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Major review

Angiogenesis in glaucoma filtration surgery and neovascular glaucoma: A review

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ABSTRACT

Angiogenesis may pose a clinical challenge in glaucoma, for example, during the wound healing phase after glaucoma filtration surgery and in the severe secondary glaucoma called neovascular glaucoma (NVG). Upregulation of vascular endothelial growth factor (VEGF), a key mediator of angiogenesis, occurs in eyes that have undergone glaucoma filtration surgery, as well as those with NVG. This has led investigation of the ability of anti–vascular endothelial growth factor therapy to improve outcomes, and we examine the findings with respect to the safety and efficacy of anti–vascular endothelial growth factor agents, mainly bevacizumab and ranibizumab, in eyes that have undergone glaucoma filtration surgery or have NVG. Combining conventional therapies—such as antimetabolites after filtration surgery and panretinal photocoagulation in NVG—and anti–vascular endothelial growth factor drugs may produce a synergetic effect, although further studies are required to evaluate the long-term efficacy of combination treatments.

1. Introduction

1.1. *Angiogenesis*

Angiogenesis is the process of new vessel growth from existing blood vessels. This essential process occurs naturally in growth, reproduction, and wound healing to supply nutrients and oxygen to tissues.[1,5] Pathologically, aberrant angiogenesis is associated with rheumatoid arthritis,[106] tumor growth and metastasis,[7,34] and eye disorders such as diabetic retinopathy, retinopathy of prematurity, retinal vein occlusions, and age-related macular degeneration.[25,37,120] The vascular endothelial growth factor (VEGF) family of cytokines promote angiogenesis in both normal development and disease.[1,7,25,34,37,100,106,120]

The endogenous members of the VEGF family are placenta growth factor and VEGF-A, VEGF-B, VEGF-C, and VEGF-D. VEGF-A serves as the principal ligand, and soluble forms of VEGF-A include VEGF-121, VEGF-145, and VEGF-165.[114] The various members of the VEGF family and their isoforms bind

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to various VEGF receptors (VEGFR)-1, VEGFR-2, or VEGFR-3.[47,91] The signaling pathways that are activated after association of VEGFRs with their ligands and the cellular responses are summarized in Table 1. The important roles of the VEGFs in angiogenesis have been demonstrated in cancers, where inhibition of the VEGF pathway inhibits the angiogenic process in various tumors.[52,73,128] In addition, hypoxia promotes VEGF transcription, indicating that the metabolic requirements of tissues can regulate angiogenesis in order to maintain the delivery of vital nutrients to hypoxic tissues through the proliferation of new capillaries.[88,121] Because angiogenesis plays a major role in a variety of pathologic conditions, angiogenic inhibitors have been the focus of numerous clinical studies,[10,18,31,32,57,124,126] with a recent focus on anti-VEGF therapies including antibodies such as bevacizumab and ranibizumab, VEGF trap or aflibercept, and small interfering RNA directed against VEGF or VEGF receptors.[2,19,86]

1.2. *Glaucoma*

Glaucoma, one of the leading causes of irreversible blindness worldwide, is normally associated with aging.[26] The number of people with glaucoma is predicted to increase from 64.3 million in 2013 to 111.8 million in 2040, disproportionately affecting Asian and African populations.[110] Glaucoma is not a single entity, but rather a term that describes a group of ocular disorders of diverse etiologies that are clinically defined as intraocular pressure (IOP)-associated optic neuropathy.[16] All forms are potentially progressive and may lead to blindness,[16] but the most prevalent is primary open-angle glaucoma (POAG). POAG is characterized by changes to the optic nerve head with corresponding defects in the visual field but retention of a normal anterior chamber.[45] Other types of glaucoma include angle-closure glaucoma, normal tension glaucoma, and secondary glaucoma such as neovascular glaucoma (NVG), exfoliative glaucoma, and uveitic glaucoma.

Normal IOP in humans is between 10 and 20 mm Hg. The IOP is mainly determined by the production of the aqueous humor and its drainage through the trabecular meshwork at the chamber angle (so-called conventional outflow pathway).[9,16] Some aqueous humor, however, also leaves the eye via the ciliary body, through the uveoscleral or nonconventional outflow pathway.[40] The pressure gradients and resistance to the aqueous outflow are likely altered in the various types of glaucoma. Primary open-angle glaucoma is frequently associated with elevated IOP.

As many as half of glaucoma cases are diagnosed in later stages of disease, because most forms of chronic glaucoma are asymptomatic.[28] Current therapy is targeted at the reduction of IOP to slow the progression of glaucoma.[9] Because of their efficacy and tolerability, the conventional first-line drugs are β-blockers and prostaglandin analogs, which reduce IOP by decreasing the formation of aqueous humor and increasing uveoscleral aqueous outflow, respectively. Other antihypertensive glaucoma medications include carbonic anhydrase inhibitors, cholinergic agonists, and α2-adrenoceptor agonists. In patients who do not respond to any of the antihypertensive medications, laser trabeculoplasty or glaucoma filtration surgery may be performed to control IOP.[21] Trabeculectomy, the most common type of glaucoma filtration surgery, is considered the mainstay of incisional antiglaucomatous surgeries.[58] The surgical goal is to bypass the trabecular meshwork by allowing the aqueous humor to exit through a subconjunctival bleb, thereby relieving IOP.[89]

With the advent of anti-VEGF therapies, many clinical studies have focused on targeting VEGF in ocular disorders, including glaucoma. Anti-VEGF therapy is expected to be an effective addition to the glaucoma treatment regimen because angiogenesis occurs in the wound healing phase after glaucoma filtration surgery to maintain the intentionally created bleb and is fundamental to the underlying pathophysiology of NVG. Inhibition of angiogenesis through anti-VEGF therapy has therefore the potential to improve the success of glaucoma filtration surgery, as well as the outcome in NVG. We describe the angiogenic events that occur after glaucoma filtration surgery and in NVG and summarize pertinent findings from recently published studies evaluating the use of anti-VEGF therapy.

2. Angiogenesis in the medical management of glaucoma

2.1. *Angiogenic response to glaucoma filtration surgery*

Although glaucoma is often controlled with antihypertensive medications, surgical intervention becomes necessary in

Table 1 – VEGF family and VEGF receptors

Receptors	Known signaling pathways	Ligands[15]	Responses
VEGFR-1 (Flt1)	ERK/MAPK PI3K/PKB/AKT[109]	VEGF-A	Weak angiogenesis[80] Soluble VEGFR-1 prevents VEGF-A binding to VEGFR-2 (negatively regulates angiogenesis)[122]
		VEGF-B	Sustains newly formed blood vessels[127]
		PlGF	Arteriogenesis[87]
VEGFR-2 (KDR)	Ras/RAFK/ERK/MAPK[63,101]	VEGF-A	Tenfold stronger angiogenic response than VEGFR-1[12] Endothelial cell proliferation, survival, migration and permeability[13]
VEGFR-3 (Flt4)	PI3K/AKT[23]	VEGF-C VEGF-D	Lymphangiogenesis[33,56,71]

PlGF, placenta growth factor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.