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Nicotinamide phosphoribosyltransferase (NAMPT) is a crucial enzyme in the biosynthesis of intracellular NAD+. NAMPT inhibitors have potent anticancer activity in several preclinical models by depleting NAD+ and ATP levels. Recently, we demonstrated that CD73 enables the utilization of extracellular NAD+/nicotinamide mononucleotide (NMN) by converting them to Nicotinamide riboside (NR), which can cross the plasmamembrane and fuel intracellular NAD+ biosynthesis in human cells. These processes are herein confirmed to also occur in a human ovarian carcinoma cell line (OVCAR-3), by means of CD73 or NRK1 specific silencing. Next, we investigated the anti-tumor activity of the simultaneous inhibition of NAMPT (with FK866) and CD73 (with α, β-methylene adenosine 5'-diphosphate, APCP), in an in vivo human ovarian carcinoma model. Interestingly, the combined therapy was found to significantly decrease intratumor NAD+, NMN and ATP levels, compared with single treatments. In addition, the concentration of these nucleotides in ascitic exudates was more remarkably reduced in animals treated with both FK866 and APCP compared with single treatments. Importantly, tumors treated with FK866 in combination with APCP contained a statistically significant lower proportion of Ki67 positive proliferating cells and a higher percentage of necrotic area. Finally, a slight but significant increase in animal survival in response to the combined therapy, compared to the single agents, could be demonstrated. Our results indicate that the pharmacological inhibition of CD73 enzymatic activity could be considered as a means to potentiate the anti-cancer effects of NAMPT inhibitors.