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Gene therapy for diabetic retinopathy: Are we ready to make the leap from bench to bedside?

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ABSTRACT

Diabetic retinopathy (DR), a chronic and progressive complication of diabetes mellitus, is a sight-threatening disease characterized in the early stages by neuronal and vascular dysfunction in the retina, and later by neovascularization that further damages vision. A major contributor to the pathology is excess production of vascular endothelial growth factor (VEGF), a growth factor that induces formation of new blood vessels and increases permeability of existing vessels. Despite the recent availability of effective treatments for the disease, including laser photocoagulation and therapeutic VEGF antibodies, DR remains a significant cause of vision loss worldwide. Existing anti-VEGF agents, though generally effective, are limited by their short therapeutic half-lives, necessitating frequent intravitreal injections and the risk of attendant adverse events. Management of DR with gene therapies has been proposed for several years, and pre-clinical studies have yielded enticing findings. Gene therapy holds several advantages over conventional treatments for DR, such as a longer duration of therapeutic effect, simpler administration, the ability to intervene at an earlier stage of the disease, and potentially fewer side-effects. In this review, we summarize the current understanding of the pathophysiology of DR and provide an overview of research into DR gene therapies. We also examine current barriers to the clinical application of gene therapy for DR and evaluate future prospects for this approach.

Contents

Abbreviations: AAV, adeno-associated virus; AGEs, accumulation of advanced glycation end products; AAV2, AAV serotype 2; AMD, age-related macular degeneration; BDNF, brain-derived neurotrophic factor; CRISPR, clustered regularly interspaced short palindromic repeats; Cas9, CRISPR associated protein 9; DCCT, Diabetes Control and Complications Trial; DD, destabilizing domains; DR, diabetic retinopathy; DME, diabetic macular edema; EDIC, Epidemiology of Diabetes Interventions and Complications; GWAS, Genome-wide association studies; HIF, hypoxia-inducible factor; IL, interleukin; ICAM-1, intercellular cell adhesion molecule-1; LCA2, Leber congenital amaurosis type 2; miRNA, microRNA; MMP, matrix metallopeptidase; MnSOD, manganese superoxide dismutase; NPDR, non-proliferative diabetic retinopathy; NF-κB, nuclear factor kappa B; Nox, NADPH oxidase; OIR, oxygen-induced retinopathy; PDR, proliferative diabetic retinopathy; PEDF, pigment epithelium-derived factor; ROS, reactive oxygen species; scAAV, self-complementary AAV; SNPs, single nucleotide polymorphisms; sFlt-1, soluble fms-like tyrosine kinase-1; siRNA, small interfering RNA; STZ, streptozotocin; VEGF, vascular endothelial growth factor.

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1. Introduction

Gene therapy for systemic disease had a chequered beginning about two decades ago (Collins & Thrasher, 2015). Although progress in gene therapies was subsequently halted for some time, recent approaches to tackling gene correction in the limited and somewhat immunoprivileged environment of the eye has rekindled interest in development of new therapeutic approaches. Here we discuss these new developments in promising gene therapies, particularly as it might apply to the coming epidemic of diabetic eye disease. Current therapeutic approaches to diabetic retinopathy (DR) leave a lot to be desired and are probably economically and ethically unsustainable.

1.1. Overview and epidemiology of diabetic retinopathy

DR, a common complication of diabetes mellitus, is one of the leading causes of blindness among working-age and elderly populations (Wong, Cheung, Larsen, Sharma, & Simo, 2016). Almost all of those with type I diabetes and more than 60% of those with type II diabetes develop some degree of DR during the first 20 years of elevated blood glucose (Fong et al., 2004).

The classification and grading of DR is based on a constellation of retinal vascular changes observed (Table 1) (Wilkinson et al., 2003). DR can be categorized as either non-proliferative (NPDR) or proliferative (PDR) based on the absence or presence of neovascularization, respectively. The earlier stage, NPDR, can be further subdivided into stages with varying degrees of severity, commonly referred to a mild, moderate and severe NPDR. Diabetic macular edema (DME) results from retinal vascular leakage in the macula, and is the most common cause of diabetes-related vision loss. It is manifest as blurring of central vision and is detected as retinal thickening, with or without the intraretinal accumulation of extravasated proteins and lipids (known clinically as hard exudates). DME can occur at any stage of DR: diagnosis and monitoring has been greatly advanced by the development of optical coherence tomography, a rapid, non-invasive imaging modality now widely regarded as the reference standard for assessment of DME (Virgili et al., 2015).

DR is an important cause of blindness and moderate to severe visual impairment, accounting for 2.6% all cases of blindness worldwide (Bourne et al., 2013). The estimated global prevalence of PDR and DME is 17 and 21 million, respectively. The presence of at least one of these forms of the disease is referred to as vision-threatening DR (Yau et al., 2012). Globally, the prevalence of diabetes is projected to rise from an estimated 415 million in 2015 to nearly 642 million by 2040 (International Diabetes Federation, 2015). Accordingly, the prevalence of DR is also anticipated to accelerate. By 2050, 16 million people aged 40 years or older are expected to show DR in the United States alone, with 3.4 million suffering vision-threatening DR (Saaddine et al., 2008). The social and economic burdens of vision-threatening DR are enormous (American Diabetes Association, 2013; Murray et al., 2012). In addition to its economic costs, DR has adverse effects on quality of life, substantially affecting the social, emotional, and physical well-being of patients (Fenwick et al., 2011, 2012). Intensive control of both hyperglycemia and hypertension is the most effective means of preventing DR, and can significantly reduce the risk of progression of established retinopathy (Au, Tang, Rong, Chen, & Yam, 2015; Chowdhury, Hopkins, Dodson, & Vafidis, 2002; Do et al., 2015; The Diabetes Control Complications Trial Research Group, 1993; UK Prospective Diabetes Study (UKPDS) Group, 1998b). A summary of the current classification and treatment of DR is presented in Table 1.

1.2. Proliferative diabetic retinopathy

PDR is a common and potentially devastating cause of vision loss in people with diabetes. It is characterized by the growth (proliferation) of abnormal new retinal blood vessels (neovascularization) that are prone to bleeding (pre-retinal and vitreous hemorrhage) and are commonly associated with the formation of fibrous tissue. Contraction of pre-retinal fibrous tissue applies traction to the retina and can predispose to retinal detachment. In response to multiple stimuli, excess production of vascular endothelial growth factor (VEGF), a growth factor that induces new blood vessel formation and increases permeability of existing vessels, has been identified as a major contributor to DR (Witmer, Vrensen, Van Noorden, & Schlingemann, 2003).

Panretinal laser photocoagulation has been the mainstay of treatment for PDR, and some cases of severe NPDR. Treatment with panretinal laser photocoagulation decreases the risk of severe visual loss by more than 50% at 12 months, as well as reducing the risk of progression of DR and vitreous hemorrhage by 50% (Evans, Michelessi, & Virgili, 2014). However, panretinal laser photocoagulation is a

Table 1
Classification and current management of diabetic retinopathy and diabetic macular edema (adapted from (Wilkinson et al., 2003)).

Condition	Clinical features	Management options
No DR	No abnormalities	None
Non-Proliferative DR (NPDR)		None
Mild NPDR	Microaneurysms only	
Moderate NPDR	More than just microaneurysms, but less than severe NPDR	
Severe NPDR	Any of the following: >20 intraretinal hemorrhages in all 4 quadrants; definite venous beading in 2 + quadrants; prominent intraretinal microvascular abnormalities in 1 + quadrant; and no signs of PDR	Consider: Panretinal laser photocoagulation, anti-VEGF drugs
Proliferative DR (PDR)	One or more of neovascularization, vitreous/pre-retinal hemorrhage	Panretinal laser photocoagulation, anti-VEGF drugs
Diabetic macular edema (DME)		
No DME	No apparent retinal thickening or hard exudates in posterior pole	None
Mild DME	Some retinal thickening or hard exudates in posterior pole but distant from center of macula	Anti-VEGF drugs, focal or grid laser photocoagulation, intraocular corticosteroids
Moderate DME	Retinal thickening or hard exudates approaching but not involving the center of the macula	
Severe DME	Retinal thickening or hard exudates involving the center of the macula	

DME: diabetic macular edema; DR: diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; VEGF: vascular endothelial growth factor.