Progress in the basic and clinical research on the Schlemm’s canal

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Received: 2019-06-20        Accepted: 2020-01-07

Abstract

- Glaucoma is a leading cause of irreversible blindness in the world. Intraocular pressure (IOP) plays a key role in glaucoma development and progression. Schlemm’s canal (SC), an important structure of the anterior chamber angle, regulates the flow of aqueous humor and maintains IOP. Because of its special function of aqueous outflow, the SC has been intensive investigated recently. Several characteristics of SC in anatomy, physiology and pathophysiology have been revealed. Compare to normal, glaucomatous SC cells are more sensitive to substrate stiffness, have higher stiffness and and lower porosity leading to higher outflow resistance. And SC collapse caused by acute IOP increase is partially or totally reversal. With advanced inspection techniques, high-quality images of the SC can be obtained \textit{in vivo}, which facilitates SC quantitative measurements clinically and allows us to investigate a new therapy paradigm for glaucoma. In this review, we summarize the basic and clinical research that focused on mechanisms of aqueous outflow resistance and SC changes in physiological, pathological, and post-treatment states.

- **KEYWORDS**: Schlemm’s canal; physiology; pathophysiology; glaucoma; progress

DOI:10.18240/ijo.2020.05.18

Citation: Wang LY, Su GY, Wei ZY, Zhang ZJ, Liang QF. Progress in the basic and clinical research on the Schlemm’s canal. Int J Ophthalmol 2020;13(5):816-821

INTRODUCTION

Glaucoma is one of the leading causes of blindness worldwide, and high intraocular pressure (IOP) contributes to the development and progression of the condition. A massive amount of evidence confirmed that conventional pathway accounted for the bulk of aqueous humor drainage, and the outflow resistance mostly lied in Schlemm’s canal (SC) and juxtacanalicular connective tissue (JCT). Of note is that the currently clinical medications of lower IOP are almost targeted at uveosceleral outflow or the formation of aqueous humor, which plays a limited role in preventing glaucoma progression especially in primary open angle glaucoma (POAG). Although the specific mechanism underlying IOP increase in glaucoma remains elusive, it is clear that the SC is a crucial structure in regulating IOP. The prognosis of glaucoma will be better by deeper understanding of how SC works and changes under different statements. Intensive researches have focused on the anatomy, physiology and pathophysiology of SC. Several theories have been well established to explained the role of SC in regulating outflow resistance, such as a “funneling effect”, the stiffness of SC cells and substrate, the porosity of inner wall (IW), SC collapse inclined to collector channel ostia. Moreover, many characteristics of glaucomatous cells have been demonstrated. The mechanism comprehending of increasing outflow resistance shed light on new strategy for reducing IOP. Hence, the basic research of SC will be reviewed in the first part. Additionally, with advanced inspection techniques, we can obtain high-quality images of the SC, which improves the accuracy of quantitative measurements and our understanding of the structure. Thus, SC change has become a more important parameter for basic glaucoma research and clinical observation. To better understand the SC in different states and provide reference values for future study, in second part, we summarized the changes of SC in physiological, pathological, and post-treatment.

BASIC RESEARCH IN SCHLEMM’S CANAL

Anatomy of the Schlemm’s Canal

In 1830, the SC was first described and named by Friedrich Schlemm, a German anatomist\cite{1}. The SC was a ring-shaped vessel located at the inner part of the corneoscleral junction, and then recognized...
as an important pathway for draining aqueous humor into the circulation system and an important structure of the blood-aqueous barrier. Due to the differences in microenvironment, the endothelia of the SC are not equal. The endothelial cells near the trabecular meshwork (TM) comprise the IW, and the remaining endothelial cells are named the outer wall. The IW has been extensively explored because it correlates to high IOP in POAG. Under the electron microscope, the IW is characterized by a smooth nucleus projected into the SC, as well as numerous giant vacuoles and pores. Giant vacuoles is formed by cell processes that cause invaginated juxtanacalicular cytoplasm by a pressure-dependent manner. The formation of giant vacuoles results in SC endothelial thinning and is thought to link with formation of pores. According to the position, pores are divided into transcellular pores and paracellular pores. Transcellular pores located where the endothelial thinning such that the apical and basal surfaces joined together and fused. Paracellular pores related to paracellular flow through SC endothelium and were dilation of intercellular space.

**Physiology of the Schlemm’s Canal** Mäepea and Bill measured SC pressure (14.3±1.0 cm H₂O), episcleral venous pressure (14.1±1.0 cm H₂O), and spontaneous IOP (IOP=19.2 cm H₂O) in monkeys. Combined with pulsatile aqueous flow, unidirectional valve-like inlets and outlets of the SC may elucidate how it functions and remains patent. Recently, several articles provided some evidence about valve-like structures in the SC endothelial wall and collector channel entrances. Pulsatile flow behavior begins with a choroidal pulse, and induces TM motion toward the SC. It decreases the volume and increases SC pressure, allowing the aqueous humor to enter collector channels. The one-way mechanism, together with cyclic motion, prevents the backflow of aqueous humor and affects the pressure differences among the anterior chamber, SC and collector channels.

Unlike normal vascular endothelial cells, the basement membrane beneath the IW is incomplete, and the pressure direction on the endothelial cells is different. The normal vascular endothelial cells have a vertical force exerts from the apical to basal, whereas that of the SC endothelial cells exerts from basal to apical, which is similar to lymphatic vessel. Recent works have further confirmed the lymphatic markers expressed in the SC. Hence, the endothelial lining of SC possesses both lymphatic vascular and blood characteristics. Moreover, in order to maintain the function of the blood-aqueous humor barriers, the SC maintains a relatively tight connection between the endothelial cells, resulting in a greater pressure difference when facing the same volume of reflux liquid. Thus, the SC is more at a risk of deformation and collapse. Additionally, a recent study revealed that IW/JCT connectivity associated with giant vacule formation, and transcellular pore formation affected by connection of and IW/IW, which provided a new direction for IOP regulation.

**Pathophysiology of the Schlemm’s Canal** It is well established that high IOP in POAG patients is mainly due to the increase outflow resistance of JCT and SC in conventional pathway. However, calculations demonstrated resistance of outflow in the paths through pores themselves is a small part of the total resistance. There must be other mechanism or structure that work with pores to regulate the resistance of outflow. A “funneling effect” was found in JCT nearest the pores, which contributed to outflow resistance exaggerated 30 folds. The “funneling effect” meat only part of the sieve-like structure to drainage aqueous humor effectively with JCT, and the density of pore would affect outflow resistance greatly, in spite of the low resistance of pores alone.

The density of pores would be affected by pressure gradient, and stiffness of substrate and IW cells. An *in vitro* study showed that pores formation had a positive relationship with perfusion pressure when the direction was from basal to apical. But if the pressure direction was apical-to-basal, this relationship would be disappeared. Studies showed that the substrate of SC had higher stiffness in glaucoma, which affected the stiffness of SC cells and had a strong negative relationship with pore formation. An *in vitro* study confirmed that, compared to normal SC cells, glaucomatous SC cells had significant higher stiffness and were more sensitive to increased substrate stiffness. The increased substrate stiffness also contributed to glaucoma-related genes expression, which would be exaggerated in glaucomatous SC cells. Considering the mechanism of pore formation, SC cell stiffness played an important role in porosity. Hence, glaucomatous SC cells had lower pore density with the suggestive of increased outflow resistance.

Several researches have revealed that the increase of perfusion pressure could contribute to SC collapse and outflow facility decrease. Battista *et al* found that the percentage effective filtration length decreased with increasing IOP. The light microscopy images also showed the collapse was inclined to occur in areas near the collector channel ostia, and the IW tissue and JCT were observed partially herniation into the collector channel, leading to a reduction in effective outflow pathway of aqueous. Zhu *et al* confirmed the morphological changes and concluded the changes were partially or completely reversed as the acute high IOP dropped to normal.

**CLINICAL RESEARCH OF THE SCHLEMM’S CANAL** Because of the small size and hidden location of the SC, early observation was based on *in vitro* method. With advanced inspection techniques, *in vivo* high-quality images of the SC can be obtained. The ultrasound biomicroscope (UBM) have be
used to obtain cross-sections of the SC with a high-resolution image using higher-frequency acoustic waves\textsuperscript{[20]}. The main advantage of the UBM was its capability to visualize structures behind the iris, which included the ciliary body and lens. But a coupling medium was always necessary, the inadvertent pressure on the eye cup would influence the quantitative results. Optical coherence tomography (OCT) is another option to observe the SC, which has a significantly finer resolution (6 µm) and faster imaging speed than other imaging modalities\textsuperscript{[21]}. But undesirable artifacts have always appeared on OCT images because of the different light reflection of coexisting tissue, such as cornea, TM, SC and sclera\textsuperscript{[22]}. Due to infrared light cannot go through iris pigment epithelium, OCT has some limitations in observation capability\textsuperscript{[23]}. UBM and OCT facilitates SC quantitative measurements, which allow us to evaluate SC morphology changes \textit{in vivo} and investigate a new therapy paradigm for glaucoma. The morphological changes in the SC under physiological, pathological, and post-treatment states would be summarized.

**Physiological States of Schlemm’s Canal**

Gao \textit{et al}\textsuperscript{[24]} observed that IOP fluctuates throughout the day and found a negative correlation between SC morphology and IOP changes only in the inferior quadrant throughout the day. They also concluded that Valsalva maneuver led to an increase in IOP and SC area. The \textit{in vivo} OCT images of the SC before and after exercise revealed the changes in the SC and lens after exercise and speculated that exercise-induced the increase of plasma colloidal osmotic pressure resulted in the shrinkage of vitreous body and then the backward axial displacement of lens. By the lens-zonular-cilioiridorectal vector and connecting fibrils between SC and ciliary body, the posterior lens displacement stretched IW and widened SC. Moreover, noradrenaline, adrenaline and nitric oxide (NO) induced by exercise could also be the factor of SC expansion. Daniel \textit{et al}\textsuperscript{[27]} measured SC size in healthy children aged 4-16y during accommodative effort and concluded that the radial diameter and cross-sections of the SC significantly increased by 0.011 mm and 0.507 mm\textsuperscript{2} respectively. Moreover, they found SC size was not correlated with gender, refractive error, TM thickness or the size of anterior chamber angle. High IOP in glaucoma development was caused by age-related cellular dysfunction in the conventional outflow tract of aqueous humor\textsuperscript{[28]}. The latest research has shown that SC size significantly decreased with age, and several speculative reasons has been used to explain the alteration. First, SC degeneration and the decreased density of giant vacuoles and pore populations were correlated to aging. Second, motor impairment of the ciliary muscle and change in limbal corneoscleral contour were observed. Third, SC size might decrease with lower production of aqueous humor, which significantly decreased with age\textsuperscript{[29]}.

**Pathological States of Schlemm’s Canal**

From a pathological perspective, Hong \textit{et al}\textsuperscript{[30]} found that the mean SC area was significantly different between participants with POAG and healthy controls (11332±2015 mm\textsuperscript{2} vs 13991±1357 mm\textsuperscript{2}). In addition, although the mean IOP showed a correlation with SC area, the relationship between severity of glaucoma damage and SC area was challenging to be estimated. Kagemann \textit{et al}\textsuperscript{[31]} identified a relationship between the SC area and acute IOP elevation (30 mm Hg) \textit{in vivo}. The mean IOP increased by 189% and the mean SC area decreased by 32% compared with the baseline. Hann \textit{et al}\textsuperscript{[32]} examined anatomical changes in the SC under 10 and 20 mm Hg perfusion pressure within two hours and concluded that SC volume was 3.3 times greater at 10 mm Hg than at 20 mm Hg in healthy participants. However, the SC volume was only two times greater at 10 mm Hg in individuals with POAG. Overall, SC volume was smaller in patients with POAG than in healthy participants.

Recent research revealed that eyes with high myopia have thinner TM and larger SC areas. On one hand, aqueous flow in high myopia patients was segmental and the inactive regions had a thinner TM, which suggested that patients with high myopia could experience decreased aqueous flow. On the other hand, three main factors contributed to larger SC area in high myopia: longer axial length, a series of collagen fiber alterations, and lesions or other obstruction of intra-scleral collector channels caused by the first two changes. The change in collector channels increased distal resistance to aqueous flow and enlarges the SC area\textsuperscript{[33]}.

**Changes in the Schlemm’s Canal after Medical Treatment**

The first-line treatment for glaucoma is the use of conventional medications. Pilocarpine, a nonselective muscarinic receptor agonist, is commonly used in the treatment of glaucoma to expand the juxtaocular region and SC area. Skaat \textit{et al}\textsuperscript{[34]} scanned the SC before administration of 1% pilocarpine in healthy eyes and 2% pilocarpine in POAG eyes and then again one hour later. Results showed that mean SC areas increased by 21% in the healthy group and 24% in the POAG group. However, there have been limited studies to determine whether travoprost could increase conventional outflow. To detect the mechanism, Chen \textit{et al}\textsuperscript{[35]} investigated 12 healthy participants who received travoprost 0.004% and found that the mean SC areas increased by 90.3% in the nasal region and 90.2% in the temporal region. The effects of travoprost lasted
48-60h. Cyclopentolate, a parasympatholytic antimuscarinic agent, relaxes the iris sphincter muscle and decreases the mean SC area by 17%. The mean SC volume in one study decreased from 6163 ± 619 462 µm³ without a significant change of mean IOP (13.9±1.5 to 14.2±1.5 mm Hg) in healthy participants.[36]. Besides traditional glaucoma drug, emerging evidence indicated that Rho kinase inhibitors, latanoprostene bunod (LBN), and latrunculin were available. Rho kinase inhibitors could decrease outflow resistance by lowering stiffness in both TM and SC cells, and separating IW and underlying JCT lead to the failure of the “funneling effect”[37]. LBN was the connection of latanoprost acid and NO-donating moiety, which had dual function in lowering IOP. The NO could increase outflow through SC and TM of conventional pathway, whereas prostaglandin analogue increased uveoscleral outflow.[38] Latrunculin is an actinepolymerizing agent and target at lowering SC cell stiffness, while some common ophthalmic solutions, such as dexamethasone and triamcinolone, increased cell stiffness and outflow resistance[39]. In the future, the SC changes should be evaluated as the new glaucoma drugs applying in clinical trials to better understand the effect of which in outflow pathway in vivo.

**Changes in the Schlemm’s Canal After Glaucoma Surgery**

When IOP remained uncontrolled despite the maximum use of a tolerated medication, surgery should be considered[40]. Hong et al[41] validated the obtained result of SC morphology expansion in POAG eyes within a month after trabeculectomy compared to baseline values (SC diameter: 34.2 vs 28.4 µm; SC area: 8117 vs 5200 µm²), and the extent of SC expansion and IOP decrease were found to be correlated. In accordance with the results, a report showed that selective laser trabeculoplasty led to 8% SC expansion[42]. Another study compared SC morphology in individuals with acute primary angle-closure glaucoma (PACG) before laser iridotomy and one week after the procedure. Results showed that the PACG SC area expanded (10600±2691 µm²) at presentation, and no significant difference was observed between normal controls (7192±1022 µm²) and post-surgical individuals with PACG (6499±1754 µm²)[43]. Conventional surgery could decrease IOP, which led to direct expansion of SC, but conventional surgery might also alter the TM’s extracellular matrix. Several changes, such as matrix metalloproteinase-3 (MMP-3) expression, have been found following laser trabeculoplasty[44]. The lower IOP and/or change of extracellular matrix could also affect the biomechanical environment of SC cells and relieve SC contraction and stiffness to finally lower aqueous flow resistance[28]. For now, we need more direct and microscopic evidence to figure out TM and SC changes following conventional surgery.

Canaloplasty is a burgeoning non-penetrating glaucoma surgery that aims to re-establish the natural trabeculo-canicular outflow using 360° circumferential catheterization and insertion of tensioning sutures. Some studies had shown that canaloplasty significantly could decrease IOP and had fewer surgical complications than trabeculectomy. One study evaluated the early anatomical SC changes after canaloplasty, and results showed that the SC expanded significantly and could be detected with OCT and UBM three months postoperatively. Moreover, the increase in SC height was more pronounced than SC width (height: +369%, width: +152%)[45]. To validate long-term anatomical changes after canaloplasty, Kuerten et al[46] examined patients who received successful surgery over a mean follow-up period of 20mo, and results have shown that the height and width of the SC increased by 351% and 144% respectively, and the dilation of the SC was persistent and stable. Canaloplasty can re-establish the natural trabeculo-canicular outflow by dilating the SC and stretching the IW and TM. Another minimally invasive glaucoma surgery, Ab-interno canaloplasty (ABiC), has been developed. During this procedure, the SC was expanded using only viscoelastic agents introduced into the SC. In comparison to conventional surgery, no tensioning suture is used in ABiC. A clinical study has shown that ABiC lowered IOP for at least one year, even though the SC was only transiently dilated by the microcatheter and viscoelastic agent[47]. Therefore, the potential mechanism of non-penetrating surgery is still being debated.

**SUMMARY**

The SC is an endothelial-lined circular channel, and it bridges the anterior chamber and bloodstream, which plays a vital role in maintaining a normal IOP. Because of the function of SC, it is a potential therapeutic target for glaucoma. Compare to normal, glaucomatous SC cells have higher stiffness and are more sensitive to substrate stiffness. And glaucomatous SC has lower porosity leading to higher outflow resistance. SC collapse caused by acute IOP increase is reversal. These results enhance our mechanism understanding of SC and outflow resistance, are great beneficial for glaucoma therapy. With the development of new instruments, we can now obtain high-resolution images of the chamber angle, which helps us understand the morphological changes of SC and investigate new therapy paradigms for glaucoma. In the future, based on the parameters provided applying imaging and biomechanics instruments, medications, gene therapy and surgical procedures that aim to expand the SC and increase conventional outflow pathways can be better assessed. The most suitable microcatheter size can be identified and applied at an early stage for better delivery of therapy.
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ACKNOWLEDGEMENTS

Foundation: Supported by the National Key R&D Program of China (No.2017YFB1302703).

Conflicts of Interest: Wang LY, None; Su GY, None; Wei ZY, None; Zhang ZJ, None; Liang QF, None.

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