Nuclear Protein Targeting

NUCLEAR PROTEIN TARGETING

In protein targeting proteins are send to different parts of the cell or exported from the cell to extracellular space, more targeting of protein into correct destination or its specific location cell have signalling system. Targeting of protein in nucleus involves signal recognition, and where the signal sequence recognises and transportation occurs through some complex molecules known as importins. These importins mediate the crossing through nuclear envelop; short stretches of basic amino acid residues form the signal sequences and these are recognised by alpha and beta importins. The involvement of nuclear pore complex (NPC) also is observed in nuclear protein targeting; NPC comprises different types of nuclear proteins. Proteins which take part in selective transport are known as nuclear localization signals (NLS), some positive charge amino acids are also involved in this process.

Process of Targeting

- Normally in nuclear protein targeting system two way of signalling happens: *in form and out form.*
  - In *in form* nucleoplasm and DNA is involved, transportation occurs inside the nucleus, with the involvement of histone protein, DNA and RNA polymerases, transcriptional factors, and transportation happens through nuclear pore or importin proteins.
  - In *out form* targeting, mRNA, tRNA and rRNA are transported across nuclear pore.
- In targeting, signalling molecules made from specific amino acid sequence like phenylalanine glycine repeats (FG Repeats), some proteins exit from nucleus by specific nucleus sequence called as NES (Nuclear exit proteins). All these types of export and import pathway is mediated by family of importin and exportin proteins; made up of soluble amino acids and collectively known as *karyopherin*. Majority study is done in NLS type of proteins in which lysine and arginine have been found to be present prominently.
- An example of a nuclear protein target is a leucine rich small sequence, a HIV Rev protein also known as Crm exportin1. The importin bids to NLS in cytoplasm and translocation occurs through NPS into the nucleus. Binding of importin to Ran-GTP occurs in nucleus. After translocation the importin-Ran GTP complex cycles back into cytoplasm, and GTP gets hydrolysed.
- Proteins that need to be transported from cytoplasm to nucleus are known as *Cargo Proteins*.

i. These are translocated by importins found in cytoplasm. Importins transfer the cargo proteins from cytoplasm to nucleus (cargo proteins bind with importin).
ii. After that cargo protein and importin are able to connect with nuclear pore by passing through channels and come inside of the nucleus.
iii. Cargo protein and Ran GTP-Importin association causes conformational changes in importin so that it gets dissociated, delivering the cargo protein inside the nucleus.
iv. Subsequently, translocation of Ran-GTP complex and importin from nucleus to cytoplasm occurs.
v. In the cytoplasm, Ran GTP complex separates from importin. In results excessive generate GTPase activated protein binds with Ran-GTP complex and this causes hydrolysis of GTP and formation of Ran-GDP takes place.
vi. Nuclear transcriptional factors bind with Ran GDP complex and translocate from cytoplasm to nucleus and inside the nucleus a guanine nucleotide exchange factor converts GDP to GTP which translocates from nucleus to cytoplasm; initiating another new cycle.

- In outer form targeting, translocation from nucleus to cytoplasm is mediated by *Exportins.* Exportins bind with their respective cargo proteins and these Exportin- Cargo proteins then bind with the Ran GTP complex, and through nuclear pore this complex gets diffused. In the cytoplasm, binding of GAP protein with Ran GTP complex occurs and this results in hydrolysis of GTP and release of the Cargo protein. Then Ran-GDP moves to nucleus and bind with ligand and in nucleus it again gets converted to Ran GTP.

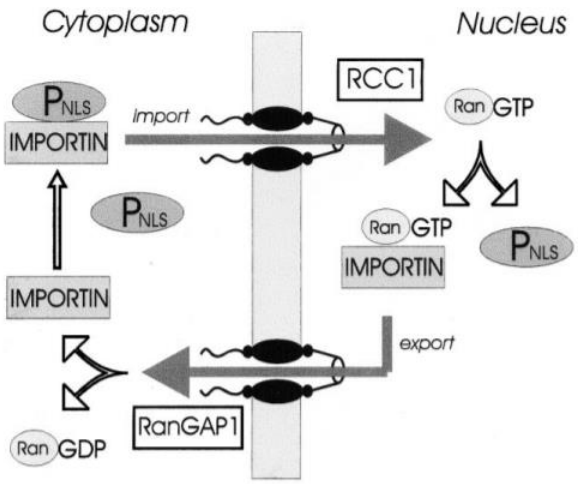

Figure 1. Schematic representation of the classical mechanism of nuclear import.

Source: D. Christophe et al. Cellular Signalling 12 (2000) 337–341

Free importin associates with a cytoplasmic NLS-bearing protein (upper left), and the resulting complex crosses the nuclear envelope. By binding the importin, GTP-bound Ran dissociates the imported complex, releasing the NLS-bearing protein in the nuclear compartment (right). The RAN-GTP/importin complex is exported back into the cytoplasm, where RanGAP1-mediated GTP hydrolysis by RAN results in the release of the free importin (lower left), ready to engage in another import cycle (*Figure 1*).

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