nutrients

MDPI

Review

Interactions between Intestinal Homeostasis and NAD$^+$ Biology in Regulating Incretin Production and Postprandial Glucose Metabolism

Taichi Nagahisa, Shotaro Kosugi and Shintaro Yamaguchi *

Division of Endocrinology, Metabolism and Nephrology, Department of Internal Medicine, Keio University School of Medicine, Shinjuku-ku, Tokyo 160-8582, Japan
* Correspondence: yama1005@a6.keio.jp; Tel.: +81-3-5363-3796; Fax: +81-3-3359-2745

Abstract: The intestine has garnered attention as a target organ for developing new therapies for impaired glucose tolerance. The intestine, which produces incretin hormones, is the central regulator of glucose metabolism. Glucagon-like peptide-1 (GLP-1) production, which determines postprandial glucose levels, is regulated by intestinal homeostasis. Nicotinamide phosphoribosyltransferase (NAMPT)-mediated nicotinamide adenine dinucleotide (NAD$^+$) biosynthesis in major metabolic organs such as the liver, adipose tissue, and skeletal muscle plays a crucial role in obesity- and aging-associated organ derangements. Furthermore, NAMPT-mediated NAD$^+$ biosynthesis in the intestines and its upstream and downstream mediators, adenosine monophosphate-activated protein kinase (AMPK) and NAD$^+$-dependent deacetylase sirtuins (SIRTs), respectively, are critical for intestinal homeostasis, including gut microbiota composition and bile acid metabolism, and GLP-1 production. Thus, boosting the intestinal AMPK–NAMPT–NAD$^+$–SIRT pathway to improve intestinal homeostasis, GLP-1 production, and postprandial glucose metabolism has gained significant attention as a novel strategy to improve impaired glucose tolerance. Herein, we aimed to review in detail the regulatory mechanisms and importance of intestinal NAMPT-mediated NAD$^+$ biosynthesis in regulating intestinal homeostasis and GLP-1 secretion in obesity and aging. Furthermore, dietary and molecular factors regulating intestinal NAMPT-mediated NAD$^+$ biosynthesis were critically explored to facilitate the development of new therapeutic strategies for postprandial glucose dysregulation.

Keywords: incretin; nicotinamide adenine dinucleotide; nicotinamide phosphoribosyltransferase; postprandial glucose metabolism; intestinal homeostasis

Citation: Nagahisa, T.; Kosugi, S.; Yamaguchi, S. Interactions between Intestinal Homeostasis and NAD$^+$ Biology in Regulating Incretin Production and Postprandial Glucose Metabolism. *Nutrients* **2023**, *15*, 1494. https://doi.org/10.3390/nu15061494

Academic Editor: Sturla Laura

Received: 21 February 2023
Revised: 17 March 2023
Accepted: 19 March 2023
Published: 20 March 2023

1. Introduction

Postprandial hyperglycemia in impaired glucose tolerance (IGT) is a crucial risk factor for type two diabetes and cardiovascular diseases (CVDs) [1–6]. The Funagata study conducted on a Japanese cohort revealed that IGT is a risk factor for CVDs and stroke [7]. In addition, the Baltimore Longitudinal Study of Aging, a long-term follow-up study of an adult caucasian population, showed that IGT, and not impaired fasting glucose tolerance, elevates the risk of coronary heart disease [8]. However, the Study To Prevent Non-insulin Dependent Diabetes Mellitus (STOP-NIDDM) trial demonstrated that the α-glucosidase inhibitor (αGI), acarbose, which specifically prevents postprandial hyperglycemia, reduces the risk of progression of IGT to type two diabetes [9] and CVDs [10]. Therefore, postprandial glucose levels are an important therapeutic target for preventing the progression of type two diabetes and its macrovascular complications. However, conventional antidiabetic medications targeting postprandial hyperglycemia, such as αGI and glinide, cause adverse effects, including abdominal symptoms and hypoglycemia, respectively [11,12]; therefore, the development of new therapeutic strategies has been sought.

Postprandial plasma glucose concentrations are regulated by gut incretin hormones, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide

(GIP), which augment insulin secretion when glucose is administered orally; this process is called glucose-stimulated insulin secretion (GSIS), regulating postprandial glucose metabolism [13,14]. GLP-1 is released from L cells, which are mainly located at the ileum, the distal part of the gastrointestinal tract, and is triggered by neuronal or hormonal stimulation and direct nutritional components, including carbohydrates, amino acids, proteins, and fatty acids [15–18]. GIP is secreted from enteroendocrine K cells in the upper small intestine [19]. Several human studies have shown that the GLP-1 secretory response is impaired in obese subjects with postprandial hyperglycemia, although conflicting results have also been reported [20–22]. In addition, fasting GLP-1 and glucose-stimulated GLP-1 secretion decreased significantly over six years in healthy older subjects aged 71.2 ± 3.8 years [23]. Consequently, the intestine and its derived incretin hormones have become potential targets for novel therapeutics to improve postprandial hyperglycemia in obesity and aging. Dipeptidyl peptidase four (DPP4) inhibitors and GLP-1 analogs, which elevate GLP-1 levels, are already commercially available. Additionally, GLP-1 analogs have been found to have preventive effects on CVDs [24]. However, the mechanisms underlying the reduced GLP-1 secretion in obesity and aging, the two major risk factors of insulin resistance and glucose intolerance, remain unclear but might be associated with the alteration of the gut environment modulated by the intake of dietary components. Emerging evidence has suggested that obesogenic diets, including high-fat components, could alter GLP-1 production by affecting the gut microbiota [25–29]. Furthermore, the number of L cells and postprandial plasma GLP-1 secretion decreases in rats fed an obesogenic high-fat diet (HFD) [30]. These findings indicate that fat-rich obesogenic diets alter intestinal homeostasis, which decreases GLP-1 production. Therefore, maintaining intestinal homeostasis could also be a novel strategy for improving GLP-1 production and thereby postprandial glucose metabolism.

We recently analyzed the impact of fat-rich obesogenic diets on intestinal homeostasis and assessed the downstream mediators of diets that affect GLP-1 secretion. It was demonstrated that HFD impairs the biosynthesis of nicotinamide adenine dinucleotide (NAD^+), a key regulator of cellular energy metabolism, which is mediated by nicotinamide phosphoribosyltransferase (NAMPT) enzymatic activity in intestines. Intestinal NAD^+ biology plays an important role in intestinal homeostasis and GLP-1 production in the ileum, consequently influencing postprandial glucose levels; boosting intestinal NAD^+ biosynthesis by administering a key NAD^+ intermediate, nicotinamide mononucleotide (NMN), augments GLP-1 production under HFD conditions [31]. However, the mechanisms by which obesogenic fat-rich diets impair intestinal NAMPT-mediated NAD^+ biosynthesis remain elusive. The aim of this review was to analyze the interplay among intestinal NAD^+ biology, nutritional components, and intestinal homeostasis, including GLP-1 production, and explore the pathophysiological significance and therapeutic potential of intestinal NAD^+ biology in systemic glucose metabolism. First, recent findings in NAD^+ research regarding glucose metabolism were analyzed, and our recent study on the novel roles of intestinal NAD^+ biology in regulating intestinal homeostasis, GLP-1 production, and postprandial glucose metabolism was highlighted. Second, the possible mechanisms by which components, including dietary nutritional contents, affect intestinal homeostasis and NAD^+ biosynthesis, are discussed. Finally, the clinical application of intestinal NAD^+ biology as a novel therapeutic target for postprandial hyperglycemia was explored.

2. Impact of NAD^+ Biology on Systemic Glucose Metabolism in an Organ-Specific Manner

2.1. Changes in NAD^+ Biology with Aging and Obesity in Metabolic Organs

NAD^+ is crucial for regulating aging, metabolism, cell growth, and inflammation [32–35]. Although NAD^+ is utilized as a cofactor or substrate by numerous enzymes to regulate redox status and cellular energy metabolism [36], sirtuins (SIRTs), which are NAD^+-dependent deacetylases, play essential roles in cellular biological processes to maintain metabolic homeostasis [35,37–39]. In rodents, NAD^+ levels decrease with aging or fat-rich diet-induced obesity in various organs, including the skeletal muscle [40–44],

liver [41,42,44–46], adipose tissue [41,42,47], brain [48], pancreas [42], heart [46], kidney [46], and lungs [46]. Similarly, in humans, NAD^+ levels decrease with aging and intake of unbalanced nutrients, such as fat and protein-rich diets, in organs such as the skin [49], skeletal muscle [50], liver [45], and brain [51,52] and in the plasma [53,54] and monocytes [55]. These findings suggest that a decrease in NAD^+ levels is involved in the pathogenesis of age- and obesity-related diseases in humans and rodents. Decreases in NAD^+ contents with age and obesity in metabolic organs may be attributed to changes in the expression or activity of NAD^+ biosynthetic and consuming enzymes [41]. For example, the enzymatic activity of poly (ADP-ribose) polymerase (PARP)1, a representative NAD^+ degrading enzyme, increases in various organs such as the liver, kidney, skeletal muscle, lung, and heart owing to the accumulation of DNA damage associated with aging and HFD-induced obesity and correlates with age- and obesity-related changes in NAD^+ levels [46,56–58].

A cluster of differentiation 38 (CD38), another major NAD^+-degrading enzyme, is highly expressed in inflammatory macrophages that infiltrate organs during aging [59,60]. Furthermore, aging and HFD-induced obesity increase CD38 expression in macrophages and the vascular endothelium. Therefore, CD38 expression increases with age and HFD-induced obesity in major organs such as the liver, skeletal muscle, and lungs, decreasing NAD^+ levels [58–63]. NAD^+ levels are maintained in CD38-deficient mice during aging and obesity stress [41,61]. In contrast to the enhanced NAD^+ consuming pathway, NAD^+ biosynthesis is impaired with aging and obesity, decreasing NAD^+ levels. In mammals, the first step of systemic NAD^+ biosynthesis depends on the salvage pathway in which nicotinamide (NAM), a water-soluble vitamin B3, is converted to NMN by NAMPT. Next, the NMN is converted to NAD^+ by a second enzyme, nicotinamide mononucleotide adenylyltransferase [58,62] (Figure 1). The expression of NAMPT, the rate-limiting enzyme in the salvage NAD^+ biosynthetic pathway, decreases with aging and obesity in various organs, including in white and brown adipose tissue, liver, skeletal muscle, hippocampus, and retina [42,47,63–66].

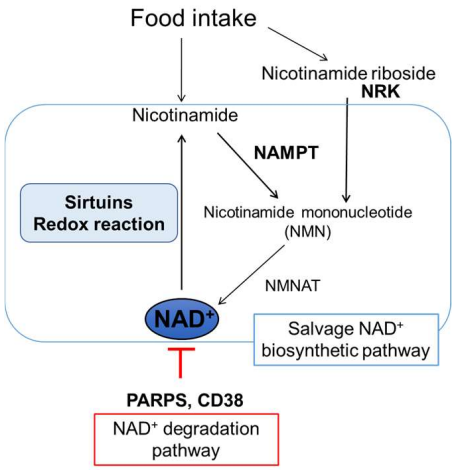

Figure 1. Mammalian NAD^+ biosynthetic salvage and degradation pathways. In mammals, NAMPT is the key enzyme in NAD^+ biosynthetic salvage pathway initiated from nicotinamide in food. SIRTs consume NAD^+ in a tissue-dependent manner, and NAD^+ degradation is mediated by PARPs and CD38. NMNAT—nicotinamide/nicotinic acid mononucleotide adenylyltransferase; NRK—nicotinamide riboside kinase; NAMPT—nicotinamide phosphoribosyltransferase; SIRTs—sirtuins; PARPs—poly ADP ribose polymerases; CD38—cluster of differentiation 38; NAD^+—nicotinamide adenine dinucleotide.

2.2. Impacts of Decrease in NAD^+ Levels with Aging and Obesity on Metabolic Organ Function

The pathophysiological importance of NAD^+ biology in metabolic organs has been investigated using genetically engineered mice models. PARP-1 knockout (KO) mice have increased NAD^+ contents in their skeletal muscle and brown fat tissues, inducing

higher mitochondrial content, increased energy expenditure, and protection against glucose intolerance and insulin resistance [57]. In addition, CD38 KO mice exhibit suppression of age-related decreases in NAD^+ levels in major organs, preserving mitochondrial function and energy and glucose metabolism [41]. For example, the genetic ablation of CD38 increases NAD^+ levels in brown adipose tissues, enhancing the thermogenic activity of brown adipocytes [67].

The impacts of decreased NAD^+ levels on various organ dysfunctions have been investigated using genetically engineered *Nampt*-knockout (NKO) mice models. Homozygous NKO mice exhibit embryonic lethality [68], whereas heterozygous NKO mice exhibit IGT due to impaired insulin secretion [68] and heart failure due to progressive mitochondrial dysfunction induced by pressure overload [69].

The roles of NAMPT-mediated NAD^+ biosynthesis in regulating organ function have also been evaluated using conditional NKO mice. Projection neuron-specific NKO mice develop synaptic dysfunction at neuromuscular junctions in the cerebral cortex and motor neuron degeneration-associated muscle atrophy, resulting in death within an average of 22 days [70]. The cortex- and hippocampus-specific NKO mice exhibit cortical and hippocampal atrophy, abnormal neuronal morphology, and impaired memory and cognitive function [66,71]. Moreover, the hippocampal CA1 region-specific NKO impairs cognitive function [72], and rod and cone cell-specific NKO mice exhibit mitochondrial dysfunction and severe retinal degeneration [73]. Furthermore, skeletal muscle-specific NKO mice develop progressive muscle atrophy [43], hepatocyte-specific NKO mice show hepatic inflammation and fibrosis and reduced liver regeneration [74,75], and proximal tubule-specific NKO mice exhibit glomerular basement membrane thickening and interstitial fibrosis, pathological features of diabetic nephropathy [76]. Vascular smooth muscle-specific NKO mice show a dilated aorta, and angiotensin II administration causes intravascular hemorrhage and aortic dissection [77].

It was recently demonstrated that decreased NAD^+ content in white adipose tissue is associated with severe insulin resistance and IGT due to hypoadiponectinemia at least partly via increased phosphorylation of serine 273 and acetylation of peroxisome proliferator-activated receptor (PPAR) γ in pan adipocyte-specific NKO (ANKO) mice [35,78,79]. Brown adipocyte-specific NKO (BANKO) mice were also established, and their metabolic phenotypes were directly compared with that of ANKO mice. Decreased NAD^+ levels in white and brown adipose tissues were associated with impaired heat production and energy metabolism in brown adipose tissue [80].

In addition to these intracellular NAMPT (iNAMPT), another type of NAMPT exists—extracellular NAMPT (eNAMPT) [68]. The interaction between iNAMPT enzymatic activity and eNAMPT secretion, and the role of plasma eNAMPT, especially in the aging process, was recently identified. The iNAMPT in adipose tissue plays an important role in white and brown adipocyte function by regulating NAD^+ levels and SIRT1 activity, one of the seven mammalian proteins of the SIRT family. Secretion of eNAMPT from the adipose tissue is determined based on the acetylation status of iNAMPT regulated by SIRT1 [81]. Furthermore, the acetylation status of iNAMPT is regulated by another nuclear SIRT, SIRT6, in cancer cells. SIRT6-mediated regulation of eNAMPT release occurs by modulating the iNAMPT acetylation status in cancer cells, contrasting with the SIRT1-mediated secretion of eNAMPT from the adipose tissues [82], although the precise mechanisms for these different regulation patterns are currently being investigated.

In ANKO mice, a reduction in plasma eNAMPT levels suppresses hypothalamic NAD^+ levels and SIRT1 activity, resulting in a defect in physical activity. Contrastingly, adipocyte-specific *Nampt* knockin (ANKI) mice exhibit increased plasma eNAMPT, hypothalamic NAD^+ levels, and SIRT1 activity, enhancing physical activity [81]. Plasma eNAMPT levels decrease with aging in mice and humans, and a positive correlation exists between plasma eNAMPT levels and life expectancy in mice. Plasma eNAMPT levels in old ANKI mice remained higher than those in the control group, and NAD^+ levels in the hypothalamus, hippocampus, pancreas, and retina remained higher in female ANKI mice. Old ANKI

mice have enhanced expression of SIRT1 target genes in the hypothalamus [83,84], which is important for physical activity and sleep quality and maintains memory and learning ability, retinal photoreceptor neurons, and further insulin secretion capacity with better glucose tolerance. Female ANKI mice maintain their body weight, especially fat mass, even during aging, showing a 13.4% increase in healthy life span compared to the control group [85]. A recent report demonstrated that peripubertal-stressed male mice exhibit increased adiposity, which triggers diminished NAMPT protein levels in adipose tissue and decreased levels of circulating eNAMPT, contributing to lifelong reductions in sociability [86]. These results suggest that maintaining both iNAMPT-mediated NAD^+ biosynthesis in major metabolic organs and plasma eNAMPT, a key effector of adipose-to-brain signaling, by boosting adipocyte iNAMPT-mediated NAD^+ biosynthesis could improve organ function and whole-body glucose metabolism and promote a healthy physical and mental status.

3. Regulators of Intestinal Homeostasis

3.1. Intestinal AMPK and NAD^+ Biosynthesis

A study demonstrated that systemic *Nampt*-inducible KO mice lost weight owing to intestinal villus atrophy-associated impaired absorption, which resulted in death within approximately 5–10 days after birth [87]. This suggests that intestinal NAD^+ biosynthesis plays a critical role in intestinal homeostasis. Although the molecular mechanism(s) underlying the association between intestinal NAD^+ biology and homeostasis remains enigmatic, AMPK has been demonstrated to upregulate NAMPT, boosting NAD^+ biosynthesis and SIRT activity [88–90]. AMPK, an energy sensor that regulates whole-body energy balance [91], is expressed in several metabolic organs, including the liver, brain, adipose tissues, skeletal muscle, and intestine [92,93]. Calorie restriction activates AMPK in intestinal stem cells and increases NAD^+ levels by stimulating *Nampt* transcription. Thus, activated intestinal NAMPT-mediated NAD^+ biosynthesis by AMPK further enhances SIRT1 activity in the intestinal stem cells, consequently increasing their number [94]. Intestinal-specific AMPK upregulation maintains intestinal homeostasis, such as barrier function, and muscle protein homeostasis by inducing autophagy during aging, ultimately extending lifespan [95].

Furthermore, pharmacological activation of AMPK enhances intestinal barrier function and epithelial differentiation by promoting the key transcription factor, caudal type homeobox two (CDX2), committing cells to intestinal epithelial lineage [96]. In contrast, high glucose contents attenuate intestinal AMPK activation. AMPK diminished in *Psammomys obesus* with insulin resistance and type 2 diabetes, possibly due to disruptions in insulin signaling at the jejunum [93]. A recent report demonstrated that genetic deletion of intestinal AMPK alters gut microbiota and their metabolites, including antimicrobial peptides, resulting in weight gain and IGT with HFD intake [97]. In addition, intestinal epithelial cell-specific deletion of AMPK results in hyperpermeability in the distal colon with a regular chow diet, accompanied by altered microbial composition [98]. Similarly, AMPK depletion in intestinal epithelial cells impairs intestinal barrier function and integrity and epithelial cell migration [96] (Figure 2). Consistent with the findings that intestinal AMPK, which mediates NAMPT activation, is impaired in glucose intolerance, HFD-induced obesity, and aging downregulates the major NAD^+-generating enzymes, including NAMPT, and reduces intestinal NAD^+ levels [31,99,100]. These findings suggest that intestinal AMPK could play a central role in maintaining intestinal homeostasis, including microbial composition, as a possible upstream mediator of intestinal NAMPT-mediated NAD^+ biosynthesis.

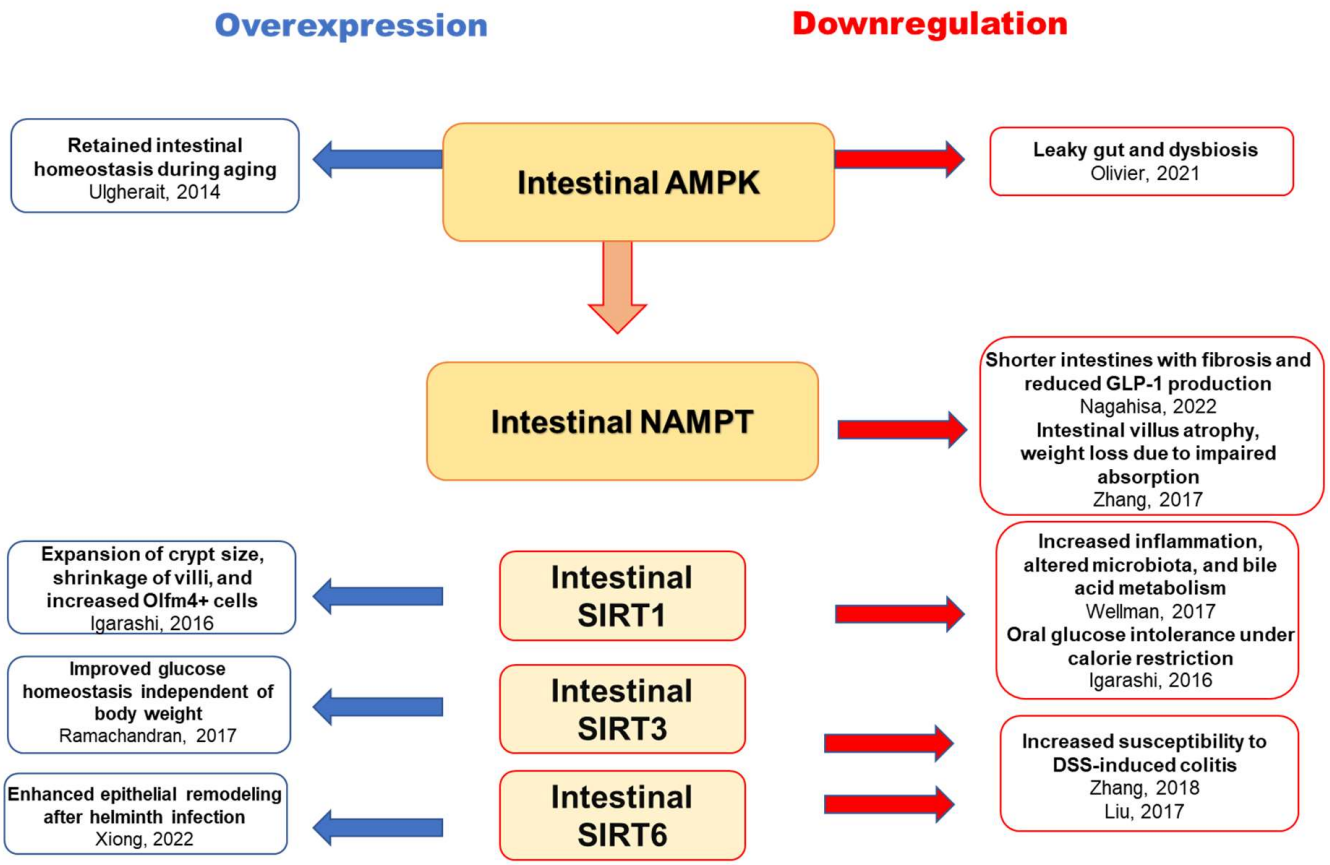

Figure 2. Intestinal phenotype induced by the overexpression or knockout of the intestinal AMPK-NAMPT-NAD^+-sirtuin pathway [31,87,94,95,98,101–105]. Olfm4—olfactomedin 4.

To explore the role of intestinal AMPK in whole-body glucose metabolism, metformin, an AMPK activator, could be the best candidate to analyze. Metformin, an antidiabetic drug, represses hepatic glucose production by inhibiting mitochondrial glycerophosphate dehydrogenase and altering hepatic redox status. Additionally, it activates intestinal AMPK [93,106–108]. Thus, its beneficial effect on glucose metabolism also depends on intestinal AMPK, which modulates gut microbial composition [97,109]; this is supported by the observation that loss of intestinal AMPK alters gut microbiota composition [98]. Metformin acts on intestinal AMPK, inhibiting the farnesoid X receptor (FXR), the nuclear receptor for maintaining bile acid homeostasis, consequently increasing the bile acid pool and stimulating GLP-1 secretion [110–112]. Additionally, metformin enhances GLP-1 secretion without affecting AMPK activity. GLP-1 secretion is stimulated by the activation of the insulin signaling pathway, followed by the wingless-related integration site (Wnt) signaling pathway in L cells [113,114]. Collectively, boosting intestinal AMPK–NAMPT—NAD^+ biosynthesis could benefit systemic glucose metabolism by maintaining intestinal homeostasis, including GLP-1 synthesis and microbial composition (Figure 3).

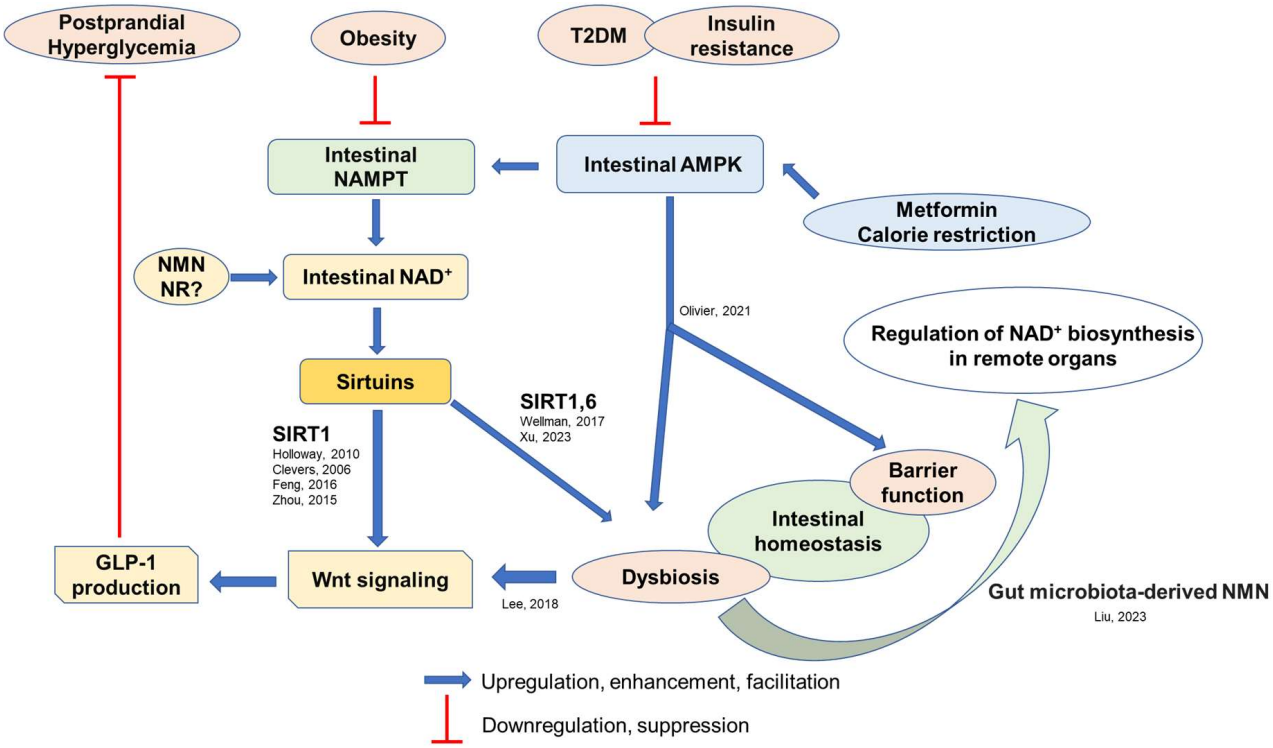

Figure 3. Vicious cycles of metabolic disorders by disrupting intestinal AMPK–NAMPT–NAD–SIRT1–gut microbiota–Wnt signaling–GLP-1 axis [98,101,115–121]. NMN—nicotinamide mononucleotide; NR—nicotinamide riboside; Wnt—wingless-related integration site; GLP-1—glucagon-like peptide-1.

3.2. Intestinal Wnt Signaling

Wnt signaling is another key regulator of intestinal homeostasis. Intestinal Wnt signaling, which is regulated by the gut microbiota [122,123], contributes to intestinal stem cell maintenance [124]. A recent study revealed that intestinal stem cell function and regenerative capacity decrease owing to impaired Wnt signaling during aging; this was evidenced by the blunted organoid formation of crypt obtained from aged mice, which was rescued by restoring canonical Wnt signaling [125]. Similarly, the impairment of intestinal stem cell function during aging was rescued by boosting the NAD^+ biosynthetic pathway by supplementing nicotinamide riboside (NR), an NAD^+ intermediate [126]. These findings suggest that impairment of Wnt signaling and intestinal NAD^+ biosynthesis synergistically or independently disrupt intestinal homeostasis. Furthermore, genetic deletion of the Wnt antagonist, Dickkopf (Dkk) 2, which increases intestinal Wnt activity, stimulates GLP-1 production, thereby improving whole-body glucose tolerance [127].

Although plausible factors underlying the relationship between intestinal NAD^+ biosynthesis and Wnt signaling remain unknown, SIRT1 is a possible contributing molecule. Halloway et al., demonstrated that SIRT1 promotes transient and constitutive Wnt signaling [115]. SIRT1 potentiates β-catenin recruitment into the nucleus, where it binds to the T cell factor/lymphoid enhancer factor [116]. Furthermore, SIRT1 regulates the transcription of downstream target genes of Wnt/β-catenin in osteogenesis [117] and adipogenesis [118]. Overall, intestinal NAD^+–SIRT1–gut microbiota–Wnt signaling could be crucial for intestinal homeostasis and systemic glucose metabolism by regulating GLP-1 production (Figure 3).

4. Pathophysiological Roles of Intestinal NAD^+ Biosynthesis

The intestine is a central regulator of glucose metabolism [128–130]. Intestinal epithelial cell-specific *Sirt1* KO mice exhibit glucose intolerance during oral glucose tolerance tests under calorie-restriction conditions [94]. As NAD^+ is essential for SIRT activity, intestinal NAD^+ biosynthetic status was investigated. HFD administration impaired intestinal NAMPT-mediated NAD^+ biosynthesis [31]. To extensively evaluate the roles of intestinal NAMPT-mediated NAD^+ biosynthesis in intestinal homeostasis and glucose metabolism, an intestinal epithelial cell-specific NKO mouse model (INKO) was established [31]. INKO mice fed a regular chow diet had shorter intestines with fibrotic changes, suggesting that intestinal NAMPT-mediated NAD^+ biosynthesis helps maintain intestinal homeostasis. Furthermore, an increased glucose excursion with reduced GLP-1 and insulin secretion was observed in INKO mice after oral glucose loading. We investigated the underlying mechanism of reduced GLP-1 in INKO mice. Silencing transcription factor 7-like 2 (TCF7L2), a crucial transcriptional factor in the canonical Wnt signaling, impacted pancreatic β cell mass and impaired GSIS by disrupting vesicle fusion of secretory granules [131,132]. Humans with genetic variants of TCF7L2 are predisposed to diabetes due to changes in GLP-1 and pulsatile insulin secretion [133–135]. In addition, functional ablation of TCF7L2 in proglucagon-expressing cells decreases proglucagon expression and GLP-1-positive cells in the gut, reducing plasma GLP-1 secretion [136]. These findings led us to investigate Wnt signaling as a possible downstream mediator connecting intestinal NAD^+ biosynthesis and GLP-1 production [136,137]. In vitro experiments using STC-1 cells as enteroendocrine cells demonstrated that ICG-001, a selective inhibitor of Wnt/βcatenin signaling, dose-dependently reduced proglucagon gene expression. Furthermore, the concurrent addition of ICG-001 negated the amelioration of GLP-1 secretion by recovering NAD^+ levels, suggesting that Wnt signaling regulates GLP-1 secretion from L cells as a downstream mediator of NAD^+ biosynthesis.

As postprandial hyperglycemia was observed in intestinal epithelial cell-specific *Sirt1* KO mice, SIRTs could be the molecule connecting intestinal NAMPT-mediated NAD^+ biosynthesis and canonical Wnt signaling to stimulate GLP-1 secretion [31,94] (Figures 2 and 3). PPARβ/δ might also be responsible for the reduced GLP-1 production due to NAD^+ depletion, as it has been demonstrated to transcriptionally regulate proglucagon expression in enteroendocrine L cells by stimulating the β-catenin/TCF7L2 pathway [138]. Collectively, intestinal NAMPT-mediated NAD^+ biosynthesis contributes to Wnt signaling, maintaining intestinal homeostasis, including GLP-1 production and postprandial glucose homeostasis (Figure 3).

5. Potential Effects of Dietary Habits and Its Associated Gut Environment on Intestinal Homeostasis and GLP-1 Secretion

Several types of food have been demonstrated to modulate intestinal homeostasis. For example, arachnoid acid, found in animal meat, promotes intestinal epithelial regeneration in cases of irradiation injury by activating Wnt signaling [139,140], and dietary vitamin D, found in sun-dried mushrooms and oily fish, such as salmon, facilitates intestinal epithelial cell turnover during bowel resection in rodents [139,140]. A high-fat ketogenic diet, which elevates circulating ketone body levels [141], boosts intestinal stem cell numbers and function, enhancing intestinal stemness [142]. Similarly, obesogenic HFD augments the number and function of intestinal stem cells and enhances their capacity to initiate tumors [143]. In addition, HFD induces dysbiosis, reducing lactobacillus, which produces lactate. Lactate acts on the lactate receptor, G-protein-coupled receptor 81 (GPR81) and augments the proliferative potential of intestinal stem cells [119,144]. Furthermore, HFD in catch up growth rat models induces lipotoxicity in the intestinal L cells, increasing intestinal L cell apoptosis and reducing GLP-1 secretion [30].

Dietary components are associated with postprandial GLP-1 secretion in humans as well. For example, habitual added sugar consumption exerts a positive effect on striatal response to food cues and a negative effect on postprandial GLP-1 response. These sugar

consumption-associated alterations could contribute to pathological overeating [145]. Oral intake of whey protein dose-dependently increases GLP-1 release in younger healthy lean males and healthy older people [146,147]. Relatively large amounts of fat (40% kcal fat diet) increase postprandial GLP-1 secretion in healthy elderlies though not in younger people [148]. Fat ingestion before a carbohydrate meal slows gastric emptying, delays the postprandial rises in blood glucose, plasma insulin, and GIP, and stimulates GLP-1 secretion in type 2 diabetes [149]. These findings support the previous notion that the effect of fat on gastric emptying and absorption of nutrients depends on when it is consumed [150]. The effect of the intake sequence of food macronutrients, including vegetables, protein, and carbohydrates, on postprandial glucose levels, insulin, and incretin secretions was evaluated in healthy adults. The postprandial glucose and insulin response was attenuated, whereas GLP-1 secretion was stimulated by the vegetable-protein-carbohydrate food intake sequence [151].

Another important factor that regulates the interplay between food, intestinal homeostasis, and GLP-1 secretion is the gut microbiota and its associated bile acid abundance and composition. The important role of microbiota in maintaining intestinal homeostasis and regulating whole-body glucose and energy metabolism has been intensely investigated [152–155]. The microbiota plays a critical role in intestinal immunity, and dysbiosis may be involved in the pathogenesis of obesity and metabolic syndrome by inducing low-grade inflammation in remote organs such as the liver or adipose tissue [156]. However, an alteration of the intestinal immune response leads to obesogenic microbiota and obesity [157]. HFD intake increases the proportion of lipopolysaccharide-containing gut microbiota, triggering metabolic endotoxemia, a low-grade inflammation factor [158]. The underlying mechanisms of such HFD-induced systemic metabolic endotoxemia due to dysbiosis might involve low-grade intestinal inflammation and enhanced gut permeability [159]. Intestinal NAD^+ biosynthesis and NAD^+-dependent deacetylase SIRTs, specifically SIRT1, is a possible molecular mechanism underlying the association between age- and obesity-associated alteration of microbiota composition, intestinal inflammation, permeability, and metabolic complications. A previous report also demonstrated that treatment with resveratrol, a potent SIRT1 activator metabolized by gut microbiota, alters microbiota composition, decreases body weight, and improves insulin sensitivity and lipid metabolism in rodents [160,161]. Contrarily, genetic ablation of *Sirt1* in the intestinal epithelium deteriorates age-associated intestinal inflammation and dysbiosis partly by modulating bile acid metabolism [101]. Our previous study also showed that INKO mice have a different gut microbiota composition than their counterparts under a regular chow diet, suggesting that intestinal NAD^+ biosynthesis is involved in maintaining gut microbiota homeostasis and possibly contributing to the reduced GLP-1 production (unpublished data). Contrastingly, normal gut microbiota variation produces NMN, enhancing pancreatic NAD^+ biosynthesis and mitochondrial deacetylase SIRT3 activity. Thus, gut microbiota-derived NMN protects against acute pancreatitis [120]. These results suggest that the gut microbiota, the gut microbiota-derived NMN, and the intestinal NAMPT–NAD^+–SIRT axis collaborate to regulate intestinal homeostasis and systemic metabolic functions (Figure. 3).

HFD intake causes an imbalance in the gut microbial community, affecting bile acid abundance and composition [162]. Several bile acid species, such as tauroursodeoxycholic acid, have disease-preventing effects [163]. Bile acids exert endocrine and metabolic effects by acting on FXR and Takeda G protein-coupled receptor five (TGR5). FXR inhibition increases GLP-1 secretion in response to glucose intake. Thus, bile acid profile alteration affects postprandial GLP-1 secretion and systemic glucose metabolism [164]. In addition, GLP-1 secretion is positively correlated with postprandial bile acid concentration in healthy individuals [165]. Therefore, diet, and its associated gut environment, may have regulatory effects on intestinal homeostasis, GLP-1 secretion, and postprandial glucose homeostasis at least partly by modulating the AMPK–NAMPT–NAD^+–SIRT1–gut microbiota–Wnt signaling, either dependent or independent of bile acid composition (Figure 3).

6. Therapeutic Potential of NAD^+ Intermediates as GLP-1 Stimulants

NAD^+ intermediates, such as NMN and NR, have attracted attention as a strategy to boost NAD^+ biosynthesis. NMN and NR are endogenously biosynthesized metabolites detected in human breast milk [166]. NMN is also found in edamame, broccoli, cucumber, avocado, tomatoes, beef, and shrimp in small quantities [167]. NMN and NR administration increases NAD^+ levels in major metabolic organs in animal models of various diseases, exerting remarkable effects on age- and obesity-associated diseases such as diabetes, CVD, cancer, and Alzheimer's disease [62,168–170]. For example, the intraperitoneal administration of NMN restores NAD^+ biosynthesis and improves glucose intolerance, insulin resistance, and dyslipidemia in age- or HFD-induced diabetic mice by activating SIRT1-catalyzed reactions [42]. Oral administration of NR also increases NAD^+ levels in the liver, brown adipose tissue, and skeletal muscle. Enhancing NAD^+ biosynthesis promotes SIRT1- and SIRT3-catalyzed reactions, improving metabolic disorders such as weight gain, insulin resistance, and dyslipidemia associated with an HFD [171].

The effects of the NAD^+ intermediates on longevity and healthy life expectancy have recently gained attention. For example, 6-week NR administration improves muscle stem cell function and prolongs the life span of 24-month-old mice. These findings indicate that boosting NAD^+ biosynthesis is associated with a life span [172]. Twelve-month oral administration of NMN suppresses weight gain and improves insulin sensitivity, adipose tissue inflammation, physical activity, skeletal muscle mitochondrial function, retinal function, and bone density in 5–17-month-old mice [167]. The details of the in vivo pharmacokinetics of NR and NMN remain unclear. Systemically administered NR may be metabolized in the liver or rapidly hydrolyzed in the blood or intestinal tract and taken up by organs as NAM [43,173,174]. The Slc12a8-encoded NMN-specific transporter has been recently demonstrated to be highly expressed in the small intestine [175], leading to the gradual understanding of the pharmacokinetics of NMN [42,167].

A recent study demonstrated that oral administration of NR could affect intestinal NAD^+ biosynthesis, mitigating ethanol-induced intestinal epithelial barrier damage by protecting mitochondrial function in a SIRT1-dependent manner [176]. We also recently discovered that HFD impairs intestinal NAMPT-mediated NAD^+ biosynthesis and disrupts the Wnt signaling pathway, GLP-1 production, and whole-body glucose metabolism. HFD-fed obese mice were administered NMN (500 mg/kg/bodyweight/day) using oral gavage for 14 days. NMN significantly increased NAD^+ concentrations and proglucagon expression in the ileum. In addition, ileum explants from NMN-treated HFD-fed obese mice exhibited higher GLP-1 secretion, which improved postprandial hyperglycemia [31]. Our findings demonstrated that NMN promotes intestinal GLP-1 secretion by restoring intestinal NAD^+ biosynthesis in HFD-induced obese mice, suggesting that NMN could be a novel therapeutic option for improving postprandial hyperglycemia in obesity.

Based on these experimental animal data, clinical trials investigating the safety and efficacy of NAD^+ intermediates in humans are currently underway worldwide. A single oral dose of NR increases the concentration of NAD^+ metabolites in a concentration-dependent manner in human peripheral blood mononuclear cells (PBMCs) [177]. Furthermore, the safety of its long-term oral administration has been confirmed [178,179]. NR administration benefits blood pressure, carotid-femoral pulse waves, maximal muscle strength, and fatigue in healthy subjects [180]. In elderly and obese subjects, it improves inflammatory blood markers, energy metabolism at bedtime, and fatty liver [181–183], though not insulin sensitivity, glucose tolerance, or skeletal muscle mitochondrial function [181,182,184]. In addition, the oral administration of NR does not affect GLP-1 secretion in nondiabetic individuals with obesity [184].

The safety and efficacy of NMN administration have been rigorously explored (Table 1). The safety study of a single oral intake of 100, 250, and 500 mg NMN in healthy middle-aged men was conducted in Japan. NMN dose-dependently increased NAM metabolites, such as *N*-methyl-2-pyridone-5-carboxamide and *N*-methyl-4-pyridone-5-carboxamide in the plasma without exerting any significant deleterious effects [185]. In healthy Japanese

participants between 20 and 65 years old, oral supplementation with 125 mg NMN twice daily for 12 weeks increased NAD^+ levels in whole blood without causing abnormalities in physiological and laboratory tests [186]. Oral administration of 1250 mg NMN once daily for four weeks was reported to be safe and well-tolerated in healthy adult men and women aged 20–65 years [187]. In older male patients over 65 years old with diabetes and impaired physical performance, 250 mg NMN supplementation for 24 weeks was safe and tolerated and did not improve grip strength and walking speed [188]. However, an oral intake of 250 mg NMN once daily in elderly men over 65 years old for 12 weeks increased whole blood NAD^+ and NAD^+-related metabolite levels, improving gait speed and performance in the left grip test without any deleterious effects [189]. Furthermore, an oral intake of 250 mg NMN once daily in the afternoon for 12 weeks effectively improved physical performance and fatigue in elderly people over 65 years old [190]. Exercise combined with 300, 600, and 1200 mg of daily NMN supplementation dose-dependently increased aerobic capacity in healthy amateur runners [191]. Oral administration of 300, 600, and 900 mg NMN daily for 60 days was well-tolerated and increased blood NAD^+ concentrations in healthy middle-aged adults, improving physical performance, blood biological age, and subjective general health assessment. However, insulin resistance assessed using the homeostasis model assessment-estimated insulin resistance was not ameliorated [192]. In contrast, oral intake of 300 mg NMN once daily after breakfast for 60 days increased the possibility that NMN could benefit insulin sensitivity in healthy subjects between the ages of 40 and 65 years [193]. Consistent supplementation with 250 mg NMN daily for 10 weeks increased NAD^+ and its metabolites in PBMCs and improved muscle insulin sensitivity in obese postmenopausal women with prediabetes [194].

Table 1. Summary of recent NMN human clinical studies.

Design	Subjects	Dose, Administration Route, and Form of NMN	Treatment Duration	Method for Validating Increased NAD^+ Level	Findings	Publication Year	Ref.
Single-arm, nonrandomized, nonblinded study	Age, 40–60 years; healthy men (n = 10)	100, 250, and 500 mg/day; oral administration; capsule	Single administration	NMN administration dose-dependently increased plasma concentrations of 2PY and 4PY.	Single oral administration of NMN did not cause significant changes in clinical symptoms, including vital signs, ophthalmic examination, sleep quality, and laboratory analysis results.	2020	[185]
Randomized, double-blind, placebo-controlled, parallel-group study	Age, 20–65 years; healthy males and females (NMN, n = 15; placebo, n = 15)	250 mg/day; oral administration; tablet	12 weeks	NMN administration increased NAD^+ and NAMN levels in whole blood.	No obvious abnormalities in physiological and laboratory tests and no adverse effects were observed.	2022	[186]
Randomized, double-blind, placebo-controlled, parallel-group study	Age, 20–65 years; healthy males and females (NMN, n = 16; placebo, n = 15)	1250 mg /day; oral administration; packaged powder dissolved in water (200 mL)	4 weeks	N/A	Oral administration of NMN 1250 mg/day for 4 weeks did not cause significant abnormalities in anthropometry, hematological, biochemical, urine, and body composition analyses.	2022	[187]
Prospective, placebo-controlled, double-blind study	Age, over 65 years; elderly males with type 2 diabetes with reduced grip strength or walking speed (NMN, n = 6; placebo, n = 7)	250 mg/day; oral administration; capsule	24 weeks	N/A	Adverse events were not observed in the NMN group. NMN did not improve grip strength and walking speed. However, an improved prevalence of frailty and central retinal thickness was observed.	2023	[188]

Table 1. *Cont.*

Design	Subjects	Dose, Administration Route, and Form of NMN	Treatment Duration	Method for Validating Increased NAD^+ Level	Findings	Publication Year	Ref.
Randomized, double-blind, placebo-controlled, parallel-group study	Age; over 65 years; elderly healthy males (NMN, *n* = 11; placebo, *n* = 11)	250 mg/day; oral administration; pill	12 weeks	NMN administration increased NAD^+ and NAD^+-related metabolites levels in whole blood, assessed by metabolomic analysis	NMN nominally but significantly improved gait speed and performance in the left grip tests without affecting body composition and glucose metabolism were observed.	2022	[189]
Randomized, double-blind, placebo-controlled study	Age, over 65 years; elderly males (NMN antemeridian, *n* = 27; post meridian, *n* = 27. Placebo antemeridian, *n* = 27; post meridian *n* = 27)	250 mg/day; oral administration; tablet	12 weeks	N/A	NMN intake in postmeridian improved lower limb function and drowsiness.	2022	[190]
Randomized, double-blind, placebo-controlled, four-arm clinical study	Age, 27–50 years; healthy recreationally trained runners (40 males and 8 females)	300, 600, 1200 mg/day, oral administration; powder	6 weeks	N/A	Exercise combined with 300, 600, and 1200 mg of daily NMN supplementation dose-dependently increased aerobic capacity.	2021	[191]
Randomized, double-blind, placebo-controlled, parallel-group study. Dose-dependent study	Age, 40–65 years; healthy males and females (NMN, 300, 600, and 900 mg; placebo, *n* = 20)	300, 600, 900 mg/day; oral administration; capsule	60 days	Blood NAD^+ concentrations were increased compared to baseline in three NMN-treated groups (300, 600, 900 mg) on days 30 and 60.	NMN administration was safely tolerated. Walking distance during the six-minute walking test, the change of biological age, and SF-36 scores were improved in the NMN 300, 600, and 900 mg groups on day 60.	2023	[192]
Randomized, double-blind, placebo-controlled, parallel-group study	Age, 40–65 years; healthy males and females (NMN, *n* = 31; placebo, *n* = 35)	300 mg/day; oral administration; capsule	60 days	Serum NAD^+/NADH levels were increased by 11.3% on day 30 and 38% on day 60 vs. baseline.	Walking endurance: SF-36 questionnaire score, a parameter for well-being, and HOMA-IR index improved with NMN administration for 60 days.	2022	[193]
Randomized, double-blind, placebo-controlled study	Age, 55–75 years; postmenopausal women with prediabetes (NMN, *n* = 13; placebo, *n* = 12)	250 mg/day; oral administration; capsule	10 weeks	Plasma concentrations of 2 PY and 4 PY and NAD^+ contents in PBMCs increased after 10 weeks of NMN treatment. *N*-methyl-nicotinamide, 2PY, and 4PY increased in quadriceps muscle tissue samples obtained 1.5 h after the last dose of NMN	NMN increased muscle insulin sensitivity assessed using the hyperinsulinemic-euglycemic clamp.	2021	[194]
Single-blind study	Age, 45–75 years; males and females with sleep disturbance without primary conditions (NMN, *n* = 32; placebo, *n* = 31)	300 mg/day; oral administration; capsule	12 weeks	N/A	NMN improved sleep quality assessed using PSQI and smart bands sleep data	2022	[195]
Open-label, single-arm exploratory study	Age, 20–70 years; healthy males and females (*n* = 10)	300 mg/day; intravenous administration; dissolved in saline (100 mL)	Single adminis-tration	Total amount of NAD^+ levels in the blood was increased.	Intravenous NMN administration reduced blood triglyceride levels without affecting blood cells, electrocardiograms, pulse, blood pressure, and metabolic markers in the liver, heart, pancreas, and kidneys.	2022	[196]

2PY—*N*-methyl-2-pyridone-5-carboxamide; 4PY—*N*-methyl-4-pyridone-5-carboxamide; PBMC—peripheral blood mononuclear cell; N/A—not applicable; NAMN—nicotinic acid mononucleotide; HOMA-IR—homeostatic model assessment for insulin resistance; SF-36—36-item short form survey instrument; PSQI—Pittsburgh sleep quality index.

Based on these findings, the safety of NMN has been demonstrated to a certain extent; however, its effects on whole-body glucose metabolism in humans remain inconclusive. Although oral administration of NR did not improve insulin sensitivity or affect GLP-1 secretion, oral intake of NMN alleviated insulin resistance in obese prediabetic females [194]. As oral NMN administration augments GLP-1 secretion and improves postprandial glucose metabolism in obese mice [31], the different effects between NMN and NR on GLP-1 production and whole-body glucose metabolism may involve the presence of the NMN transporter in the small intestine [175]. Human studies investigating the effects of orally administered NMN on intestinal NAD^+ biology, GLP-1 secretion, and postprandial glucose metabolism should be comprehensively conducted. The results from the human clinical study will further validate that boosting intestinal NAD^+ biosynthesis by orally administering NMN could be a new therapeutic approach to improve intestinal homeostasis, postprandial glucose metabolism, and ultimately, healthy life expectancy.

7. Conclusions and Prospects

Postprandial hyperglycemia in obesity and aging is an important treatment target to reduce the risk of progression to type 2 diabetes and the incidence of CVDs [1–6]. Several medications for postprandial hyperglycemia, such as αGI, glinide, DPP4 inhibitors, and GLP-1 analogs, have been commercially available for the past decade and have been shown to exert efficient antihyperglycemic effects and additional protective effects against CVDs [9,10,24]. However, they can induce adverse effects, and there is a lack of evidence to support their ability to promote healthy aging and life expectancy [11,12,197]. Therefore, the development of novel therapies targeting postprandial hyperglycemia, which could improve both cardiovascular outcomes and healthy life expectancy, has been sought.

The overall findings of several rodent studies targeting intestines have indicated that the intestinal AMPK–NAMPT–NAD–SIRTs axis plays an important role in maintaining intestinal homeostasis, thereby regulating GLP-1 production and postprandial glucose metabolism. Thus, these findings provide important mechanistic and therapeutic insights into the disruption of intestinal homeostasis and postprandial glucose dysregulation, particularly in obesity and aging. Nevertheless, several important questions remain unanswered and require further investigation. First, elucidating the molecular mechanism underlying the regulation of intestinal *Nampt* expression is warranted. Furthermore, given that calorie restriction-induced AMPK activation stimulates *Nampt* transcription [94], and metformin, an AMPK activator, activates intestinal AMPK [93,106–108], the effects of metformin administration on *Nampt* expression and GLP-1 production should be comprehensively tested in HFD-fed obese mice with impaired intestinal NAMPT-mediated NAD^+ biosynthesis [31]. In different cell types, *Nampt* gene transcription is regulated by the circadian locomotor output cycles kaput/brain and muscle ARNT-like one (CLOCK:BMAL1) complex [38,198]. As the ileal diurnal rhythms of microbiome and transcriptome are disrupted in HFD-fed obese mice [199], changes in intestinal *Nampt* transcription and intestinal bacterial composition should be examined in mice with disturbed lifestyles such as diet and the timing of meals. Second, the involvement of gut microbiota and NMN transporter in NMN absorption should be investigated. Orally administered NAM is first converted to nicotinic acid (NA) by the gut microbiota and absorbed as NA from the colon [200], and orally administered NR is converted to NAM and then to NA by the microbiota [201]. These findings suggest that the uptake of orally administered NAD^+ precursors requires microflora. Consistently, normal gut microbiota variation is required to produce NMN, enhancing NAD^+ biosynthesis in remote organs [120]. Therefore, the Slc12a8 NMN transporter and microbiota in the small intestine might work synergistically to regulate intestinal and whole-body NAD^+ biosynthesis. Thus, NMN transporter expression, microbiota composition, and NAD^+ metabolism in multiple organs in INKO mice should be further explored. Lastly, the effects of NMN on GLP-1 production, postprandial glucose regulation, gut microbiota, and healthy life expectancy in aged individuals with obesity should be evaluated in random-

ized, controlled clinical trials. Such studies will elucidate the novel therapeutic potential of intestinal NAD^+ biology for improving postprandial hyperglycemia and healthy longevity.

Author Contributions: Conceptualization, S.Y.; Writing—Original Draft Preparation, T.N., S.K. and S.Y.; Writing—Review & Editing, S.Y. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Scientific Research Fund of the Ministry of Education, Culture, Sports, Science, and Technology of Japan (grant no. 21K07377), Keio University Global Research Institute Pre-Start-up Grant 2022, and research grants from Daiwa Securities Health Foundation, Takeda Science Foundation, and the 2021 Inamori Research Grant Program.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Tominaga, M.; Eguchi, H.; Manaka, H.; Igarashi, K.; Kato, T.; Sekikawa, A. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. *Diabetes Care* **1999**, *22*, 920–924. [CrossRef]
2. Abbott, R.D.; Donahue, R.P.; MacMahon, S.W.; Reed, D.M.; Yano, K. Diabetes and the risk of stroke. The Honolulu Heart Program. *JAMA* **1987**, *257*, 949–952. [CrossRef] [PubMed]
3. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: Comparison of fasting and 2-h diagnostic criteria. *Arch. Intern. Med.* **2001**, *161*, 397–405. [CrossRef] [PubMed]
4. Hanefeld, M.; Fischer, S.; Julius, U.; Schulze, J.; Schwanebeck, U.; Schmechel, H.; Ziegelasch, H.J.; Lindner, J. Risk factors for myocardial infarction and death in newly detected NIDDM: The Diabetes Intervention Study, 11-year follow-up. *Diabetologia* **1996**, *39*, 1577–1583. [CrossRef] [PubMed]
5. Nakagami, T.; DECODA Study Group. Hyperglycaemia and mortality from all causes and from cardiovascular disease in five populations of Asian origin. *Diabetologia* **2004**, *47*, 385–394. [CrossRef]
6. Fujishima, M.; Kiyohara, Y.; Kato, I.; Ohmura, T.; Iwamoto, H.; Nakayama, K.; Ohmori, S.; Yoshitake, T. Diabetes and cardiovascular disease in a prospective population survey in Japan: The Hisayama Study. *Diabetes* **1996**, *45* (Suppl. 3), S14–S16. [CrossRef]
7. Oizumi, T.; Daimon, M.; Jimbu, Y.; Wada, K.; Kameda, W.; Susa, S.; Yamaguchi, H.; Ohnuma, H.; Tominaga, M.; Kato, T. Impaired glucose tolerance is a risk factor for stroke in a Japanese sample—The Funagata study. *Metabolism* **2008**, *57*, 333–338. [CrossRef]
8. Blake, D.R.; Meigs, J.B.; Muller, D.C.; Najjar, S.S.; Andres, R.; Nathan, D.M. Impaired glucose tolerance, but not impaired fasting glucose, is associated with increased levels of coronary heart disease risk factors: Results from the Baltimore Longitudinal Study on Aging. *Diabetes* **2004**, *53*, 2095–2100. [CrossRef]
9. Chiasson, J.L.; Josse, R.G.; Gomis, R.; Hanefeld, M.; Karasik, A.; Laakso, M.; STOP-NIDDM Trail Research Group. Acarbose for prevention of type 2 diabetes mellitus: The STOP-NIDDM randomised trial. *Lancet* **2002**, *359*, 2072–2077. [CrossRef]
10. Chiasson, J.L.; Josse, R.G.; Gomis, R.; Hanefeld, M.; Karasik, A.; Laakso, M.; STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: The STOP-NIDDM trial. *JAMA* **2003**, *290*, 486–494. [CrossRef]
11. Fujisawa, T.; Ikegami, H.; Inoue, K.; Kawabata, Y.; Ogihara, T. Effect of two α-glucosidase inhibitors, voglibose and acarbose, on postprandial hyperglycemia correlates with subjective abdominal symptoms. *Metabolism* **2005**, *54*, 387–390. [CrossRef]
12. Wei, Y.; Lin, F.J.; Lin, S.Y.; Wang, C.C. Risk of hypoglycemia and concomitant use of repaglinide and clopidogrel: A population-based nested case-control Study. *Clin. Pharmacol. Ther.* **2019**, *106*, 1346–1352. [CrossRef] [PubMed]
13. Meier, J.J.; Nauck, M.A. Incretins and the development of type 2 diabetes. *Curr. Diab. Rep.* **2006**, *6*, 194–201. [CrossRef] [PubMed]
14. Todd, J.F.; Bloom, S.R. Incretins and other peptides in the treatment of diabetes. *Diabet. Med.* **2007**, *24*, 223–232. [CrossRef]
15. Carr, R.D.; Larsen, M.O.; Winzell, M.S.; Jelic, K.; Lindgren, O.; Deacon, C.F.; Ahrén, B. Incretin and islet hormonal responses to fat and protein ingestion in healthy men. *Am. J. Physiol. Endocrinol. Metab.* **2008**, *295*, E779–E784. [CrossRef] [PubMed]
16. Elliott, R.M.; Morgan, L.M.; Tredger, J.A.; Deacon, S.; Wright, J.; Marks, V. Glucagon-like peptide-1 (7-36)amide and glucose-dependent insulinotropic polypeptide secretion in response to nutrient ingestion in man: Acute post-prandial and 24-h secretion patterns. *J. Endocrinol.* **1993**, *138*, 159–166. [CrossRef]
17. Lindgren, O.; Carr, R.D.; Holst, J.J.; Deacon, C.F.; Ahrén, B. Dissociated incretin hormone response to protein versus fat ingestion in obese subjects. *Diabetes Obes. Metab.* **2011**, *13*, 863–865. [CrossRef]
18. Kuhre, R.E.; Holst, J.J.; Kappe, C. The regulation of function, growth and survival of GLP-1-producing L-cells. *Clin. Sci.* **2016**, *130*, 79–91. [CrossRef]
19. Phillips, R. Incretin pathway regulates β-cell survival. *Nat. Rev. Endocrinol.* **2016**, *12*, 64. [CrossRef]

20. Hira, T.; Pinyo, J.; Hara, H. What is GLP-1 really doing in obesity? *Trends Endocrinol. Metab.* **2020**, *31*, 71–80. [CrossRef]
21. Færch, K.; Torekov, S.S.; Vistisen, D.; Johansen, N.B.; Witte, D.R.; Jonsson, A.; Pedersen, O.; Hansen, T.; Lauritzen, T.; Sandbæk, A.; et al. GLP-1 Response to oral glucose is reduced in prediabetes, screen-detected type 2 diabetes, and obesity and influenced by sex: The ADDITION-PRO study. *Diabetes* **2015**, *64*, 2513–2525. [CrossRef] [PubMed]
22. Matikainen, N.; Bogl, L.H.; Hakkarainen, A.; Lundbom, J.; Lundbom, N.; Kaprio, J.; Rissanen, A.; Holst, J.J.; Pietiläinen, K.H. GLP-1 responses are heritable and blunted in acquired obesity with high liver fat and insulin resistance. *Diabetes Care* **2014**, *37*, 242–251. [CrossRef]
23. Pham, H.; Marathe, C.S.; Phillips, L.K.; Trahair, L.G.; Hatzinikolas, S.; Huynh, L.; Wu, T.; Nauck, M.A.; Rayner, C.K.; Horowitz, M.; et al. Longitudinal changes in fasting and glucose-stimulated GLP-1 and GIP in healthy older subjects. *J. Clin. Endocrinol. Metab.* **2019**, *104*, 6201–6206. [CrossRef] [PubMed]
24. Marso, S.P.; Bain, S.C.; Consoli, A.; Eliaschewitz, F.G.; Jódar, E.; Leiter, L.A.; Lingvay, I.; Rosenstock, J.; Seufert, J.; Warren, M.L.; et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N. Engl. J. Med.* **2016**, *375*, 1834–1844. [CrossRef] [PubMed]
25. Chimerel, C.; Emery, E.; Summers, D.K.; Keyser, U.; Gribble, F.M.; Reimann, F. Bacterial metabolite indole modulates incretin secretion from intestinal enteroendocrine L cells. *Cell Rep.* **2014**, *9*, 1202–1208. [CrossRef] [PubMed]
26. Miyamoto, J.; Igarashi, M.; Watanabe, K.; Karaki, S.I.; Mukouyama, H.; Kishino, S.; Li, X.; Ichimura, A.; Irie, J.; Sugimoto, Y.; et al. Gut microbiota confers host resistance to obesity by metabolizing dietary polyunsaturated fatty acids. *Nat. Commun.* **2019**, *10*, 4007. [CrossRef]
27. Miyamoto, J.; Watanabe, K.; Taira, S.; Kasubuchi, M.; Li, X.; Irie, J.; Itoh, H.; Kimura, I. Barley β-glucan improves metabolic condition via short-chain fatty acids produced by gut microbial fermentation in high fat diet fed mice. *PLoS ONE* **2018**, *13*, e0196579. [CrossRef]
28. Yoon, H.S.; Cho, C.H.; Yun, M.S.; Jang, S.J.; You, H.J.; Kim, J.H.; Han, D.; Cha, K.H.; Moon, S.H.; Lee, K.; et al. Akkermansia muciniphila secretes a glucagon-like peptide-1-inducing protein that improves glucose homeostasis and ameliorates metabolic disease in mice. *Nat. Microbiol.* **2021**, *6*, 563–573. [CrossRef]
29. Wang, B.; Kong, Q.; Li, X.; Zhao, J.; Zhang, H.; Chen, W.; Wang, G. A high-fat diet increases gut microbiota biodiversity and energy expenditure due to nutrient difference. *Nutrients* **2020**, *12*, 3197. [CrossRef]
30. Zheng, J.; Xiao, K.L.; Chen, L.; Wu, C.; Hu, X.; Zeng, T.; Chen, X.Q.; Li, W.J.; Deng, X.; Li, H.; et al. Insulin sensitizers improve the GLP-1 secretion and the amount of intestinal L cells on high-fat-diet-induced catch-up growth. *Nutrition* **2017**, *39–40*, 82–91. [CrossRef]
31. Nagahisa, T.; Yamaguchi, S.; Kosugi, S.; Homma, K.; Miyashita, K.; Irie, J.; Yoshino, J.; Itoh, H. Intestinal epithelial NAD+ biosynthesis regulates GLP-1 production and postprandial glucose metabolism in mice. *Endocrinology* **2022**, *163*, bqac023. [CrossRef] [PubMed]
32. Yoshino, J.; Imai, S. Accurate measurement of nicotinamide adenine dinucleotide (NAD^+) with high-performance liquid chromatography. *Methods Mol. Biol.* **2013**, *1077*, 203–215. [CrossRef] [PubMed]
33. Imai, S.; Yoshino, J. The importance of NAMPT/NAD/SIRT1 in the systemic regulation of metabolism and ageing. *Diabetes Obes. Metab.* **2013**, *15* (Suppl. 3), 26–33. [CrossRef] [PubMed]
34. Imai, S.; Guarente, L. NAD+ and sirtuins in aging and disease. *Trends Cell Biol.* **2014**, *24*, 464–471. [CrossRef]
35. Yamaguchi, S.; Yoshino, J. Adipose tissue NAD^+ biology in obesity and insulin resistance: From mechanism to therapy. *Bioessays* **2017**, *39*, 1600227. [CrossRef]
36. Kulkarni, C.A.; Brookes, P.S. Cellular compartmentation and the redox/nonredox functions of NAD+. *Antioxid. Redox Signal.* **2019**, *31*, 623–642. [CrossRef]
37. Nakagawa, T.; Guarente, L. SnapShot: Sirtuins, NAD, and aging. *Cell Metabol.* **2014**, *20*, 192. [CrossRef]
38. Ramsey, K.M.; Yoshino, J.; Brace, C.S.; Abrassart, D.; Kobayashi, Y.; Marcheva, B.; Hong, H.K.; Chong, J.L.; Buhr, E.D.; Lee, C.; et al. Circadian clock feedback cycle through NAMPT-mediated NAD+ biosynthesis. *Science* **2009**, *324*, 651–654. [CrossRef]
39. Porter, L.C.; Franczyk, M.P.; Pietka, T.; Yamaguchi, S.; Lin, J.B.; Sasaki, Y.; Verdin, E.; Apte, R.S.; Yoshino, J. NAD^+-dependent deacetylase SIRT3 in adipocytes is dispensable for maintaining normal adipose tissue mitochondrial function and whole body metabolism. *Am. J. Physiol. Endocrinol. Metab.* **2018**, *315*, E520–E530. [CrossRef]
40. Gomes, A.P.; Price, N.L.; Ling, A.J.; Moslehi, J.J.; Montgomery, M.K.; Rajman, L.; White, J.P.; Teodoro, J.S.; Wrann, C.D.; Hubbard, B.P.; et al. Declining NAD(+) induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. *Cell* **2013**, *155*, 1624–1638. [CrossRef] [PubMed]
41. Camacho-Pereira, J.; Tarrago, M.G.; Chini, C.C.S.; Nin, V.; Escande, C.; Warner, G.M.; Puranik, A.S.; Schoon, R.A.; Reid, J.M.; Galina, A.; et al. CD38 dictates age-related NAD decline and mitochondrial dysfunction through an SIRT3-dependent mechanism. *Cell Metab.* **2016**, *23*, 1127–1139. [CrossRef]
42. Yoshino, J.; Mills, K.F.; Yoon, M.J.; Imai, S. Nicotinamide mononucleotide, a key NAD(+) intermediate, treats the pathophysiology of diet- and age-induced diabetes in mice. *Cell Metab.* **2011**, *14*, 528–536. [CrossRef] [PubMed]
43. Frederick, D.W.; Loro, E.; Liu, L.; Davila, A., Jr.; Chellappa, K.; Silverman, I.M.; Quinn, W.J., 3rd; Gosai, S.J.; Tichy, E.D.; Davis, J.G.; et al. Loss of NAD homeostasis leads to progressive and reversible degeneration of skeletal muscle. *Cell Metab.* **2016**, *24*, 269–282. [CrossRef]

44. Mouchiroud, L.; Houtkooper, R.H.; Moullan, N.; Katsyuba, E.; Ryu, D.; Canto, C.; Mottis, A.; Jo, Y.S.; Viswanathan, M.; Schoonjans, K.; et al. The NAD(+)/sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling. *Cell* **2013**, *154*, 430–441. [CrossRef] [PubMed]
45. Zhou, C.C.; Yang, X.; Hua, X.; Liu, J.; Fan, M.B.; Li, G.Q.; Song, J.; Xu, T.Y.; Li, Z.Y.; Guan, Y.F.; et al. Hepatic NAD(+) deficiency as a therapeutic target for non-alcoholic fatty liver disease in ageing. *Br. J. Pharmacol.* **2016**, *173*, 2352–2368. [CrossRef] [PubMed]
46. Braidy, N.; Guillemin, G.J.; Mansour, H.; Chan-Ling, T.; Poljak, A.; Grant, R. Age related changes in NAD+ metabolism oxidative stress and Sirt1 activity in wistar rats. *PLoS ONE* **2011**, *6*, e19194. [CrossRef]
47. Wei, X.; Jia, R.; Wang, G.; Hong, S.; Song, L.; Sun, B.; Chen, K.; Wang, N.; Wang, Q.; Luo, X.; et al. Depot-specific regulation of NAD^+/SIRTs metabolism identified in adipose tissue of mice in response to high-fat diet feeding or calorie restriction. *J. Nutr. Biochem.* **2020**, *80*, 108377. [CrossRef]
48. Stein, L.R.; Imai, S. Specific ablation of Nampt in adult neural stem cells recapitulates their functional defects during aging. *EMBO J.* **2014**, *33*, 1321–1340. [CrossRef]
49. Massudi, H.; Grant, R.; Braidy, N.; Guest, J.; Farnsworth, B.; Guillemin, G.J. Age-associated changes in oxidative stress and NAD+ metabolism in human tissue. *PLoS ONE* **2012**, *7*, e42357. [CrossRef]
50. Seyssel, K.; Alligier, M.; Meugnier, E.; Chanseaume, E.; Loizon, E.; Canto, C.; Disse, E.; Lambert-Porcheron, S.; Brozek, J.; Blond, E.; et al. Regulation of energy metabolism and mitochondrial function in skeletal muscle during lipid overfeeding in healthy men. *J. Clin. Endocrinol. Metab.* **2014**, *99*, E1254–E1262. [CrossRef]
51. Zhu, X.H.; Lu, M.; Lee, B.Y.; Ugurbil, K.; Chen, W. In vivo NAD assay reveals the intracellular NAD contents and redox state in healthy human brain and their age dependences. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 2876–2881. [CrossRef]
52. Bagga, P.; Hariharan, H.; Wilson, N.E.; Beer, J.C.; Shinohara, R.T.; Elliott, M.A.; Baur, J.A.; Marincola, F.M.; Witschey, W.R.; Haris, M.; et al. Single-Voxel ^{1} H MR spectroscopy of cerebral nicotinamide adenine dinucleotide (NAD^+) in humans at 7T using a 32-channel volume coil. *Magn. Reson. Med.* **2020**, *83*, 806–814. [CrossRef]
53. Clement, J.; Wong, M.; Poljak, A.; Sachdev, P.; Braidy, N. The plasma NAD^+ metabolome is dysregulated in "normal" aging. *Rejuvenation Res.* **2019**, *22*, 121–130. [CrossRef] [PubMed]
54. Seyedsadjadi, N.; Berg, J.; Bilgin, A.A.; Braidy, N.; Salonikas, C.; Grant, R. High protein intake is associated with low plasma NAD+ levels in a healthy human cohort. *PLoS ONE* **2018**, *13*, e0201968. [CrossRef]
55. Minhas, P.S.; Liu, L.; Moon, P.K.; Joshi, A.U.; Dove, C.; Mhatre, S.; Contrepois, K.; Wang, Q.; Lee, B.A.; Coronado, M.; et al. Macrophage de novo NAD^+ synthesis specifies immune function in aging and inflammation. *Nat. Immunol.* **2019**, *20*, 50–63. [CrossRef]
56. Wang, G.; Han, T.; Nijhawan, D.; Theodoropoulos, P.; Naidoo, J.; Yadavalli, S.; Mirzaei, H.; Pieper, A.A.; Ready, J.M.; McKnight, S.L. P7C3 neuroprotective chemicals function by activating the rate-limiting enzyme in NAD salvage. *Cell* **2014**, *158*, 1324–1334. [CrossRef] [PubMed]
57. Bai, P.; Cantó, C.; Oudart, H.; Brunyánszki, A.; Cen, Y.; Thomas, C.; Yamamoto, H.; Huber, A.; Kiss, B.; Houtkooper, R.H.; et al. PARP-1 inhibition increases mitochondrial metabolism through SIRT1 activation. *Cell Metab.* **2011**, *13*, 461–468. [CrossRef]
58. Jokinen, R.; Pirnes-Karhu, S.; Pietilainen, K.H.; Pirinen, E. Adipose tissue NAD^+-homeostasis, sirtuins and poly(ADP-ribose) polymerases-important players in mitochondrial metabolism and metabolic health. *Redox Biol.* **2017**, *12*, 246–263. [CrossRef]
59. Amici, S.A.; Young, N.A.; Narvaez-Miranda, J.; Jablonski, K.A.; Arcos, J.; Rosas, L.; Papenfuss, T.L.; Torrelles, J.B.; Jarjour, W.N.; Guerau-de-Arellano, M. CD38 is robustly induced in human macrophages and monocytes in inflammatory conditions. *Front. Immunol.* **2018**, *9*, 1593. [CrossRef] [PubMed]
60. Matalonga, J.; Glaria, E.; Bresque, M.; Escande, C.; Carbó, J.M.; Kiefer, K.; Vicente, R.; León, T.E.; Beceiro, S.; Pascual-García, M.; et al. The nuclear receptor LXR limits bacterial infection of host macrophages through a mechanism that impacts cellular NAD metabolism. *Cell Rep.* **2017**, *18*, 1241–1255. [CrossRef]
61. Barbosa, M.T.; Soares, S.M.; Novak, C.M.; Sinclair, D.; Levine, J.A.; Aksoy, P.; Chini, E.N. The enzyme CD38 (a NAD glycohydrolase, EC 3.2.2.5) is necessary for the development of diet-induced obesity. *FASEB J.* **2007**, *21*, 3629–3639. [CrossRef]
62. McReynolds, M.R.; Chellappa, K.; Baur, J.A. Age-related NAD^+ decline. *Exp. Gerontol.* **2020**, *134*, 110888. [CrossRef] [PubMed]
63. Liu, L.Y.; Wang, F.; Zhang, X.Y.; Huang, P.; Lu, Y.B.; Wei, E.Q.; Zhang, W.P. Nicotinamide phosphoribosyltransferase may be involved in age-related brain diseases. *PLoS ONE* **2012**, *7*, e44933. [CrossRef] [PubMed]
64. Jadeja, R.N.; Powell, F.L.; Jones, M.A.; Fuller, J.; Joseph, E.; Thounaojam, M.C.; Bartoli, M.; Martin, P.M. Loss of NAMPT in aging retinal pigment epithelium reduces NAD^+ availability and promotes cellular senescence. *Aging* **2018**, *10*, 1306–1323. [CrossRef]
65. de Guia, R.M.; Agerholm, M.; Nielsen, T.S.; Consitt, L.A.; Søgaard, D.; Helge, J.W.; Larsen, S.; Brandauer, J.; Houmard, J.A.; Treebak, J.T. Aerobic and resistance exercise training reverses age-dependent decline in NAD^+ salvage capacity in human skeletal muscle. *Physiol. Rep.* **2019**, *7*, e14139. [CrossRef]
66. Stein, L.R.; Wozniak, D.F.; Dearborn, J.T.; Kubota, S.; Apte, R.S.; Izumi, Y.; Zorumski, C.F.; Imai, S. Expression of Nampt in hippocampal and cortical excitatory neurons is critical for cognitive function. *J. Neurosci.* **2014**, *34*, 5800–5815. [CrossRef] [PubMed]
67. Benzi, A.; Sturla, L.; Heine, M.; Fischer, A.W.; Spinelli, S.; Magnone, M.; Sociali, G.; Parodi, A.; Fenoglio, D.; Emionite, L.; et al. CD38 downregulation modulates NAD^+ and NADP(H) levels in thermogenic adipose tissues. *Biochim. Biophys. Acta Mol. Cell Biol. Lipids* **2021**, *1866*, 158819. [CrossRef]

68. Revollo, J.R.; Korner, A.; Mills, K.F.; Satoh, A.; Wang, T.; Garten, A.; Dasgupta, B.; Sasaki, Y.; Wolberger, C.; Townsend, R.R.; et al. Nampt/PBEF/Visfatin regulates insulin secretion in beta cells as a systemic NAD biosynthetic enzyme. *Cell Metab.* **2007**, *6*, 363–375. [CrossRef] [PubMed]
69. Byun, J.; Oka, S.I.; Imai, N.; Huang, C.Y.; Ralda, G.; Zhai, P.; Ikeda, Y.; Ikeda, S.; Sadoshima, J. Both gain and loss of Nampt function promote pressure overload-induced heart failure. *Am. J. Physiol. Heart Circ. Physiol.* **2019**, *317*, H711–H725. [CrossRef]
70. Wang, X.; Zhang, Q.; Bao, R.; Zhang, N.; Wang, Y.; Polo-Parada, L.; Tarim, A.; Alemifar, A.; Han, X.; Wilkins, H.M.; et al. Deletion of Nampt in projection neurons of adult mice leads to motor dysfunction, neurodegeneration, and death. *Cell Rep.* **2017**, *20*, 2184–2200. [CrossRef]
71. Stein, L.R.; Zorumski, C.F.; Imai, S.; Izumi, Y. Nampt is required for long-term depression and the function of GluN2B subunit-containing NMDA receptors. *Brain Res. Bull.* **2015**, *119*, 41–51. [CrossRef] [PubMed]
72. Johnson, S.; Wozniak, D.F.; Imai, S. CA1 Nampt knockdown recapitulates hippocampal cognitive phenotypes in old mice which nicotinamide mononucleotide improves. *npj Aging Mech. Dis.* **2018**, *4*, 10. [CrossRef]
73. Lin, J.B.; Kubota, S.; Ban, N.; Yoshida, M.; Santeford, A.; Sene, A.; Nakamura, R.; Zapata, N.; Kubota, M.; Tsubota, K.; et al. NAMPT-mediated NAD(+) biosynthesis is essential for vision in mice. *Cell Rep.* **2016**, *17*, 69–85. [CrossRef] [PubMed]
74. Dall, M.; Hassing, A.S.; Niu, L.; Nielsen, T.S.; Ingerslev, L.R.; Sulek, K.; Trammell, S.A.J.; Gillum, M.P.; Barrès, R.; Larsen, S.; et al. Hepatocyte-specific perturbation of NAD^+ biosynthetic pathways in mice induces reversible nonalcoholic steatohepatitis-like phenotypes. *J. Biol. Chem.* **2021**, *297*, 101388. [CrossRef] [PubMed]
75. Mukherjee, S.; Chellappa, K.; Moffitt, A.; Ndungu, J.; Dellinger, R.W.; Davis, J.G.; Agarwal, B.; Baur, J.A. Nicotinamide adenine dinucleotide biosynthesis promotes liver regeneration. *Hepatology* **2017**, *65*, 616–630. [CrossRef]
76. Muraoka, H.; Hasegawa, K.; Sakamaki, Y.; Minakuchi, H.; Kawaguchi, T.; Yasuda, I.; Kanda, T.; Tokuyama, H.; Wakino, S.; Itoh, H. Role of Nampt-Sirt6 axis in renal proximal tubules in extracellular matrix deposition in diabetic nephropathy. *Cell Rep.* **2019**, *27*, 199–212. [CrossRef]
77. Watson, A.; Nong, Z.; Yin, H.; O'Neil, C.; Fox, S.; Balint, B.; Guo, L.; Leo, O.; Chu, M.W.A.; Gros, R.; et al. Nicotinamide phosphoribosyltransferase in smooth muscle cells maintains genome integrity, resists aortic medial degeneration, and is suppressed in human thoracic aortic aneurysm disease. *Circ. Res.* **2017**, *120*, 1889–1902. [CrossRef]
78. Stromsdorfer, K.L.; Yamaguchi, S.; Yoon, M.J.; Moseley, A.C.; Franczyk, M.P.; Kelly, S.C.; Qi, N.; Imai, S.; Yoshino, J. NAMPT-mediated NAD(+) biosynthesis in adipocytes regulates adipose tissue function and multi-organ insulin sensitivity in mice. *Cell Rep.* **2016**, *16*, 1851–1860. [CrossRef]
79. Franczyk, M.P.; Qi, N.; Stromsdorfer, K.L.; Li, C.; Yamaguchi, S.; Itoh, H.; Yoshino, M.; Sasaki, Y.; Brookheart, R.T.; Finck, B.N.; et al. Importance of adipose tissue NAD+ Biology in Regulating Metabolic Flexibility. *Endocrinology* **2021**, *162*, bqab006. [CrossRef]
80. Yamaguchi, S.; Franczyk, M.P.; Chondronikola, M.; Qi, N.; Gunawardana, S.C.; Stromsdorfer, K.L.; Porter, L.C.; Wozniak, D.F.; Sasaki, Y.; Rensing, N.; et al. Adipose tissue NAD^+ biosynthesis is required for regulating adaptive thermogenesis and whole-body energy homeostasis in mice. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 23822–23828. [CrossRef]
81. Yoon, M.J.; Yoshida, M.; Johnson, S.; Takikawa, A.; Usui, I.; Tobe, K.; Nakagawa, T.; Yoshino, J.; Imai, S. SIRT1-mediated eNAMPT secretion from adipose tissue regulates hypothalamic NAD+ and function in mice. *Cell Metab.* **2015**, *21*, 706–717. [CrossRef] [PubMed]
82. Sociali, G.; Grozio, A.; Caffa, I.; Schuster, S.; Becherini, P.; Damonte, P.; Sturla, L.; Fresia, C.; Passalacqua, M.; Mazzola, F.; et al. SIRT6 deacetylase activity regulates NAMPT activity and NAD(P)(H) pools in cancer cells. *FASEB J.* **2019**, *33*, 3704–3717. [CrossRef] [PubMed]
83. Satoh, A.; Brace, C.S.; Rensing, N.; Cliften, P.; Wozniak, D.F.; Herzog, E.D.; Yamada, K.A.; Imai, S. Sirt1 extends life span and delays aging in mice through the regulation of Nk2 homeobox 1 in the DMH and LH. *Cell Metab.* **2013**, *18*, 416–430. [CrossRef]
84. Satoh, A.; Brace, C.S.; Rensing, N.; Imai, S. Deficiency of Prdm13, a dorsomedial hypothalamus-enriched gene, mimics age-associated changes in sleep quality and adiposity. *Aging Cell* **2015**, *14*, 209–218. [CrossRef]
85. Yoshida, M.; Satoh, A.; Lin, J.B.; Mills, K.F.; Sasaki, Y.; Rensing, N.; Wong, M.; Apte, R.S.; Imai, S.I. Extracellular vesicle-contained eNAMPT delays aging and extends lifespan in mice. *Cell Metab.* **2019**, *30*, 329–342.e5. [CrossRef]
86. Morató, L.; Astori, S.; Zalachoras, I.; Rodrigues, J.; Ghosal, S.; Huang, W.; Guillot de Suduiraut, I.; Grosse, J.; Zanoletti, O.; Cao, L.; et al. eNAMPT actions through nucleus accumbens NAD^+/SIRT1 link increased adiposity with sociability deficits programmed by peripuberty stress. *Sci. Adv.* **2022**, *8*, eabj9109. [CrossRef]
87. Zhang, L.Q.; Van Haandel, L.; Xiong, M.; Huang, P.; Heruth, D.P.; Bi, C.; Gaedigk, R.; Jiang, X.; Li, D.Y.; Wyckoff, G.; et al. Metabolic and molecular insights into an essential role of nicotinamide phosphoribosyltransferase. *Cell Death Dis.* **2017**, *8*, e2705. [CrossRef] [PubMed]
88. Gong, H.; Chen, H.; Xiao, P.; Huang, N.; Han, X.; Zhang, J.; Yang, Y.; Li, T.; Zhao, T.; Tai, H.; et al. miR-146a impedes the anti-aging effect of AMPK via NAMPT suppression and NAD^+/SIRT inactivation. *Signal Transduct. Target Ther.* **2022**, *7*, 66. [CrossRef]
89. Han, X.; Tai, H.; Wang, X.; Wang, Z.; Zhou, J.; Wei, X.; Ding, Y.; Gong, H.; Mo, C.; Zhang, J.; et al. AMPK activation protects cells from oxidative stress-induced senescence via autophagic flux restoration and intracellular NAD(+) elevation. *Aging Cell* **2016**, *15*, 416–427. [CrossRef]
90. Cantó, C.; Jiang, L.Q.; Deshmukh, A.S.; Mataki, C.; Coste, A.; Lagouge, M.; Zierath, J.R.; Auwerx, J. Interdependence of AMPK and SIRT1 for metabolic adaptation to fasting and exercise in skeletal muscle. *Cell Metab.* **2010**, *11*, 213–219. [CrossRef]

91. Long, Y.C.; Zierath, J.R. AMP-activated protein kinase signaling in metabolic regulation. *J. Clin. Investig.* **2006**, *116*, 1776–1783. [CrossRef] [PubMed]
92. Lin, S.C.; Hardie, D.G. AMPK: Sensing Glucose as well as Cellular Energy Status. *Cell Metab.* **2018**, *27*, 299–313. [CrossRef]
93. Harmel, E.; Grenier, E.; Bendjoudi Ouadda, A.; El Chebly, M.; Ziv, E.; Beaulieu, J.F.; Sané, A.; Spahis, S.; Laville, M.; Levy, E. AMPK in the small intestine in normal and pathophysiological conditions. *Endocrinology* **2014**, *155*, 873–888. [CrossRef]
94. Igarashi, M.; Guarente, L. mTORC1 and SIRT1 Cooperate to foster expansion of gut adult stem cells during calorie restriction. *Cell* **2016**, *166*, 436–450. [CrossRef] [PubMed]
95. Ulgherait, M.; Rana, A.; Rera, M.; Graniel, J.; Walker, D.W. AMPK modulates tissue and organismal aging in a non-cell-autonomous manner. *Cell Rep.* **2014**, *8*, 1767–1780. [CrossRef]
96. Sun, X.; Yang, Q.; Rogers, C.J.; Du, M.; Zhu, M.J. AMPK improves gut epithelial differentiation and barrier function via regulating Cdx2 expression. *Cell Death Differ.* **2017**, *24*, 819–831. [CrossRef]
97. Zhang, E.; Jin, L.; Wang, Y.; Tu, J.; Zheng, R.; Ding, L.; Fang, Z.; Fan, M.; Al-Abdullah, I.; Natarajan, R.; et al. Intestinal AMPK modulation of microbiota mediates crosstalk with brown fat to control thermogenesis. *Nat. Commun.* **2022**, *13*, 1135. [CrossRef] [PubMed]
98. Olivier, S.; Pochard, C.; Diounou, H.; Castillo, V.; Divoux, J.; Alcantara, J.; Leclerc, J.; Guilmeau, S.; Huet, C.; Charifi, W.; et al. Deletion of intestinal epithelial AMP-activated protein kinase alters distal colon permeability but not glucose homeostasis. *Mol. Metab.* **2021**, *47*, 101183. [CrossRef]
99. Liao, X.; Huang, X.; Li, X.; Qiu, X.; Li, M.; Liu, R.; He, T.; Tang, Q. AMPK phosphorylates NAMPT to regulate NAD^+ homeostasis under ionizing radiation. *Open Biol.* **2022**, *12*, 220213. [CrossRef]
100. Zhu, X.; Shen, W.; Wang, Y.; Jaiswal, A.; Ju, Z.; Sheng, Q. Nicotinamide adenine dinucleotide replenishment rescues colon degeneration in aged mice. *Signal Transduct. Target Ther.* **2017**, *2*, 17017. [CrossRef]
101. Wellman, A.S.; Metukuri, M.R.; Kazgan, N.; Xu, X.; Xu, Q.; Ren, N.S.X.; Czopik, A.; Shanahan, M.T.; Kang, A.; Chen, W.; et al. Intestinal epithelial Sirtuin 1 regulates intestinal inflammation during aging in mice by altering the intestinal microbiota. *Gastroenterology* **2017**, *153*, 772–786. [CrossRef] [PubMed]
102. Ramachandran, D.; Clara, R.; Fedele, S.; Hu, J.; Lackzo, E.; Huang, J.Y.; Verdin, E.; Langhans, W.; Mansouri, A. Intestinal SIRT3 overexpression in mice improves whole body glucose homeostasis independent of body weight. *Mol. Metab.* **2017**, *6*, 1264–1273. [CrossRef]
103. Xiong, X.; Yang, C.; He, W.Q.; Yu, J.; Xin, Y.; Zhang, X.; Huang, R.; Ma, H.; Xu, S.; Li, Z.; et al. Sirtuin 6 maintains epithelial STAT6 activity to support intestinal tuft cell development and type 2 immunity. *Nat. Commun.* **2022**, *13*, 5192. [CrossRef]
104. Zhang, Y.; Wang, X.L.; Zhou, M.; Kang, C.; Lang, H.D.; Chen, M.T.; Hui, S.C.; Wang, B.; Mi, M.T. Crosstalk between gut microbiota and Sirtuin-3 in colonic inflammation and tumorigenesis. *Exp. Mol. Med.* **2018**, *50*, 1–11. [CrossRef] [PubMed]
105. Liu, F.; Bu, H.F.; Geng, H.; De Plaen, I.G.; Gao, C.; Wang, P.; Wang, X.; Kurowski, J.A.; Yang, H.; Qian, J.; et al. Sirtuin-6 preserves R-spondin-1 expression and increases resistance of intestinal epithelium to injury in mice. *Mol. Med.* **2017**, *23*, 272–284. [CrossRef]
106. Madiraju, A.K.; Erion, D.M.; Rahimi, Y.; Zhang, X.M.; Braddock, D.T.; Albright, R.A.; Prigaro, B.J.; Wood, J.L.; Bhanot, S.; MacDonald, M.J.; et al. Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. *Nature* **2014**, *510*, 542–546. [CrossRef] [PubMed]
107. MacDonald, M.J.; Ansari, I.H.; Longacre, M.J.; Stoker, S.W. Metformin's therapeutic efficacy in the treatment of diabetes does not involve inhibition of mitochondrial glycerol phosphate dehydrogenase. *Diabetes* **2021**, *70*, 1575–1580. [CrossRef] [PubMed]
108. Alshawi, A.; Agius, L. Low metformin causes a more oxidized mitochondrial NADH/NAD redox state in hepatocytes and inhibits gluconeogenesis by a redox-independent mechanism. *J. Biol. Chem.* **2019**, *294*, 2839–2853. [CrossRef]
109. Shin, N.R.; Lee, J.C.; Lee, H.Y.; Kim, M.S.; Whon, T.W.; Lee, M.S.; Bae, J.W. An increase in the Akkermansia spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. *Gut* **2014**, *63*, 727–735. [CrossRef]
110. Lien, F.; Berthier, A.; Bouchaert, E.; Gheeraert, C.; Alexandre, J.; Porez, G.; Prawitt, J.; Dehondt, H.; Ploton, M.; Colin, S.; et al. Metformin interferes with bile acid homeostasis through AMPK-FXR crosstalk. *J. Clin. Investig.* **2014**, *124*, 1037–1051. [CrossRef]
111. Thomas, C.; Gioiello, A.; Noriega, L.; Strehle, A.; Oury, J.; Rizzo, G.; Macchiarulo, A.; Yamamoto, H.; Mataki, C.; Pruzanski, M.; et al. TGR5-mediated bile acid sensing controls glucose homeostasis. *Cell Metab.* **2009**, *10*, 167–177. [CrossRef] [PubMed]
112. Napolitano, A.; Miller, S.; Nicholls, A.W.; Baker, D.; Van Horn, S.; Thomas, E.; Rajpal, D.; Spivak, A.; Brown, J.R.; Nunez, D.J. Novel gut-based pharmacology of metformin in patients with type 2 diabetes mellitus. *PLoS ONE* **2014**, *9*, e100778. [CrossRef]
113. Yi, F.; Sun, J.; Lim, G.E.; Fantus, I.G.; Brubaker, P.L.; Jin, T. Cross talk between the insulin and Wnt signaling pathways: Evidence from intestinal endocrine L cells. *Endocrinology* **2008**, *149*, 2341–2351. [CrossRef]
114. Kim, M.H.; Jee, J.H.; Park, S.; Lee, M.S.; Kim, K.W.; Lee, M.K. Metformin enhances glucagon-like peptide 1 via cooperation between insulin and Wnt signaling. *J. Endocrinol.* **2014**, *220*, 117–128. [CrossRef]
115. Holloway, K.R.; Calhoun, T.N.; Saxena, M.; Metoyer, C.F.; Kandler, E.F.; Rivera, C.A.; Pruitt, K. SIRT1 regulates Dishevelled proteins and promotes transient and constitutive Wnt signaling. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 9216–9221. [CrossRef] [PubMed]
116. Clevers, H. Wnt/beta-catenin signaling in development and disease. *Cell* **2006**, *127*, 469–480. [CrossRef]
117. Feng, G.; Zheng, K.; Song, D.; Xu, K.; Huang, D.; Zhang, Y.; Cao, P.; Shen, S.; Zhang, J.; Feng, X.; et al. SIRT1 was involved in TNF-α-promoted osteogenic differentiation of human DPSCs through Wnt/β-catenin signal. *In Vitro Cell Dev. Biol. Anim.* **2016**, *52*, 1001–1011. [CrossRef]

118. Zhou, Y.; Zhou, Z.; Zhang, W.; Hu, X.; Wei, H.; Peng, J.; Jiang, S. SIRT1 inhibits adipogenesis and promotes myogenic differentiation in C3H10T1/2 pluripotent cells by regulating Wnt signaling. *Cell Biosci.* **2015**, *5*, 61. [CrossRef]
119. Lee, Y.S.; Kim, T.Y.; Kim, Y.; Lee, S.H.; Kim, S.; Kang, S.W.; Yang, J.Y.; Baek, I.J.; Sung, Y.H.; Park, Y.Y.; et al. Microbiota-derived lactate accelerates intestinal stem-cell-mediated epithelial development. *Cell Host Microbe* **2018**, *24*, 833–846.e6. [CrossRef] [PubMed]
120. Liu, L.W.; Xie, Y.; Li, G.Q.; Zhang, T.; Sui, Y.H.; Zhao, Z.J.; Zhang, Y.Y.; Yang, W.B.; Geng, X.L.; Xue, D.B.; et al. Gut microbiota-derived nicotinamide mononucleotide alleviates acute pancreatitis by activating pancreatic SIRT3 signalling. *Br. J. Pharmacol.* **2023**, *180*, 647–666. [CrossRef]
121. Xu, K.; Guo, Y.; Wang, Y.; Ren, Y.; Low, V.; Cho, S.; Ping, L.; Peng, K.; Li, X.; Qiu, Y.; et al. Decreased Enterobacteriaceae translocation due to gut microbiota remodeling mediates the alleviation of premature aging by a high-fat diet. *Aging Cell* **2023**, *22*, e13760. [CrossRef] [PubMed]
122. Chen, D.; Jin, D.; Huang, S.; Wu, J.; Xu, M.; Liu, T.; Dong, W.; Liu, X.; Wang, S.; Zhong, W.; et al. Clostridium butyricum, a butyrate-producing probiotic, inhibits intestinal tumor development through modulating Wnt signaling and gut microbiota. *Cancer Lett.* **2020**, *469*, 456–467. [CrossRef] [PubMed]
123. Swafford, D.; Shanmugam, A.; Ranganathan, P.; Hussein, M.S.; Koni, P.A.; Prasad, P.D.; Thangaraju, M.; Manicassamy, S. Canonical Wnt Signaling in CD11c(+) APCs Regulates Microbiota-Induced Inflammation and Immune Cell Homeostasis in the Colon. *J. Immunol.* **2018**, *200*, 3259–3268. [CrossRef] [PubMed]
124. Novellasdemunt, L.; Antas, P.; Li, V.S. Targeting Wnt signaling in colorectal cancer. A review in the theme: Cell signaling: Proteins, pathways and mechanisms. *Am. J. Physiol. Cell Physiol.* **2015**, *309*, C511–C521. [CrossRef]
125. Nalapareddy, K.; Nattamai, K.J.; Kumar, R.S.; Karns, R.; Wikenheiser-Brokamp, K.A.; Sampson, L.L.; Mahe, M.M.; Sundaram, N.; Yacyshyn, M.B.; Yacyshyn, B.; et al. Canonical Wnt signaling ameliorates aging of intestinal stem cells. *Cell Rep.* **2017**, *18*, 2608–2621. [CrossRef]
126. Igarashi, M.; Miura, M.; Williams, E.; Jaksch, F.; Kadowaki, T.; Yamauchi, T.; Guarente, L. NAD^+ supplementation rejuvenates aged gut adult stem cells. *Aging Cell* **2019**, *18*, e12935. [CrossRef]
127. Li, X.; Shan, J.; Chang, W.; Kim, I.; Bao, J.; Lee, H.J.; Zhang, X.; Samuel, V.T.; Shulman, G.I.; Liu, D.; et al. Chemical and genetic evidence for the involvement of Wnt antagonist Dickkopf2 in regulation of glucose metabolism. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 11402–11407. [CrossRef]
128. Kawano, Y.; Nakae, J.; Watanabe, N.; Kikuchi, T.; Tateya, S.; Tamori, Y.; Kaneko, M.; Abe, T.; Onodera, M.; Itoh, H. Colonic pro-inflammatory macrophages cause insulin resistance in an intestinal Ccl2/Ccr2-dependent manner. *Cell Metab.* **2016**, *24*, 295–310. [CrossRef]
129. Luck, H.; Tsai, S.; Chung, J.; Clemente-Casares, X.; Ghazarian, M.; Revelo, X.S.; Lei, H.; Luk, C.T.; Shi, S.Y.; Surendra, A.; et al. Regulation of obesity-related insulin resistance with gut anti-inflammatory agents. *Cell Metab.* **2015**, *21*, 527–542. [CrossRef]
130. Garidou, L.; Pomié, C.; Klopp, P.; Waget, A.; Charpentier, J.; Aloulou, M.; Giry, A.; Serino, M.; Stenman, L.; Lahtinen, S.; et al. The gut microbiota regulates intestinal CD4 T cells expressing RORγt and controls metabolic disease. *Cell Metab.* **2015**, *22*, 100–112. [CrossRef]
131. Da Silva Xavier, G.; Loder, M.K.; McDonald, A.; Tarasov, A.I.; Carzaniga, R.; Kronenberger, K.; Barg, S.; Rutter, G.A. TCF7L2 regulates late events in insulin secretion from pancreatic islet beta-cells. *Diabetes* **2009**, *58*, 894–905. [CrossRef]
132. Takamoto, I.; Kubota, N.; Nakaya, K.; Kumagai, K.; Hashimoto, S.; Kubota, T.; Inoue, M.; Kajiwara, E.; Katsuyama, H.; Obata, A.; et al. TCF7L2 in mouse pancreatic beta cells plays a crucial role in glucose homeostasis by regulating beta cell mass. *Diabetologia* **2014**, *57*, 542–553. [CrossRef] [PubMed]
133. Laurenti, M.C.; Dalla Man, C.; Varghese, R.T.; Andrews, J.C.; Rizza, R.A.; Matveyenko, A.; De Nicolao, G.; Cobelli, C.; Vella, A. Diabetes-associated genetic variation in TCF7L2 alters pulsatile insulin secretion in humans. *JCI Insight* **2020**, *5*, e136136. [CrossRef]
134. Grant, S.F.; Thorleifsson, G.; Reynisdottir, I.; Benediktsson, R.; Manolescu, A.; Sainz, J.; Helgason, A.; Stefansson, H.; Emilsson, V.; Helgadottir, A.; et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nat. Genet.* **2006**, *38*, 320–323. [CrossRef] [PubMed]
135. Schäfer, S.A.; Tschritter, O.; Machicao, F.; Thamer, C.; Stefan, N.; Gallwitz, B.; Holst, J.J.; Dekker, J.M.; t'Hart, L.M.; Nijpels, G.; et al. Impaired glucagon-like peptide-1-induced insulin secretion in carriers of transcription factor 7-like 2 (TCF7L2) gene polymorphisms. *Diabetologia* **2007**, *50*, 2443–2450. [CrossRef]
136. Shao, W.; Wang, D.; Chiang, Y.T.; Ip, W.; Zhu, L.; Xu, F.; Columbus, J.; Belsham, D.D.; Irwin, D.M.; Zhang, H.; et al. The Wnt signaling pathway effector TCF7L2 controls gut and brain proglucagon gene expression and glucose homeostasis. *Diabetes* **2013**, *62*, 789–800. [CrossRef] [PubMed]
137. Ni, Z.; Anini, Y.; Fang, X.; Mills, G.; Brubaker, P.L.; Jin, T. Transcriptional activation of the proglucagon gene by lithium and beta-catenin in intestinal endocrine L cells. *J. Biol. Chem.* **2003**, *278*, 1380–1387. [CrossRef]
138. Daoudi, M.; Hennuyer, N.; Borland, M.G.; Touche, V.; Duhem, C.; Gross, B.; Caiazzo, R.; Kerr-Conte, J.; Pattou, F.; Peters, J.M.; et al. PPARβ/δ activation induces enteroendocrine L cell GLP-1 production. *Gastroenterology* **2011**, *140*, 1564–1574. [CrossRef]
139. Hadjittofi, C.; Coran, A.G.; Mogilner, J.G.; Pollak, Y.; Matter, I.; Sukhotnik, I. Dietary supplementation with vitamin D stimulates intestinal epithelial cell turnover after massive small bowel resection in rats. *Pediatr. Surg. Int.* **2013**, *29*, 41–50. [CrossRef]

140. Holick, M.F. Sunlight, ultraviolet radiation, vitamin D and skin cancer: How much sunlight do we need? *Adv. Exp. Med. Biol.* **2014**, *810*, 1–16.
141. Newman, J.C.; Covarrubias, A.J.; Zhao, M.; Yu, X.; Gut, P.; Ng, C.P.; Huang, Y.; Haldar, S.; Verdin, E. Ketogenic diet reduces midlife mortality and improves memory in aging mice. *Cell Metab.* **2017**, *26*, 547–557. [CrossRef] [PubMed]
142. Cheng, C.W.; Biton, M.; Haber, A.L.; Gunduz, N.; Eng, G.; Gaynor, L.T.; Tripathi, S.; Calibasi-Kocal, G.; Rickelt, S.; Butty, V.L.; et al. Ketone body signaling mediates intestinal stem cell homeostasis and adaptation to diet. *Cell* **2019**, *178*, 1115–1131.e15. [CrossRef] [PubMed]
143. Beyaz, S.; Mana, M.D.; Roper, J.; Kedrin, D.; Saadatpour, A.; Hong, S.J.; Bauer-Rowe, K.E.; Xifaras, M.E.; Akkad, A.; Arias, E.; et al. High-fat diet enhances stemness and tumorigenicity of intestinal progenitors. *Nature* **2016**, *531*, 53–58. [CrossRef] [PubMed]
144. Ishihara, S.; Hata, K.; Hirose, K.; Okui, T.; Toyosawa, S.; Uzawa, N.; Nishimura, R.; Yoneda, T. The lactate sensor GPR81 regulates glycolysis and tumor growth of breast cancer. *Sci. Rep.* **2022**, *12*, 6261. [CrossRef]
145. Dorton, H.M.; Luo, S.; Monterosso, J.R.; Page, K.A. Influences of dietary added sugar consumption on striatal food-cue reactivity and postprandial GLP-1 response. *Front. Psychiatry* **2018**, *8*, 297. [CrossRef]
146. Hutchison, A.T.; Piscitelli, D.; Horowitz, M.; Jones, K.L.; Clifton, P.M.; Standfield, S.; Hausken, T.; Feinle-Bisset, C.; Luscombe-Marsh, N.D. Acute load-dependent effects of oral whey protein on gastric emptying, gut hormone release, glycemia, appetite, and energy intake in healthy men. *Am. J. Clin. Nutr.* **2015**, *102*, 1574–1584. [CrossRef]
147. Giezenaar, C.; Hutchison, A.T.; Luscombe-Marsh, N.D.; Chapman, I.; Horowitz, M.; Soenen, S. Effect of age on blood glucose and plasma insulin, glucagon, ghrelin, CCK, GIP, and GLP-1 responses to whey protein ingestion. *Nutrients* **2017**, *10*, 2. [CrossRef]
148. Di Francesco, V.; Barazzoni, R.; Bissoli, L.; Fantin, F.; Rizzotti, P.; Residori, L.; Antonioli, A.; Graziani, M.S.; Zanetti, M.; Bosello, O.; et al. The quantity of meal fat influences the profile of postprandial hormones as well as hunger sensation in healthy elderly people. *J. Am. Med. Dir. Assoc.* **2010**, *11*, 188–193. [CrossRef]
149. Gentilcore, D.; Chaikomin, R.; Jones, K.L.; Russo, A.; Feinle-Bisset, C.; Wishart, J.M.; Rayner, C.K.; Horowitz, M. Effects of fat on gastric emptying of and the glycemic, insulin, and incretin responses to a carbohydrate meal in type 2 diabetes. *J. Clin. Endocrinol. Metab.* **2006**, *91*, 2062–2067. [CrossRef]
150. Cunningham, K.M.; Read, N.W. The effect of incorporating fat into different components of a meal on gastric emptying and postprandial blood glucose and insulin responses. *Br. J. Nutr.* **1989**, *61*, 285–290. [CrossRef]
151. Sun, L.; Goh, H.J.; Govindharajulu, P.; Leow, M.K.; Henry, C.J. Postprandial glucose, insulin and incretin responses differ by test meal macronutrient ingestion sequence (PATTERN study). *Clin. Nutr.* **2020**, *39*, 950–957. [CrossRef]
152. Ridaura, V.K.; Faith, J.J.; Rey, F.E.; Cheng, J.; Duncan, A.E.; Kau, A.L.; Griffin, N.W.; Lombard, V.; Henrissat, B.; Bain, J.R.; et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* **2013**, *341*, 1241214. [CrossRef] [PubMed]
153. Turnbaugh, P.J.; Ley, R.E.; Mahowald, M.A.; Magrini, V.; Mardis, E.R.; Gordon, J.I. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* **2006**, *444*, 1027–1031. [CrossRef] [PubMed]
154. Tilg, H.; Zmora, N.; Adolph, T.E.; Elinav, E. The intestinal microbiota fuelling metabolic inflammation. *Nat. Rev. Immunol.* **2020**, *20*, 40–54. [CrossRef] [PubMed]
155. Le Roy, T.; Llopis, M.; Lepage, P.; Bruneau, A.; Rabot, S.; Bevilacqua, C.; Martin, P.; Philippe, C.; Walker, F.; Bado, A.; et al. Intestinal microbiota determines development of non-alcoholic fatty liver disease in mice. *Gut* **2013**, *62*, 1787–1794. [CrossRef]
156. Scheithauer, T.P.M.; Rampanelli, E.; Nieuwdorp, M.; Vallance, B.A.; Verchere, C.B.; van Raalte, D.H.; Herrema, H. Gut microbiota as a trigger for metabolic inflammation in obesity and type 2 diabetes. *Front. Immunol.* **2020**, *11*, 571731. [CrossRef] [PubMed]
157. Petersen, C.; Bell, R.; Klag, K.A.; Lee, S.H.; Soto, R.; Ghazaryan, A.; Buhrke, K.; Ekiz, H.A.; Ost, K.S.; Boudina, S.; et al. T cell-mediated regulation of the microbiota protects against obesity. *Science* **2019**, *365*, eaat9351. [CrossRef]
158. Cani, P.D.; Amar, J.; Iglesias, M.A.; Poggi, M.; Knauf, C.; Bastelica, D.; Neyrinck, A.M.; Fava, F.; Tuohy, K.M.; Chabo, C.; et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* **2007**, *56*, 1761–1772. [CrossRef]
159. Winer, D.A.; Luck, H.; Tsai, S.; Winer, S. The intestinal immune system in obesity and insulin resistance. *Cell Metab.* **2016**, *23*, 413–426. [CrossRef]
160. Borra, M.T.; Smith, B.C.; Denu, J.M. Mechanism of human SIRT1 activation by resveratrol. *J. Biol. Chem.* **2005**, *280*, 17187–17195. [CrossRef]
161. Chaplin, A.; Carpéné, C.; Mercader, J. Resveratrol, metabolic syndrome, and gut microbiota. *Nutrients* **2018**, *10*, 1651. [CrossRef] [PubMed]
162. Li, H.; Perino, A.; Huang, Q.; Von Alvensleben, G.V.G.; Banaei-Esfahani, A.; Velazquez-Villegas, L.A.; Gariani, K.; Korbelius, M.; Bou Sleiman, M.; Imbach, J.; et al. Integrative systems analysis identifies genetic and dietary modulators of bile acid homeostasis. *Cell Metab.* **2022**, *34*, 1594–1610. [CrossRef]
163. Kusaczuk, M. Tauroursodeoxycholate-bile acid with chaperoning activity: Molecular and cellular effects and therapeutic perspectives. *Cells* **2019**, *8*, 1471. [CrossRef] [PubMed]
164. Trabelsi, M.S.; Daoudi, M.; Prawitt, J.; Ducastel, S.; Touche, V.; Sayin, S.I.; Perino, A.; Brighton, C.A.; Sebti, Y.; Kluza, J.; et al. Farnesoid X receptor inhibits glucagon-like peptide-1 production by enteroendocrine L cells. *Nat. Commun.* **2015**, *6*, 7629. [CrossRef] [PubMed]
165. Roberts, R.E.; Glicksman, C.; Alaghband-Zadeh, J.; Sherwood, R.A.; Akuji, N.; le Roux, C.W. The relationship between postprandial bile acid concentration, GLP-1, PYY and ghrelin. *Clin. Endrocrinol.* **2011**, *74*, 67–72. [CrossRef] [PubMed]

166. Ummarino, S.; Mozzon, M.; Zamporlini, F.; Amici, A.; Mazzola, F.; Orsomando, G.; Ruggieri, S.; Raffaelli, N. Simultaneous quantitation of nicotinamide riboside, nicotinamide mononucleotide and nicotinamide adenine dinucleotide in milk by a novel enzyme-coupled assay. *Food Chem.* **2017**, *221*, 161–168. [CrossRef]
167. Mills, K.F.; Yoshida, S.; Stein, L.R.; Grozio, A.; Kubota, S.; Sasaki, Y.; Redpath, P.; Migaud, M.E.; Apte, R.S.; Uchida, K.; et al. Long-term administration of nicotinamide mononucleotide mitigates age-associated physiological decline in mice. *Cell Metab.* **2016**, *24*, 795–806. [CrossRef]
168. Yoshino, J.; Baur, J.A.; Imai, S.I. NAD^+ intermediates: The biology and therapeutic potential of NMN and NR. *Cell Metab.* **2018**, *27*, 513–528. [CrossRef]
169. Rajman, L.; Chwalek, K.; Sinclair, D.A. Therapeutic potential of NAD-boosting molecules: The in vivo evidence. *Cell Metab.* **2018**, *27*, 529–547. [CrossRef]
170. Johnson, S.; Imai, S.I. NAD^+ biosynthesis, aging, and disease. *F1000Res* **2018**, *7*, 132. [CrossRef]
171. Cantó, C.; Houtkooper, R.H.; Pirinen, E.; Youn, D.Y.; Oosterveer, M.H.; Cen, Y.; Fernandez-Marcos, P.J.; Yamamoto, H.; Andreux, P.A.; Cettour-Rose, P.; et al. The NAD(+) precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity. *Cell Metab.* **2012**, *15*, 838–847. [CrossRef] [PubMed]
172. Zhang, H.; Ryu, D.; Wu, Y.; Gariani, K.; Wang, X.; Luan, P.; D'Amico, D.; Ropelle, E.R.; Lutolf, M.P.; Aebersold, R.; et al. NAD^+ repletion improves mitochondrial and stem cell function and enhances life span in mice. *Science* **2016**, *352*, 1436–1443. [CrossRef] [PubMed]
173. Liu, L.; Su, X.; Quinn, W.J., 3rd; Hui, S.; Krukenberg, K.; Frederick, D.W.; Redpath, P.; Zhan, L.; Chellappa, K.; White, E.; et al. Quantitative analysis of NAD synthesis-breakdown fluxes. *Cell Metab.* **2018**, *27*, 1067–1080.e5. [CrossRef] [PubMed]
174. Ratajczak, J.; Joffraud, M.; Trammell, S.A.; Ras, R.; Canela, N.; Boutant, M.; Kulkarni, S.S.; Rodrigues, M.; Redpath, P.; Migaud, M.E.; et al. NRK1 controls nicotinamide mononucleotide and nicotinamide riboside metabolism in mammalian cells. *Nat. Commun.* **2016**, *7*, 13103. [CrossRef]
175. Grozio, A.; Mills, K.F.; Yoshino, J.; Bruzzone, S.; Sociali, G.; Tokizane, K.; Lei, H.C.; Cunningham, R.; Sasaki, Y.; Migaud, M.E.; et al. Slc12a8 is a nicotinamide mononucleotide transporter. *Nat. Metab.* **2019**, *1*, 47–57. [CrossRef]
176. Li, W.; Zhou, Y.; Pang, N.; Hu, Q.; Li, Q.; Sun, Y.; Ding, Y.; Gu, Y.; Xiao, Y.; Gao, M.; et al. NAD supplement alleviates intestinal barrier injury induced by ethanol via protecting epithelial mitochondrial function. *Nutrients* **2022**, *15*, 174. [CrossRef]
177. Trammell, S.A.; Schmidt, M.S.; Weidemann, B.J.; Redpath, P.; Jaksch, F.; Dellinger, R.W.; Li, Z.; Abel, E.D.; Migaud, M.E.; Brenner, C. Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. *Nat. Commun.* **2016**, *7*, 12948. [CrossRef]
178. Airhart, S.E.; Shireman, L.M.; Risler, L.J.; Anderson, G.D.; Nagana Gowda, G.A.; Raftery, D.; Tian, R.; Shen, D.D.; O'Brien, K.D. An open-label, non-randomized study of the pharmacokinetics of the nutritional supplement nicotinamide riboside (NR) and its effects on blood NAD+ levels in healthy volunteers. *PLoS ONE* **2017**, *12*, e0186459. [CrossRef]
179. Conze, D.; Brenner, C.; Kruger, C.L. Safety and metabolism of long-term administration of NIAGEN (nicotinamide riboside chloride) in a randomized, double-blind, placebo-controlled clinical trial of healthy overweight adults. *Sci. Rep.* **2019**, *9*, 9772. [CrossRef]
180. Martens, C.R.; Denman, B.A.; Mazzo, M.R.; Armstrong, M.L.; Reisdorph, N.; McQueen, M.B.; Chonchol, M.; Seals, D.R. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD^+ in healthy middle-aged and older adults. *Nat. Commun.* **2018**, *9*, 1286. [CrossRef]
181. Dollerup, O.L.; Christensen, B.; Svart, M.; Schmidt, M.S.; Sulek, K.; Ringgaard, S.; Stødkilde-Jørgensen, H.; Møller, N.; Brenner, C.; Treebak, J.T.; et al. A randomized placebo-controlled clinical trial of nicotinamide riboside in obese men: Safety, insulin-sensitivity, and lipid-mobilizing effects. *Am. J. Clin. Nutr.* **2018**, *108*, 343–353. [CrossRef] [PubMed]
182. Remie, C.M.E.; Roumans, K.H.M.; Moonen, M.P.B.; Connell, N.J.; Havekes, B.; Mevenkamp, J.; Lindeboom, L.; de Wit, V.H.W.; van de Weijer, T.; Aarts, S.; et al. Nicotinamide riboside supplementation alters body composition and skeletal muscle acetylcarnitine concentrations in healthy obese humans. *Am. J. Clin. Nutr.* **2020**, *112*, 413–426. [CrossRef]
183. Elhassan, Y.S.; Kluckova, K.; Fletcher, R.S.; Schmidt, M.S.; Garten, A.; Doig, C.L.; Cartwright, D.M.; Oakey, L.; Burley, C.V.; Jenkinson, N.; et al. Nicotinamide riboside augments the aged human skeletal muscle NAD(+) metabolome and induces transcriptomic and anti-inflammatory signatures. *Cell Rep.* **2019**, *28*, 1717–1728.e6. [CrossRef] [PubMed]
184. Dollerup, O.L.; Trammell, S.A.J.; Hartmann, B.; Holst, J.J.; Christensen, B.; Møller, N.; Gillum, M.P.; Treebak, J.T.; Jessen, N. Effects of nicotinamide riboside on endocrine pancreatic function and incretin hormones in nondiabetic men with obesity. *J. Clin. Endocrinol. Metab.* **2019**, *104*, 5703–5714. [CrossRef]
185. Irie, J.; Inagaki, E.; Fujita, M.; Nakaya, H.; Mitsuishi, M.; Yamaguchi, S.; Yamashita, K.; Shigaki, S.; Ono, T.; Yukioka, H.; et al. Effect of oral administration of nicotinamide mononucleotide on clinical parameters and nicotinamide metabolite levels in healthy Japanese men. *Endocr. J.* **2020**, *67*, 153–160. [CrossRef] [PubMed]
186. Okabe, K.; Yaku, K.; Uchida, Y.; Fukamizu, Y.; Sato, T.; Sakurai, T.; Tobe, K.; Nakagawa, T. Oral administration of nicotinamide mononucleotide is safe and efficiently increases blood nicotinamide adenine dinucleotide levels in healthy subjects. *Front. Nutr.* **2022**, *9*, 868640. [CrossRef]
187. Fukamizu, Y.; Uchida, Y.; Shigekawa, A.; Sato, T.; Kosaka, H.; Sakurai, T. Safety evaluation of β-nicotinamide mononucleotide oral administration in healthy adult men and women. *Sci. Rep.* **2022**, *12*, 14442. [CrossRef]

188. Akasaka, H.; Nakagami, H.; Sugimoto, K.; Yasunobe, Y.; Minami, T.; Fujimoto, T.; Yamamoto, K.; Hara, C.; Shiraki, A.; Nishida, K.; et al. Effects of nicotinamide mononucleotide on older patients with diabetes and impaired physical performance: A prospective, placebo-controlled, double-blind study. *Geriatr. Gerontol. Int.* **2023**, *23*, 38–43. [CrossRef]
189. Igarashi, M.; Nakagawa-Nagahama, Y.; Miura, M.; Kashiwabara, K.; Yaku, K.; Sawada, M.; Sekine, R.; Fukamizu, Y.; Sato, T.; Sakurai, T.; et al. Chronic nicotinamide mononucleotide supplementation elevates blood nicotinamide adenine dinucleotide levels and alters muscle function in healthy older men. *npj Aging* **2022**, *8*, 5. [CrossRef]
190. Kim, M.; Seol, J.; Sato, T.; Fukamizu, Y.; Sakurai, T.; Okura, T. Effect of 12-week intake of nicotinamide mononucleotide on sleep quality, fatigue, and physical performance in older japanese adults: A randomized, double-blind placebo-controlled study. *Nutrients* **2022**, *14*, 755. [CrossRef]
191. Liao, B.; Zhao, Y.; Wang, D.; Zhang, X.; Hao, X.; Hu, M. Nicotinamide mononucleotide supplementation enhances aerobic capacity in amateur runners: A randomized, double-blind study. *J. Int. Soc. Sports. Nutr.* **2021**, *18*, 54. [CrossRef] [PubMed]
192. Yi, L.; Maier, A.B.; Tao, R.; Lin, Z.; Vaidya, A.; Pendse, S.; Thasma, S.; Andhalkar, N.; Avhad, G.; Kumbhar, V. The efficacy and safety of β-nicotinamide mononucleotide (NMN) supplementation in healthy middle-aged adults: A randomized, multicenter, double-blind, placebo-controlled, parallel-group, dose-dependent clinical trial. *Geroscience* **2023**, *45*, 29–43. [CrossRef] [PubMed]
193. Huang, H. A multicentre, randomised, double blind, parallel design, placebo controlled study to evaluate the efficacy and safety of uthever (NMN supplement), an orally administered supplementation in middle aged and older adults. *Front. Aging* **2022**, *3*, 851698. [CrossRef]
194. Yoshino, M.; Yoshino, J.; Kayser, B.D.; Patti, G.J.; Franczyk, M.P.; Mills, K.F.; Sindelar, M.; Pietka, T.; Patterson, B.W.; Imai, S.I.; et al. Nicotinamide mononucleotide increases muscle insulin sensitivity in prediabetic women. *Science* **2021**, *372*, 1224–1229. [CrossRef]
195. Zhao, B.; Liu, C.; Qiang, L.; Liu, J.; Qiu, Z.; Zhang, Z.; Zhang, J.; Li, Y.; Zhang, M. Clinical observation of the effect of nicotinamide mononucleotide on the improvement of insomnia in middle-aged and old adults. *Am. J. Transl. Res.* **2022**, *6*, 167–176.
196. Kimura, S.; Ichikawa, M.; Sugawara, S.; Katagiri, T.; Hirasawa, Y.; Ishikawa, T.; Matsunaga, W.; Gotoh, A. Nicotinamide mononucleotide is safely metabolized and significantly reduces blood triglyceride levels in healthy individuals. *Cureus* **2022**, *14*, e28812. [CrossRef]
197. Sharma, D.; Verma, S.; Vaidya, S.; Kalia, K.; Tiwari, V. Recent updates on GLP-1 agonists: Current advancements & challenges. *Biomed. Pharmacother.* **2018**, *108*, 952–962. [CrossRef]
198. Nakahata, Y.; Sahar, S.; Astarita, G.; Kaluzova, M.; Sassone-Corsi, P. Circadian control of the NAD+ salvage pathway by CLOCK-SIRT1. *Science* **2009**, *324*, 654–657. [CrossRef]
199. Dantas Machado, A.C.; Brown, S.D.; Lingaraju, A.; Sivaganesh, V.; Martino, C.; Chaix, A.; Zhao, P.; Pinto, A.F.M.; Chang, M.W.; Richter, R.A.; et al. Diet and feeding pattern modulate diurnal dynamics of the ileal microbiome and transcriptome. *Cell Rep.* **2022**, *40*, 111008. [CrossRef]
200. Shats, I.; Williams, J.G.; Liu, J.; Makarov, M.V.; Wu, X.; Lih, F.B.; Deterding, L.J.; Lim, C.; Xu, X.; Randall, T.A.; et al. Bacteria boost mammalian host NAD metabolism by engaging the deamidated biosynthesis pathway. *Cell Metab.* **2020**, *31*, 564–579.e7. [CrossRef]
201. Yaku, K.; Palikhe, S.; Izumi, H.; Yoshida, T.; Hikosaka, K.; Hayat, F.; Karim, M.; Iqbal, T.; Nitta, Y.; Sato, A.; et al. BST1 regulates nicotinamide riboside metabolism via its glycohydrolase and base-exchange activities. *Nat. Commun.* **2021**, *12*, 6767. [CrossRef] [PubMed]