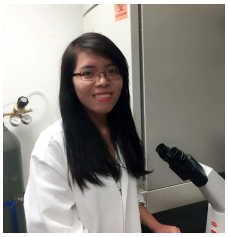

UC San Diego
PHYSICAL SCIENCES
Student Success Center

Hoang Nguyen

EXPAND Mentor

Mechanistic insights into the internal targeting signal carrying preproteins import into mitochondria

Herzik Lab (Winter, 2021-22)

What you will do

Mitochondria are an integral cellular hub that perform many vital functions in eukaryotic cells, including oxidative phosphorylation, heme and lipid biosynthesis, metabolism, and other essential cellular processes necessary for normal eukaryotic physiology[1]. Consequently, mitochondrial dysfunction has been shown to contribute to a variety of disorders including neurodegeneration, metabolic diseases, cancers and heart failure[2–4]. Of the estimated ~1500 proteins that are necessary for human mitochondria to perform their functions, only 13 of these proteins are encoded on mitochondrial DNA while the remaining ~99% of the mitochondrial proteome result from nuclear-encoded genes which must be translated by cytosolic ribosomes and subsequently imported into mitochondria. These cytosolically-synthesized precursor proteins (preproteins) contain endogenous signals that target them to their respective import pathways. To accommodate the complexity of mitochondrial proteome, there are several membrane-embedded complexes that are responsible for the import, folding, processing, and sorting of the different classes of mitochondrial proteins. Among them, the translocase of the outer membrane (TOM) complex is the primary entry gate locating to the outer mitochondrial membrane (OMM) that imports nearly all mitochondrial preproteins. The TOM complex comprises the protein-conducting channel Tom40, scaffolding proteins Toms 5, 6, and 7, the chaperone Tom22, and the preprotein receptors Toms 20 and 70. While Tom20 recognizes those preproteins that contain N-terminal targeting signal, termed matrix-targeting sequences (MTSs), Tom70 serves as the main receptor for preproteins with internal targeting signals (ITS), like those proteins destined for the IMM. Most intriguingly, there is no absolutely conserved import recognition motif for these preprotein substrates, rather, topological features appear to be important. As such, these preprotein receptors, such as Tom70, are required to recognize substantial variations in the primary amino sequence for mitochondrial preprotein import. Yet, despite the TOM complex having been the most well-studied of these import complexes, fundamental questions regarding Tom70-mediated protein import remain. Structural, computational and biochemical approaches will be utilized to elucidate Tom70 preprotein interaction governing mitochondrial protein import pathway.

Skills you will acquire

- Basic wet lab skills (buffer making, gel pouring, lab maintenance tasks).
- Cloning, protein purification.
- Literature review, lab meeting and presentation.
- Common structural softwares (Chimera, NAMD, VMD).