A Transgenic Rodent Model with Dietary Niacin Controlled Nicotinamide Adenine Dinucleotide (NAD) (ANDY Mouse)

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Abstract

Transgenic Mouse Model with Tunable NAD+ Deficiency: NAD+ deficiency is a common factor of aging and a number of metabolic and neurodegenerative diseases. USU researchers have developed methods to create a mouse model with tunable and reversible NAD+ deficiency, creating the first practical mouse model of NAD + metabolism.

Problem

The lack of a rodent model in which low NAD+ levels could be achieved presents a major hurdle to studying basic mechanisms that could corroborate claims of health benefits of preventing and reverting low NAD+.

Solution

Researchers are able to achieve NAD+ deficiency in a mouse model, without accumulation of toxic intermediates such as quinolinic acid.

Value Proposition

This model has potential to increase the scientific community's understanding of metabolic disorders, neurodegenerative diseases, cancer treatment recovery, and aging.

Benefit

NAD+ is a cofactor required for enzymes involved in metabolism and DNA repair mechanisms, and is used as an extracellular signaling molecule with roles in cell-to-cell communication and neurotransmission. NAD+ acts as an electron carrier in redox reactions in the Krebs cycle, glycolysis, beta oxidation, gluconeogenesis, and lipid and steroid synthesis – making it vital to catabolic and anabolic reactions in the body. Additionally, NAD+ dependent enzymes are involved in aging, and various human diseases including cancer, neurodegeneration, multiple sclerosis, Alzheimer disease, and Huntington disease. Thus, NAD+ is an attractive target for drug discovery. The lack of a rodent model in which low NAD + levels could be achieved presents a major hurdle to studying basic mechanisms that could corroborate claims of health benefits of preventing and reverting low NAD+.

Unfortunately, creating a rodent model of NAD+ metabolism is difficult, because unlike humans, they are able to efficiently convert tryptophan into NAD+ through the kynurenine pathway. In order for a mouse model to mimic the human situation, the ability of mouse metabolism to convert tryptophan to NAD+ must be eliminated. Although various knockout mouse models have attempted to achieve this, a practical knockout model is yet to be established.

USU researchers have established an effective rodent model of NAD+ deficiency. The acquired niacin dependency (ANDY) mouse model is a transgenic mouse model with inducible human alpha-amino-beta-carboxy-muconate-semialdehyde decarboxylase (ACMSD) expression. Overexpression of the ACMSD enzyme allows

for NAD+ synthesis in the ANDY mouse to be tuned and reversed. By controlling ACMSD expression through administration of doxycycline and adjustments to the M2 reverse tetracycline transactivator, researchers are able to achieve NAD+ deficiency in a mouse model, without accumulation of toxic intermediates such as quinolinic acid.

This model has potential to increase the scientific community's understanding of metabolic disorders, neurodegenerative diseases, cancer treatment recover, and aging. This model is especially interesting because the nature of its methods allow it to be reversible and tunable. This makes it valuable for both observation of negative effects of NAD+ deficiency and the effects of reverting back to normal/adequate NAD+ levels.

Market Application

The model of tunable NAD+ deficiency offered by this model would be especially useful for entities involved in research of aging, energy metabolism, and neurodegenerative diseases such as Parkinson's disease, Alzheimer disease or Huntington disease.

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