• Review Article •

Mechanism of selective laser trabeculoplasty: a systemic review

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Abstract

● Although selective laser trabeculoplasty (SLT) is a recognized method for the treatment of glaucoma, the exact changes in the target tissue and mechanism for its intraocular pressure lowing effect are still unclear. The purpose of this review is to summarize the potential mechanisms of SLT on trabecular meshwork both *in vivo* and *in vitro,* so as to reveal the potential mechanism of SLT. SLT may induce immune or inflammatory response in trabecular meshwork (TM) induced by possible oxidative damage *etc*, and remodel extracellular matrix. It may also induce monocytes to aggregate in TM tissue, increase Schlemm's canal (SC) cell conductivity, disintegrate cell junction and promote permeability through autocrine and paracrine forms. This provides a theoretical basis for SLT treatment in glaucoma.

● **KEYWORDS:** mechanisms; selective laser trabeculoplasty; glaucoma; trabecular meshwork

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INTRODUCTION

Glaucoma is a group of progressive optic neuropathy, which is the most frequent cause of irreversible blindness worldwide[1-3]. Many management strategies have been explored to control the disease progression, but so far, the only definite management method is to lower intraocular pressure (IOP)[4]. Currently, medical therapies with topical drugs, laser therapy, or surgical intervention are the only available approaches for IOP control[5-7].

Argon laser trabeculoplasty (ALT) was introduced as a therapy for primary open angle glaucoma in 1979[8] and came to the fore more than 20 years ago[9-10]. Selective laser trabeculoplasty (SLT) was first described in 1995[11] and was listed as a procedure separate from ALT by Food and Drug Administration in 2002[12]. With less than 1% ALT energy[12-13], less damage to trabecular meshwork (TM) and fewer adverse event reports, and may have better repeatability and better cost-effectiveness, SLT has overtaken ALT as the preferred technique to increase conventional aqueous outflow through the TM[10,14-17].

SLT was reported to effectively reduce the IOP for various types of glaucoma patients, regardless of whether they have undergone previous glaucoma or cataract surgeries or have not undergone any surgery at all[18]. Even low-energy SLT can achieve good results in glaucoma patients[19]. At present, it has become an essential treatment modality, and increasing evidences support its use as the first-line intervention for glaucoma patients[20-23].

It has been confirmed from clinical observations that SLT can increase TM outflow facilities[24-26] and expand Schlemm's canal (SC)[27-28], which may be the mechanism of SLT to lower IOP, but its changes in target tissues still need to be studied[29-30]. A study found that SLT induces prominent increases in ciliary body and iris returning to baseline thickness in a month, which may be caused by inflammation, vascular engorgement, or mechanical muscular contraction[31]. The purpose of this review is to summarize the effects of SLT on TM in cell culture experiments and some animal studies, so as to reveal the potential mechanism and targets of SLT, and provide a theoretical basis for treatment choices for glaucoma patients.

EFFECT ON ULTRASTRUCTURE

In Vitro An *in vitro* study of cultured bovine TM cells has reported that, when treated within threshold Q-switched Nd YAG (532 nm, 10 nanoseconds), melanin particles in pigment TM cells were broken and lysosomal membrane was broken 4h post-laser exposure; while adjacent TM cells without melanin showed no evidence of ultrastructural damage, which indicated that laser damages were limited to TM cells containing melanin. However, irradiation exceeding 20 times of the threshold resulted in 100% non-selective cytotoxicity of both pigmented and non-pigmented TM cells[11].

In another *in vitro* study of human primary TM (hTM) cells showed that, when treated with 1.0 mJ SLT, melanin containing hTM cells immediately showed obvious signs of cell shrinkage and necrosis; 4h post-SLT, the cells at the ablation zone were cleared, the morphology of adjacent hTM cells changed significantly, with cellular shrinkage and fragmentation extending outside of the ablation zone. However non-melanin-treated hTM showed no obvious morphological changes under low magnification, and only cellular shrinkage and vacuolization at ablation zone under high magnification[32]. These two *in vitro* studies both showed that SLT laser targeted the TM cells containing melanin, which could be damaged and died immediately after SLT treatment.

Micropulse laser trabeculoplasty is also a kind of laser trabeculoplasty[33-34], which is considered to induce a common cellular biochemical reaction with SLT[35]. A study performed micropulse laser irradiation to hTM cells, which were exposed to melanin granules to artificially introduce different levels of pigmentation. They found that the pigmentation intensity of the TM tissues may affect the treatment efficacy of micropulse laser trabeculoplasty, because TM cells with strong staining intensity showed a significantly enhanced response to micropulse laser irradiation[36].

These results are consistent with the clinical observation that glaucoma patients with more pigmentation in TM have a greater range of IOP reduction after SLT treatment[37-39]. However, some studies do not support this view[40-42], which may be related to the complex cellular and molecular processes of SLT.

Eye Bank Eyes Several studies observed the effect of SLT on TM tissues from eye bank eyes. Three or 6h after 0.5 mJ SLT, TM was well conserved and showed intact trabecular beams under scanning electron microscope (SEM)[43].

While after 0.6-1.0 mJ SLT, except for artifactual cracklike defects on the beams, the ropelike beams of the uveal and sheets of corneoscleral TM were intact, and there was no evidence of coagulative damage of corneoscleral or uveal trabecular beams under SEM; transmission electron microscope (TEM) observed that, there was little evidence of mechanical damage post-SLT, and the only ultrastructural evidence was that some pigmented trabecular endothelial cells contained disrupted, cracked and fragmented pigment granules and some of the endothelial cells are vacuolated[44].

However, under higher power, such as 2.0 mJ, the edges of SLT treated areas showed the destruction of trabecular beams with tissue scrolling under SEM[45].

Since these studies were conducted *in vitro*, it only reflects the immediate tissue response to laser energy without the effect of tissue response and remodeling, which may be very important in the clinical environment.

Recently, one study[46] treated corneoscleral rim from eye bank human donor eyes with 0.6-1.2 mJ SLT and then returned to culture *in vitro* for 27d to observe the ultrastructural changes of aqueous humor outflow channel. Mild destruction of uveal TM was observed under light microscope, SEM and TEM, but overall relatively TM and SC structure were preserved between 2-7d of observation. The authors claimed that SLT had less destructive on TM. After 2d of SLT application, there was no significant changes in DNA synthesis compared to the control. By 7d, DNA synthesis tended to increase in the laser-treated eyes, and mitotic cells were mainly in the inner wall of the SC. Although this study did not fully simulate tissue responses *in vivo*, it provides important clues and evidences that changes in nucleic acid levels may affect outflow channels in many ways after SLT treatment.

In Vivo SLT, with the mean energy level of 0.7 mJ/pulse, was performed on patients 1-5d prior to enucleation due to choroid malignant melanoma. Specimens showed that a sharp demarcation line was visible between the laser treated and untreated TM after SLT. In the SLT treated TM, disruption of trabecular beams and desquamated of some endothelial cells were observed, but the extent of damage was smaller than ALT, and the long spacing collagen is more abundant after SLT. No inflammatory reaction was observed between tissues, and the extent of the tissue alterations between day 1 and 5 after SLT had no difference[47].

The results of ultrastructural changes were similar to those observed in eye bank eyes, that SLT could cause ultrastructural changes, but it had smaller damage to TM tissue than ALT, especially in low power settings.

Longer observation on histological and ultrastructural changes is lacking in human study. Histological sections from cat eyes 2wk after 1.32-1.91 mJ SLT treatment were observed. Compared with the untreated TM tissue, the light microscopy showed no significant morphological changes or inflammatory reaction[48], while study of the biological mechanism in-depth was lacking.

EFFECT ON CELL ACTIVITY: APOPTOSIS AND NECROSIS

The change of TM cell activity caused by SLT is related to whether the cells contain melanin. For hTM cells without melanin, the cell metabolic activity increased 4h after SLT, and returned to the basic level 24h later. There was no obvious necrosis change during the observation period. The apoptosis rate decreased by 50.4%±11.0% at 3h post-SLT 1.0 mJ[32].

Nighty-four genes activating cell death by apoptosis or necrosis in hTM cells were detected by cDNA microarray 2-6h post-SLT 0.5 mJ, and no significant change was observed[43]. These finds indicated that, 0.5-1.0 mJ SLT would not directly induce cell death in non-melanin-treated hTM *in vitro*.

When melanin-treated and non-melanin-treated bovine TM co-cultured 1:1, the level of cell necrosis increased after 0.15 mJ or higher radiation, reached the peak after 60min, and returned to the basic level within 8h; the number of apoptotic cells in the irradiation area increased significantly 3-4d after treatment, then decreased, and lowered to the non-significant level on 10d[49].

0.2 mJ SLT selectively killed melanin-treated TM cells, but at a higher laser energy of 0.35 mJ, all cells were killed[49]. A similar phenomenon was observed in co-cultured hTM cells after 0.5-1.0 mJ SLT[32].

EFFECTS ON CELL PROLIFERATION AND MIGRATION

Human primary TM cells proliferated actively and migrated to the ablation zone 24h post-SLT 1.0 mJ in co-cultured melanin-treated and non-melanin-treated hTM cells[32]. Others also observed that bovine TM cells could migrate to the laser affected zone post-SLT 0.2-0.35 mJ *in vitro* after one day or more[49]. However, TM cells have the ability to proliferate *in vitro*. We are not sure yet that the TM cells appeared within the laser affected zone were stimulation by SLT from these studies, and further research is needed to explore this.

EFFECTS ON EXTRACELLULAR MATRIX REMODELING

By cDNA microarray, genes related to extracellular matrix removal were up-regulated; however, genes related to extracellular matrix formation were down-regulated[43]. This indicated that SLT may increase extracellular matrix degradation and promote remodeling.

Twenty-four hours after 1.0 mJ SLT, in co-cultured melanin-treated and non-melanin-treated hTM cells, mitochondrial membrane potential 3 (MMP-3) release increased significantly by 91.2%. Interestingly, the level of MMP-3 secretion in melanin-treated hTM alone decreased[32].

Elevated levels of biglycan and keratin were detected in cat TM treated with 1.32-1.91 mJ SLT laser[48]. The in-depth understanding of TM protein glycosylation induced by laser trabeculoplasty may provide a new method for TM to reduce outflow resistance. These insights are of great significance for new drug development in the treatment of glaucoma by reducing IOP.

MMP-2 and tissue inhibitor of metalloproteinase 2 (TIMP-2) levels in aqueous humor were detected after SLT in pseudoexfoliative glaucoma (PEXG-SLT)[50]. Patients in PEXG-SLT group received trabeculectomy for uncontrolled IOP in the eye that showed increased IOP despite the maximum extent of β-blockers and dorzolamide eye drops after ineffective SLT. Patients in PEXG and cataracts (PEXG-C) group received cataracts with well controlled IOP by β-blockers and dorzolamide. It was found that the TIMP-2 and TIMP-2/MMP-2 ratio in PEXG-SLT and PEXG-C were significantly higher than those in the control group, but the MMP-2, TIMP-2 and TIMP-2/MMP-2 ratio in PEXG-SLT and PEXG-C patients were equivalent, that is, SLT treatment did not increase the MMP-2 level or decreased the TIMP-2/MMP-2 ratio in PEXG-SLT patients' aqueous humor. However, this study had some limitations. First, patients in PEXG-SLT group were all failed for SLT; second, the study did not specifically explain the time interval between aqueous humor detection and SLT treatment.

In conclusion, both *in vivo* and *in vitro* studies suggest that SLT may have an impact on extracellular matrix remodeling. Since the biological impact of SLT on TM cells may be related to intracellular pigment particles, more rigorous studies are needed to confirm the underneath mechanism.

PROMOTING CYTOKINE RELEASE

Studies from ALT has suggested that laser treatment can cause cytokine release and lead to TM tissue biological changes[51]. Result from rabbits found that lipid peroxidation (LPO) in aqueous humor of SLT treated eyes was significantly higher than that of untreated eyes 7d after SLT[52]. The increase of aqueous LPO level indicates that free radicals should be formed in TM during SLT, which may be the cause of inflammatory reactions after SLT.

After that, studies found that SLT could induce a large number of cytokines synthesis and secretion in TM cells, such as interleukin 1α (IL-1α), IL-1β, tumor necrosis factor α (TNF-α) and IL-8[53-55]. By affymetrix microarray analysis, enzyme linked immunosorbent assay (ELISA) and protein antibody array, Alvarado *et al*[55] found that gene expression level of several cytokines and their receptors were changed in both TM and SC cells after SLT *in vitro*. Moreover, the change of cytokines and their receptors expression in TM or SC cells, which were exposed to supernatant conditioned by SLT-irradiated TM or SC cells, was also be induced. Recently, a report from Mayo clinic found that patients received systemic immunosuppressive therapy had obviously less IOP reduction at 12mo following SLT than control patients not receiving systemic immunosuppressive medications[56]. Dahlgren *et al*[57] found that topical non-steroidal anti-inflammatory drugs decreased relative IOP reduction after SLT than the control group. These studies implicate that immune or inflammatory response might involve in IOP-reduction following SLT. The expression changes of these cytokines and their receptors may be involved in the therapeutic effect of SLT in IOP control, and also lay a foundation for cytokine-based glaucoma therapies in the future.

EFFECTS ON MONOCYTES

SLT laser treatment was performed on patients who planned to undergo enucleation to remove malignant choroidal melanoma[58]. It was observed that the number of monocytes

in TM tissue increased five times compared with the control group. Although the actual number of monocytes in monkey eyes was much smaller than that in human eyes, the proportion of monocytes recruited was similar to that in human eyes. The number of monocytes in irradiated animals was 4 times higher than that in control animals. Monocytes increase aqueous humor outflow *in vivo* and SC permeability *in vitro* by further secreting cytokines or directly phagocytizing fragments in TM[53,55,59].

EFFECTS ON SC CELLS

Alvarado[53] found that TM endothelial cells (TMEs) can release a large number of factors into the culture medium when activated by SLT, and these factors could increase the permeability and conductivity of SC cell barrier after binding with SC endothelial cells (SCEs). They also proved that SLT regulates the permeability of cultured human SC cells by inducing intercellular junction decomposition in a manner similar to prostaglandin analogues[59-60]. Skaat *et al*[27] performed SLT on 13 primary open angle glaucoma patients and found that the average SC cross-sectional area increased by 8% 4wk after SLT; the average SC volume has also increased. And there was a significant correlation between this increase and the IOP decrease. These studies may indicate that the cytokines secreted by TM cells after SLT may affect the biological function of surrounding tissue cells in the form of autocrine or/and paracrine to regulate aqueous humor outflow.

EFFECTS ON SC ADJACENT TISSUES

Though there is no evidence of histopathological effect of SLT on the choroid or ciliary body, researchers found that SLT has effects on the adjacent tissues including ciliary body, iris and even choroid using imaging modalities. Aykan *et al*[31] found that, by using ultrasound biomicroscopy, SLT results higher thickness of ciliary body and iris at day 3 and 7. Özer *et al*[61] evaluated the anterior chamber parameters by anterior segment optical coherence tomography, and conclude that SLT results in anterior chamber angle expansion and an increase in angle opening distance as well as trabecular-iris space area 1d after SLT application. However, these changes return to baseline level in a longer time, such as 1mo after SLT. Kim *et al*[62] reported a case with choroidal detachment and hypotony after SLT, and they thought that this is a rare complication after SLT. We speculate that changes on the adjacent tissues after SLT may be a result of biological effects, such as immune or inflammatory response.

CONCLUSIONS

Current studies suggest that SLT mainly acts on TM. SLT has little damage to the ultrastructure of TM cells. Its mechanism of reducing IOP is mainly caused by biological changes, including inducing immune or inflammatory response in TM induced by possible oxidative damage *etc*, and remodeling extracellular matrix. It may also induce monocytes to aggregate in TM tissue, increase SC cell conductivity, disintegrate cell junction and promote permeability through autocrine and paracrine forms. Further revealing the biological and molecular changes of SLT targeted TM cells may provide direction for the search of targeted molecules for anti-glaucoma agents in the future. With the understanding of the pathogenesis of glaucoma and the in-depth understanding of the treatment mechanism of SLT, it may provide direction for the individualized treatment of glaucoma patients.

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