NAD(+) (--- NICOTINAMIDE ADENINE DINUCLEOTIDE)

NAD(+) is both a coenzyme and a substrate for NAD(+)–consuming enzymes.

NAD(+) metabolism plays important roles in the random patterns of aging, (= what NUTRI-SPEC recognizes as Exogenous INFLAM_AGING), and also in the more programmatic aspects associated with Metabolic Clocks (= what NUTRI-SPEC labels as Endogenous INFLAM-AGING).

NAD(+) also activates sirtuins --- linked to controlling INFLAM-AGING as it relates to both the causes and the effects of fading glycemic control, weight gain, maintaining healthy brain and nerve function, and Th-2-medicated Immune System Imbalances. (But more is not better. Large doses of NAD(+) can actually inhibit sirtuins, and exacerbate other aspects of Endogenous Aging. Supplementing with a physiological (not pharmacological "nutrition" megadose) quantity effectively enhances supplementation with other Rejuvenins.)

The contribution NAD(+) metabolism makes to Lifespan extension in model systems indicates that therapies to boost NAD(+) might promote some of the longevity benefits of calorie restriction. NAD(+)-dependent enzymes are increasingly appreciated for their regulatory role in the timing of changes (Metabolic Clocks) that lead to Endogenous Aging.

The derivatives of NAD(+), such as reduced and oxidized forms of NAD(P)(+), play important roles in maintaining cellular redox state, Ca(2+) stores, DNA damage and repair, stress responses, cell cycle timing, chromatin remodeling, circadian rhythm regulation, insulin secretion and sensitivity, expression of inflammatory cytokines, and lipid and energy metabolism.

NAD(+) coenzyme activity is important in energy metabolism processes such as mitochondrial electron transport, glycolysis, and citric acid cycle --- to generate ATP.

The NAD(+)/NADH ratio influences reactive oxygen species and oxidative stress formation through regulation of intracellular ATP production, different metabolic enzymes, and redox state. An increase of NAD(+) and/or NAD(+)/ NADH ratio can increase cellular defense, induce DNA repair and apoptosis, activates sirtuins --- thus playing an important role in controlling INFLAM-AGING.

Caloric restriction stimulates the NAD(+) salvage pathway leading to increased NAD(+) bioavailability. Caloric restriction increases NAD(+), while lowering NADH and activating sirtuins. Thus, activation of sirtuins with NAD(+) is a necessary condition for the life-span extension provided by calorie restriction. Studies on caloric restriction reveal that it is more important to improve the

ratio between NAD(+) and NADH than to raise the overall amount of cellular NAD(+). Caloric restriction reduces NADH more than it increases NAD(+).

Besides by caloric restriction, NAD(+) can be increased with food and supplements. Ingestion of the amino acid tryptophan will increase NAD(+) --- but --- since tryptophan accelerates aging by other mechanisms, such supplementation or a high tryptophan diet is not recommended. But supplements that do effectively increase NAD(+) include niacinamide, nicotinic acid, as well as nicotinamide riboside (NR), nicotinamide mononucleotide (NMN), and nicotinic acid riboside (NaR), 15 mg per day of combined niacin and niacinamide (somewhat easily obtained by meat, fish, and dairy foods) are required for NAD(+) synthesis. Using niacinamide, niacin, and NR has been shown in human clinical trials to increase NAD(+).

Increased acetyl-L-carnitine in skeletal muscle, plus minor changes in body composition and sleeping metabolic rate are reported in studies on NR supplementation in otherwise healthy obese humans.

The three vitamin precursors to NAD(+) (Nicotinic Acid (NA)), niacinamide (NAM), and nicotinamide riboside (NR) are available in unprocessed foods. Human digestion and each individual's microbiota play critical roles in the absorption of these vitamins in ways that are not yet fully defined. Immuno-Synbiotic may do more to increase NAD(+) than supplementation with its precursors.

NAD endogenous production decreases with age and with overnutrition.

While it takes only about 15 mg per day of NA or NAM to prevent pellagra, pharmacological doses of NA as high as 2-4 g are foolishly taken to treat high cholesterol --- by the same harmful mechanism as statin drugs. Research seems to indicate that if there are truly beneficial effects of NA on plasma cholesterol, they might simply depend on NA functioning as an NAD(+) booster. Sirtuin activation is likely a part of the mechanism because NAM is an NAD(+) precursor in most cells, but inhibits sirtuins at high doses.

NR has been employed in mice to elevate NAD(+) metabolism and improve health in models of Metabolic Stress. Particularly, increased NAD(+) allows mice to resist weight gain, prevent noise-induced hearing loss, and maintain the regenerative potential of stem cells in aging mice --- providing a longevity advantage. The data indicate that the level of liver NADP(+) and NADPH, which are required for resistance to ROS–mediated Exogenous Aging, are severely challenged by diet-induced obesity, and that glycemic control is maintained by oral NR.

Effects on longevity:

Studies suggest that increasing NAD(+) appears to mediate several beneficial effects of calorie restriction, supporting the life-prolonging effects. These effects are mediated via improvement of metabolism and decrease in chronic inflammation, a hallmark of aging.

In addition to its role as a substrate for signaling sirtuins, NAD(+) plays a prominent role in cellular processes such as transcription, recombination, cell division, proliferation, genome maintenance, Apoptosis, stress resistance, and senescence.

Aging is characterized by chronic inflammation and increased production of Senescent Cells --- the hallmark of Endogenous INFLAM-AGING. Increasing NAD(+) and related metabolites in skeletal muscle significantly reduces levels of circulating inflammatory cytokines --- such as IL-6, IL-5, IL-2 & TNF-alpha.

Senescence is increasingly defined by Gerontologists as the Key to Endogenous Aging. Elevating NAD(+) alleviates senescence by enhancing Autophagy, thus maintaining healthy mitochondrial function.

NAD(+)-dependent enzymes play an important role in neuroplasticity. NAD(+) depletion in brain cells is common during aging. Emerging findings reveal a critical role for NAD(+) in neural resilience and in the molecular mechanisms of the signs of brain aging.

NAD+ is the central redox coenzyme in cellular metabolism. It functions as a hydride group acceptor, forming NADH as it oxidizes metabolites derived from carbohydrates, amino acids and fats. The NAD+/NADH ratio controls the degree to which such reactions proceed in oxidative versus reductive directions.

While fuel oxidation reactions require NAD+ as a hydride acceptor --- gluconeogenesis, oxidative phosphorylation, ketogenesis, detoxification of reactive oxygen species, and lipogenesis require reduced cofactors, NADH and NADPH, as hydride donors.

In addition to this role as a coenzyme, NAD+ is the consumed substrate of enzymes such as PARPs, sirtuins, and cyclic ADPribose Synthetases. In redox reactions, the biosynthetic structures of NAD+, NADH, NADP+ and NADPH are preserved. PARP, sirtuin and cyclic ADPribose Synthetase activities hydrolyze the linkage between the nicotinamide and the ADPribosyl moieties of NAD+ to signal DNA damage, alter gene expression, control post-translational modifications and regulate calcium signaling.

Adult stem cells are essential for tissue maintenance and regeneration, yet are susceptible to senescence during aging. Research shows the importance of the amount of the oxidized form of cellular NAD(+) and its effect on mitochondrial activity as a pivotal switch to modulate muscle stem cell senescence. NAD(+) reduces the mitochondrial unfolded protein response, which rejuvenates muscle stem cells in aged mice.

It is also shown that increasing NAD(+) delays senescence of neural stem cells and melanocyte stem cells, and increases mouse life span. Boosting cellular NAD(+) may reprogram dysfunctional stem cells and improve life span in humans.