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Review

Targeting NAD$^+$ degradation: The therapeutic potential of flavonoids for Alzheimer's disease and cognitive frailty

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ABSTRACT

Flavonoids are efficacious candidates as pharmaceuticals or nutraceuticals in the treatment of Alzheimer's disease (AD), aging and other age-related chronic inflammatory diseases. Natural flavonoids reduce pathological hallmarks, extracellular amyloid deposits and neurofibrillary tangles by mediating amyloid precursor protein (APP) processing, Aβ accumulation and tau pathology. The antioxidant and anti-inflammatory actions as well as modulation of sirtuins and telomeres are also involved in the amelioration of aging, neurodegeneration and other age-related diseases. Recently, some flavonoids were shown to inhibit poly (ADP-ribose) polymerases (PARPs) and cyclic ADP-ribose (cADP) synthases (CD38 and CD157), elevate intracellular nicotinamide adenine dinucleotide$^+$ (NAD$^+$) levels and activate NAD$^+$ dependent sirtuin −mediated signaling pathways. We summarized how flavonoids reduce the degradation of NAD$^+$ with an emphasis on the mechanisms through which flavonoids affect the NAD$^+$-sirtuin axis to protect against AD. Aging and age-related diseases as well as a decline in the physiological reserve are the risk factors for cognitive frailty. Flavonoids with multiple therapeutic targets may also be potential candidates for the prevention and treatment of cognitive frailty.

Contents

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1. Introduction

Changes in the cellular nicotinamide adenine dinucleotide$^+$ (NAD^+) concentration mediated by biosynthetic salvage and consuming pathways might play an important role in aging and age-related diseases [1,2]. The coenzyme NAD^+ is consumed in redox reactions and is a cosubstrate for three enzyme classes NAD^+-dependent sirtuins, adenosinediphosphate (ADP)–ribose transferase (ARTs)/poly (ADP-ribose) polymerases (PARPs), and cyclic ADP-ribose (cADP) synthases (e.g., CD38 and CD157). A decrease in NAD+ degradation via inhibition of the over activation of NAD^+ consuming enzymes, including PARPs, CD38 and CD157, resulting in sirtuin activation, might be an efficient intervention for aging and age-related diseases [1–3]. Some flavonoids inhibit PARPs and/or CD38 [4–6], leading to an increase in the intercellular NAD^+ levels. Flavonoids, the largest and the most important group of polyphenols, are composed of different subgroups (Table 1) [7]. Flavonoids are effective bioactive chemical components with antioxidant and anti-inflammatory targets, among others, and anti-apoptotic and neuroprotective effects. They have been widely used to treat various chronic metabolic and inflammatory diseases and neurodegenerative disorders in humans and animals [8–11]. Cognitive frailty is a clinical syndrome with the simultaneous presence of physical frailty and reversible or potentially reversible cognitive impairment [12]. Aging and chronic physical diseases are risk factors for both Alzheimer's disease (AD) and cognitive frailty [13]. Many previous studies showed that flavonoids can prevent AD and slow down its progress. Flavonoids also act on multiple targets including amyloid precursor protein (APP) processing, extracellular β-amyloidosis, tauopathy, neuroinflammation and acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) activity [9,14]. Previous studies have demonstrated that some flavonoids slow down aging and AD by regulating the activity or expression of sirtuins [15]. Since flavonoids decrease the NAD^+ consumption and activate NAD^+-dependent sirtuins by inhibiting PARPs and CD38, these compounds have been widely used to protect against aging, physical diseases [15–18] and the cognitive impairment they induce [19–22]. Flavonoids might also have therapeutic potential for cognitive frailty. Some flavonoids had been approved in preclinical (in vitro and animal models) and clinical trials (Table 2). The present study summarizes PARP and CD38 inhibition by polyphenolic flavonoids, and sirtuin activation in age-related diseases. We then focus on flavonoid treatment to slow down AD and cognitive frailty progression via a new mechanism based on a link between NAD^+-dependent sirtuins and NAD degradation.

2. The degradation of NAD^+

NAD^+ can be a coenzyme for the hydride-transfer of redox enzymes to redox reactions in energy metabolism. The NAD^+/NADH equilibrium in the cytosol/nucleus and mitochondria is determined by their specific redox states. Cytoplasmic glycolysis and the mitochondrial tricarboxylic acid (TCA) cycle transform NAD^+ into NADH. The electron transport chain is a major contributor to NADH oxidation into NAD^+, coupling glycolysis and the TCA cycle to ATP synthesis via oxidative phosphorylation. The cytosol and the mitochondria can exchange redox equivalents through the malate/aspartate and glyceraldehyde 3-phosphate shuttles. NAD^+ is also a cosubstrate for ARTs/PARPs, cADP-ribose synthases (CD38 and CD157) and type III lysine deactylases found in all living cells, known as sirtuins. In the cytosol/nucleus or mitochondria, NAD^+ consuming enzyme activity can cause the production of nicotinamide (NAM) that is salvaged for NAD^+ synthesis via nicotinamide phosphoribosyl transferase (NAMPT). The NAD^+ pool balance is mediated by NAD^+ synthesis and consumption. A simultaneous increase of ARTs/PARPs and CD38 activity results in lower NAD^+ levels and less activity of NAD^+-dependent sirtuins (Fig. 1). NAD^+ degradation suppression by inhibiting PARPs or CD38/CD157 enhances NAD^+ levels and activates sirtuins [1–3].

PARPs, a major NAD^+-consuming nuclear enzyme in eukaryotes, are activated by oxidative stress and DNA injury, including single and double strand breaks [23,24]. PARP-1 accounts for approximately 85% of the total cellular poly (ADP-ribosylation) (PARylation) activity. Under physiological conditions, PARP-1 basal activity is necessary to promote the expression of certain genes, such as RNA polymerase II transcribed genes, by nucleosome binding properties [25]. After DNA is damaged, PARP-1 binds to the damaged DNA, and increases ADP ribose transfer from NAD^+ to itself and the nuclear proteins for PARylation, which induces DNA repair or cell death. PARylation of mild or moderate DNA damage recruits DNA repair enzymes to the damage sites, facilitates DNA base excision repair, and promotes cell survival [26–29]. If the repair of damaged DNA fails, PARP-1 becomes a substrate and is cleaved by apoptosis-, autophagy- or parthanatos-related suicidal proteases into different peptide fragments [30]. PARP-1 overactivation due to extensive DNA damage leads to the rapid depletion of intracellular NAD^+ and ATP. The energy deficiency slows the glycolysis and mitochondrial respiration rates and causes necrosis [31].

CD38 is a type II transmembrane glycoprotein that functions as another major NAD^+-consuming enzyme in mammals and is a receptor ubiquitously distributed in mammalian tissues. The primary activity of this multifunctional enzyme is NAD^+ glycohydrolase (NADase) activity. It is also a cyclic ADP-ribose (cADPR) synthase or an ADP-ribosyl cyclase and cADPR hydrolase [32]. CD38 catalyzes NAD and nicotinamide adenine dinucleotide phosphate (NADP) transformation to the $Ca2^+$-mobilizing messengers cADPR and nicotinic acid adenine dinucleotide phosphate (NAADP), and mediates intracellular $Ca2^+$ stores [33–35]. CD38 also hydrolyzes NAD and cADPR into another $Ca2^+$ messenger, ADPR (Fig. 1), which targets the $Ca2^+$ influx channel TRPM2 [35]. CD38 knockout studies show that the messenger-mediated calcium signaling pathway modulates important physiological functions, such as insulin secretion [36], neutrophil migration to infection sites [37], and hypothalamic neuropeptide oxytocin release to stimulate maternal and social behavior [38]. Beyond its role as a secondary messenger enzyme, CD38 is a critical mediator of NAD^+ levels and the NAD^+ dependent deacetylase activity of sirtuins. The NAD^+ level in most tissues of CD38 deficient mice was 10-20-fold higher than in the wild-type control due to the absence of NADase in various organelles and the nucleus [39]. CD38 knockout neuronal cells showed no ADP ribosyl cyclase and NADase activity, and greater than a 5-fold increase in the NAD^+ concentration, and an greater than a 10-fold increase in SIRT1 activity compared to control neurons, as assessed via siRNA [40].

Sirtuins in mammals include seven subtypes with different subcellular locations: nuclear for SIRT1, SIRT 6 and SIRT7, mitochondrial for SIRT3-SIRT5, and cytoplasmic for SIRT2. Sirtuins use NAD^+ as a substrate to remove acetyl moieties from lysine residues on histones and proteins, releasing NAM and O-acetyl ADP-ribose (Fig. 1) [41]. SIRT1, SIRT2 and SIRT3 have stronger deacetylase activity than SIRT4, SIRT5 and SIRT6 [42]. Sirtuins also transduce the signal of intracellular NAD^+ concentration changes via acyl, succinyl, malonyl, glutaryl, palmitoyl groups and fatty acids [43–45]. All mammalian sirtuins also indicate long-chain deacylation [45]. To evaluate sirtuin activity with the Michaelis constant (K_m) for a given intracellular NAD^+, SIRT1, SIRT3 and SIRT5 activity is rate-limited by NAD^+ and these subtypes can sense NAD^+ alteration [45]. The product of the sirtuin reaction NAM is a potent sirtuin deacetylase inhibitor. SIRT6 has been demon-