Structures and mechanisms of nuclear import and export

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Research Abstract

DESCRIPTION (provided by applicant): Karyopherinß proteins mediate nucleocytoplasmic transport through recognition of distinct nuclear localization or export signals (NLSs or NESs). Although there are 19 known Kaps in humans, only three classes of signals for Kap?/Kapß1, Kapß2 (or Transportin) and CRM1, respectively, are known at this time. Most other Kaps recognize diverse sequences that occlude the identity of their signals. This proposal describes structural and biochemical analyses of import systems Kapß2 and Imp5/Kap121 as well as the

export-Kap CRM1. Kapß2 mediates nuclear import of RNA binding proteins through their PY-NLSs. Our discovery and understanding of the PY-NLS contributed to the discovery of a defective PY-NLS that causes a subset of amyotrophic lateral sclerosis (ALS). Here, we propose to understand the role of Kapß2 in protein mislocalization and aggregation in ALS. In another aim, we will apply the combined structural, biochemical and bioinformatics approach that we used to discover the PY-NLS to the Imp5/Kap121p pathway with the goal of discovering a set of characteristics to unify the diverse sequences recognized by the Kaps, hence revealing a new class of NLS. Finally, we will study CRM1, which mediates nuclear export of hundreds of proteins; most of them identified using the small molecule inhibitor Leptomycin B. This proposal aims to determine the mechanism of how CRM1 mediates conjugation of leptomycin B to inhibit nuclear export.

Further information available at:

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