Molecular basis for nucleocytoplasmic transport of tRNA by Exportin-t

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Export of mature, fully processed tRNA molecules from nucleus to cytoplasm is carried out by Exportin-t (Xpot) protein in mammals (Los1p homolog in *S. cerevisiae).* It belongs to a family of nuclear import/export proteins called Karyopherins, formed by a repeating motif of 35-40 amino acids called HEAT repeats. The export and subsequent release of tRNA cargo by Xpot involves Ran-GTP hydrolysis in the cytoplasm which is associated with Xpot. Despite the availability of crystal structures of nuclear and cytosolic forms of Xpot, the details regarding the sequential events leading to tRNA release and conformational change in Xpot remain unclear. We have studied a range of molecular complexes including free Xpot protein and intermediate state complexes bound either to Ran or tRNA, to understand the gross structural motions in Xpot after cargo release and identified various molecular determinants responsible for cargo binding. A combination of classical all atom MD and accelerated MD simulations have been performed to study the molecular complexes involving Xpot. This combinatorial approach provided a statistically reliable estimate of the conformational space explored by Xpot in cargo free forms. The overall conformational change in Xpot due to cargo release was attributed to a highly fluctuating C-terminal region. In ternary Xpot-Ran-tRNA complexes (GTP/GDP), immediate effect of GTP hydrolysis was observed in terms of loss of contacts between Xpot and tRNA at tRNA TΨC stem-loop/D-loop region and Heats 9/16-19.