About NAD biosynthesis -- de novo and salvage pathways Nicotinamide adenine dinucleotideis an essential cofactor for cellular redox reactions and energy metabolism. NAD also has been shown to be an important substrate in a variety of biological processes, including transcriptional regulation, DNA repair, calcium-dependent signaling pathways, calorie-restriction-mediated life-span extension and age-associated diseases. NAD appears to affect these processes by regulating the Sir2p family of NAD-dependent deacetylases. There are a number of pathways for NAD biosynthesis. In yeast and most other organisms, the two major pathways are de novo synthesis of NADand regeneration of NAD from its nicotinamide degradation products. NAD is synthesized de novo from tryptophan via kynurenine. In this pathway tryptophan is converted to nicotinic acid mononucleotidein 6 enzymatic stepsand one non-enzymatic step. At NaMN the de novo pathway converges with the NAD salvage pathway and the last two steps to NAD are shared. In the yeast NAD salvage pathway, the vitamin precursors nicotinamide and nicotinic acid are converted to NaMN, the point of convergence with the de novo pathway. The steps from nicotinic acid to NAD were elucidated by Preiss and Handler and are sometimes referred to as the Preiss-Handler pathway. Yeast can also import extracellular nicotinic acid into the cell by the permease Tna1p and then convert it to NAD via the Preiss-Handler pathway. There are four additional pathways for synthesizing NAD in yeast: two salvage pathways from the vitamin precursor nicotinamide ribosideand two salvage pathways from nicotinic acid riboside. Only one of these pathways, the NR salvage pathway I, is independent of the NAD salvage pathway. In the NR salvage pathway I, NR is phosphorylated to nicotinamide mononucleotide by the kinase Nrk1p, and then adenylated to NAD by Nma1p or Nma2p. In the NR salvage pathway II, the hydrolase Urh1p or the phosphorylase Pnp1p split NR into a ribosyl product and nicotinamide, which subsequently is converted to NAD via the NAD salvage pathway. The initial steps in the NaR salvage pathways I and II are similar to those of the NR salvage pathways I and II and are catalyzed by the same enzymes, respectively. In the NaR salvage pathway I, Nrk1p phosphorylates NaR to NaMN, which subsequently is converted to NAD via the enzymes shared by the de novo and NAD salvage pathways. In the NaR salvage pathway II, Urh1p or Pnp1p split NR into a ribosyl product and nicotinic acid, which is first converted to NaMN and then is converted similarly to NAD.