Review

Eyeballing cholesterol efflux and macrophage function in disease pathogenesis

Abdoulaye Sene[1] and Rajendra S. Apte[1,2]

[1] Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, 660 South Euclid Avenue, Saint Louis, Missouri 63110, USA
[2] Department of Developmental Biology, Washington University School of Medicine, 660 South Euclid Avenue, Saint Louis, Missouri 63110, USA

Disorders of lipid metabolism are strongly associated with cardiovascular disease. Recently, there has been significant focus on how tissues process lipid deposits. Impaired cholesterol efflux has been shown to be crucial in mediating lipid deposition in atherosclerosis. The inability of macrophages to effectively efflux cholesterol from tissues initiates inflammation, plaque neovascularization, and subsequent rupture. Recent studies suggest that inability to effectively efflux cholesterol from tissues may have global implications far beyond atherosclerosis, extending to the pathophysiology of unrelated diseases. We examine the unifying mechanisms by which impaired cholesterol efflux facilitates tissue-specific inflammation and disease progression in age-related macular degeneration (AMD), a blinding eye disease, and in atherosclerosis, a disease associated with significant cardiovascular morbidity.

AMD lipid deposition and innate immunity

AMD (see Glossary) is the leading cause of blindness in individuals over 50 years of age in the industrialized world [1]. Accumulation of lipid-rich deposits termed drusen underneath the retina is a hallmark of AMD, and disease progression is often initially characterized by an increase in drusen number and size. Advanced AMD is characterized by photoreceptor loss associated with either atrophic changes in the macula or development of new blood vessels underneath the retina, a process termed choroidal neovascularization (CNV) (Figure 1) [1]. The majority of blindness in AMD is secondary to CNV. Although AMD is a multifactorial disease, and aging is the major risk factor, inflammation is central to the pathological process [2,3]. Numerous genetic analyses including several genome wide association studies (GWAS) have strongly linked innate immunity and several complement pathway components to susceptibility to both the development and severity of AMD [4]. There is emerging evidence showing progressive accumulation of macrophages underneath the retina of AMD patients that correlates with the clinical stage of the disease [5,6], supporting an important role for macrophages in disease pathogenesis in AMD. GWAS studies have also linked lipid metabolism to the pathogenesis of AMD [7,8]. Indeed, accumulation of intracellular cholesterol in macrophages underneath the retina might be crucial for disease pathogenesis because decreased expression of macrophage cholesterol-transporter proteins that results in impaired cholesterol efflux also promotes CNV.

Here we critically assess new findings that mechanistically connect impaired cholesterol efflux and tissue-specific inflammation, both hallmarks of atherosclerosis, to age-related macular degeneration. We suggest that pharmacotherapeutic, genetic, or RNA interference approaches to modify cholesterol metabolic pathways warrant future investigation as potential beneficial therapies for both AMD and atherosclerosis.

Glossary

Age-related macular degeneration (AMD): a medical condition and major cause of blindness and visual impairment in older adults. It results in a loss of vision due to damage to the retina. AMD may occur in 'dry' and 'wet' forms. Dry AMD is characterized by accumulation of drusen between the retina and the choroid. The more severe wet form is characterized by abnormal blood vessel growth (choroidal neovascularization).
ATP-binding cassette (ABC) transporters: members of a superfamily of transmembrane proteins that utilize ATP hydrolysis to transport a wide variety of substrates such as lipids, sterols, and drugs across membranes. ABCA1 and ABCG1 are involved in macrophage cholesterol and phospholipid transport, and may also regulate cellular lipid homeostasis in other cell types.
Cholesteryl ester transfer protein (CETP): a plasma protein that helps the transport of cholesteryl esters and triglycerides between lipoprotein molecules.
Choroidal neovascularization (CNV): the creation of new blood vessels in the choroid layer of the eye often seen in AMD.
Drusen: tiny yellow or white deposits made up of lipids in a layer of the retina termed Bruchs membrane. They are considered to be an early sign of age-related macular degeneration.
Hepatic lipase (LIPC): a lipolytic enzyme that promotes the hydrolysis of triglycerides and phospholipids in lipoproteins. This enzyme has a dual function because its binding to lipoproteins also facilitates their uptake and metabolism through cell surface receptors.
Liver X receptors (LXRs): members of the nuclear receptor superfamily of transcription factors. LXRs regulate cholesterol, fatty acid, and glucose homeostasis. There are two LXR isoforms, LXRα and LXRβ, both of which bind to and are activated by endogenous oxysterol ligands.

Corresponding author: Apte, R.S. (apte@vision.wustl.edu).
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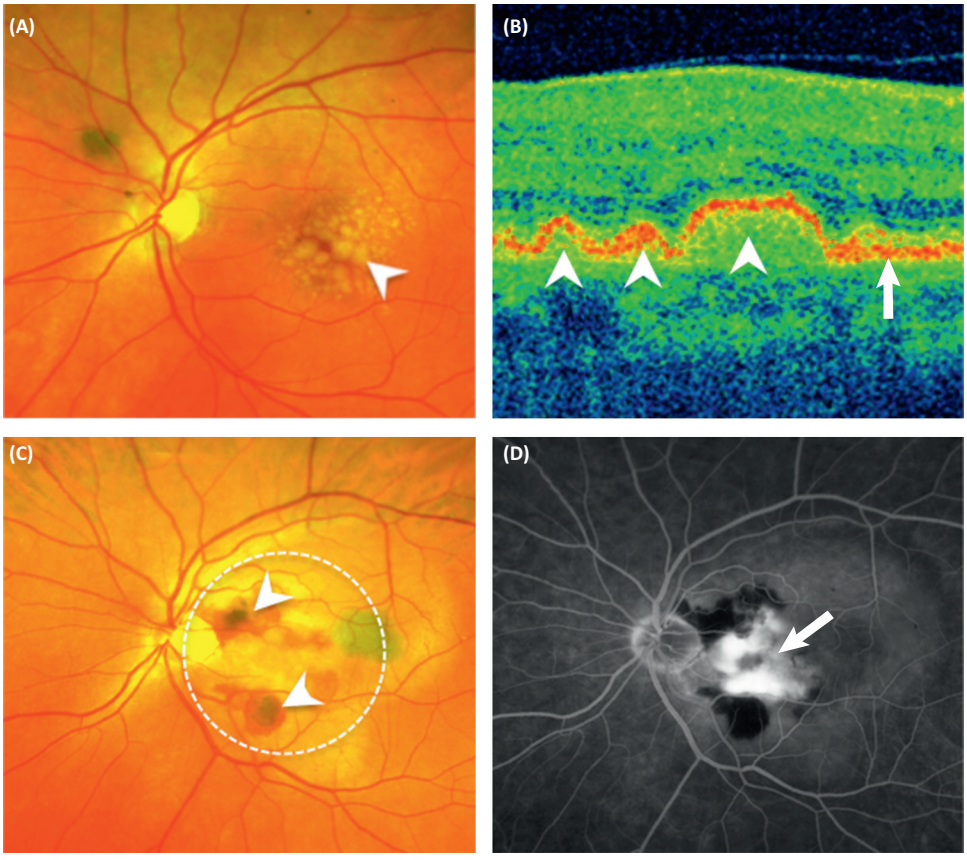

Figure 1. Clinical features of age-related macular degeneration (AMD). **(A)** Fundus photograph of the retina of a patient with dry AMD demonstrating large lipid-laden drusen (arrowhead) underneath the retina. **(B)** Corresponding optical coherent tomography (OCT) of the central retina (macula) confirming the presence of multiple drusen (arrowheads) underneath the retinal pigment epithelium layer (RPE; arrowed). **(C)** Fundus photograph of a patient with the wet form of AMD illustrating subretinal hemorrhage and fluid (arrowhead) secondary to choroidal neovascularization (CNV, dotted circle). **(D)** A fluorescein angiogram demonstrates leakage of dye from the CNV (arrow).

Macrophage-mediated inflammation: the mechanistic link

Extensive characterization of existing mouse models that exhibit some of the clinical features of AMD has revealed that defective chemotaxis of macrophages in the eye resulted in accelerated accumulation of drusen-like deposits under the retina [9,10]. Furthermore, in support of the central role of macrophages in the disease process, studies using murine models of injury-induced CNV, that accurately demonstrate pathophysiologic characteristics of neovascular AMD seen in human patients, have clearly established the determinant role of macrophages in the progression of pathological angiogenesis [11–13]. However, their precise contribution to the AMD phenotype was initially unclear; in early studies there was conflicting evidence regarding whether macrophages were involved in promoting or repressing CNV in murine models of AMD. It is now apparent that these results could be attributed to macrophage heterogeneity and the status of their activation and polarization. Indeed, in response to microenvironmental signals, macrophages have been shown to exhibit classic (M1) or alternative (M2) activation characterized by differential cytokine production, receptor expression, and effector function [14,15]. A variety of specific markers have been identified for the different populations of activated macrophages. Proinflammatory M1 macrophages express high levels of TNF-α, IL-12, iNOS, IL-6, IL-1β, PTGS2, CCL2, and MMP9. Conversely, pro-angiogenic M2 macrophages mediate wound healing and are characterized by low M1 signature markers but increased expression of IL-10, CD163, and TGF-β. Previous studies in murine models of AMD demonstrated that the switch of macrophage polarization from M1 to M2, also seen during normal aging, is a key event in CNV progression [11,16]. By contrast, macrophages recruited under the retina at the initial stage of disease exhibit a proinflammatory M1 phenotype [17]. An analysis of the histopathological features of human AMD, with subsequent phenotypic profiling of infiltrated macrophages, also revealed that in the early stages of AMD macrophages are polarized to M1 whereas in later stages they are alternatively M2 activated [5,6] (Figure 2).

The efficacy of macrophages to efflux and remove intracellular cholesterol engulfed from lipid-rich drusen underneath the retina might also be crucial for their ability to regulate pathological angiogenesis. Along these lines, an age-associated decrease in the expression of the cholesterol transporter ABCA1 (ATP binding cassette A1) resulted in impaired cholesterol efflux in macrophages and promoted CNV [18]. Moreover, cholesterol buildup in senescent macrophages polarizes them to a pro-angiogenic and