When Less is MORE: Functional Proteomics of ABC Importers reveal Essential Roles of Cellular Abundances and Counterintuitive Stoichiometries

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Prokaryotes acquire essential nutrients primarily through ABC importers, consisting of an ATPase, a permease, and a substrate-binding protein. These importers are highly underrepresented in proteomic databases, limiting our knowledge about their cellular copy numbers, component stoichiometry, and the mechanistic implications of these parameters. We developed a tailored proteomic approach to compile the most comprehensive dataset to date of the E. coli 'ABC importome'. Functional assays and analysis of deletion strains revealed mechanistic features linking molecular mechanisms to cellular abundances, co-localization, and component stoichiometries. We observed 4-5 orders of magnitude variation in import system abundances, with copy numbers tuned to nutrient hierarchies essential for growth. Abundances of substrate-binding proteins are unrelated to their substrate binding affinities but are tightly, yet inversely, correlated with their interaction affinity with permeases. Counterintuitive component stoichiometries are crucial for function, offering insights into the design principles of multi-component protein systems, potentially extending beyond ABC importers.