

Grozio A, Sociali G, Sturla L, Caffa I, Soncini D, Salis A, Raffaelli N, De Flora A, Nencioni A, Bruzzone S. (2013). CD73 protein as a source of extracellular precursors for sustained NAD⁺ biosynthesis in FK866-treated tumor cells. *J Biol Chem.* 288, 25938-49.

NAD(+) is mainly synthesized in human cells via the "salvage" pathways starting from nicotinamide, nicotinic acid, or nicotinamide riboside (NR). The inhibition with FK866 of the enzyme nicotinamide phosphoribosyltransferase (NAMPT), catalyzing the first reaction in the "salvage" pathway from nicotinamide, showed potent antitumor activity in several preclinical models of solid and hematologic cancers. In the clinical studies performed with FK866, however, no tumor remission was observed. Here we demonstrate that low micromolar concentrations of extracellular NAD(+) or NAD(+) precursors, nicotinamide mononucleotide (NMN) and NR, can reverse the FK866-induced cell death, this representing a plausible explanation for the failure of NAMPT inhibition as an anti-cancer therapy. NMN is a substrate of both ectoenzymes CD38 and CD73, with generation of NAM and NR, respectively. In this study, we investigated the roles of CD38 and CD73 in providing extracellular NAD(+) precursors for NAD(+) biosynthesis and in modulating cell susceptibility to FK866. By specifically silencing or overexpressing CD38 and CD73, we demonstrated that endogenous CD73 enables, whereas CD38 impairs, the conversion of extracellular NMN to NR as a precursor for intracellular NAD(+) biosynthesis in human cells. Moreover, cell viability in FK866-treated cells supplemented with extracellular NMN was strongly reduced in tumor cells, upon pharmacological inhibition or specific down-regulation of CD73. Thus, our study suggests that genetic or pharmacologic interventions interfering with CD73 activity may prove useful to increase cancer cell sensitivity to NAMPT inhibitors.

KEYWORDS:

CD73, Cancer Therapy, Cell Death, NAD, NAD Biosynthesis, Nicotinamide, Nicotinamide Mononucleotide, Nicotinamide Riboside