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The importance of NAMPT/NAD/SIRT1 in the systemic regulation of metabolism and ageing

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Ageing is associated with a variety of pathophysiological changes, including development of insulin resistance, progressive decline in β-cell function and chronic inflammation, all of which affect metabolic homeostasis in response to nutritional and environmental stimuli. SIRT1, the mammalian nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylase, and nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting NAD biosynthetic enzyme, together comprise a novel systemic regulatory network, named the 'NAD World', that orchestrates physiological responses to internal and external perturbations and maintains the robustness of the physiological system in mammals. In the past decade, an accumulating body of evidence has demonstrated that SIRT1 and NAMPT, two essential components in the NAD World, play a critical role in regulating insulin sensitivity and insulin secretion throughout the body. In this article, we will summarize the physiological significance of SIRT1 and NAMPT-mediated NAD biosynthesis in metabolic regulation and discuss the ideas of functional hierarchy and frailty in determining the robustness of the system. We will also discuss the potential of key NAD intermediates as effective nutriceuticals for the prevention and the treatment of age-associated metabolic complications, such as type 2 diabetes.

Keywords: inflammation, insulin secretion, insulin sensitivity, NAD, NAD World, NAMPT, SIRT1

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Introduction

Ageing is one of the most serious risk factors for many metabolic complications, including obesity, atherosclerosis and type 2 diabetes. For example, among US residents aged 65 years and older, 10.9 million or 26.9% of all people in this age group suffered diabetes in 2010, based on the 2011 National Diabetes Fact Sheet from the Center for Disease Control and Prevention. Indeed, it has been well known that insulin resistance develops over time [1]. It has also been shown that β-cell function declines progressively during ageing [2], contributing to the pathogenesis of type 2 diabetes. Another important factor of ageing that affects metabolic homeostasis is chronic inflammation. It has been known that levels of inflammatory cytokines and markers, including interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and C-reactive protein (CRP), elevate with age in healthy old individuals [3]. The elevation of these inflammatory cytokines and markers is tightly associated with the development of insulin resistance and β-cell dysfunction [4,5]. Therefore, one would speculate that factors that contribute to the regulation of systemic metabolic robustness and anti-inflammatory responses could play a crucial role in the pathogenesis of these age-associated metabolic complications, such as atherosclerosis and type 2 diabetes.

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One such factor is the mammalian nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylase SIRT1, one of the seven family members of mammalian sirtuins [6,7]. In the past decade, an accumulating body of evidence suggests that SIRT1 plays an important role in the regulation of glucose and lipid metabolism, providing a hope that SIRT1 will be a promising therapeutic target for age-associated metabolic complications, particularly type 2 diabetes [8]. Because SIRT1 requires NAD for its enzymatic activity, understanding the regulation of mammalian NAD biosynthesis has also become a critical issue in the field of metabolism and ageing research. Particularly, nicotinamide phosphoribosyltransferase (NAMPT), a key NAD biosynthetic enzyme in mammals, has recently become a focus of intensive investigation [9]. In this review, we will focus on the importance of a systemic regulatory network, named the 'NAD World', mediated by these two major players, SIRT1 and NAMPT. We will also discuss the translational aspect of the studies on SIRT1 and NAMPT for the treatment and prevention of type 2 diabetes.

SIRT1, a Key Mediator that Regulates Metabolic Responses to Nutritional Input

The biology of SIR2 family proteins, called 'sirtuins', has been evolving dramatically in the past decade since the discovery of their unique NAD-dependent deacetylase activity [8]. Through these tremendous amounts of studies on sirtuins, it has become clear that sirtuins function to maintain and/or enhance

the robustness of the physiological system and secure the survival of individuals when organisms are exposed to internal and external perturbations [6,7]. Among these perturbations, energy limitation, such as fasting and diet restriction (DR), is one of the most important ones that are known to increase sirtuin dosages and/or enhance their activities. Sirtuins also respond to other types of stresses and damages, such as oxidative stresses and DNA damages. In this regard, it is likely that sirtuins have evolved primarily to prevent the physiological system from any destruction due to a wide variety of environmental perturbations, such as a famine. This particular evolutional trait of sirtuins might have likely put themselves to a universal position of mediating anti-ageing effects in many different organisms.

Indeed, in yeast, worms and flies, sirtuins have been shown to play an important role in the regulation of ageing and longevity [10–12]. However, some of those results, particularly the effects of SIR2 orthologs, Sir-2.1 and dSir2, on longevity in worms and flies, respectively, have been called into a question [13], generating a serious controversy regarding the importance of sirtuins for ageing and longevity. Although this controversy still remains in the field, recent studies in yeast, flies and mice have provided further supportive evidence for the importance of sirtuins as key regulators of ageing and longevity [14–16]. In mammals, it has been firmly established that sirtuins are critical metabolic mediators in multiple tissues [6,7]. In particular, SIRT1, the mammalian SIR2 ortholog, regulates a variety of metabolic responses to changes in nutritional input in multiple tissues, including the liver, skeletal muscle, adipose tissue, pancreatic islets and the brain (figure 1). SIRT1 also plays a critical role in the regulation of phenotypes induced by DR, a well-known regimen that delays ageing and extends life span in a wide variety of organisms. Whereas the whole-body and brain-specific *Sirt1* knockout mice fail to respond to DR [17–19], *Sirt1*-overexpresing transgenic mice display phenotypes similar to DR mice [20] or prevention against metabolic complications caused by high-fat diet (HFD) and ageing [21,22]. However, whole-body *Sirt1*-overexpressing mice have been reported to fail to show life span extension, although they show a lower incidence of spontaneous carcinomas and sarcomas and a reduced susceptibility to HFD/carcinogen-induced liver tumours [23]. Therefore, whether and how sirtuins, SIRT1 in particular, regulate ageing and longevity in mammals still remains a critical question, and intensive investigation is currently in progress in the field of sirtuin biology to address this long-standing question.

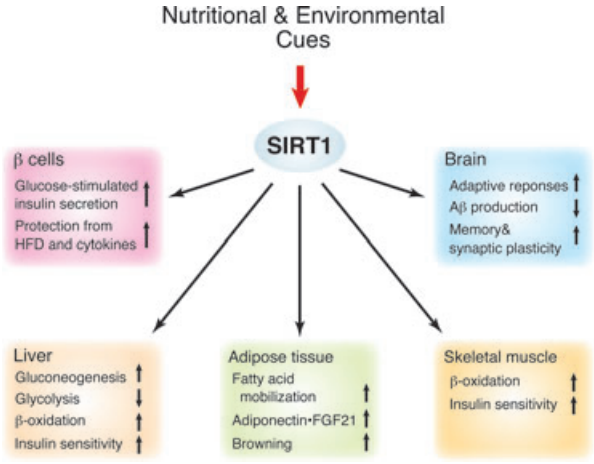

Figure 1. The function of silent information regulator T1 (SIRT1) as a key mediator that coordinates metabolic responses to nutritional and environmental cues and maintains physiological robustness in mammals. Major roles of SIRT1 in the liver, adipose tissue, skeletal muscle, pancreatic β cells and the brain are summarized in this scheme. Through these functions illustrated here, SIRT1 regulates the balance between insulin sensitivity and insulin secretion throughout the body and provides protection against nutritional and environmental perturbations, such as high-fat diet (HFD) and chronic inflammation. More details are given in the text.

Regulation of Insulin Sensitivity by SIRT1

Nonetheless, a number of genetic studies have so far strongly suggested that SIRT1 is important to maintain both insulin sensitivity and insulin secretion throughout the body. For example, in the liver, hepatic deletion of SIRT1 impairs peroxisome proliferator-activated receptor (PPAR) α function and decreases fatty acid β-oxidation, causing hepatic steatosis, inflammation and endoplasmic reticulum stress when exposed to a HFD [24]. Another study has demonstrated that hepatic *Sirt1* deficiency impairs the mammalian target of rapamycin complex 2 (mTORC2)/AKT signalling pathway, causing chronic hyperglycaemia, oxidative stress and systemic insulin resistance on a regular diet [25]. In adipose tissue, adipose tissue-specific *Sirt1* deficiency causes increased adiposity and leads to insulin resistance under a HFD and during ageing [26]. Interestingly, *Sirt1* deficiency in adipose tissue causes changes in gene expression that largely overlap with those caused by a HFD [26]. Most recently, it has been shown that SIRT1 promotes 'browning' of white adipose tissue by deacetylating PPARγ and recruiting Prdm16, a key co-activator for the development and function of brown adipose tissue, to PPARγ, potentially contributing to the improvement of insulin sensitivity [27]. In skeletal muscle, DR increases SIRT1 activity and enhances insulin-stimulated phosphoinositide 3-kinase (PI3K) signalling and glucose uptake through SIRT1-mediated STAT3 deacetylation [28]. These adaptive responses in skeletal muscle are completely abrogated by skeletal muscle-specific *Sirt1* deletion. These findings clearly demonstrate that SIRT1 plays a critical role in maintaining and improving insulin sensitivity in response to nutritional perturbations in major insulin sensitive tissues.

Regulation of Insulin Secretion by SIRT1

On the other hand, SIRT1 has also been demonstrated to positively regulate glucose-stimulated insulin secretion (GSIS) in pancreatic β-cells. Our group has previously demonstrated that an increased dosage of SIRT1 in β cells significantly enhances GSIS and improves glucose tolerance in pancreatic β-cell specific SIRT1-overexpressing (BESTO) transgenic mice [29]. Given that DR enhances postprandial insulin secretion [30], the BESTO phenotype is an interesting

phenocopy of this DR-induced response of insulin secretion. Contrarily, *Sirt1*-deficient mice and islets show blunted GSIS [31], further supporting the importance of SIRT1 in the regulation of GSIS in pancreatic β-cells. SIRT1 is also important for β-cell adaptation in response to increasing insulin resistance. Our group has shown that BESTO mice are able to maintain improved glucose tolerance with enhanced GSIS even under a long-term (up to 30 weeks) HFD treatment [32]. Consistent with our finding, other groups have also shown that SIRT1 protects pancreatic β-cells from metabolic stress- and cytokine-induced β-cell death by deacetylating FOXO1 and the p65 subunit of NF-κB, respectively [33,34]. Therefore, these findings indicate that SIRT1 is critical to protect pancreatic β-cells from dysfunction caused by metabolic and age-induced perturbations.

Regulation of Central Adaptive Response by SIRT1

In addition to regulating the balance between insulin sensitivity and insulin secretion in peripheral tissues and organs, SIRT1 is also required to regulate central adaptive responses to acute and chronic energy limitations. For example, DR significantly increases SIRT1 protein levels and induces neural activation in the dorsomedial and lateral hypothalamic nuclei (DMH and LH, respectively) [19]. Brain-specific SIRT1-overexpressing (BRASTO) mice mimics DR-induced neural activation in the DMH and LH, promotes physical activity and counteract the decrease in body temperature in response to different diet-restricting paradigms [19]. These adaptive responses are all abrogated in *Sirt1*$^{-/-}$ mice. In the DMH and LH, SIRT1 upregulates expression of the orexin type 2 receptor to mediate these adaptive responses. Furthermore, it has been reported that SIRT1 decreases the production of Aβ amyloid [35], prevents tau-mediated neurodegeneration [36] and maintain memory and synaptic plasticity [37], contributing to the prevention of age-associated cognitive disorders. These findings also provide strong support for the notion that SIRT1 functions to maintain physiological robustness against different kinds of perturbations, mediating beneficial effects against ageing.

Expanding Roles of Other Sirtuins in Metabolic Regulation

Recent studies have clearly proven the importance of other sirtuins in the regulation of insulin sensitivity and insulin secretion. For example, SIRT3, one of the mitochondrial sirtuin family members (SIRT3-5), regulates insulin sensitivity in skeletal muscle [38], and *Sirt3* deficiency is associated with the pathogenesis of metabolic syndrome including insulin resistance [39]. SIRT4, another mitochondrial sirtuin, controls amino acid-stimulated insulin secretion in pancreatic β-cells [40]. It has also been reported that SIRT6 promotes GSIS in β cells [41], whereas it suppresses gluconeogenesis in the liver [42]. Currently, intensive investigation is being undertaken to understand the roles of mitochondrial sirtuins and SIRT6 in cancer metabolism [43,44]. It has now become apparent that sirtuins have extensively divergent, complex functions in the regulation of metabolism under many different pathophysiological conditions. Given that they all require NAD for their functions, sirtuins are likely the critical keys to connect between NAD availability and metabolic regulation.

NAMPT, a Key NAD Biosynthetic Enzyme That Functions as a Pacemaker and Fine-Tunes SIRT1 Activity

The pathophysiological significance of SIRT1 and other sirtuins has fuelled more enthusiasm to investigate NAD biosynthetic pathways. NAD is a universal and essential co-enzyme involved in many cellular redox reactions. To generate NAD, mammals utilize four different precursors, including tryptophan, nicotinamide and nicotinic acid (also known as two forms of vitamin B_3) and nicotinamide riboside (NR) [45]. It is known that the salvage pathway starting from nicotinamide is a predominant NAD biosynthetic pathway in mammals [46]. In this pathway, NAMPT produces nicotinamide mononucleotide (NMN) from nicotinamide and 5′-phosphoribosyl-1-pyrophosphate. NMN, together with ATP, is then converted into NAD by the second enzyme, nicotinamide/nicotinic acid mononucleotide adenylyltransferase (NMNAT, figure 2). Studies have demonstrated that NAMPT is a dimeric type II phosphoribosyltransferase which functions as the rate-limiting enzyme in mammalian

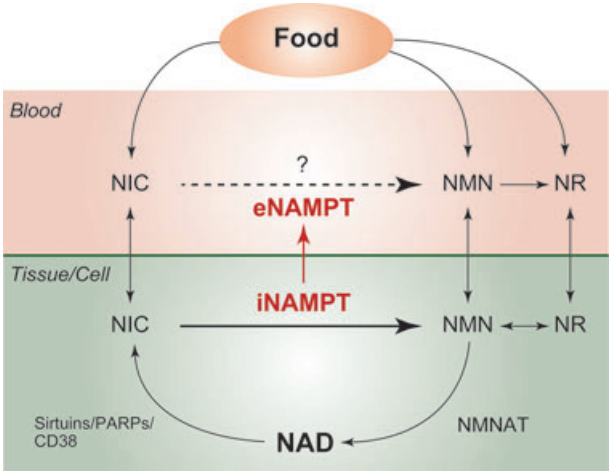

Figure 2. Nicotinamide phosphoribosyltranferase (NAMPT)-mediated nicotinamide adenine dinucleotide (NAD) biosynthetic pathways in mammals. In mammals, nicotinamide (NIC) is converted to nicotinamide mononucleotide (NMN) by the rate-limiting enzyme, NAMPT. There are two forms of NAMPT: intracellular and extracellular NAMPT (iNampt and eNampt, respectively). eNAMPT has significantly higher enzymatic activity than iNAMPT and likely synthesizes NMN in blood circulation. Extracellular NMN might be directly transferred into tissues/cells or is first converted to nicotinamide riboside (NR) and then transferred into tissues/cells. NR is reconverted to NMN by nioctinamide riboside kinase and utilized for NAD biosynthesis. NAD is generated from NMN by nicotinamide/nicotinic acid mononucleotide adenylyltransferase (NMNAT) and consumed by sirtuins, poly(ADP-ribose) polymerases (PARPs) and CD38.

NAD biosynthetic pathway and directly regulates SIRT1 activity [47,48]. Interestingly, mammals possess two different forms of NAMPT: intracellular and extracellular NAMPT (iNampt and eNampt, respectively, figure 2) [9,49]. In the past decade, the role of iNAMPT has been extensively studied in many biological processes. Particularly, iNAMPT plays an important role in regulating metabolic function by modulating SIRT1 activity. For example, FoxOs regulate *Nampt* transcription in the liver, and overexpression of iNAMPT reduces hepatic triglyceride levels [50]. It has also been reported that the levels of hepatic iNAMPT protein decrease in the patients with non-alcoholic fatty liver disease (NAFLD) [51]. In skeletal muscle, both glucose restriction and exercise increase iNAMPT protein levels [52,53], and iNAMPT levels correlate with mitochondrial contents in humans [52]. iNAMPT also plays a protective role in the stress associated with ageing and high-glucose in endothelial cells [54]. Interestingly, we and other groups have reported that the *Nampt* gene is regulated by the core clock machinery and thereby iNAMPT and NAD levels display circadian oscillation patterns in peripheral metabolic tissues, such as the liver and adipose tissue [55–57]. In turn, SIRT1 negatively regulates the transcriptional activation of clock genes. In other words, iNAMPT and SIRT1 together comprises a novel circadian-regulatory feedback loop, connecting circadian rhythm regulation to metabolic regulation. These findings suggest that NAD functions as a 'metabolic oscillator' that dynamically influences rhythmic regulation of metabolic responses [55]. We have recently found that both iNAMPT and NAD levels are reduced in multiple metabolic tissues and organs by HFD feeding and ageing, contributing to the pathogenesis of type 2 diabetes [58]. It appears that inflammatory cytokines and oxidative stress cause the reduction in iNAMPT-mediated NAD biosynthesis, implicating an interesting connection between chronic inflammation and NAMPT-mediated NAD biosynthesis.

The physiological function of eNAMPT is still under debate. It has been reported that eNAMPT is positively secreted from fully differentiated adipocytes [49], mononuclear cells [59], hepatocytes [60] and cardiomyocytes [61]. Our previous study has demonstrated that eNAMPT, secreted from adipocytes, has higher enzymatic activity compared with iNAMPT, and it might be involved in the extracellular synthesis of NMN, possibly in the blood circulation (figure 2) [49]. However, one recent study shows the contradictory data that recombinant NAMPT is not capable of producing NMN in plasma *in vitro* [62]. To further elucidate the function of eNAMPT *in vivo*, employing genetic approach, as well as biochemical approach, is important, and the detailed analysis of adipose tissue-specific *Nampt* knockout mice is currently in progress.

The NAD World: a Systemic Regulatory Network Connecting Metabolism and Ageing

As summarized above, the functional interplay between SIRT1 and NAMPT-mediated NAD biosynthesis plays a crucial role in the regulation of a variety of biological processes, particularly metabolic regulation. NAMPT-mediated NAD biosynthesis functions as a 'pacemaker' that controls a novel transcriptional-enzymatic arm of circadian regulation and fine-tunes SIRT1 activity. In response to the alterations in NAMPT-mediated NAD biosynthesis, SIRT1 functions as a key mediator that coordinates a number of metabolic responses throughout the body. Through this tight interplay, NAMPT-mediated NAD biosynthesis and SIRT1 together comprise a novel systemic regulatory network, named the 'NAD World', that orchestrates physiological responses to internal and external perturbations and maintains the robustness of the physiological system in mammals [55,63–65].

The significance of this concept is that it conveys the ideas of functional hierarchy and frailty in determining the robustness of the systemic regulation of metabolism and ageing. In this concept of the NAD World, critical frailty points are the tissues and organs that have very low levels of iNAMPT. Such tissues and organs likely rely on extracellular sources of NAD intermediates, such as NMN and NR, to maintain sufficient NAD levels for their functions (figure 3). In this regard, pancreatic β-cells and neurons are likely the most critical frailty points in the mammalian physiological system because both cell types have very low levels of iNAMPT compared with other cell types. Our previous studies have clearly shown that pancreatic β-cells are indeed an important frailty point in the NAD World that is susceptible to changes in NAMPT-mediated NAD biosynthesis. Genetic, pharmacological and pathophysiological reductions in NAMPT-mediated NAD biosynthesis all impairs β-cell function, causing defects in GSIS and impaired glucose tolerance *in vivo* [32]. Similarly, neurons are also likely another critical frailty point in the NAD World. It has been demonstrated that SIRT1 regulates memory and synaptic plasticity in the hippocampus [37] and neurobehavioral adaptation in the hypothalamus [19]. Therefore, NAD supply for SIRT1 in these brain regions must be critical, and its reduction could cause neurological problems, including dementia and neurobehavioral complications.

As briefly described in the previous section, we have shown that tumour necrosis factor-α (TNF-α) and oxidative stress significantly reduce NAMPT and NAD levels in primary hepatocytes [58]. Given that both inflammatory cytokines and oxidative stress contribute to age-associated chronic inflammation [3], the development of chronic inflammation could be the reason why NAMPT-mediated NAD biosynthesis is compromised during ageing, leading to reduction in SIRT1 activity and thereby a variety of metabolic complications in multiple tissues. Therefore, it will be of great interest to examine whether inflammatory cytokines, such as TNF-α, and/or oxidative stress indeed affects NAD levels in pancreatic β-cells and central neurons. If this is the case, serious dysfunction of these two cell types would be caused by chronic inflammation through defects in NAMPT-mediated NAD biosynthesis. Such dysfunction of pancreatic β-cells and central neurons would affect many other tissues and organs through insulin action and central metabolic regulation, resulting in the gradual deterioration of physiological robustness over time. We speculate that this cascade of robustness breakdown triggered by defects in NAMPT-mediated NAD biosynthesis underlies in the induction of age-associated pathophysiology. If so, is

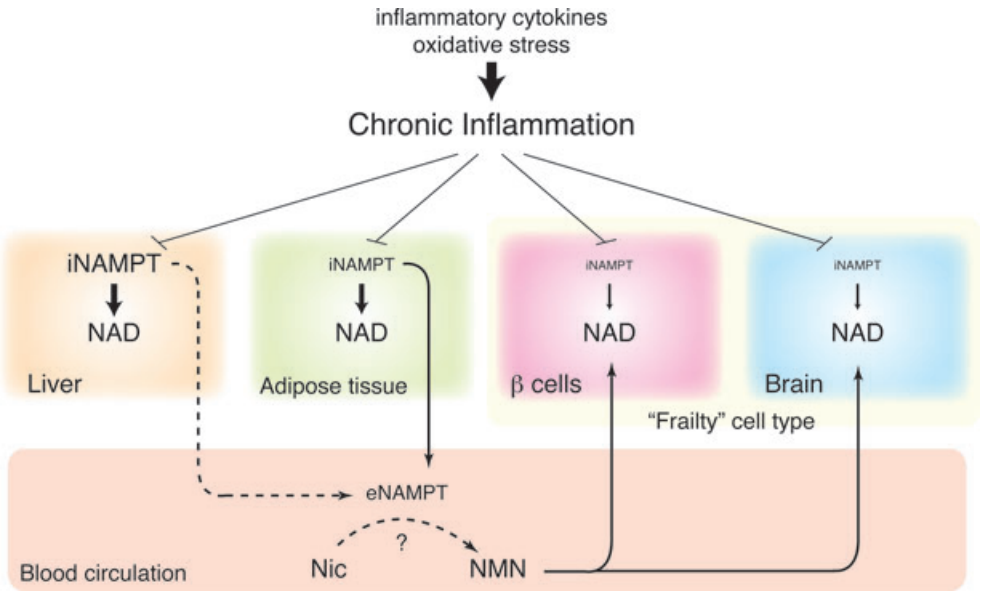

Figure 3. The concept of the NAD World and the possible effect of chronic inflammation. Pancreatic β-cells and neurons (the brain) are two major frailty points in the NAD World because these two cell types have very low levels of intracellular nicotinamide phosphoribosyltranferase (iNAMPT). These particular cell types likely depend on extracellular nicotinamide mononucleotide (NMN), which is speculated to be synthesized by extracellular nicotinamide phosphoribosyltranferase (eNAMPT) secreted by adipose tissue, and maintain optimal nicotinamide adenine dinucleotide (NAD) levels for their functions. Chronic inflammation, which is caused by inflammatory cytokines and oxidative stress, decreases NAMPT and NAD levels in multiple tissues, contributing to the pathogenesis of age-associated metabolic complications, such as type 2 diabetes. It still remains unclear whether chronic inflammation in adipose tissue also decreases plasma eNAMPT levels and remotely affects the functions of 'frailty' cell types. More details for the concept of the NAD World are given in the text.

it possible to prevent this systemic robustness breakdown by enhancing NAD biosynthesis at a systemic level? We will discuss this interesting possibility in the next section.

Key NAD Intermediates: a Translational Perspective

Given the importance of SIRT1 in the regulation of metabolic responses in multiple tissues and organs, it has been speculated that modulating NAD levels may influence metabolic functions and provide an effective intervention to treat metabolic disorders such as type 2 diabetes, obesity and insulin resistance [66]. Indeed, recent studies, including our own, show that enhancing NAD biosynthesis has beneficial effects on glucose and lipid metabolism by increasing SIRT1 activity. For example, genetically engineered mouse models demonstrate that inactivation of poly(ADP-ribose) polymerase-1 (NAD consuming enzyme) [67] or CD38 (NAD degrading enzyme) [68] significantly improves mitochondrial function in skeletal muscle and prevents diet-induced obesity by enhancing energy expenditure. Slow Wallerian degeneration (WldS) mutant mice that contain a spontaneous mutation containing full-length NMNAT1 enhance insulin secretion, and they are also protective against HFD-induced glucose intolerance and streptozotocin-induced hyperglycaemia in a SIRT1 dependent manner [69]. Furthermore, administration of apigenin (a potent CD38 inhibitor) [70] and leucine [71] also increases tissue NAD levels and improves metabolic complications, such as glucose intolerance and insulin resistance, in HFD-fed mice.

Our group has demonstrated that administration of a key NAD intermediate, NMN, treats the pathophysiology of metabolic disorders associated with haplodeficiency of *Nampt*, HFD-feeding and ageing. NMN is a product of NAMPT enzymatic reaction and found in our daily food sources (our unpublished finding). NMN administration restores GSIS in *Nampt* heterozygous knockout mice [49] and old BESTO and wild-type mice [32]. Furthermore, NMN increases GSIS and insulin sensitivity in HFD-fed type 2 diabetic model mice by restoring the defects in NAMPT-mediated NAD biosynthesis [58]. Interestingly, NMN appears to ameliorate inflammatory response, leading to the improvement in hepatic insulin sensitivity in HFD-fed mice. Indeed, NMN administration enhances the deacetylation of the p65 subunit of NF-κB through the activation of SIRT1 in the liver. Our bioinformatics analyses confirm that biological pathways associated with inflammatory response and NF-κB target genes, such as IL-1β and SA100 calcium binding proteins A8 and A9 (S100a8 and S100a9), are also reduced by NMN treatment. Consistent with our findings, NMN administration reduces the expression of IL-1β and restores β-cell function in fructose-rich diet-fed mice [72]. Additionally, NMN restores insulin secretion in pro-inflammatory cytokine-treated islets [72,73]. These findings indicate that NMN treatment has anti-inflammatory effects in pancreatic islets and the liver, improving insulin secretion and action in diabetic model mice. NR is another promising NAD intermediate to treat metabolic disorders. It has been reported that NR administration also improves mitochondrial function in skeletal muscle and brown adipose tissue, glucose tolerance,

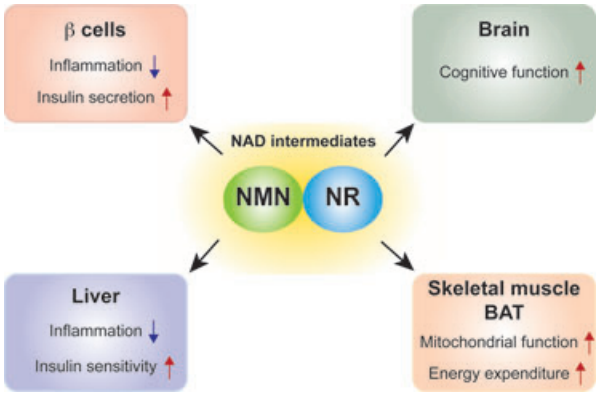

Figure 4. Therapeutic potential of key nicotinamide adenine dinucleotide (NAD) intermediates against age-associated diseases. Supplementation of key NAD intermediates, nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR), improves insulin secretion, insulin action, energy expenditure, and cognitive function and prevents inflammatory reactions in mice. These NAD intermediates are expected to be translatable as effective anti-ageing nutriceuticals into humans in the near future.

insulin secretion and action, plasma lipid panel and energy expenditure through activating SIRT1 and SIRT3 in HFD-fed mice [74]. Because SIRT1 functions to prevent a variety of age-associated diseases [6,8], it is likely that enhancing NAD levels through supplementation with NAD intermediates, such as NMN and NR, could prevent not only metabolic disorders but also other age-associated diseases (figure 4). One recent study has shown that NR treatment significantly attenuates cognitive deterioration in the AD mouse model [75]. Furthermore, it is also possible that NMN/NR supplementation directly affects NAD-dependent redox metabolism such as β-oxidation and glycolysis. Therefore, it will be of great importance to investigate the effect of NMN/NR supplementation on those biological processes. Given that both NMN and NR are natural compounds (unpublished data) and derivatives of vitamin B_3, these compounds are expected to be translatable as effective anti-ageing nutriceuticals into humans in the near future. To this end, it will be of great importance to carefully evaluate the effects of long-term NMN/NR supplementation, as well as their potential side effects, on metabolism and other pathophysiological parameters in rodents and then possibly humans.

Conclusion

On the verge of historically unprecedented increases in elderly demographics through the globe, it is now of great importance to understand the spatial and temporal dynamics of the systemic regulatory network that integrates metabolic regulation to the ageing/longevity control in mammals. In this regard, the concept of the NAD World provides critical insight into how to dissect such system dynamics, focusing on two critical components, namely SIRT1 and NAMPT-mediated NAD biosynthesis. Several important questions still remain unanswered. If chronic inflammation is a major cause for defects in NAMPT-mediated biosynthesis at a systemic level, how and where does it happen during the process of ageing? Are 'frailty' cell types, such as pancreatic β-cells and neurons, indeed sensitive to inflammation-induced dysfunction of NAD biosynthesis? Can we reverse this destruction process by enhancing NAD biosynthesis with key NAD intermediates as nutriceuticals? Can we really improve the quality of life and eventually achieve longevity by administering these NAD intermediates in humans? Further investigation will be definitely required to address these questions. We hope that understanding the NAD World will guide us towards reasonable solutions for social and economic problems caused by heavily ageing societies.

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Conflict of Interest

S. I. serves as a scientific advisory board member for Sirtris, a GSK company, and has a Sponsored Research Agreement with Oriental Yeast Co., Tokyo, Japan. J. Y. has no conflict of interest.

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