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Maculoplasty for age-related macular degeneration: Reengineering Bruch's membrane and the human macula

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Abstract

Age-related macular degeneration (AMD) is the leading cause of blindness in the western world. Over the last decade, there have been significant advances in the management of exudative AMD with the introduction of anti-VEGF drugs; however, many patients with exudative AMD continue to lose vision and there are no effective treatments for advanced exudative AMD or geographic atrophy. Initial attempts at macular reconstruction using cellular transplantation have not been effective in reversing vision loss. Herein we discuss the current status of surgical attempts to reconstruct damaged subretinal anatomy in advanced AMD. We reinforce the concept of maculoplasty for advanced AMD, which is defined as reconstruction of macular anatomy in patients with advanced vision loss. Successful maculoplasty is a three-step process that includes replacing or repairing damaged cells (using transplantation, translocation or stimulation of autologous cell proliferation); immune suppression (if allografts are used to replace damaged cells); and reconstruction or replacement of Bruch's membrane (to restore the integrity of the substrate for proper cell attachment).

In the current article we will review the rationale for maculoplasty in advanced AMD, and discuss the results of initial clinical attempts at macular reconstruction. We will then discuss the role of Bruch's membrane damage in limiting transplant survival and visual recovery, and discuss the effects of age-related changes within human Bruch's membrane on the initial attachment and subsequent proliferation of transplanted cells. We will discuss attempts to repair Bruch's membrane by coating with extracellular matrix ligands, anatomic reconstitution of the inner collagen layer, and the effects of Bruch's membrane reconstruction of ultrastuctural anatomy and subsequent cell behavior. Lastly, we will emphasize the importance of continued efforts required for successful maculoplasty.

Contents

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1. Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly population in the Western world (West, 2000). Ninety percent of severe visual loss from AMD is due to the complications of choroidal neovascularization (Smith et al., 2001). Developing new treatments that prevent or reverse vision loss in AMD is the holy grail of ophthalmology, due to the severe visual loss that occurs with this condition and the knowledge that disease prevalence will increase with a shift demographics of western populations to older age groups.

The last 5 years have witnessed significant advances in the management of exudative AMD. Prior to these recent advances, the only proven treatment for subfoveal exudation in AMD was thermal laser photocoagulation, which was advocated to stop the progression of vision loss in this disease (Moisseiev et al., 1995; Tezel et al., 1996). Thermal laser coagulates choroidal new vessels at the cost of destroying the overlying sensory retina and creating an absolute central scotoma (Tezel et al., 1996). In addition half of patients treated with thermal laser for exudative AMD develop persistent or recurrent neovascularization after laser photocoagulation (Moisseiev et al., 1995). The limitations of this approach are clear. Over the last 5 years several drugs have become available for treatment of exudative AMD; the first approved therapy in the USA was photodynamic therapy with verteporfin. This treatment is performed by injecting a photosensitizing dye (verteporfin) intravenously, followed by application of focused light to the area of subretinal neovascularization under direct visualization. Photodynamic therapy reduces the rate of visual loss in patients with subfoveal choroidal neovascularization but does not lead to significant visual improvement in most individuals (Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) Study Group, 1999; Miller et al., 1999). These limitations have led to the investigation of alternative treatment modalities for subfoveal exudative AMD, such as systemic interferon (Fung 1991; Engler et al., 1993; Donahue et al., 1994), brachytherapy (Bergink et al., 1998; Finger et al., 1998; Spaide et al., 1998), subfoveal membranectomy with and without retinal pigment epithelium (RPE) transplantation or translocation (Thomas and Kaplan, 1991; Berger and Kaplan, 1992; Lambert et al., 1992; Thomas et al., 1992; Coscas and Meunier, 1993), macular translocation (Lai et al., 2002), and pharmacological therapy with intravitreal triamcinolone (Penfold et al., 2000) and posterior juxtascleral subTenon's anecortave acetate (D'Amico et al., 2003).

The most significant advances in the management of exudative AMD have come from the development of anti-VEGF drugs, such an the anti-VEGF aptamer pegaptanib (Gragoudas et al., 2004, 2005; Cunningham et al., 2005; Fraunfelder, 2005; Gonzales, 2005; Moshfeghi and Puliafito, 2005; Rakic et al., 2005; Rosenfeld et al., 2005b; Sullivan, 2005; Adamis et al., 2006; D'Amico et al., 2006; Ng et al., 2006; Pieramici et al., 2006; Tobin, 2006), which was the first anti-VEGF compound approved for use for exudative AMD, the anti-VEGF antibody fragment ranibizumab (Gaudreault et al., 2005; Husain et al., 2005; Michels and Rosenfeld, 2005; Kim et al., 2006; Rosenfeld, 2006; Rosenfeld et al., 2006), and the widespread off-label use of intravitreal bevacizumab (Michels et al., 2005; Rosenfeld et al., 2005a; Avery et al., 2006; Bakri et al., 2006; Luke et al., 2006; Manzano et al., 2006; Maturi et al.,