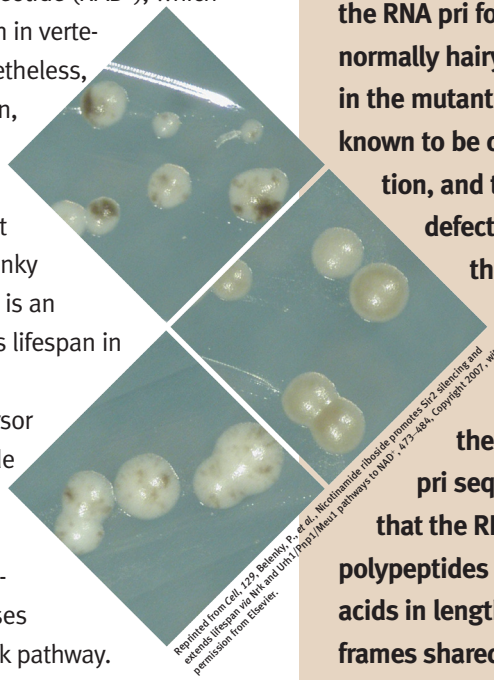
Nicotinamide Riboside: Two Routes to Longevity

Ponce de León never found the fountain of youth, but chemical biologists continue to look for biological factors and pathways that contribute to vitality. In yeast, lifespan can be extended by calorie restriction (CR) *via* a pathway dependent on the protein lysine deacetylase Sir2 and the coenzyme nicotinamide adenine dinucleotide (NAD^+), which is also a Sir2 substrate. CR also extends lifespan in vertebrates and increases brain and liver NAD^+. Nonetheless, lifespan had never been extended with a vitamin, even in yeast cells. Nicotinamide riboside (NR) is a newly discovered NAD^+ precursor vitamin whose contribution to NAD^+ metabolism has not been fully characterized. A new report from Belenky *et al.* (*Cell* 2007, *129*, 473–484) reveals that NR is an NAD^+-boosting vitamin that significantly extends lifespan in yeast cells grown in non-CR conditions.



Reprinted from *Cell*, *129*, Belenky, P., *et al.*, Nicotinamide riboside promotes Sir2 silencing and extends lifespan *via* Nrk and Urh1/Pnp1/Meu1 pathways to NAD$^+$, 473–484, Copyright 2007, with permission from Elsevier.

NR was initially discovered as an NAD^+ precursor whose activity depends on nicotinamide riboside kinase (Nrk), which is conserved between yeast and humans. Using yeast mutants, the authors observed that adding NR promotes Sir2-dependent repression of recombination, increases gene silencing, and extends longevity *via* the Nrk pathway. In addition, they determined that a second, Nrk-independent pathway exists that converts NR to NAD^+. Further studies of the two NR salvage pathways suggested that NR is a normal NAD^+ metabolite, even in the absence of NR supplementation, and established that NR extends the lifespan of wild-type yeast cells on high glucose through both pathways. Genetic evidence in mice suggests that NR may be valuable in the treatment of neurodegenerative diseases and in the prevention of chemotherapy-induced peripheral neuropathy. Further evidence suggests that NR may protect against *Candida glabrata* infection and that NR might provide the high-density lipoprotein-elevating effects of nicotinic acid without causing painful flushing. Accordingly, clarification of the basic chemical biology of endogenous NR metabolism and identification of the gene expression consequences of varied NAD^+ levels may lead to new medicines and new insights into drug mechanisms.

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for the RNA was implicated when the researchers found exoskeleton defects in a fly mutant lacking the RNA. They named the RNA pri for polished rice, because the normally hairy cuticle fibers were smooth in the mutant. Filamentous actins are known to be critical for the cuticle formation, and the pri mutant showed a defect in the normal assembly of these proteins during development. But how might pri RNA regulate actins? On further examination of the *Drosophila melanogaster* pri sequence, the authors found that the RNA could encode five short polypeptides that are 11 or 32 amino acids in length. Four of the reading frames shared a common septamer peptide motif. Comparing genomes with the other 11 flies helped solve this mystery, because other species often displayed different pri nucleotide sequences but the same encoded peptide. The four related peptides appear functionally redundant, as a re-expression of just one peptide in the mutant pri line provided a full rescue. These results are striking and give researchers a good reason to take another look at the tiny open reading frames that might be hiding in the genomes. Jason G. Underwood, Ph.D.