Deciphering the unknown - structure and function of NIF3 protein

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The NIF3 protein stands out as one of the most enduring enigmas awaiting characterization. Eukaryotic NIF3 remains relatively unexplored, with only a limited number of scientific publications linked to it, leaving its function shrouded in mystery. Our project endeavors to bridge this knowledge gap through an integrative approach encompassing structural and cell biology, complemented by proteomics and transcriptomics.

While NIF3 exhibits conservation across Bacteria, Archaea, and Eukaryotes, its prokaryotic counterparts have received the lion's share of attention in previous studies. However, insights into the specific function of NIF3 have been scant. Its association with diverse biological contexts such as DNA repair, DNA methylation, iron homeostasis, cellular stress, and virulence has been noted. Moreover, links between NIF3 expression in humans and various diseases, including cancer, osteoporosis, and degenerative neurological conditions, have been identified, though these associations appear highly pleiotropic. Notably, while the molecular structure of prokaryotic NIF3 homologs has been elucidated, no such information exists for any eukaryotic homologue, including the human variant.

Despite the limited understanding of NIF3's function, our research indicates its involvement in the hypusination of eukaryotic translation factor 5A (eIF5A). NIF3 has demonstrated binding capabilities with DHS and eIF5A-2, suggesting a role in hypusine synthesis.

The primary scientific significance of our project lies in furnishing the community with comprehensive and innovative functional and structural insights into the yet-undefined regulatory mechanism of the hypusination process, impacting protein translation. The proposal's strength lies in the dual approach—targeted and hypothesis-driven research on NIF3's role in hypusination, coupled with untargeted exploration to uncover novel functions. Our research employs structural biology methodologies, including X-ray crystallography, mass spectrometry (MS), and cryoelectron microscopy (cryoEM). Additionally, advanced proteomics will be employed to unveil the potential role of human NIF3 in cellular metabolism and discern its cellular interactome.