CellPress

NAD+ Metabolism and Signaling

We caught up with some of the leading researchers in the NAD+ metabolism and signaling field as they gathered in Dublin for the 2019 FASEB Science Research Conference. Here they share their excitement from the rich history of NAD+ biology dating back over 100 years ago to a future of translation benefiting human health and aging.

The Chemical Road to NAD+ Biology

Marie Migaud
University of South Alabama, Mobile, USA

As a chemical, it has been a long road for NAD to make its mark in the field of biology. First, its precursors, nicotinamide and nicotinic acid, were isolated and characterized as vitamins, shown to have life-saving properties. Then came the relationship between these precursors and their functional forms, as NAD, NADH, NADP, and NADPH. The biochemical complexity that stems from the chemical versatility of these four cofactors has given rise to decades of enzymatic and mechanistic investigations and explorations of biosynthetic and metabolic pathways. There, enzymatic and chemical syntheses of modified precursors and derivatives have enabled the studies of flux and biodistribution of these chemical entities at organism, cellular, and sub-cellular levels and the dissection of NAD biosynthetic pathways and their dynamics. As a result, informed functional investigations are going full speed ahead as the numerous NAD biosynthetic pathways can be manipulated to accentuate the levels of NAD with the view of benefiting health and improving the quality of aging, through function. Many of these stunning biological advances have been made possible by the constant contribution of chemistry to the field of NAD biology. From the earliest days of NAD, step changes in exploring NAD biology have been enabled by new and exciting physical, chemical, and biochemical tools to probe specific aspects of this multifaceted molecule. I am proud and excited to be part of that effort and make a small chemical contribution to this vibrant field that has been spearheaded over this century by scientific giants of biochemistry, enzymology, and biology.

Coming Full Circle with NAD+

W. Lee Kraus
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When I was an undergraduate student, biochemistry lecture and laboratory were the courses that steered me away from a career as a veterinarian toward a career as a research scientist. The enzymes and molecules in the myriad metabolic pathways in the cell captured my interest and held sway over my thinking. Yet somehow in those days, I never really thought of myself as a metabolic biochemist. So thinking back decades later, I am amused (but not surprised) to find my thoughts and science immersed in NAD+ biosynthesis and metabolism. Although my entry into the NAD+ field was through PARPs and ADP-ribosylation, I found myself asking, "Where does the NAD+ that PARPs use come from?" This simple question led me back to the same metabolic pathways that intrigued me so much as a student. In my own work with PARPs, I have been struck by the intimate functional connections between the PARP enzymes (NAD+ "consumers" and ADP-ribose "writers") and the NAD+ synthases ("feeders," e.g., NMNATs 1, 2, and 3). In addition, my lab's discoveries demonstrating compartmentalization of NAD+ biosynthesis and functions have changed my view about the distinct biological roles of NAD+ in the cell. Simply put, the nuclear NAD+ synthase NMNAT-1 makes NAD+ for nuclear PARPs, while the cytosolic NAD+ synthase NMNAT-2 makes NAD+ for cytosolic PARPs. This is undoubtedly an overly reductive view, but it has been a useful way to shape my thinking about this process and where the NAD+ field might go in the future.

Aging and Rejuvenation

Danica Chen
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Promising Alzheimer's disease drug trials just ended in failure. A plausible explanation is that it is often too late to start treatment as there exists a point of no return. It is therefore more urgent than ever to understand the reversibility of aging-associated degeneration and use that knowledge to guide the drug development for aging-associated diseases. What aspects of aging-associated conditions are reversible? Is the cause of aging reversible?

Will NAD fill the bill for rejuvenation? The biology of sirtuins, the major NAD-consuming enzymes, has been guiding and will continue to guide the potential applications of NAD. Recent advances have demonstrated that sirtuins function to prevent and reverse aging-associated mitochondrial stress, stem cell decay, tissue degeneration, and degenerative diseases. Fittingly, NAD repletion improves mitochondrial health, stem cell maintenance, and tissue regeneration, and extends lifespan, at least in mouse models. Time will tell if NAD will serve the same purposes in humans. This also spurs the interest in identifying the bona fide sirtuin activators for these applications.

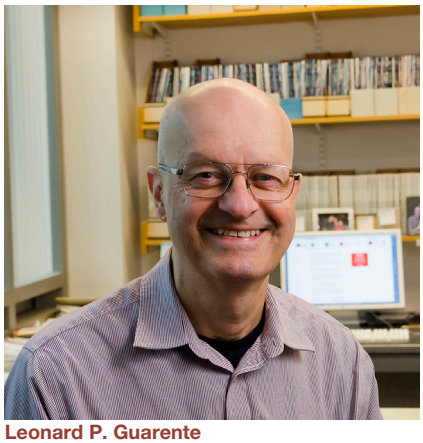
Sirtuin biology also guides our understanding in NAD signaling. Sirtuins have well-defined deacylase activities and numerous substrates have been identified for sirtuins. However, evidence is lacking to support whether deacylation of these substrates is indeed mediating the effects of sirtuins *in vivo*, and this remains a major challenge for sirtuin biology as well as NAD biology.

Balancing the Needs

Mathias Ziegler
University of Bergen, Norway

About 20 years ago, I got excited about NAD metabolism. Poly-ADP-ribosylation changed the view on regulation of DNA repair, unusual NAD(P) derivatives that mediate calcium signaling were discovered, and not least, NAD-dependent protein deacetylation by sirtuins emerged as a new mechanism of epigenetic and metabolic regulation. Interestingly, these fields co-existed with little overlap, even though the enzymes involved have one important aspect in common: they all consume NAD. While not degrading NAD themselves, hundreds of dehydrogenases in essentially all biochemical pathways depend on NAD. Perhaps for this reason, it was assumed that NAD is plentiful and everywhere. But is that so? It turns out that NAD-dependent signaling, and thereby NAD degradation, is surprisingly active, and there are even circadian changes in tissue NAD levels. On a daily basis, we need to re-synthesize, perhaps, twice the amount of the NAD reservoirs in our body to keep up with the enormous NAD consumption in signaling processes. Therefore, an adequate supply of NAD precursors is key for balanced metabolism, especially for healthy aging. There is an intimate interplay and cross-regulation between NAD-dependent signaling and NAD biosynthesis. We now know many molecular details about human NAD biosynthesis and NAD-consuming signaling processes, and we are beginning to exploit this knowledge for therapeutic applications. However, to take full advantage, we need to understand the cellular details. I believe that compartmentalization and dynamic interactions between subcellular NAD pools are key elements of maintaining NAD homeostasis.

NAD^+ and a Healthy Future



Leonard P. Guarente
Massachusetts Institute of Technology, Cambridge, USA

About 30 years ago, I was searching for a new area to investigate and became fascinated with aging. It seemed like a critical yet understudied problem, albeit one that was difficult to approach conventionally. After several years, sirtuins emerged as conserved proteins that slow aging in times of stress, including food scarcity, thus providing one explanation for calorie restriction extension of lifespan. Biochemically, sirtuins are NAD^+-dependent protein deacetylases (including histones), which link NAD^+, epigenetics, and aging. NAD^+ and its reduced form NADH were long known as cofactors for metabolic enzymes, and NADH as the driver of ATP production in mitochondria. NAD^+ is also a co-substrate for poly-ADP-ribosylation by PARPs (poly-ADP-ribose polymerases) at DNA damage sites.

NAD^+ levels decrease during aging in mice, worms, and humans, thereby turning down the activities of sirtuins. Dietary NAD^+ precursors are effectively taken up by cells, mice, and humans and offset this NAD^+ decline, leading to health benefits, including a reversal of stem cell aging and an extended lifespan in mice. Numerous genetic diseases with DNA damage repair deficits display premature aging. Murine models display a cycle of NAD^+ depletion (via PARPs), sirtuin deactivation, and mitochondrial dysfunction, and are ameliorated by provision of NAD^+ precursors, but only if the sirtuin SIRT1 is intact.

Sirtuin activation by NAD^+ repletion may be the most actionable item to emerge from aging research and could result in health benefits in the near term. It will be exciting to see how wide ranging these benefits will be.

Improve Neurodegeneration

Villhelm A. Bohr
National Institute on Aging, NIH, Bethesda, USA

I have worked in the fields of genome stability, aging, and neurodegeneration and have seen many theories and interventions come and go. Through the last decade, I have become convinced that NAD^+ is a central metabolite in the organism and that its regulation and abundance are critically important for human health. I was glad to be invited to the past FASEB NAD^+ biology meeting in New Orleans. I learned a lot and met an interesting and enthusiastic group of scientists, many of whom I have come to know better in the past years. I have also enjoyed collaborations with many of these colleagues and found that there is an open and constructive atmosphere in this group.

Metabolism is a very complex process, and we are at an exciting time in this field. Many new tools and insights are being developed rapidly with direct implications for human health. In my group, we have had very positive results with NAD^+ supplementation at the translational level against neurodegeneration, using mice, cells, and nematodes, and this has also provided important mechanistic insight. Since there appear to be no significant side effects with NAD^+ supplementation in humans, it is a very promising approach for human intervention. Many types of neurodegeneration are associated with mitochondrial dysfunction, and this is where NAD^+ supplementation has a major effect and where there are great opportunities to get more insight into its mechanism of action.

Rediscovering a True Classic: NAD+ and Aging

Eric Verdin
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I am fascinated by the cyclical nature of discoveries in science, how specific research topics wax and wane, why progress stalls, and how to be at the front of new areas of research. The story of NAD^+ offers a rich example of this phenomenon. From its discovery as a "coferment" that accelerated alcoholic fermentation in yeast by Harden in 1906, to its identification as a nucleotide sugar phosphate by Hans Von Euler, and finally to its demonstrated role in hydride transfer reactions by Otto Warburg, the field of NAD^+ research has an incredibly rich history of pioneering discoveries. As biology moved from metabolism into the molecular biology revolution in the 50s, NAD^+ metabolism took a back stage. Who would have thought that NAD^+ would take center stage again in aging research 100 years after its discovery? A convergence of serendipitous observations, the realization that the sirtuins are NAD^+-dependent enzymes and NAD^+ consuming, the recently proposed model that sirtuins and PARPs are competing for a fixed pool of NAD^+, and finally, the realization that NAD^+ levels globally decrease during aging, have together created a perfect storm of interest in this amazing molecule. I am fascinated by the idea that progressive depletion of NAD^+ during aging, now documented in multiple organs and in multiple species, could play a key pathogenic role in the aging process. What are the reasons for its depletion in aging? Is it tissue specific? What is the role of NAD^+ in specific cellular subcompartments during aging? This field is now brimming with new questions and the potential to devise novel therapies that affect aging and its associated diseases.

Comparative Biology Coming out of the Woods

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We were always fascinated by nature, wildlife, and the diversity of species. At the same time, we wanted to know how things work and delve deep into mechanistic studies. When we opened our laboratories side-by-side at the University of Rochester, we wanted to bring these two fields together; to use the diversity of wild species to understand molecular mechanisms. Our research is focused on aging and cancer, and we have been fascinated by naturally long-lived and cancer-resistant species. One of such species is the naked mole rat, for which our groups have discovered several mechanisms contributing to longevity and cancer resistance. More recently, we examined DNA repair in 18 species of rodents. We found that long-lived species have more efficient double-strand break repair that is mediated by the NAD-dependent enzyme SIRT6. On the biochemical level, SIRT6 from longer-lived species turned out to be a more active deacetylase and mono-ADP ribosylase. Excitingly, earlier works from the Alex Burkle lab report a positive correlation between PARP activity in cell extracts and species longevity. We hypothesize that sirtuins and PARPs may be regulating genome and epigenome stability more efficiently in long-lived species. Together these findings reveal that metabolic pathways such as the function of NAD-dependent enzymes have been shaped by the evolution of longevity. We hope that in understanding specific differences in these enzymes in long-lived species, we will achieve a deeper understanding of the mechanisms of longevity and illuminate new paths for clinical interventions to increase healthspan.