Role of CD38 in age-related NAD+ depletion: implication for age-related metabolic dysfunction and “NAD+ replacement” therapy.

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A decrease in intracellular levels of nicotinamide adenine dinucleotide (NAD+) has been shown to occur during the aging process. This decrease in NAD+ levels has a causal role on the development of age-related mitochondrial dysfunction and metabolic decline. To date, the mechanisms responsible for the age-related NAD+ decline have not been identified. It has been proposed that accumulation of DNA damage driven PARP activation may be involved. However, we identify that PARP levels and activity decline with aging. In contrast, we demonstrate for the first time that the expression and activity of the enzyme CD38 increases with aging and plays an active role in the age-related NAD+ decline in vivo and the subsequent development of age related mitochondrial dysfunction. In addition, we also identify CD38 as the main enzyme involved in the degradation of NAD+ precursors such as nicotinamide mononucleotide (NMN) in vivo and to have a role in the modulation of the response to NAD+ replacement therapy in aging. These data demonstrates the key role of CD38 in age-related NAD+ and metabolic decline, and highlights the potential role of CD38 inhibition for the development of an effective “NAD+ replacement therapy” for aging and other metabolic diseases.

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