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Literature Review: The Role of Adipose Stem Cell Secretome In Caspase-3 Regulation and Endothelial Cell Density Preservation in Corneal Regeneration Post-Phacoemulsification

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ABSTRACT

Phacoemulsification is the most widely used surgical technique for cataract removal; however, it poses risks of corneal endothelial damage, leading to complications such as corneal edema and vision impairment. The corneal endothelium plays a crucial role in maintaining corneal transparency, yet it has limited regenerative capacity. Endothelial cell loss following phacoemulsification results from mechanical trauma, oxidative stress, and apoptosis, with caspase-3 acting as a key mediator of programmed cell death. Excessive apoptosis leads to a critical reduction in endothelial cell density (ECD), causing corneal decompensation and potential vision loss. Current treatments, including endothelial keratoplasty, are limited by donor shortages and surgical risks. Stem cell-derived secretomes, particularly from adipose-derived stem cells (ASCs), have emerged as a promising therapeutic approach for corneal endothelial repair. ASC secretomes contain bioactive molecules such as growth factors and cytokines that promote endothelial cell survival, reduce apoptosis by downregulating caspase-3, and enhance tissue regeneration. Preclinical studies suggest that ASC secretomes may effectively support endothelial recovery post-phacoemulsification. This literature review explores the mechanisms of endothelial damage, the role of apoptosis in corneal cell loss, and the therapeutic potential of ASC secretomes as a novel intervention for protecting and restoring corneal endothelium following cataract surgery. Additionally, the use of New Zealand white rabbits as an animal model for studying endothelial regeneration is discussed.

Keywords: *Phacoemulsification, corneal endothelial damage, endothelial cell density, caspase-3, adipose-derived stem cell secretome, New Zealand white rabbit*

1. INTRODUCTION

Cataract surgery, particularly phacoemulsification, remains the most common surgical procedure for restoring vision in individuals with cataracts. However, despite its effectiveness, phacoemulsification can result in corneal endothelial damage, leading to potential long-term complications such as corneal edema and vision impairment. The corneal endothelium plays a crucial role in maintaining corneal transparency through its barrier and pump functions. Damage to this non-regenerative cell layer can result in fluid imbalance, leading to corneal swelling and visual deterioration. (1, 2, 3, 4)

Current therapeutic approaches, such as keratoplasty, have limitations including donor tissue scarcity and the risk of graft rejection. In recent years, researchers have explored alternative therapeutic approaches to mitigate corneal endothelial damage following cataract surgery. One of the most promising developments is the use of stem cell-derived secretomes, which contain bioactive molecules that can stimulate corneal endothelial cell survival, proliferation, and repair. Adipose-derived stem cell (ASC) secretomes, in particular, have shown potential in modulating apoptosis and enhancing corneal endothelial cell survival. (5)(6). This literature review examines the impact of phacoemulsification on corneal endothelial health, the role of caspase-3 in apoptosis, the therapeutic potential of ASC secretomes in mitigating endothelial damage, and the use of animal models to study these therapeutic approaches.

Cataract and Phacoemulsification

Cataract is the leading cause of blindness worldwide, particularly among the aging population. The condition is characterized by the clouding of the lens due to protein aggregation, which interferes with light transmission to the retina, leading to blurred vision and, ultimately, blindness. While cataract formation is commonly associated with aging, other risk factors such as diabetes, ultraviolet (UV) exposure, smoking, and genetic predisposition can accelerate its development (1, 7).

Phacoemulsification is the preferred surgical method for cataract removal, involving the use of ultrasound energy to break

up the cloudy lens before replacing it with an intraocular lens (IOL). This technique offers several advantages, including smaller incisions, reduced recovery time, and improved postoperative visual outcomes. However, despite its benefits, phacoemulsification is not without risks. The ultrasound energy used in the procedure generates mechanical and thermal stress that can result in endothelial cell loss, corneal edema, and long-term complications such as bullous keratopathy(4). Efforts to minimize endothelial damage during surgery include optimizing ultrasound power settings, using dispersive viscoelastic agents, and implementing surgical techniques that reduce direct endothelial trauma.

Corneal Endothelial Damage During Phacoemulsification

The corneal endothelium is a monolayer of hexagonal cells that lines the posterior surface of the cornea, playing an essential role in regulating corneal hydration. Unlike epithelial cells, endothelial cells have limited proliferative capacity, making them vulnerable to damage from surgical interventions. The loss of endothelial cells disrupts the delicate balance of fluid transport, leading to corneal swelling and opacification (3).

During phacoemulsification, endothelial damage primarily occurs due to direct mechanical trauma from ultrasound waves, fluid turbulence from intraocular irrigation, and oxidative stress caused by free radicals (8). The endothelial cell damage during phacoemulsification can also occur as an inflammatory responses that involves the activation of interleukin-1α (IL-1α), interleukin-1β (IL-1β), and damage-associated molecular patterns (DAMPs) which triggers inflammatory cascades that lead to endothelial cell loss (9).

Studies have shown that endothelial cell loss can range between 8.0-16.7% following phacoemulsification, with the degree of damage influenced by factors such as cataract density, surgical technique, and surgeon experience (10). While endothelial cells attempt to compensate for cell loss through cell spreading and migration, excessive loss can lead to corneal decompensation, necessitating corneal transplantation.

Endothelial Cell Density and Its Clinical Importance

Endothelial cell density (ECD) is a key parameter used to assess corneal health. In healthy adults, the normal ECD ranges from 2,500 to 3,000 cells/mm², with a gradual decline occurring as part of the aging process. The endothelium maintains corneal transparency by actively pumping excess fluid out of the cornea. When ECD falls below the critical threshold of 400-500 cells/mm², corneal edema develops, impairing vision and leading to conditions such as pseudophakic bullous keratopathy (8).

Patients with pre-existing endothelial dysfunction are particularly at risk of severe complications following phacoemulsification. Factors such as diabetes, prolonged surgical time, and intraoperative complications can exacerbate endothelial cell loss, accelerating the progression toward corneal decompensation. Strategies aimed at preserving ECD include the use of intraocular pharmacological agents, endothelial keratoplasty, and, more recently, stem cell-based therapies.

Caspase-3 and Apoptosis in Corneal Endothelial Cells

Apoptosis, also known as programmed cell death, is a carefully controlled process crucial for preserving tissue balance and function. However, excessive apoptosis in the corneal endothelium can result in significant cell loss, compromising corneal function. Caspase-3 is a central executioner enzyme in the apoptotic pathway, activated by both intrinsic and extrinsic signals. Once activated, caspase-3 cleaves key structural and regulatory proteins, leading to cell shrinkage, chromatin condensation, and DNA fragmentation (11, 12).

Following phacoemulsification, oxidative stress and mechanical injury trigger apoptosis in corneal endothelial cells, with caspase-3 playing a pivotal role in mediating cell death. Studies have shown that increased caspase-3 activity correlates with higher rates of endothelial cell loss, underscoring the need for therapeutic interventions that can modulate apoptotic pathways. Suppressing caspase-3 activation through pharmacological inhibitors or regenerative therapies may help preserve endothelial integrity and enhance corneal recovery.

Stem Cell Therapy and Secretome Applications

Given the limited regenerative potential of corneal endothelial cells, stem cell-based therapies have emerged as a promising approach to corneal repair. Mesenchymal stem cells (MSCs) have garnered particular interest due to their ability to secrete paracrine factors that promote cell survival, inhibit apoptosis, and enhance tissue regeneration. MSC-derived secretomes consist of bioactive molecules like growth factors, cytokines, and extracellular vesicles, which contribute to tissue repair and possess anti-inflammatory properties (13, 6).

Preclinical and clinical studies have demonstrated the potential of MSC-derived secretomes in promoting corneal endothelial repair. Research has shown that secretomes from bone marrow, umbilical cord, and limbal stem cells can enhance endothelial cell proliferation and suppress apoptotic signaling pathways. However, the challenges associated with obtaining and culturing these stem cell sources have led researchers to explore alternative sources, such as adipose-derived stem cells (ASCs) (14).

Adipose Stem Cell Secretome as a Potential Therapy

Adipose-derived stem cells (ASCs) are an attractive source of regenerative therapy due to their high yield, ease of isolation, and robust paracrine activity (Figure 1). ASC-derived secretomes contain a diverse array of growth factors and cytokines beneficial for corneal repair (Figure 2), including: transforming growth factor-beta (TGF-β) which modulates inflammation and promotes wound healing; vascular endothelial growth factor (VEGF) which stimulates endothelial survival and angiogenesis; and Extracellular Vehicles (EVs) which facilitate cell-to-cell communication and enhance corneal regeneration (15, 16).

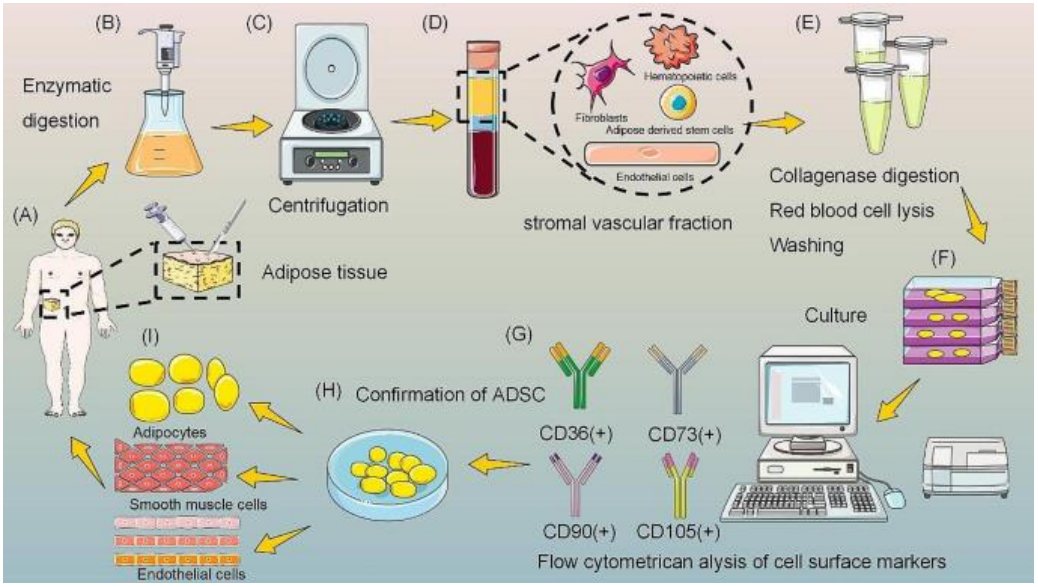

Figure 1. Process of obtaining adipose stem cell (17)

Recent studies conducted in vitro and in vivo have revealed that ASC secretomes can enhance endothelial cell survival by downregulating caspase-3 activity, thereby reducing apoptosis. Additionally, ASC-derived factors have been shown to modulate oxidative stress, mitigate inflammation, and support endothelial cell migration, further contributing to corneal recovery (18). Future research should prioritize enhancing the delivery of ASC secretomes and assessing their long-term safety and effectiveness in clinical settings.

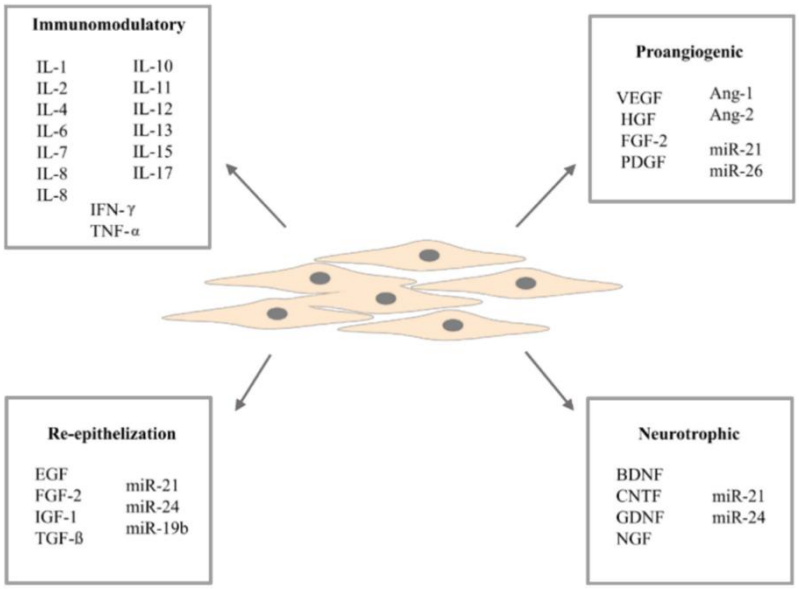

Figure 2. Various array of growth factors and cytokines from adipose stem cell secretomes (19)

New Zealand white rabbits as an animal model for corneal endothelial research

New Zealand white rabbits (Oryctolagus cuniculus) are widely used as an animal model in ophthalmic research due to

their similar corneal structure to humans, large eye size, and ease of handling in experimental conditions. Their corneal endothelial cells exhibit regenerative properties that make them an ideal model for testing therapeutic interventions for endothelial damage (20, 21).

One of the advantages of using New Zealand white rabbits are the morphological similarity to human cornea, where the hexagonal endothelial cell pattern in rabbits is comparable to that in humans. Moreover, New Zealand white rabbits have rapid healing and proliferation where unlike human endothelial cells, rabbit corneal endothelial cells exhibit higher mitotic potential, allowing for dynamic assessment of regenerative therapies. Additionally, New Zealand white rabbits can be made as a standardized model for endothelial damage, where phacoemulsification-induced endothelial damage in rabbits accurately mimics human surgical outcomes, making them suitable for evaluating treatments like ASC secretome therapy (22).

2. CONCLUSION

Endothelial damage following phacoemulsification remains a significant concern in cataract surgery. While corneal transplantation has been the standard treatment, ASC secretome represents a novel and promising approach for corneal endothelial regeneration. The ability of ASC secretome to modulate caspase-3 expression, reduce oxidative stress, and promote endothelial cell survival makes it a viable alternative for maintaining corneal transparency and preventing post-phacoemulsification complications. The use of New Zealand white rabbit as an animal model provides valuable insights into the efficacy of ASC secretome therapy in corneal endothelial repair. Future studies should focus on refining ASC secretome formulations, optimizing delivery techniques, and conducting extensive clinical trials to establish its clinical efficacy as a viable intervention for patients at risk of corneal endothelial damage post-phacoemulsification.

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