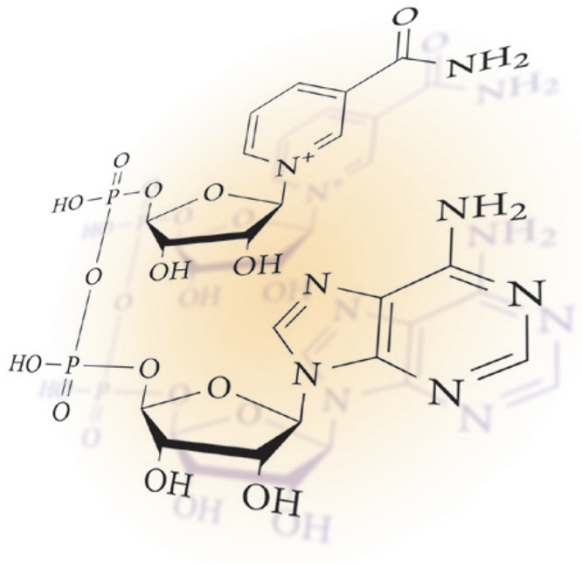
FUNGAL VIRULENCE

Salvageable research

DOI:
10.1038/nrmicro1781

NAD^+ is an important coenzyme that has essential roles in many metabolic pathways. Researchers from Brendan Cormack's laboratory are interested in the connections between this coenzyme and virulence in *Candida glabrata*. They have now successfully defined the NAD^+-biosynthesis pathways in this opportunistic fungal pathogen, and the results are presented in a recent issue of *Molecular Microbiology*.

C. glabrata is an NAD^+ auxotroph and must therefore synthesize NAD^+ from the vitamin precursors that are present in the environment. Ma and colleagues began by investigating which precursors *C. glabrata* can salvage, and they found that, like *Saccharomyces cerevisiae*, *C. glabrata* can use nicotinic acid (NA), nicotinamide (NAM) and nicotinamide riboside (NR) as sources of NAD^+. In *S. cerevisiae*, which, unlike *C. glabrata*, can also synthesize NAD^+ *de novo*, NA and NAM are both salvaged through the evolutionarily conserved Preiss–Handler pathway. Npt1 and Qns1, which catalyse the first and last steps, respectively, are essential enzymes in this pathway. The presence of a functional Preiss–Handler pathway in *C. glabrata*, and its involvement in the conversion of NA to NAD^+, was confirmed by deletion of the *C. glabrata* orthologues of these key *S. cerevisiae* enzymes, as the authors found that, with NA as the sole NAD^+ source, the *npt1*Δ and *qns1*Δ *C. glabrata* strains were unable to grow.



Ma and colleagues went on to investigate the pathways that *C. glabrata* uses to salvage the other two vitamin precursors, NAM and NR. In *S. cerevisiae*, Pnc1 converts NAM to NA, which can then enter the Preiss–Handler pathway for conversion to NAD^+. The *npt1*Δ, *qns1*Δ and *pnc1*Δ strains of *C. glabrata* could not grow in media that contained NAM as the only source of NAD^+, indicating that the same NAM-salvage pathway is used by *C. glabrata*. For NR, it was known that *S. cerevisiae* can salvage this precursor independently of the Preiss–Handler pathway using a pathway that requires the NR kinase Nrk1. Ma *et al.* confirmed that *C. glabrata* can salvage NR using this same pathway. Surprisingly, however, it was also found that *C. glabrata* *nrk1*Δ strains grow as well as the parent strain if NR is the sole source of NAD^+, indicating that, in addition to this Nrk1-dependent pathway, *C. glabrata* also possesses an Nrk1-independent NR-salvage pathway.

The authors postulated that this alternative pathway might involve the combined action of the nicotinamidase Pnc1 and a nucleosidase to form NA, which can then be funnelled into the Preiss–Handler pathway. Using a range of deletion mutants, they were able to demonstrate that Urh1 and Pnp1 are the main nucleosidases that are involved, with a minor role for a third nucleosidase, Meu1. Finally, studies using a mouse model revealed that NR is the primary NAD^+ source during *C. glabrata* disseminated infection *in vivo*.

Previous work in the Cormack laboratory has shown that the availability of NAD^+ vitamin precursors is a key regulator of *C. glabrata* virulence. This detailed paper has now fully delineated the salvage pathways by which these precursors are converted to NAD^+.

Sheilagh Molloy

ORIGINAL RESEARCH PAPER Ma, B., Pan, S. J., Zupancic, M. L. & Cormack, B. P. Assimilation of NAD^+ precursors in *Candida glabrata*. *Mol. Microbiol.* **66**, 14–25 (2007)