

INTERCELLULAR AND INTRACELLULAR TRAFFICKING OF NAD⁺ AND NAD⁺ PRECURSORS, INTERMEDIATE METABOLITES AND SIGNAL METABOLITES

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Although being currently illustrated in Biochemistry textbooks, NAD⁺ metabolism is still largely undefined in its features. Specifically, enzymes involved in NAD⁺ biosynthesis and some of the enzymes involved in its utilization localize to distinct subcellular compartments of the same cell and, functionally, also to different cell types of the same organism. These findings lead to revolutionize current ideas. For instance,

1)NAD⁺ biosynthesis from several precursors (e.g., Nicotinamide, Nicotinic Acid, Nicotinamide mononucleotide, Nicotinamide riboside, Tryptophan, collectively defined Vit. B3) is a systemic yet segmentary process, whose individual steps may occur in different cells/tissues/organs. These activate a crosstalk via the exchange of intermediate metabolites in biological fluids and the eventual NAD⁺ biosynthesis takes place in selected cells able to utilize it in diverse, fundamental processes. Therefore, NAD⁺ metabolism is an organismal process encompassing local events.

2)Utilization of NAD⁺ for regulation of cell functions involves the trafficking, both subcellular (autocrine) and intercellular (paracrine), of signal-metabolites including NAD⁺ itself and NAD⁺-derived second messengers, e.g. Cyclic ADP-ribose and ADP-ribose. This hitherto unrecognized trafficking involves a complex interplay of ectoenzymes (e.g. CD38), plasmamembrane receptors and related signal transduction pathways, equilibrative and concentrative transporters, ion channels, whose outcome is the fine control of intracellular Ca²⁺ homeostasis and of Ca²⁺-dependent cell functions.

Further elucidation of compartmentation of NAD⁺ and more extensive identification of its precursors/metabolites is expected to unveil at the mechanistic level a number of physiological and pathological processes, e.g. aging and age-related diseases.

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