Bioengineering Techniques for Mitochondrial Self-Sufficiency

Mitochondria, often referred to as the powerhouses of the cell, are critical organelles responsible for generating the majority of the cellular energy in the form of adenosine triphosphate (ATP). Mitochondrial dysfunction is implicated in a range of diseases, from rare genetic disorders to common conditions such as cancer, neurodegenerative diseases, and aging. Enhancing mitochondrial self-sufficiency and function is therefore a significant focus within the field of bioengineering, with the aim of developing therapeutic strategies to treat mitochondrial-related diseases.

Mitochondrial-Targeted Nanomedicine

One of the most promising bioengineering approaches to enhance mitochondrial function is the use of mitochondrial-targeted nanomedicine. Nanoparticles (NPs) can be engineered to selectively deliver therapeutic agents directly to mitochondria, thereby increasing the efficacy and reducing the systemic toxicity of treatments. Lipid-based NPs, for example, have been successfully used to deliver COVID-19 vaccines, demonstrating the potential of this technology for rapid clinical translation (Alsudir et al., 2021). Similarly, mitochondrial-targeting NPs could be tailored for the selective delivery of nucleic acids, potentially accelerating the translation of gene editing therapies into clinics and promoting the development of personalized nanomedicine (PMC9508646).

The hyperpolarization and hydrophobicity of the mitochondrial membrane are key factors that can be exploited to tailor mitochondrial-targeting NPs. By moderating the degree of hydrophobicity and charge density of the NPs, and governing their size and shape, it is possible to create NPs that can effectively target and penetrate the mitochondrial membrane. Significant efforts have been made to develop mitochondrial targeting NPs, including polymeric, lipid, organic, or inorganic NPs. However, none of these NPs has yet been utilized to deliver the genetic materials required for gene therapy, indicating an urgent need to investigate optimal mitochondrial-targeting nanoplatforms (PMC9508646).

Mitochondrial Disorders and Clinical Trials

The rarity of primary mitochondrial disorders has historically impacted the conduction of successful clinical trials, design, and funding. However, significant breakthroughs in developing new therapeutic approaches are expected to continue through advances in gene therapy and screening assays to improve mitochondrial function. Innovative approaches to clinical trial design, the development of new technologies, and the creation of virtual controls will herald a new era in personalized medicine for patients with mitochondrial diseases (PMC9508646).

Mitochondrial Transfer and Augmentation

Another bioengineering technique involves the transfer of exogenous mitochondria for therapeutic purposes. In vitro uptake of purified mitochondria has been shown to occur at low efficacy but can be maintained under selective pressure. Injection of mitochondria into human cells can lead to rapid replacement of endogenous mitochondrial DNA (mtDNA), reconstituting recipient cells with exogenous normal mtDNA content. Several methods are being developed to utilize mitochondrial transfer of exogenous mitochondria for therapeutic purposes, with existing

preclinical feasibility of in vitro mitochondrial uptake and in vivo intercellular mitochondrial transfer (s41536-021-00167-7).

Mitochondrial augmentation therapy (MAT) is a process where human hematopoietic stem/progenitor cells (HSPCs) from healthy or diseased subjects are enriched with exogenous, functional mitochondria. This has been demonstrated to provide long-term functional benefits to patient-derived HSPCs administered to an immunocompromised murine model. Moreover, mitochondria from infused ex vivo augmented cells have shown the capacity to transfer to hematopoietic cells in the peripheral blood, supporting MAT as a potential therapeutic avenue for patients with mtDNA deletions or mutations (s41536-021-00167-7).

Mitochondrial Biogenesis and Autophagy

Research into mitochondrial biogenesis and autophagy has become a hot spot, with studies exploring whether certain interventions can play a therapeutic role by regulating these processes. For instance, nobiletin has been shown to regulate mitochondrial autophagy and biosynthesis by activating the SIRT-1/FOXO3α pathway, improving hepatic ischemia-reperfusion injury. Similarly, the nuclear receptor Rev-erb-alpha and progranulin have been implicated in regulating mitochondrial biosynthesis and autophagy, suggesting that maintaining mitochondrial homeostasis is important for normal physiological function (PMC9833928).

Mitochondria-Targeted Cancer Therapy

In the context of cancer therapy, targeting mitochondria and their metabolisms has been recognized as a promising strategy. Recent efforts have focused on developing mitochondria-targeted pharmaceuticals, including small molecular drugs, peptides, proteins, and genes. Advances in nanotechnology have led to the development of self-assembled peptide-nanomaterials that integrate biomarker-targeting, stimuli-response, self-assembly, and therapeutic effects. In situ mitochondria-targeted self-assembling peptides that can assemble on the surface or inside mitochondria have opened new dimensions for mitochondria-targeted cancer therapy (pubmed.ncbi.nlm.nih.gov/34900970).

Conclusion

The field of bioengineering has made significant strides in developing techniques to enhance mitochondrial self-sufficiency and function. Mitochondrial-targeted nanomedicine, mitochondrial transfer and augmentation, and the regulation of mitochondrial biogenesis and autophagy are all promising approaches that hold potential for the treatment of mitochondrial-related diseases. As research continues to advance, these techniques may lead to breakthrough therapies that could transform the management of mitochondrial disorders and other conditions associated with mitochondrial dysfunction.

References

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