Biomere

COMMUNITY BLOG

PROGERIA: NEW THERAPIES FOR THE "BENJAMIN BUTTON" DISEASE

Progeria or Hutchinson-Gilford syndrome is a rare disease characterized by accelerated dramatic aging. It is estimated that one in 4 million live births have progeria, and currently about 400 children have been diagnosed with the disease. Progeria does not develop at birth and symptoms appear about a year after birth, and the average lifespan of progeria patients is 14 years. Along with characteristic physical features such as a large head, small facial features and baldness, children with progeria suffer from joint issues and heart diseases that can lead to fatal heart attacks or stroke. In 2003, scientists discovered that a single point mutation (GGC > GGT) in the Lamin A gene was the genetic disease driver of progeria[1]. The point mutation resulted in the truncation of the Lamin A protein causing destabilization of the nuclear membranes in cells. The truncated Lamin A protein is also called progerin. The impact of nuclear membrane destabilization results in dysregulated transcription, mitochondrial dysfunction and accelerated cell death and senescence. The effects are prominently seen in tissues subject to external forces such as cardiovascular and musculoskeletal tissues.

There is a genomic test to identify the presence of point mutations in the Lamin A gene (*LMNA*) clinically, and this facilitates early diagnosis and treatment. In November 2020, the first therapy for progeria was approved by the FDA[2] – lonafarnib (Zokinvy) was developed by Eiger BioPharmaceuticals and is a farnesyltransferase inhibitor. Lonafarnib acts by inhibiting the farnesylation of the progerin protein (truncated Lamin A) so that it does not bind to the nuclear membrane and this helps reduce the destabilization of the nuclear membrane[3]. Lonafarnib was found to increase the lifespan of progeria patients by 2.5 years in the 11 year follow up time frame of the trial cohort compared to natural history controls. Due to its inhibitory effect on truncated Lamin A protein, lonfarnib is also being investigated as a potential therapy for other rare laminopathies.

Recently, researchers at Harvard University and the Broad Institute published a ground-breaking new study using CRISPR based DNA editing technology to correct the point mutation in Lamin A[4]. Conventional CRISPR Cas9 system nicks both strands of DNA at specific locations allowing the insertion or deletion of a DNA sequence but it does not correct point mutations. David Liu's lab at the Broad Institute has advanced CRISPR technology to develop single strand base editing capabilities, which were successfully shown to correct the point mutation in Lamin A. Base editing technology uses engineered bacterial deaminase enzymes that convert an adenine (A) base to cytosine (C) and a guanine (G) to thymidine (T). The deaminase enzymes are targeted to the DNA sequence that requires editing by the Cas9 enzyme that performs the same function in conventional CRISPR technology.

The researchers delivered the base editing system via adeno-associated viruses (AAV) to correct the error in the Lamin A gene in mouse models of progeria, resulting in an increase in the amount of normal Lamin A protein in the heart and muscles. This correction resulted in doubling of the lifespan of treated mice compared to control despite the efficiency of base correction being in the 20-60% range[5]. The study demonstrated a critical point that 100% efficiency of correction is not required to see improvement in the disease phenotype. While minimal off target effects were detected in this study, safety issues must be thoroughly investigated before using base editing in human patients.

Nevertheless, this study demonstrates that pinpoint accuracy of DNA sequence correction can be a ground breaking approach to fix disease causing point mutations and improve patient quality of life and increase life span[6].

References:

[1] https://pubmed.ncbi.nlm.nih.gov/12714972/
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