


Chapter 10


Advances in CRISPR–Cas9– Based Mitochondrial Gene Editing and Delivery Systems for Precision Medicine: Targeting the Powerhouse

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ABSTRACT

The powerhouse of cells, mitochondria, play a crucial role in homeostasis, energy metabolism, apoptosis and stress response. Mitochondria possess a separate set of DNA (mtDNA), which is associated with a wide range of metabolic, degenerative and age-related disorders. The CRISPR-Cas 9 system revolutionised medicine with its discoveries in the nucleus; however, its application in mitochondria remains constrained due to the challenges of delivery, due to the double membrane and repair mechanisms, since mitochondria lack the conventional repair mechanisms, unlike the nucleus. These limitations directed CRISPR-independent and CRISPR-inspired strategies aiming at overcoming the hurdles. This chapter discusses the obstacles in achieving precise mitochondrial genome editing in order to shed light on new therapeutic possibilities.

INTRODUCTION

Imagine stepping into a sprawling metropolis, where every building, street, and park has a purpose. In this city, energy flows like electricity through power lines, information is transmitted through networks of sensors, and the citizens follow complex rules to maintain order. This is not a city on Earth; it is one within a cell. At the heart of this microscopic city lie mitochondria, the organelles often referred to as the cell's powerhouses. Yet, as in any well-planned urban centre, power generation is only one aspect of their role. Mitochondria are also command centres, capable of sensing stress, orchestrating responses to fluctuating resources, and determining the fate of the cell. Understanding this organisation is key to grasping how mitochondria contribute to health and, when hijacked, disease.

As the central regulators of energy metabolism and apoptosis, mitochondria play essential roles in cellular function. Mutations in mitochondrial DNA (mtDNA) contribute to a wide range of degenerative and metabolic diseases. The CRISPR/Cas9 system has revolutionised nuclear genome editing and offers numerous therapeutic possibilities. However, despite its feat in the nucleus, mitochondrial editing remains difficult due to hurdles in delivering guide RNA and repairing the resulting DNA breaks. Therefore, recent studies are shifting toward CRISPR-inspired, but CRISPR-independent approaches.

This chapter aims to study the potential of emerging genome-editing technologies in mitochondrial genetic engineering by highlighting the advances, challenges and future directions.

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