Progress in Neurobiology 95 (2011) 14–25

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Age related macular degeneration and drusen: Neuroinflammation in the retina

Elisa Buschini [a,b,1,*], Antonio Piras [a,1], Raffaele Nuzzi [b], Alessandro Vercelli [a]

[a] NICO, Neuroscience Institute of the Cavalieri Ottolenghi Foundation, University of Torino, Regione Gonzole 10, Orbassano (TO), Italy
[b] Department of Clinical Pathophysiology, Ophthalmic Section, University of Torino, Via Juvarra 19, 10121 Torino, Italy

ARTICLE INFO

Article history:
Received 1 April 2011
Received in revised form 3 May 2011
Accepted 9 May 2011
Available online 28 June 2011

Keywords:
Aging
Retinal pigmented epithelium
Inflammation
Complement
Microglia
Autophagy

ABSTRACT

Inflammation protects from dangerous stimuli, restoring normal tissue homeostasis. Inflammatory response in the nervous system ("neuroinflammation") has distinct features, which are shared in several diseases. The retina is an immune-privileged site, and the tight balance of immune reaction can be disrupted and lead to age-related macular disease (AMD) and to its peculiar sign, the druse. Excessive activation of inflammatory and immunological cascade with subsequent induction of damage, persistent activation of resident immune cells, accumulation of byproducts that exceeds the normal capacity of clearance giving origin to a chronic local inflammation, alterations in the activation of the complement system, infiltration of macrophages, T-lymphocytes and mast-cells from the bloodstream, participate in the mechanisms which originate the drusen. In addition, aging of the retina and AMD involve also para-inflammation, by which immune cells react to persistent stressful stimuli generating low-grade inflammation, aimed at restoring function and maintaining tissue homeostasis by varying the set point in relation to the new altered conditions. This mechanism is also seen in the normal aging retina, but, in the presence of noxious stimuli as in AMD, it can become chronic and have an adverse outcome. Finally, autophagy may provide new insights to understand AMD pathology, due to its contribution in the removal of defective proteins. Therefore, the AMD retina can represent a valuable model to study neuroinflammation, its mechanisms and therapy in a restricted and controllable environment. Targeting these pathways could represent a new way to treat and prevent both exudative and dry forms of AMD.

Contents

Abbreviations: AMD, age-related macular degeneration; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CEP, carboxyethylpyrrole; CatD, cathepsin D; CNS, central nervous system; Ccl2, chemokine (C–C motif) ligand 2; CCR2, chemokine (C–C motif) receptor 2; CX3CL1, chemokine (C–X3–C motif) ligand 1; CX3CR1, chemokine (C–X3–C motif) receptor 1; CXCR4, chemokine (C–X–C motif) receptor 4; CNV, choroidal neovascularization; CD, cluster of differentiation antigens; CFB, complement factor B; CFD, complement factor D; CFH, complement factor H; CFHR, complement factor H-related; CFI, complement factor I; DAF, decay accelerating factor; DHA, docosahenoic acid; DKO, double knockout; FasL, Fas Ligand; HSP, heat shock protein; HLD-DR, human leukocyte antigen-DR; HD, Huntington's disease; IL, interleukin; LAMP-2, lysosomal-associated membrane protein-2; MHC, major histocompatibility complex; MAC, membrane attack complex; MCP-1, monocyte chemoattractant protein-1; MS, multiple sclerosis; PD, Parkinson's disease; RCA, regulators of complement activation; RPE, retinal pigmented epithelium; SDF-1, stromal cell derived factor 1; SOD1, superoxide dismutase 1; TNF-α, tumor necrosis factor-alpha; TRAIL, tumor necrosis factor-related apoptosis inducing ligand; Y402H, tyrosine → histidine substitution at the amino acid 402 of the CFH protein; VEGF, vascular endothelial growth factor.

* Corresponding author at: NICO – Neuroscience Institute of the Cavalieri Ottolenghi Foundation, Regione Gonzole 10, Orbassano (TO), Italy. Tel.: +39 0116706617; fax: +39 0112367700.
E-mail address: elisa.buschini@tiscali.it (E. Buschini).
[1] These two authors equally contributed to the manuscript.

0301-0082/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.pneurobio.2011.05.011

1. Introduction

1.1. Neuroinflammation

Inflammation is a defensive process which protects from dangerous stimuli, restoring normal tissue homeostasis. Inflammatory response in the nervous system ("neuroinflammation") has its unique features, found in many different neurodegenerative diseases, including multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD) and age-related macular degeneration (AMD). They are all characterized by progressive neuronal dysfunction and loss. Although the triggers are different and disease-specific, such as stroke, hypoxia, genetic factors, infections, neurotoxins, aggregation of abnormal proteins, trauma, and immune-mediated mechanisms, the shared component is a chronic immune process which leads to uncontrolled inflammation resulting in neuronal damage by production of neurotoxic factors (Block and Hong, 2005; Glass et al., 2010).

The central nervous system (CNS) has been for many years considered as a site of "immune privilege", i.e. inert and isolated from the periphery through anatomical barriers. Nowadays, the concept has changed and it has become clear that the CNS has resident immune cells and can be invaded by peripheral ones. According to some authors, therefore, the privilege consists in a different kind of immunomodulation (Carson et al., 2006). In the retina, disruption of these mechanisms has been linked to neuronal degeneration and a growing body of evidence highlights its relevance in the pathogenesis and progression of AMD.

1.2. Age-related macular degeneration (AMD)

AMD is a widespread macular disorder that represents a leading cause of irreversible visual function impairment. Its prevalence increases with aging and, according to some recent studies, it is likely to increase significantly over the next 40 years (Rein et al., 2009). AMD is a multifactorial disease and its pathogenesis remains largely unknown, implying a complex interplay of genetic, environmental, metabolic and functional factors (Nowak, 2006). Recently, a growing body of evidence confirmed that inflammation, immune system and autophagy play a key role in triggering this pathology. This progressive disease can develop in a "wet" and a "dry" forms (Fig. 1). The shared clinical sign, which characterizes both in the early stages, consists in the drusen, pathological extracellular deposits that accumulate between the basal lamina of the retinal pigmented epithelium (RPE) and the inner collagenous layer of the Bruch's membrane (Green, 1999). In the commonest dry form (90% of cases), visual loss is usually gradual, depending on the extent of drusen in the macular area. These lesions often remain asymptomatic for a long time or may evolve, along with the

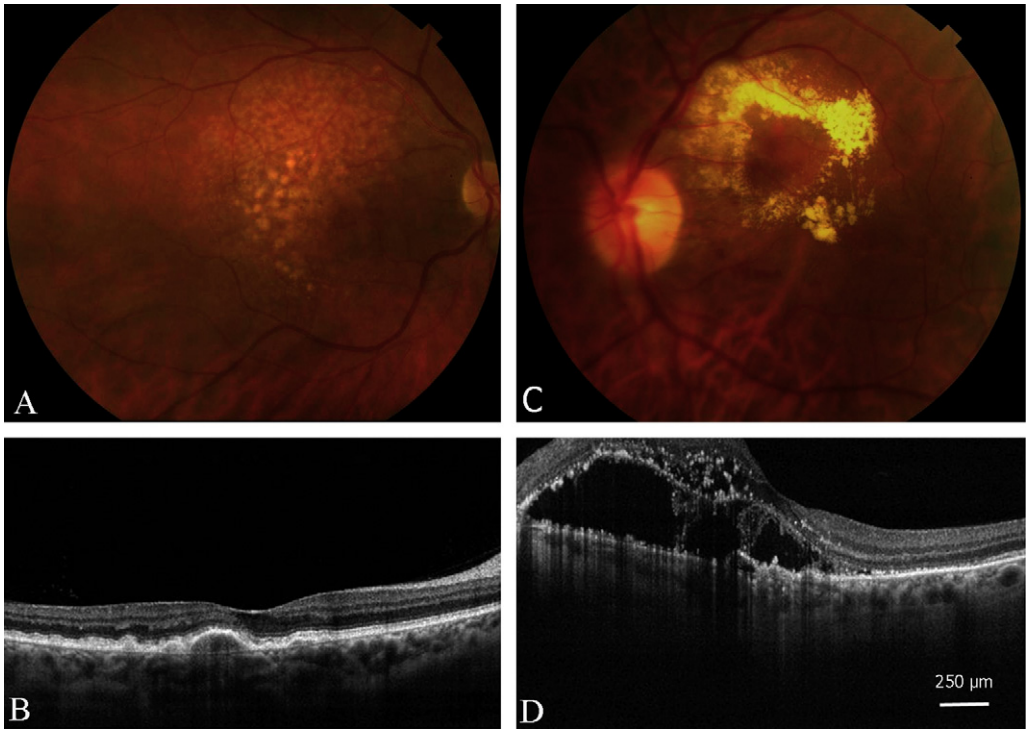

Fig. 1. Morphological features of dry (A and B) and wet (C and D) AMD. (A) Macular soft druse. (B) Optical Coherence Tomography (OCT) imaging showing druse deposits between the RPE and the Bruch's membrane with distortion of the retinal photoreceptor layer. (C) Juxtafoveal CNV surrounded by exudates. (D) Evidence of RPE and photoreceptor degeneration with accumulation of sub/intra-retinal fluid and loss of the normal foveal architecture. Scale bar = 250 μm in C and D.