Annual highlight: Bypassing NAD^+ recycling as a targetable vulnerability in cancer cells

The intricate orchestration of enzymatic activities involving nicotinamide adenine dinucleotide (NAD^+) is essential for maintaining metabolic homeostasis and preserving genomic integrity. As a co-enzyme, NAD^+ plays a key role in regulating metabolic pathways, such as glycolysis and Kreb's cycle. ADP-ribosyltransferases (PARPs) and sirtuins rely on NAD^+ to mediate post-translational modifications of target proteins. The activation of PARP1 in response to DNA breaks leads to rapid depletion of cellular NAD^+ compromising cell viability. Therefore, the levels of NAD^+ must be tightly regulated. Our new data show that that NAD^+ can directly be taken up by the cell's energy factories, called mitochondria, and thereby influence the production of energy. Short-term incubation with NAD^+ boosts Kreb's cycle and the electron transport chain and enhances pyrimidine biosynthesis. On the other hand, extended incubation with NAD^+ results in depletion of pyrimidines, accumulation of purines, activation of the replication stress response and cell cycle arrest. Some cancer cell types, which are characterized by aggressive and rapid cell growth, rely on de novo pyrimidine synthesis and are particularly sensitive to treatment with NAD^+. Importantly, a treatment combination of NAD^+ and 5-fluorouridine can be used to effectively target and eliminate such cancer cells. For now, the mechanism has only been investigated in cells, but the prospects are to further explore the clinical potential of these findings for future cancer therapy. Based on these data, we propose an integrated model of how NAD^+ regulates nucleotide metabolism, with relevance to health span, ageing and cancer therapy. So far, the mechanism has been investigated only in cultured cells, but our plan is to further explore the clinical potential of these findings for future cancer therapy.

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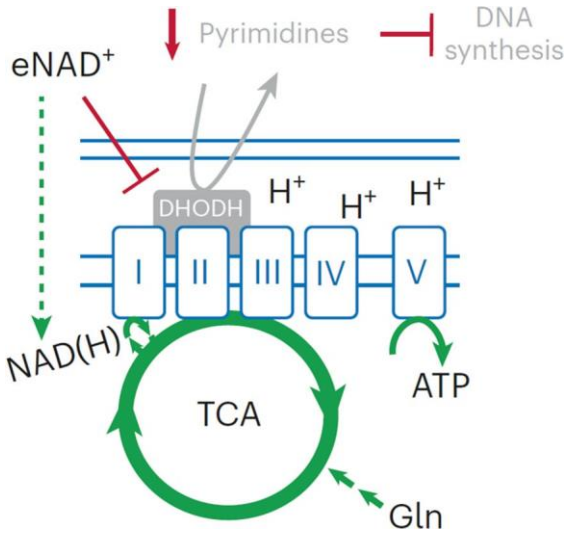

Figure 1. Exogenous NAD^+ affects mitochondrial energy production the synthesis of DNA building blocks.