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Proteomic Study of Aqueous Humor in Neovascular Glaucoma after Anti-VEGF Therapy

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Abstract

Proteomics is a large-scale study of proteins, which affects our understanding of genetic function to a large extent since we usher in genomic period. The most important breakthrough in proteomics is generally acknowledged as the identification of proteins via mass spectrometry, which excels over simple protein display supported by traditional technology in both accuracy and efficiency. Recently, mass spectrometry has been utilized to analyze differentially expressed proteins between pathological state and normal individual. Hence, changes of aqueous humor proteomics in neovascular glaucoma (NVG) patients before and after anti-VEGF therapy was briefly reviewed.

Keywords: Proteome; Aqueous humor; Neovascular glaucoma; Vascular endothelial growth factor receptor; Anti-VEGF

Introduction

Aqueous Humor (AH) is predominantly secreted by non-pigmented epithelial cells of ciliary and contributive to maintenance of stable intraocular pressure and constant micro-environment. Proteome analysis of AH is essential to overall comprehension of its physiological and pathophysiological functions. To date, 825 (43.7%) proteins are in correspondence with plasma proteome in human AH proteome data (1,888 in total) [1]. Proteomic analysis has been applied for ophthalmic disease such as Adav et al. Mass spectrometric technique was adopted to analyze AH of Primary Open Angle Glaucoma (POAG) and respective controls. Significant changes in proteins of the complement system was confirmed, which was related to pathogenesis of POAG, including changes in complement cascade, astrocyte activation, neurodegeneration and apoptosis [2].

NVG, as secondary glaucoma, is generally secondary to Diabetic Retinopathy (DR), ischemic Retinal Vein Occlusion (RVO) and ocular ischemic syndrome. Vascular Endothelial Growth Factor (VEGF) is an important factor of angiogenesis which could accelerate endothelial growth accompanied with higher vascular permeability. Intravitreal injection of anti-VEGF drugs is widely used in treatment of Age-related Macular Degeneration (AMD), Diabetic Macular Edema (DME), Proliferative Diabetic Retinopathy (PDR) and Retinal Vessel Occlusion (RVO) [3]. Accordingly, we briefly reviewed changes of aqueous humor proteomics in NVG patients before and after anti-VEGF therapy.

VEGFR-1 (Vascular Endothelial Growth Factor Receptor 1)

Proteomic study and differential AH proteomic analysis of aqueous humor was conducted by Yu et al. in NVG patients before and after intravitreal injection of anti-VEGF drugs in NVG treatment, which revealed that AH proteome is reliable to reflect pathophysiological changes of drug treatment. Angiogenesis and thrombus coagulation progression are deeply involved in NVG treatment. The abovementioned results indicated that there were significant interactions among 26 up-regulated DEPs (differential expression proteins), and most of which, such as FLT1 (Vascular endothelial growth factor receptor 1, VEGFR-1), IGFBP3 (Insulin-like growth factor-binding protein 3), PTPRZ1 (Receptor-type tyrosine-protein phosphatase zeta), FN1 (Fibronectin) and KNG1 (Kininogen-1), were involved in angiogenesis. VEGFR-1, as cell-surface receptor for VEGFA, VEGFB, and PGF, is potent to make VEGF (the key target in NVG treatment) less accessible for VEGFR-2 thus engaging in “negative role” during vasculogenesis [1]. Expression of VEGFR-1 was increased in VH (Vitreous Humor) in PDR patients after intravitreal injection of anti-VEGF drugs [4]. Soluble VEGFR-1 (sVEGFR-1) concentration in subjects with active PDR was significantly lower than subjects with quiescent PDR. sVEGFR-1 chimeric protein is contributive to suppress retinal neovascularization in vivo [5]. In addition, according to study by Bainbridge et al., adenovirus-mediated expression of sVEGFR-1 is reported to inhibit neovascularization in oxygen-induced retinopathy and prevent progression of diabetic retinopathy in vivo [6]. High concentrations of sVEGFR-1 in vitreous fluid is likely to decrease risk of intraocular angiogenesis. Conversely, low level of sVEGFR-1 in vitreous fluid is likely to increase risk of developing ocular neovascularization [5]. VEGFR1 is a promising novel cell therapy for treatment of angiogenic ocular diseases in the long term.

Fibronectin

Fibronectin (FN1), an important constituent of the vertebrate extracellular matrix (ECM), is widely distributed in choroid and retinal pigment epithelium (RPE). Fibronectin is a key component in basement membrane of retinal vessels. Animal models of diabetic retinopathy (DR) and samples from diabetic patients indicated increased fibronectin staining in retinal micro-vessels and increased fibronectin expression measured by mRNA level [7]. Intravitreal injection of antisense oligonucleotides containing fibronectin, collagen type IV and laminin in diabetic rats is conducive to reduce vascular leakage induced by hyperglycemia [8]. Fibronectin has been shown to engage in "dual role" during angiogenesis, which was known as hallmark of PDR. First, as a component of vascular basement membrane, fibronectin is important to constructing architecture of new vessel. In addition, binding domain of fibronectin has been verified to interact with VEGF, the key modulator of neovascularization and currently the predominant therapeutic target in PDR and neovascular AMD [7]. Intravitreal injection of fibronectin siRNA in diabetic rats was believed to impede thickening of basement membrane, which was usually associated with DR as well as other markers of vascular compromise [9]. In view of discovery by Wei et al., Fibronectin was significantly greater in intravitreal anti-VEGF injection (IVI) group than control group via proteomic analysis of VH samples in PDR patients. [4]. Fibronectin was elevated in AH samples of NVG patients after IVI. FN1 was confirmed as active participant during angiogenesis and coagulation cascades pathway according to constructed PPI (protein-protein interaction) network [1]. Based upon accumulated studies, IVI is acknowledged to increase degree of fibrosis in patients with proliferative vitreoretinopathy or exudative age-related macular degeneration, thereby reducing vision. In correspondence with recent report, fibrin-fibronectin complex is the main factor that directly improves progression of fibrosis, while CTGF (connective tissue growth factor) elevates tissue fibrosis by enhancing affinity of fibronectin to fibrin under pathologic conditions [10]. Fibrin– fibronectin complex formation is a molecular mechanism underlying development of TRD (tractional retinal detachment) following IVI. This is conducive to explain why patients diagnosed with preexisting TRD are more likely to develop severe TRD after IVI.

F13 B (Coagulation Factor XIII B)

FXIII is a transglutaminase (TG) that circulates in tetrameric form (FXIII-A2B2), consisted of two A subunits (FXIII-A) and two B subunits (FXIII-B). Coagulation factor XIII is essential for blood coagulation and fibrinolysis. FXIII-B is a carrier protein and essential for stabilization of FXIII-A, which accelerates cross-linking of fibrin by accelerating formation of ternary complex between FXIII proenzyme, pre-matrix fibrinogen and activated thrombin. FXIII is also an important participant during angiogenesis. VEGF receptor-2 (VEGFR-2) and αvβ3 on surface of vascular endothelial cells are both signal molecules during angiogenesis, which can be activated by fibronectin and vitronectin once cross-linked with FXIII [11]. The expression of F13B in aqueous humor of NVG patients after IVI was higher than that before IVI. F13B participates in susceptibility to venous thrombosis. In present study, increase of F13B may be in parallel with hypercoagulated state of ocular microvasculature [1]. According to study by Jo et al., microcirculatory disturbances at retina and acute vision loss were detected in four patients with NVG who received intravitreal bevacizumab [12]. This may be related to release of hypercoagulated state of ocular microvasculature after IVI. Systemic use of anti-VEGF agents in oncology is associated with increased risk of arterial hypertension, cardiovascular events and arterial embolism [13]. It is uncertain whether such intravitreal administration could increase risks as mentioned before. Acute stroke with unilateral carotid artery occlusion caused by intravitreal injection of anti-VEGF drugs in treatment of NVG secondary to ocular ischemic syndrome is accessible to the public for further study [14]. Therefore, NVG patients with severe carotid stenosis should be treated by anti-VEGF therapy with special caution.

MMP2

MMPs (Matrix metalloproteinases) is classified to a family of extracellular matrix (ECM)-degrading enzymes and deemed as important participant in regulation of various developmental processes, including morphogenesis, angiogenesis and vascular remodeling. By degrading the junction proteins, occluding and cadherin, MMPs disrupt the BRB (blood–retinal barrier) – junction complex is conducive to increase vascular permeability. MMP-2 and MMP-9, are considered as indispensable prerequisite for angiogenesis [15]. In proliferative diabetic retinopathy, HIF (Hypoxia inducible factor)-1α-mediated secretion of VEGF from hypoxic Muller cells was confirmed to up regulate and activate MMP-2 in adjacent endothelial cells [16]. MMP2 was elevated in aqueous humor, vitreous, retina and neovascular membranes in patients with diabetic retinopathy [17]. The expression of MMP2 in aqueous humor of NVG patients was decreased after anti-VEGF treatment [1]. MMP2 was considered as attractive therapeutic targets of retinal neovascular diseases. Further researches are yet to be implemented concentrated upon application of drugs such as atorvastatin, to inhibit MMP2 [18].

Conclusion

In summary, overall comprehension of AH proteomic changes in NVG patients is conducive to unveil new therapeutic target molecules which can be used for pharmaceutical development. In the coming future, it is promising to apply proteomic analysis for personalized treatment of NVG patients.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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