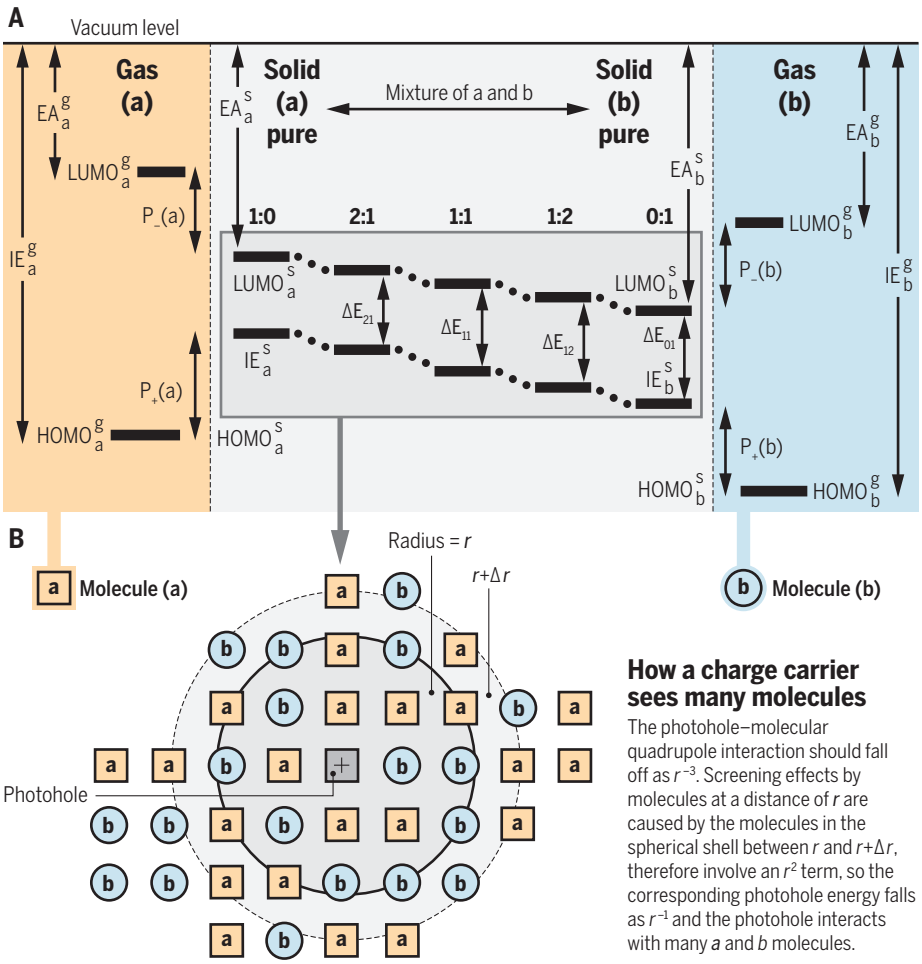

How a charge carrier sees many molecules

The photohole–molecular quadrupole interaction should fall off as r^{-3}. Screening effects by molecules at a distance of r are caused by the molecules in the spherical shell between r and $r+\Delta r$, therefore involve an r^2 term, so the corresponding photohole energy falls as r^{-1} and the photohole interacts with many *a* and *b* molecules.

Smooth changes. (**A**) Schwarze *et al*. found that mixtures of organic semiconductor molecules, 1 and 2, change their electron affinities (EA) and ionization energies (IE) smoothly; the solid-state values are offset by polarization terms. (**B**) The origin of this smooth change can be explained by considering a photogenerated charge carrier. It interacts with the quadrupole moment of many nearby molecules, sampling a population of both 1 and 2.

these phenomena with different molecular systems, such as mixtures of subphthalocyanine and its hexachlorinated derivative.

This effect can likely be exploited in a number of other molecules. The present IE tuning may have generality as a band-structure engineering method for organic semiconductors. This phenomenon is unexpected but was confirmed by the authors, who measured V_{oc} and current density–voltage curves of organic solar cells and field-effect mobility for the ZnPc-F_xZnPc blends.

Although the spatial range of this tuning effect and the required molecules for intermixing need further investigation, the present phenomena are the result of weak intermolecular interactions in organic semiconductors and the quadrupole of large-size molecules, both of which are well-known features of organic molecular solids. These studies may motivate entirely new designs of device architectures for organic semiconductors that take advantage of gap states–mediated Fermi-level tuning (*9*, *10*), doping effects (*5*), and effects of intermolecular charge transfer (*11*, *12*). ■

Graduate School of Advanced Integration Science, Chiba University, Inage-ku, Chiba 263-8522, Japan. Email: uenon@faculty.chiba-u.jp

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CELL METABOLISM

The resurgence of NAD+

Restoring a mitochondrial metabolite slows stem cell loss and aging

By **Leonard Guarente**

Interventions that can slow mammalian aging have been rare. On pages 1436 and 1474 of this issue, Zhang *et al*. (*1*) and Cambronne *et al*. (*2*), respectively, highlight nicotinamide adenine dinucleotide (NAD^+) as a major intervention point to slow or ameliorate phenotypes of aging.

NAD was discovered over a century ago, and its role in cells as a redox conduit in metabolism was subsequently established. More recently, its oxidized form, NAD^+, resurfaced as a key molecule in aging in organisms ranging from yeast to mammals by the finding that the antiaging proteins, sirtuins, are NAD^+-dependent deacylases (*3*). These proteins play a key role in mitochondrial function. Indeed, aging is also associated with loss of sirtuin and mitochondrial function.

This NAD^+-sirtuin axis plays a crucial role in maintaining health and staving off diseases of aging (*4*). The amount of cellular NAD^+ declines during normal aging, as revealed in mice engineered to overexpress the sirtuin SIRT1 in pancreatic β-cells (*5*). The novel phenotypes conferred in young mice by this overexpression, such as glucose tolerance and increased insulin secretion, were lost in old mice, but could be restored by supplementing their diet with the NAD^+ precursor, nicotinamide mononucleotide. Numerous subsequent studies of aging in worms and mice have shown that NAD^+ replenishment is associated with better metabolic health and restored mitochondrial function (*6*). One possible explanation for the NAD^+ loss during aging is that getting old is associated with the accumulation of DNA damage, which triggers chronic activation of poly(ADP-ribose) polymerases (PARPs) and the resulting depletion of the substrate used by PARP for protein PARylation, NAD^+ (*7*).

Mitochondrial dysfunction in aging mammals may be due to a disharmony between nuclear and mitochondrial gene expression, and this phenotype could be rescued by NAD^+

Department of Biology, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, USA. Email: leng@mit.edu

replenishment (*8*). This dysfunction was also demonstrated in premature aging diseases resulting from genetic defects in DNA repair, and this deficit appears to be due to NAD^+ depletion and the resulting SIRT1 inactivation. Metabolic maladies in these mice could also be corrected by supplementation with an NAD^+ precursor, nicotinamide riboside (*9*). Thus, a model emerges in which aging is associated with PARP activation, NAD^+ depletion, sirtuin inactivation, mitochondrial dysfunction, and degeneration of cells and tissues, and where this calamity can be corrected or forestalled by supplementation with NAD^+ precursors (see the figure).

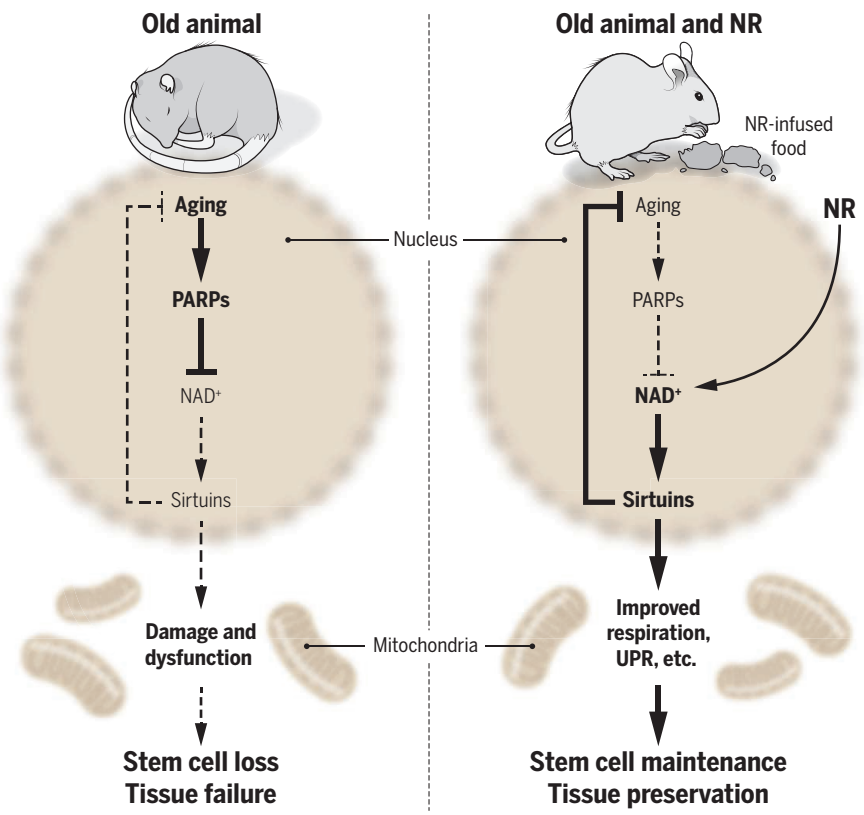
Zhang *et al.* show that adult mouse stem cells (i.e., muscle stem cells) are lost during normal aging, and this could be ameliorated by supplementing their diet with nicotinamide riboside. This salutary effect of nicotinamide riboside involved an improvement of mitochondrial function in these stem cells, including respiration, membrane potential, production of adenosine triphosphate (ATP), and the mitochondrial unfolded protein response, and did not occur in stem cells lacking SIRT1. Nicotinamide riboside also suppressed dysfunction in a mouse model of muscular dystrophy, which is consistent with earlier findings that overexpressing SIRT1 in muscle also rescued this disease model (*10*). Generalizing the findings in muscle stem cells, Zhang *et al.* also found that nicotinamide riboside countered senescence in adult neural stem cells and adult melanocyte stem cells. The loss of adult stem cells may be an important cause of organ dysfunction,

"...NAD^+ replenishment may also provide health benefits in people."

and this process may limit the life span of animals. Indeed, the authors show that nicotinamide riboside supplementation extended the life span of wild-type mice fed the normal chow diet, joining a short list of compounds with this ability (SIRT1 activators, metformin, and rapamycin). These findings suggest that preserving mitochondrial function by way of nicotinamide riboside may be a key to maintaining adult stem cells, which in turn may slow or counter degenerative effects of aging and, possibly, diseases.

Cambronne *et al.* describe an NAD^+ sensor consisting of a fusion of Venus fluorescence protein to the NAD^+ binding domain of bacterial DNA ligase. This ligase uses NAD^+ instead of ATP to activate the DNA ends for joining. The binding of NAD^+ to this hybrid sensor protein partially quenches the fluorescence signal, and this decline can be quantitatively measured. The authors targeted this NAD^+ sensor to different cellular compartments of mammalian cells and could determine the amount of NAD^+ in the local environment. As a further proof of principle, Cambronne *et al.* demonstrate that they could detect an inhibition of NAD^+ synthesis due to reducing the expression of specific biosynthetic enzymes. It will be important to determine whether the sensor can also detect the perhaps more subtle changes in NAD^+ amounts that occur as a function of diet, aging, or disease. The possibility that the NAD^+ sensor may respond to aging is exciting because a reliable and versatile biomarker for aging has long been sought without success.

As to whether NAD^+ replenishment can improve health maintenance in humans, it has been reported that cellular NAD^+ amounts decline during human aging (*11*). Also, the strict conservation in the relevant pathways of NAD^+ synthesis, sirtuins, and PARPs suggests that NAD^+ replenishment may also provide health benefits in people. Still, it will be important to test in humans whether dietary supplementation with NAD^+ precursors will raise cellular NAD^+ concentrations sufficiently to compensate for the loss due to aging. If so, it will also be necessary to test, in rigorously controlled trials, whether raising NAD^+ concentrations improves health parameters, such as blood glucose and lipid profile, as well as inflammation. More expanded trials could measure effects on bone density, endothelial cell function, muscle mass, or even cognition. If NAD^+ precursors can positively affect health parameters, it is reasonable to anticipate their place at the table alongside more traditional pharmaceutical drugs in the treatment of diseases. ■



Restorative intervention. In old mice, aging may trigger NAD^+ loss by activating poly(ADP-ribose) polymerases (PARPs). NAD^+ reduction lowers the activity of the antiaging proteins, sirtuins, leading to a feedforward cycle of aging. Nicotinamide riboside (NR) restores NAD^+ amounts and reverses this cycle, resulting in better stem cell maintenance and tissue function. UPR, unfolded protein response.

GRAPHIC: C. BICKEL/*SCIENCE*

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The resurgence of NAD$^+$

Leonard Guarente

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