in glaucomatous optic neuropathy? Of course such a paravascular system would also be vulnerable to the passage of micro-organisms, tumor cells, and immune cells with potential implications for our understanding of the progression of infection, cancer, and immune responses within the eye.

In summary, we hypothesize the existence of a retinal paravascular transport system analogous to the described glymphatic system of the brain. Evidence from AO studies of patients with retinal vasculitis appears supportive of this hypothesis. The elucidation of such a transport system by emerging imaging technologies is an exciting possibility with important ramifications for many sight-threatening retinal diseases.

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