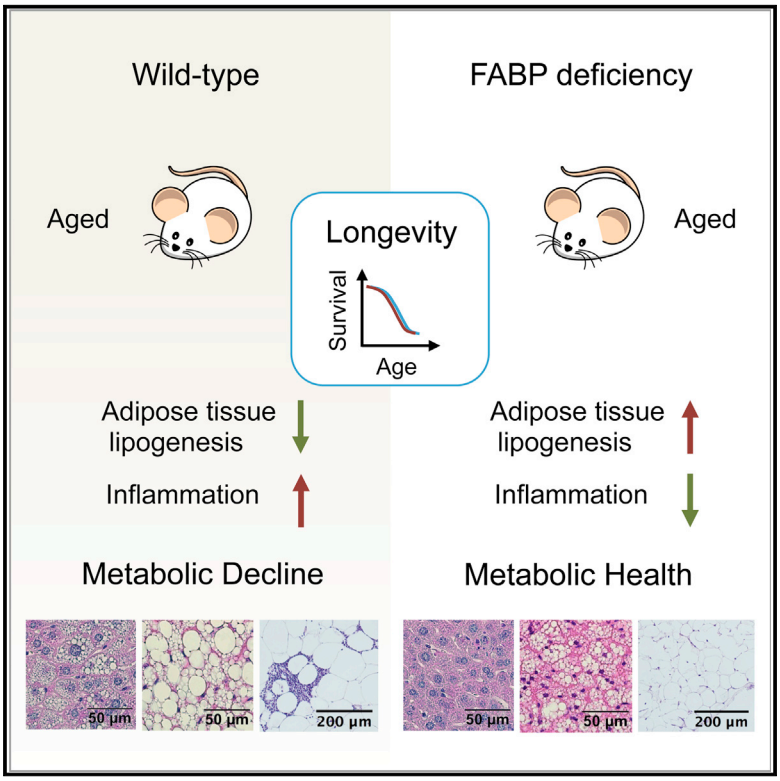
Article

Cell Reports

Uncoupling of Metabolic Health from Longevity through Genetic Alteration of Adipose Tissue Lipid-Binding Proteins

Graphical Abstract



Highlights

- Fabp deficiency protects against age-related inflammation and metabolic diseases
- Calorie restriction and Fabp deficiency share many molecular features
- Unlike calorie restriction, Fabp deficiency does not extend lifespan
- Lifelong metabolic health may not be uniformly associated with extended longevity

Authors

Khanichi N. Charles, Min-Dian Li, Feyza Engin, Ana Paula Arruda, Karen Inouye, Gökhan S. Hotamisligil

Correspondence

ghotamis@hsph.harvard.edu

In Brief

Deterioration of metabolic health is a hallmark of aging and generally thought to be detrimental to longevity. Charles et al. utilize FABP-deficient mice as a model to demonstrate that the preservation of metabolic health in this model persists throughout life, even under metabolic stress, but does not increase longevity.

Charles et al., 2017, Cell Reports *21*, 393–402
October 10, 2017
https://doi.org/10.1016/j.celrep.2017.09.051

Cell Reports
Article

Uncoupling of Metabolic Health from Longevity through Genetic Alteration of Adipose Tissue Lipid-Binding Proteins

Khanichi N. Charles,[1,3,5] Min-Dian Li,[1,5] Feyza Engin,[1,4] Ana Paula Arruda,[1] Karen Inouye,[1] and Gökhan S. Hotamisligil[1,2,6,*]

[1]Department of Genetics and Complex Diseases and Sabri Ülker Center, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA
[2]Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA
[3]Present address: Marlborough School, 250 South Rossmore Avenue, Los Angeles, CA 90004, USA
[4]Present address: Departments of Biomolecular Chemistry and Medicine, Division of Endocrinology, Diabetes, and Metabolism, University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI 53706, USA
[5]These authors contributed equally
[6]Lead Contact
*Correspondence: ghotamis@hsph.harvard.edu
https://doi.org/10.1016/j.celrep.2017.09.051

SUMMARY

Deterioration of metabolic health is a hallmark of aging and generally assumed to be detrimental to longevity. Exposure to a high-calorie diet impairs metabolism and accelerates aging; conversely, calorie restriction (CR) prevents age-related metabolic diseases and extends lifespan. However, it is unclear whether preservation of metabolic health is sufficient to extend lifespan. We utilized a genetic mouse model lacking *Fabp4/5* that confers protection against metabolic diseases and shares molecular and lipidomic features with CR to address this question. *Fabp*-deficient mice exhibit extended metabolic healthspan, with protection against insulin resistance and glucose intolerance, inflammation, deterioration of adipose tissue integrity, and fatty liver disease. Surprisingly, however, *Fabp*-deficient mice did not exhibit any extension of lifespan. These data indicate that extension of metabolic healthspan in the absence of CR can be uncoupled from lifespan, indicating the potential for independent drivers of these pathways, at least in laboratory mice.

INTRODUCTION

Deterioration of metabolic health, including the emergence of increased adiposity, insulin resistance, and dyslipidemia, is a key pathological manifestation of aging (López-Otín et al., 2016), and it contributes to age-related diseases, such as diabetes, cancer, cardiovascular disease, and neurodegenerative diseases. In the past two decades, much has been learned about the etiology and underlying mechanisms of the decline in metabolic health (Hotamisligil, 2017; Shulman, 2014). For example, metabolically driven chronic inflammation or metaflammation, ectopic fat deposition and metabolism, and organelle dysfunction all contribute to insulin resistance and abnormal glucose homeostasis. Metabolic stress associated with hyperlipidemia engages key inflammatory and stress-signaling modules, including c-Jun N-terminal kinase (JNK), inhibitor of nuclear factor kappa-B kinase (IKK), and protein kinase C (PKC); interferes with metabolic physiology orchestrated by nutrient-sensing pathways, e.g., insulin signaling, adenine-monophosphate-activated protein kinase (AMPK), and mammalian target of rapamycin (mTOR); and ultimately leads to metabolic dysfunction and disease (Arruda and Hotamisligil, 2015; Hotamisligil, 2017). Dietary restriction regimens, prominently calorie restriction, on the other hand, delay the onset of aging and age-associated diseases and impact the aforementioned mechanisms in a corrective manner (Anderson and Weindruch, 2010; Fontana et al., 2010; Yang et al., 2016). In fact, mounting studies targeting these inflammatory modules and nutrient-sensing pathways lend support to the concept that increasing metabolic fitness may extend healthspan and lifespan across the phyla.

As demonstrated in the early genetic studies in round worms and flies, the mechanisms linking metabolic health and aging are finely controlled and context dependent (Kenyon, 2010). For example, while blunting insulin/insulin-like growth factor (IGF) signaling extends lifespan, total ablation of this pathway is detrimental to metabolic health and even longevity (Accili et al., 1996; Joshi et al., 1996). Holzenberger et al. (2003) report that heterozygous knockout of IGF receptor increases the lifespan in female mice by 33%, but it does not alter the lifespan of males, possibly due to severely impaired glucose tolerance. Our group has shown that, in mice, obesity-induced JNK activation suppresses insulin signaling and impairs metabolic health (Hirosumi et al., 2002); however, studies in fruit flies suggest that hyperactivation of JNK can increase lifespan by tuning down insulin signaling (Wang et al., 2005). These observations call into the question the direction and nature of the relationship between metabolic health and lifespan and how nutrients and their metabolism regulate the action of these pathways (Hansen et al., 2013).

Fatty acid-binding proteins (FABPs) are known as intracellular buffer proteins for fatty acids that are involved in lipid trafficking, metabolism, and signaling (Hotamisligil and Bernlohr, 2015). Of