Chapter 1

Introduction

1.1 Background

Metabolic diseases such as obesity will continue to pose significant public health challenges globally (Zhang et al., 2024). Approximately 1.9 billion adults are estimated to be living with obesity, with around 650 million classified as obese (Mohajan & Mohajan, 2023). Furthermore, obesity, which is characterized by an excess accumulation of adipose tissue, contributes to various complications, leading to a substantial increase in overall mortality, with 2.8 million people dying each year (WHO, 2021). In addition, another chronic metabolic disease, diabetes, which can progress from obesity, has shown that an estimated 537 million adults suffer from this disease (Magliano & Boyko, 2021). The mortality rates associated with these conditions are equally concerning, as diabetes is linked to approximately 6.7 million deaths annually (IDF, 2022). Furthermore, adipose tissue functions as an energy reservoir, and its dysregulation can lead to obesity, a significant risk factor for conditions like type 2 diabetes and other metabolic-related diseases. Therefore, the interplay between these metabolic disorders underscores the urgent need for effective public health strategies. Thus, exploring the mechanism between obesity and adipose tissue could be a strategy to facilitate the development of these novel treatments.

Adipose tissue (AT) is critical in maintaining the body's energy balance, mainly through energy storage and thermogenesis (Machado et al., 2022). Previously considered only as passive lipid storage, AT is now recognized for its dynamic influence on metabolism throughout the body. The two primary types, white adipose tissue (WAT) and brown adipose tissue (BAT), serve distinct functions. Schirinzi et al. (2023) state that WAT is mainly an energy reserve. Still, it can undergo a "browning" process to form beige adipocytes with BAT-like characteristics, such as increased mitochondria and enhanced thermogenesis (Kuryłowicz & Puzianowska-Kuźnicka, 2020). This distinction arises from differences in developmental origins, where brown adipocytes originate

from a muscle-like lineage. In contrast, beige adipocytes were hypothesized to arise from preadipocytes in iWAT under stimuli like cold exposure or hormonal stimuli and retain their distinct identity. This heat-generating adaptation, which can be stimulated through binding of β-adrenergic receptors by a synthetic agonist such as isoproterenol, aids in releasing energy as heat rather than as ATP, thereby enhancing energy expenditure (Zhang et al., 2021).

MTHFD2 has recently gained attention as a key enzyme due to its critical role in cellular metabolism and its potential as a therapeutic target. While most previous studies have focused on its anti-cancer properties when inhibited, emerging evidence suggests its involvement in adipose tissue metabolism and thermogenesis. For example, MTHFD2 induction has been observed in the white adipose tissue of mice exposed to cold, with upregulation detected as early as 12 hours post-exposure. Additionally, Seale et al. (2021) identified altered MTHFD2 expression in their BAT microarray analysis, showing upregulation in vivo, which was further enhanced following acute cold exposure. However, despite these findings, the direct correlation between MTHFD2 expression and mitochondrial respiration under thermogenic activation remains unexplored. As such, in terms of mitochondrial function that is directly linked with metabolic activity, MTHFD2 plays a pivotal role in folate and one-carbon metabolism, regulating redox homeostasis by utilizing both NAD+ and NADP+ as cofactors. This regulation influences the intracellular redox state through the production of NADPH (Shin et al., 2017). Therefore, the inhibition of MTHFD2 leads to a decrease in NADPH levels, resulting in heightened oxidative stress that can compromise mitochondrial function and overall cellular health, emphasizing the enzyme's broader physiological importance extending beyond its anti-cancer properties.

1.2 Objective

This study aims to investigate the role of MTHFD2 in regulating mitochondrial respiration in beige adipocytes. Specifically, to evaluate the effects of MTHFD2 inhibition both under basal conditions and thermogenic activation, assessing its potential as a target for enhancing metabolic function.

1.3 Hypothesis

H0 = The inhibition of MTHFD2 in beige adipose does not cause significant changes in mitochondrial respiration or in the expression of both thermogenic and mitochondrial genes, under both basal and thermogenically stimulated conditions.

H1 = The inhibition of MTHFD2 in beige adipose results in a decrease in mitochondrial respiration, accompanied by reduced mRNA expression of thermogenic and mitochondrial genes under both basal and thermogenically stimulated conditions.