Aging and Nicotinamide Adenine Dinucleotide Deficiency

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Under normal physiological conditions, nicotinamide adenine dinucleotide (NAD+) consumption is matched by its synthesis primarily via the salvage pathway catalyzed by nicotinamide phosphoribosyltransferase (NAMPT). However, aging and muscular contraction enhance NAD+ utilization, whereas NAD+ replenishment is limited by cellular sources of NAD+ precursors and/or enzyme expression.

Keywords: Aging ; nicotinamide adenine dinucleotide ; Muscle

1. Muscle Nicotinamide Adenine Dinucleotide (NAD+) Level Decreases with Aging

The discovery that aging could cause declines in cellular nicotinamide adenine dinucleotide (NAD+) levels came from the observation that sirtuins (SIRTs) activities were lowered in aged animals [1][2]. It was noticed that transgenic mice overexpressing SIRT1 stimulated insulin secretion and ameliorated glucose metabolism when they were young, but the positive effects faded when mice grew older. Subsequent research revealed that SIRT1 activity was compromised because of diminished NAD+, the mandatory substrate for SIRTs [2]. Supplementation of NAD+ precursor nicotinamide mononucleotide (NMN) was able to restore NAD+ due to the conversion of NMN to NAD+ by NAMN transferase (NMNAT) and ameliorated the aging effect. Since then, a number of studies confirmed that NAD+ levels in mammals, as well as in several species of invertebrates, decrease with advanced age in tissues and organs such as the liver, brain, and muscle [1][3][4][5][6]. Skeletal muscle is one of the organs dramatically demonstrating this phenomenon [7][8][9][10][11].

In living cells, NAD+ is much more abundant than 3-hydroxylacyl coenzyme A dehydrogenase (NADH) [12], presumably because the latter is readily converted back to NAD+ by the ETC under normal physiological conditions. Thus, most studies use the NAD+ level as an indication of the total cellular nicotinamide adenine dinucleotide pool. Although cellular NAD+ levels have been shown to decline as much as 80% at old age [4][13], the extent of NAD+ change in skeletal muscle is less clear and variable data have been reported in the literature. Gomes et al. [1] showed that NAD+ content in the gastrocnemius muscle of 6-month-old mice was ~230 pmol/mg protein. Frederic et al. [8] showed that NAD+ concentrations in the mixed hindlimb muscles (quadriceps, gastrocnemius, and tibialis anterior) of both male and female mice were about 500 pmol/mg muscle. It is unclear whether wet or dry muscle weight was used to normalize NAD+ concentration. Researchers also showed that NAD+ concentration in isolated muscle mitochondria was in several nmole ranges per mg protein. In a recent study, Yeo et al. [14] measured NAD+ concentration at 250 pmol/mg protein in mouse gastrocnemius and quadriceps muscles, similar to that of Gomes et al. [1]. Since NAD+ concentration is highly compartmented in the cell, it is difficult to know the extent of age-related NAD+ deficit in muscle. Yeo et al. [14] found that NAD+ concentration in the homogenate of mouse quadriceps and gastrocnemius muscle decreased about 50%, comparing 12 months and 24 months of age with 6 months of age. The nuclear NAD+ level was also decreased by approximately half, whereas cytoplasmic NAD+ showed only a modest decrease of ~20%. Because nuclear poles are large enough for NAD+ to exit into the cytosol, the exact concentration of NAD+ in cytosol is often uncertain. Since skeletal muscle is highly heterogeneous in fiber type compositions with different genotypic sources of originality and metabolic profile, the NAD+ level is likely to be different in different fiber types [15]. Furthermore, different fiber types age at different rates, giving even greater diversity of biochemical and physiological endowments [16]. Currently, there is a paucity of data regarding fiber-specific alteration of NAD+ turnover during aging.

2. Consequences of NAD+ Deficit in Aging Muscle

A hallmark of aging is decreased mitochondrial function, demonstrated by a reduced ability to utilize metabolic fuels, decreased ATP production, and oxygen consumption [17][18]. Mitochondrial volume also decreases in aged muscle, largely

explained by decreased mitochondrial biogenesis controlled by the SIRT/PGC-1α/Tfam axis [19]. However, the mechanism of age-related decline in mitochondrial quality and quantity is not entirely clear. The discovery that aged organisms, including muscle suffer from diminished NAD+ pools, has provided a new insight to this decade-old puzzle in age research.

The enzyme that is most affected by a diminished NAD+ level with aging is SIRTs, especially SIRT1 and SIRT3. SIRT activity systematically declines in aging despite the relatively stable enzyme protein content [20]. This decline can directly affect its ability to deacetylate PGC-1α, leading to a lower Tfam, the primary nuclear factor to activate mitochondrial biogenesis [12]. SIRT1 is also known to activate mitochondrial enzyme expressions via a PGC-1α-independent, but HIF-dependent pathway [8]. In addition, decreased NAD+ also inactivates SIRT3, the mitochondrial sirtuin, thus causing inhibition of enzymes in the TCA cycle through increased acetylation [21]. Moreover, lower mitochondrial NAD+ could hinder the ability of Complex I to oxidize NADH and restrict electron flow through the ETC [22][23][24][25]. Thus, a compromised NAD+ level may provide a direct explanation of the age-related loss of mitochondrial homeostasis, which leads to muscle functional loss and sarcopenia. Indeed, in a recent study, Yeo et al. [14] demonstrated that NAD+ deficit in 24-month-old mice was associated with increased acetylation of a wide range of proteins, such as PGC-1α, GCN5, p65, and SOD2 in mouse hindlimb muscles and heart. Ironically, protein levels of SIRT1, 3, 5, and 6 were upregulated comparing old vs. young muscles. Other researchers have also reported decays of SIRT activities with aging, and directly attributed SIRT downregulation to NAD+ deficit [1][2][26]. These data emphasized the importance of cellular NAD+ in controlling overall acetylation status and thus, muscle functionality.

Another serious consequence of decreased NAD+ availability in an aged organism is compromised antioxidant defense, leading to increased oxidative stress and inflammation, termed “inflammaging” [27]. First, aged muscle is known to generate high levels of ROS primarily in the mitochondria, but also due to inflammation [19][28]. Diminished NAD+ levels and SIRT3 activity can attenuate SOD2 deacetylation and thus, the ability of removing superoxide anion. Acetylation increases the binding activity of p65, a crucial step in the transactivation of pro-inflammatory cytokine expression [29][30]. Moreover, lowered NAD+ level limits the ability of PARP-1 to utilize pADPr to repair DNA damage that occurs at old age [31][32].

3. Potential Mechanisms of Age-Related NAD+ Decline

Cellular mechanisms for decreased NAD+ levels with aging are multifaceted, related to both NAD+ consumption and synthesis. The most important reason is probably related to increased protein acetylation in aging organisms [20][27]. Proteomic analysis reveals that over 100 lysine sites in mitochondrial proteins are acetylated, which can be one of the most common post-translational modifications of mitochondrial homeostasis [33]. Aging is a prominent inducer of mitochondrial protein hyperacetylation, the major cause of mitochondrial enzyme dysfunction in the TCA cycle and ETC, loss of redox homeostasis, and increased organelle oxidative damage [34][35]. A recent study revealed that hindlimb muscles of 24-month-old mice had enhanced acetylation of PGC-1α by 6-fold, p65 by 4-fold, SOD2 level by 8-fold, GCN5 by 50%, and total protein level by 3-fold, compared to those of 6-month-old counterparts [14]. Importantly, most of these parameters showed significant elevations at 12 months of age, indicating age-dependent NAD+ deficit might start earlier than previously thought. Increased protein acetylation requires higher SIRT activity for deacetylation, and in turn, more NAD+ to accept acetyl moieties from acetylated proteins [20][36]. Whether aging upregulates or downregulates SIRT1 is still controversial. The ironic finding was that despite increased protein expression of SIRT1 in response to aging, its activity is unchanged or even decreased due to diminished NAD+ supply in muscle cells [10][37].

Besides increased consumption by SIRTs, aging has been shown to increase CD38 and CD157 activities [38]. Cleavage of NAD+ generates ADP-ribose and NAM, used as DNA damage repair and for NAD+ salvage, respectively. Recent studies reported that aging gradually increases CD38 protein levels and its NADase activity [7][9][39][40]. CD38 gene knockout and 78c, a specific CD38 inhibitor, rescued intracellular NAD+ and preserved SIRTs activity [7][9]. It was demonstrated that CD38 expression increased by 2–6-fold in the skeletal muscle of mid-aged mice and by 5–13-fold in the old mice, supporting the view that upregulation of this enzyme, could be the main reason for muscle NAD+ deficit at old aged [14][41][42].

Another explanation for age-associated decreases in muscleNAD+ is an upregulation of PARP-1, which uses NAD + as a substrate to catalyze the covalent transfer of ADP-ribose for DNA repair [20]. Elevated PARP-1 levels may be an inevitable process of aging due to an accumulation of DNA damage [31]. Treatment of PARP-1 inhibitor was shown to increase NAD+ pools and elevate SIRT activity [31][43][44]. Skeletal muscles of old mice accumulated higher levels of cleaved pADPr, suggesting that PARP-1 activity was increased during aging [14]. Taken together, aged muscles clearly suffer from a NAD+

deficit, which might be attributed to the enhanced deacetylation demand catalyzed by SIRTs and the upregulation of two enzymes that consume NAD+, namely CD38, and PARP-1.

While clear evidence exists that aging increases NAD+ degradation in muscle, research also indicates that NAD+ synthesis may diminish at old age. As previously mentioned, the primary means to replenish cellular NAD+ is the NAD+ salvage pathway catalyzed by its rate-limiting enzyme NAMPT. There is a consensus that aging decreases NAMPT expression in several tissues, including skeletal muscle [12][45]. Age-associated downregulation of NAMPT is probably caused by a defective circadian rhythm regulation by CLOCK and BMAL [3][46]. BMAL and CLOCK control the expression of NAMPT, whereas they are regulated by SIRT1 through the deacetylation of a central clock component in the liver [47][48]. An age-related decline in SIRT1 activity may be the primary reason for the observed downregulation of NAMPT.

NAMPT downregulation during aging may also be triggered by increased inflammation, marked by elevated pro-inflammatory cytokine expression. TNF-α inhibits BMAL/CLOCK-mediated transcription in hepatocytes and hence, NAMPT expression [3][49]. Since aging is associated with increased muscle inflammation, marked by elevated TNF-α and other inflammatory triggers, such as cyclooxygenase 2 (COX2), suppression of muscle inflammation may provide an alternative strategy to maintain proper NAD+ and SIRT levels during aging [50].

4. Supplementation of NAD+ Precursors Ameliorates Muscle Aging

At a young age and in a healthy state, NAD+ levels do not seem to limit cardiac and skeletal muscle physiology [51]. However, decreases in NAD+ content are apparent in the brain, liver, and muscle, coincident with functional declines in these tissues at older age [1][4][6][43]. Furthermore, increased NAD+ levels are associated with increased longevity in the invertebrates and improve metabolic function in rodents [12][27]. Therefore, various strategies have been postulated and experimented aiming to restore and boost cellular NAD+ pools, making NAD+ supplementation a hot area of both basic research and human clinical trials. It is noticed that supplementation of four different NAD+ precursors has demonstrated age-specific efficacy not necessarily in agreement with the observation of younger animals or humans.

Since mitochondrial dysfunction is considered the hallmark of muscle aging, the majority of research has linked NAD+ precursor supplementation to mitochondrial function. It is generally agreed that the primary reason for NR supplementation to restore NAD+ levels and ameliorate aging effects in muscle is due to increased SIRT1 activity, thus activating the SIRT1/PGC-1α/Tfam axis and improving mitochondrial homeostasis [52][53][54][55]. NAMPT overexpression alone augmented endurance performance in mice, demonstrating the efficacy of the salvage pathway [56]. While NAM supplementation alone may not be effective in raising cellular NAD+ levels, physical exercise in conjunction with NAM has shown some promise. For example, Pajk et al. [57] supplemented NAM in drinking water to young and old mice in conjunction with endurance training. NAM treatment increased SIRT1 deacetylation activity in both age groups, accompanied by an increased PGC-1α level in older mouse muscle. These data provided some promise that oral NAM supplementation, especially combined with exercise, may not cause SIRT1 inhibition in vivo. Recently, Das et al. [58] demonstrated that supplementation of NAM increased blood flow and endurance capacity in old mice by promoting SIRT1-mediated capillary density. The role of blood flow in aging muscle and highlighted the role of SIRT1 in angiogenesis to elevate hydrogen sulfide (H2S) and restore NAD+ levels in the endothelial cells. Long-term administration of NMN was found to be an effective regimen to mitigate an age-associated physiological decline in mice [59]. Twelve months of NMN supplementation with a regular chow diet in C57BL/6N mice suppressed body weight gain, enhanced energy metabolism, promoted physical activity, and improved insulin sensitivity during normal aging. Thus, NMN may be a more direct and simpler dietary source to ameliorate aging effects.

Another potential site of action for NAD+ precursors to ameliorate muscle aging is muscle stem cells (MuSC), as revealed in a study by Zhang et al. [60]. NAD+ concentration in MuSC from aged mice was lower than that from young mice, indicating NAD+ deficit was the main reason for these mice demonstrating a range of muscle dysfunctions, whereas supplementation of NR increased NAD+ levels in MuSC. NR rejuvenated age-associated MuSC regeneration, mitochondrial function, and SIRT1 activity. Importantly, NR also increased muscle strength, running duration, and life span in aged mice [60]. A study shed new light to the role of NAD+ in improving not only the existing senescent myocyte function but also the ability to reverse muscle morphological and physiological declines at old age via stem cell rejuvenation.

Due to the importance of the salvage pathway in recycling NAM to synthesize NAD+, the role of NAMPT as the rate-limiting enzyme for this pathway, and as a key factor for ameliorating aging, was highlighted in[61]. Transgenic overexpression of NAMPT has been reported to improve cellular functions and attenuate the onset of senescence in several tissues, including skeletal muscle [51]. NAD+ levels were shown to increase by 2-fold in transgenic lines of mouse

embryotic fibroblast (MEF) compared to WT MEF cells [61]. Increased SIRT1 activity, elevated antioxidant enzyme expression, and resistance to oxidative stress were also observed in this cell line.

It is noteworthy that NAD+ precursor supplementation is still a controversial subject and the research outcome of its efficacy, especially in humans, is mixed. Several recent clinical trials revealed that chronic NR supplementation did not improve mitochondrial volume and function in humans [62][63][64][65], even though NAM and nicotinic acid riboside (NAR) contents were elevated [62]. These studies challenged the proposition that aged people should increase consumption of vitamin B3 compounds for the sake of preserving muscle function. For example, Connell et al. [66] failed to observe increases in NAD+ levels or limb muscle functional improvement conducted by MRI scanning after one-month supplementation of a mixture of niacin equivalent (tryptophan, NA, and NAM). Noticeably, NR was missing from the ascribed dietary source. Stocks et al. [62] also did not observe a significant change in muscle NAD+ content or mitochondrial functional capacity following 7-days of NR supplementation. Clearly, the efficacy and mechanism of NR supplementation in ameliorating functional improvement of aging muscle require more innovative and thorough investigation, and the effects of exercise in ameliorating dietary supplementation seem to be critically important [67].

References

1. 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.
2. Ramsey, K.M.; Mills, K.F.; Satoh, A.; Imai, S. Age-associated loss of Sirt1-mediated enhancement of glucose-stimulated insulin secretion in beta cell-specific Sirt1-overexpressing (BESTO) mice. Aging Cell 2008, 7, 78–88.
3. 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.
4. 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.
5. Pugh, T.D.; Conklin, M.W.; Evans, T.D.; Polewski, M.A.; Barbian, H.J.; Pass, R.; Anderson, B.D.; Colman, R.J.; Eliceiri, K.W.; Keely, P.J.; et al. A shift in energy metabolism anticipates the onset of sarcopenia in rhesus monkeys. Aging Cell 2013, 12, 672–681.
6. 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.
7. 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.
8. 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.
9. Tarrago, M.G.; Chini, C.C.S.; Kanamori, K.S.; Warner, G.M.; Caride, A.; de Oliveira, G.C.; Rud, M.; Samani, A.; Hein, K.Z.; Huang, R.; et al. A Potent and Specific CD38 Inhibitor Ameliorates Age-Related Metabolic Dysfunction by Reversing Tissue NAD(+) Decline. Cell Metab. 2018, 27, 1081–1095.
10. Koltai, E.; Szabo, Z.; Atalay, M.; Boldogh, I.; Naito, H.; Goto, S.; Nyakas, C.; Radak, Z. Exercise alters SIRT1, SIRT6, NAD and NAMPT levels in skeletal muscle of aged rats. Mech. Ageing Dev. 2010, 131, 21–28.
11. Schultz, M.B.; Sinclair, D.A. Why NAD(+) Declines during Aging: It's Destroyed. Cell Metab. 2016, 23, 965–966.
12. Verdin, E. NAD(+) in aging, metabolism, and neurodegeneration. Science 2015, 350, 1208–1213.
13. Braidy, N.; Poljak, A.; Grant, R.; Jayasena, T.; Mansour, H.; Chan-Ling, T.; Guillemin, G.J.; Smythe, G.; Sachdev, P. Mapping NAD(+) metabolism in the brain of ageing Wistar rats: Potential targets for influencing brain senescence. Biogerontology 2014, 15, 177–198.
14. Yeo, D.; Kang, C.; Ji, L.L. Aging alters acetylation status in skeletal and cardiac muscles. Geroscience 2020, 42, 963–976.
15. Deschenes, M.R. Effects of aging on muscle fibre type and size. Sports Med. 2004, 34, 809–824.
16. Giacomello, E.; Crea, E.; Torelli, L.; Bergamo, A.; Reggiani, C.; Sava, G.; Toniolo, L. Age Dependent Modification of the Metabolic Profile of the Tibialis Anterior Muscle Fibers in C57BL/6J Mice. Int. J. Mol. Sci. 2020, 21, 3923.

17. Wallace, D.C. Mitochondrial DNA mutations in disease and aging. Environ. Mol. Mutagen. 2010, 51, 440–450.

18. Lanza, I.R.; Nair, K.S. Mitochondrial function as a determinant of life span. Pflug. Arch. 2010, 459, 277–289.

19. Ji, L.L. Redox signaling in skeletal muscle: Role of aging and exercise. Adv. Physiol. Educ. 2015, 39, 352–359.

20. Imai, S.; Guarente, L. NAD+ and sirtuins in aging and disease. Trends Cell Biol. 2014, 24, 464–471.

21. Lombard, D.B.; Alt, F.W.; Cheng, H.L.; Bunkenborg, J.; Streeper, R.S.; Mostoslavsky, R.; Kim, J.; Yancopoulos, G.; Valenzuela, D.; Murphy, A.; et al. Mammalian Sir2 homolog SIRT3 regulates global mitochondrial lysine acetylation. Mol. Cell. Biol. 2007, 27, 8807–8814.

22. Someya, S.; Yu, W.; Hallows, W.C.; Xu, J.; Vann, J.M.; Leeuwenburgh, C.; Tanokura, M.; Denu, J.M.; Prolla, T.A. Sirt3 mediates reduction of oxidative damage and prevention of age-related hearing loss under caloric restriction. Cell 2010, 143, 802–812.

23. Hebert, A.S.; Dittenhafer-Reed, K.E.; Yu, W.; Bailey, D.J.; Selen, E.S.; Boersma, M.D.; Carson, J.J.; Tonelli, M.; Balloon, A.J.; Higbee, A.J.; et al. Calorie restriction and SIRT3 trigger global reprogramming of the mitochondrial protein acetylome. Mol. Cell 2013, 49, 186–199.

24. Qiu, X.; Brown, K.; Hirschey, M.D.; Verdin, E.; Chen, D. Calorie restriction reduces oxidative stress by SIRT3-mediated SOD2 activation. Cell Metab. 2010, 12, 662–667.

25. Hirschey, M.D.; Shimazu, T.; Goetzman, E.; Jing, E.; Schwer, B.; Lombard, D.B.; Grueter, C.A.; Harris, C.; Biddinger, S.; Ilkayeva, O.R.; et al. SIRT3 regulates mitochondrial fatty-acid oxidation by reversible enzyme deacetylation. Nature 2010, 464, 121–125.

26. Chang, H.C.; Guarente, L. SIRT1 mediates central circadian control in the SCN by a mechanism that decays with aging. Cell 2013, 153, 1448–1460.

27. Chini, C.C.S.; Tarrago, M.G.; Chini, E.N. NAD and the aging process: Role in life, death and everything in between. Mol. Cell Endocrinol. 2017, 455, 62–74.

28. Ji, L.L.; Kang, C.; Zhang, Y. Exercise-induced hormesis and skeletal muscle health. Free Radic. Biol. Med. 2016, 98, 113–122.

29. Yeung, F.; Hoberg, J.E.; Ramsey, C.S.; Keller, M.D.; Jones, D.R.; Frye, R.A.; Mayo, M.W. Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. EMBO J. 2004, 23, 2369–2380.

30. Kawahara, T.L.; Michishita, E.; Adler, A.S.; Damian, M.; Berber, E.; Lin, M.; McCord, R.A.; Ongaigui, K.C.; Boxer, L.D.; Chang, H.Y.; et al. SIRT6 links histone H3 lysine 9 deacetylation to NF-kappaB-dependent gene expression and organismal life span. Cell 2009, 136, 62–74.

31. Fang, E.F.; Kassahun, H.; Croteau, D.L.; Scheibye-Knudsen, M.; Marosi, K.; Lu, H.; Shamanna, R.A.; Kalyanasundaram, S.; Bollineni, R.C.; Wilson, M.A.; et al. NAD(+) Replenishment Improves Lifespan and Healthspan in Ataxia Telangiectasia Models via Mitophagy and DNA Repair. Cell Metab. 2016, 24, 566–581.

32. Fouquerel, E.; Sobol, R.W. ARTD1 (PARP1) activation and NAD(+) in DNA repair and cell death. DNA Repair 2014, 23, 27–32.

33. Kim, S.C.; Sprung, R.; Chen, Y.; Xu, Y.; Ball, H.; Pei, J.; Cheng, T.; Kho, Y.; Xiao, H.; Xiao, L.; et al. Substrate and functional diversity of lysine acetylation revealed by a proteomics survey. Mol. Cell 2006, 23, 607–618.

34. Sack, M.N.; Finkel, T. Mitochondrial metabolism, sirtuins, and aging. Cold Spring Harb. Perspect. Biol. 2012, 4, a013102.

35. Wagner, G.R.; Payne, R.M. Mitochondrial acetylation and diseases of aging. J. Aging Res. 2011, 2011, 234875.

36. Johnson, S.; Imai, S.I. NAD (+) biosynthesis, aging, and disease. F1000Research 2018, 7, 132.

37. Kilic, U.; Gok, O.; Erenberk, U.; Dundaroz, M.R.; Torun, E.; Kucukardali, Y.; Elibol-Can, B.; Uysal, O.; Dundar, T. A remarkable age-related increase in SIRT1 protein expression against oxidative stress in elderly: SIRT1 gene variants and longevity in human. PLoS ONE 2015, 10, e0117954.

38. Chini, E.N. CD38 as a regulator of cellular NAD: A novel potential pharmacological target for metabolic conditions. Curr. Pharm. Des. 2009, 15, 57–63.

39. Chini, E.N.; Chini, C.C.S.; Espindola Netto, J.M.; de Oliveira, G.C.; van Schooten, W. The Pharmacology of CD38/NADase: An Emerging Target in Cancer and Diseases of Aging. Trends Pharmacol. Sci. 2018, 39, 424–436.

40. Chini, C.; Hogan, K.A.; Warner, G.M.; Tarrago, M.G.; Peclat, T.R.; Tchkonia, T.; Kirkland, J.L.; Chini, E. The NADase CD38 is induced by factors secreted from senescent cells providing a potential link between senescence and age-related cellular NAD(+) decline. Biochem. Biophys. Res. Commun. 2019, 513, 486–493.

41. Aksoy, P.; Escande, C.; White, T.A.; Thompson, M.; Soares, S.; Benech, J.C.; Chini, E.N. Regulation of SIRT 1 mediated NAD dependent deacetylation: A novel role for the multifunctional enzyme CD38. Biochem. Biophys. Res. Commun. 2006, 349, 353–359.

42. Aksoy, P.; White, T.A.; Thompson, M.; Chini, E.N. Regulation of intracellular levels of NAD: A novel role for CD38. Biochem. Biophys. Res. Commun. 2006, 345, 1386–1392.

43. 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.

44. Fang, E.F.; Scheibye-Knudsen, M.; Brace, L.E.; Kassahun, H.; SenGupta, T.; Nilsen, H.; Mitchell, J.R.; Croteau, D.L.; Bohr, V.A. Defective mitophagy in XPA via PARP-1 hyperactivation and NAD(+)/SIRT1 reduction. Cell 2014, 157, 882–896.

45. 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.

46. 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.

47. Asher, G.; Gatfield, D.; Stratmann, M.; Reinke, H.; Dibner, C.; Kreppel, F.; Mostoslavsky, R.; Alt, F.W.; Schibler, U. SIRT1 regulates circadian clock gene expression through PER2 deacetylation. Cell 2008, 134, 317–328.

48. Nakahata, Y.; Kaluzova, M.; Grimaldi, B.; Sahar, S.; Hirayama, J.; Chen, D.; Guarente, L.P.; Sassone-Corsi, P. The NAD+-dependent deacetylase SIRT1 modulates CLOCK-mediated chromatin remodeling and circadian control. Cell 2008, 134, 329–340.

49. Cavadini, G.; Petrzilka, S.; Kohler, P.; Jud, C.; Tobler, I.; Birchler, T.; Fontana, A. TNF-alpha suppresses the expression of clock genes by interfering with E-box-mediated transcription. Proc. Natl. Acad. Sci. USA 2007, 104, 12843–12848.

50. 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.

51. Frederick, D.W.; Davis, J.G.; Davila, A., Jr.; Agarwal, B.; Michan, S.; Puchowicz, M.A.; Nakamaru-Ogiso, E.; Baur, J.A. Increasing NAD synthesis in muscle via nicotinamide phosphoribosyltransferase is not sufficient to promote oxidative metabolism. J. Biol. Chem. 2015, 290, 1546–1558.

52. Canto, 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.

53. Ryu, D.; Zhang, H.; Ropelle, E.R.; Sorrentino, V.; Mazala, D.A.; Mouchiroud, L.; Marshall, P.L.; Campbell, M.D.; Ali, A.S.; Knowels, G.M.; et al. NAD+ repletion improves muscle function in muscular dystrophy and counters global PARylation. Sci. Transl. Med. 2016, 8, 361ra139.

54. Khan, N.A.; Auranen, M.; Paetau, I.; Pirinen, E.; Euro, L.; Forsstrom, S.; Pasila, L.; Velagapudi, V.; Carroll, C.J.; Auwerx, J.; et al. Effective treatment of mitochondrial myopathy by nicotinamide riboside, a vitamin B3. EMBO Mol. Med. 2014, 6, 721–731.

55. Cerutti, R.; Pirinen, E.; Lamperti, C.; Marchet, S.; Sauve, A.A.; Li, W.; Leoni, V.; Schon, E.A.; Dantzer, F.; Auwerx, J.; et al. NAD(+)-dependent activation of Sirt1 corrects the phenotype in a mouse model of mitochondrial disease. Cell Metab. 2014, 19, 1042–1049.

56. Costford, S.R.; Brouwers, B.; Hopf, M.E.; Sparks, L.M.; Dispagna, M.; Gomes, A.P.; Cornnell, H.H.; Petucci, C.; Phelan, P.; Xie, H.; et al. Skeletal muscle overexpression of nicotinamide phosphoribosyl transferase in mice coupled with voluntary exercise augments exercise endurance. Mol. Metab. 2018, 7, 1–11.

57. Pajk, M.; Cselko, A.; Varga, C.; Posa, A.; Tokodi, M.; Boldogh, I.; Goto, S.; Radak, Z. Exogenous nicotinamide supplementation and moderate physical exercise can attenuate the aging process in skeletal muscle of rats. Biogerontology 2017, 18, 593–600.

58. Das, A.; Huang, G.X.; Bonkowski, M.S.; Longchamp, A.; Li, C.; Schultz, M.B.; Kim, L.J.; Osborne, B.; Joshi, S.; Lu, Y.; et al. Impairment of an Endothelial NAD(+)-H2S Signaling Network Is a Reversible Cause of Vascular Aging. Cell 2019, 176, 944–945.

59. 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.

60. 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.

61. Khaidizar, F.D.; Nakahata, Y.; Kume, A.; Sumizawa, K.; Kohno, K.; Matsui, T.; Bessho, Y. Nicotinamide phosphoribosyltransferase delays cellular senescence by upregulating SIRT1 activity and antioxidant gene expression in mouse cells. Genes Cells 2017, 22, 982–992.
62. Stocks, B.; Ashcroft, S.P.; Joanisse, S.; Dansereau, L.C.; Koay, Y.C.; Elhassan, Y.S.; Lavery, G.G.; Quek, L.E.; O'Sullivan, J.F.; Philp, A.M.; et al. Nicotinamide riboside supplementation does not alter whole-body or skeletal muscle metabolic responses to a single bout of endurance exercise. J. Physiol. 2021, 599, 1513–1531.
63. 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.
64. 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.e1716.
65. Dollerup, O.L.; Chubanava, S.; Agerholm, M.; Sondergard, S.D.; Altintas, A.; Moller, A.B.; Hoyer, K.F.; Ringgaard, S.; Stodkilde-Jorgensen, H.; Lavery, G.G.; et al. Nicotinamide riboside does not alter mitochondrial respiration, content or morphology in skeletal muscle from obese and insulin-resistant men. J. Physiol. 2020, 598, 731–754.
66. Connell, N.J.; Grevendonk, L.; Fealy, C.E.; Moonen-Kornips, E.; Bruls, Y.M.H.; Schrauwen-Hinderling, V.B.; de Vogel, J.; Hageman, R.; Geurts, J.; Zapata-Perez, R.; et al. NAD+-Precursor Supplementation With L-Tryptophan, Nicotinic Acid, and Nicotinamide Does Not Affect Mitochondrial Function or Skeletal Muscle Function in Physically Compromised Older Adults. J. Nutr. 2021, 151, 2917–2931.
67. Custodero, C.; Saini, S.K.; Shin, M.J.; Jeon, Y.K.; Christou, D.D.; McDermott, M.M.; Leeuwenburgh, C.; Anton, S.D.; Mankowski, R.T. Nicotinamide riboside-A missing piece in the puzzle of exercise therapy for older adults? Exp. Gerontol. 2020, 137, 110972.
