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Review

Atomic basis of CRM1-cargo recognition, release and inhibition

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ABSTRACT

CRM1 or XPO1 is the major nuclear export receptor in the cell, which controls the nuclear-cytoplasmic localization of many proteins and RNAs. CRM1 is also a promising cancer drug target as the transport receptor is overexpressed in many cancers where some of its cargos are misregulated and mislocalized to the cytoplasm. Atomic level understanding of CRM1 function has greatly facilitated recent drug discovery and development of CRM1 inhibitors to target a variety of malignancies. Numerous atomic resolution CRM1 structures are now available, explaining how the exporter recognizes nuclear export signals in its cargos, how RanGTP and cargo bind with positive cooperativity, how RanBP1 causes release of export cargos in the cytoplasm and how diverse inhibitors such as Leptomycin B and the new KPT-SINE compounds block nuclear export. This review summarizes structure–function studies that explain CRM1-cargo recognition, release and inhibition.

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1. Introduction

Nucleocytoplasmic transport is an essential process that governs the localization of numerous proteins and RNAs in eukaryotic cells. While small molecules can diffuse passively across through the nuclear pore complex (NPC), the majority of macromolecular transport across the nuclear envelope is mediated by nuclear transport receptors of the Karyopherin β (Kap) family. There are 19 known Kaps in human cells and they include import receptors called Importins, export receptors called Exportins and bidirectional Kaps that have both Importin and Exportin functions [1–9]. Kap proteins share low sequence identities (10–20%) but have similar physical properties such as molecular weights (90–150 kDa) and isoelectric points (pI = 4.0–5.0) [10]. Nuclear transport is achieved through interactions of cargos with Kap proteins, which in turn interact with nucleoporins that make up the NPC. Kap-cargo interactions are controlled by the GTPase Ran.

There are seven known Exportins in human cells. Of these, CRM1 (Chromosome region maintenance 1, also known as Exportin-1 or XPO1) is the most general and prevalently used export receptor. Other Exportins such as Cas, Exportin-t and Exportin-5 seem to be more specialized as they primarily export the import adaptor Importin-α, tRNAs and pre-miRNAs, respectively [11–13]. CRM1 was first identified through a mutation in its gene, which caused distortion in chromosome structure in *Schizosaccharomyces pombe* and was thus named Chromosomal Region Maintenance 1 [14]. CRM1 was later found to be an essential nuclear export receptor [15–21]. The discovery of CRM1's nuclear export function was also accompanied by the finding that the natural product inhibitor Leptomycin B (LMB) is a very potent and specific inhibitor of CRM1 [17,22,23]. LMB facilitated the identification of numerous CRM1 cargos [24].

Like other Kaps, CRM1 also uses the Ran GTPase to load and unload cargos [25]. CRM1 binds cooperatively with cargos and RanGTP to form export complexes in the nucleus, which then translocate through the NPC via CRM1-nucleoporin interactions [21,26–30]. CRM1 recognizes its export cargos through nuclear export signals or NESs in their polypeptide chains known as classical- or leucine-rich-NESs. These export signals are stretches of 8–15 amino acids, which contain patterns of hydrophobic residues [31–35]. Approximately 300 functionally diverse CRM1 cargos have been reported in the literature and information about these NES-containing proteins are archived in databases such as NESdb and ValidNESs [24,36]. CRM1 cargos include many tumor suppressors and cell growth regulators such as p53, BRCA1/2, FOXO3, IκBα and Survivin [37–41]. Many of these cargo proteins are misregulated and then mislocalized to the cytoplasm in cancer cells [42]. CRM1 itself is also overexpressed in several malignancies and high levels of CRM1 protein is associated with lower survival rates in the patients [43–48]. CRM1 has recently been shown to be an effective drug target for various cancers as CRM1 inhibition restores nuclear localization and nuclear functions of tumor suppressors, leading to apoptosis of the cancer cells [43,49–63].

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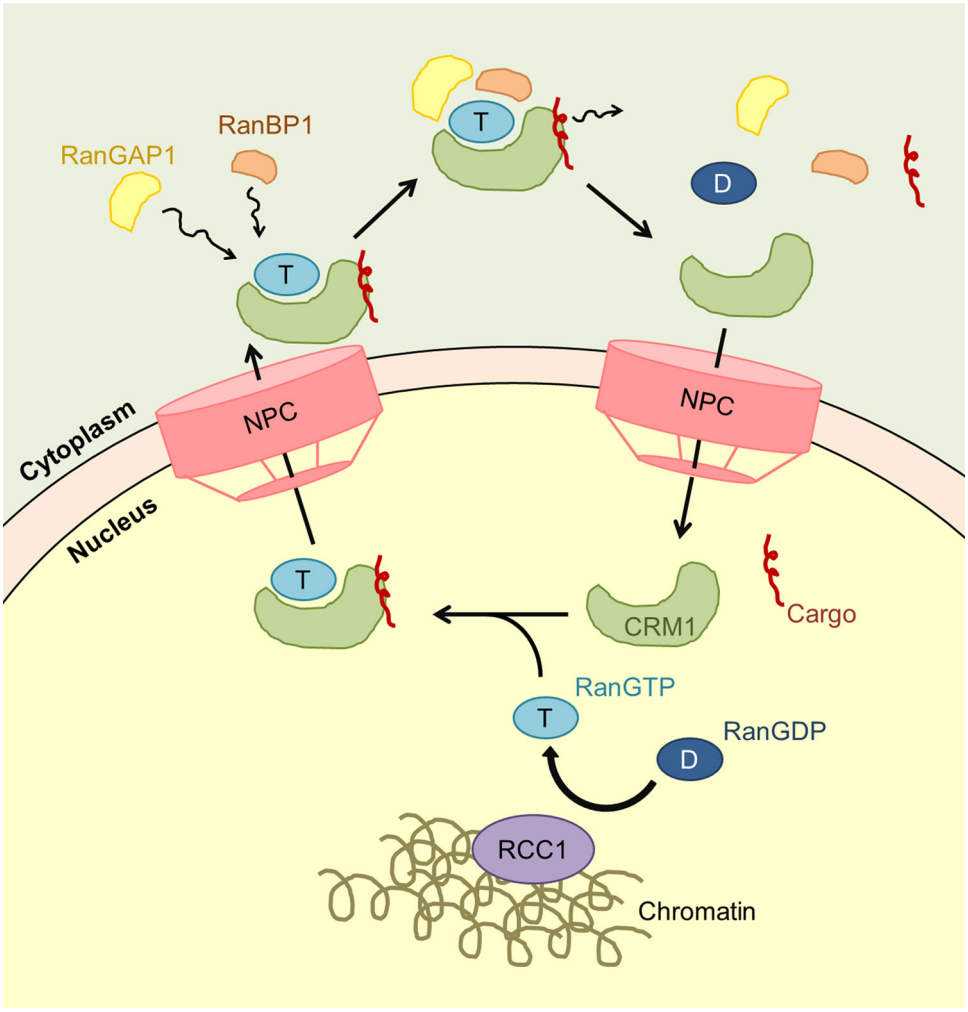

Fig. 1. Schematic of the CRM1 nuclear export cycle. In the nucleus, RanGTP is efficiently loaded with GTP by RCC1. RanGTP and cargo forms a complex with CRM1 and is exported through the nuclear pore complex to the cytoplasm. RanGAP1 and RanBP1 facilitate cargo release and RanGTP hydrolysis. CRM1 is then recycled back to the nucleus for another round of export.

Atomic level understanding of CRM1 function obtained from numerous structural studies was critical in the drug discovery endeavor to target this essential cellular process.

This review focuses on the atomic basis of CRM1-mediated nuclear export. There are now 27 crystal structures of CRM1 in the Protein Data Bank (PDB) (www.rcsb.org) [64]. Collectively, this large body of work explains various aspects of CRM1 function. Here we summarize the structure–function studies that explain CRM1-cargo recognition, release and inhibition.

2. CRM1 and the Ran cycle

CRM1-mediated nuclear export requires the action of the small GTPase Ran. A RanGTP-RanGDP gradient is maintained across the nuclear envelope through compartmentalization of Ran regulators. Ran is predominantly in the GTP state in the nucleus because of efficient nucleotide exchange by its guanidine nucleotide exchange factor RCC1, which is tethered to chromatin through interactions with histones H2A and H2B (Fig. 1) [65–67]. In contrast, cytoplasmic Ran is predominantly in the GDP state because the GTPase-activating protein RanGAP1 that catalyzes hydrolysis of RanGTP to RanGDP is located in the cytoplasm or at the cytoplasmic fibrils of the NPC (Fig. 1) [68–70].

Binary interactions of CRM1 with either RanGTP or export cargos are very weak, but CRM1 binds both ligands cooperatively to form the CRM1-cargo-RanGTP export complex (Fig. 1) [71,72]. The loading process is further facilitated by the Ran binding protein RanBP3 through a still unknown mechanism [73,74]. The CRM1-cargo-RanGTP export complex binds various nucleoporins in the NPC including Nup98 on the nucleoplasmic side, Nup214-Nup88 on the cytoplasmic side of the NPC and various FG repeat-containing nucleoporins [21,26–30]. In the cytoplasm, the CRM1-cargo-RanGTP complex encounters RanBP1 and Nup358 (also known as RanBP2), which facilitate cargo release and interactions of RanGTP with RanGAP1 (Fig. 1) [75–79]. Finally, RanGAP1 catalyzes hydrolysis of RanGTP to RanGDP to end the nuclear export process and CRM1 is then recycled back to the nucleus for additional rounds of export (Fig. 1) [68].

3. A summary of CRM1 structures

Many crystal structures of CRM1 have been published in the last five years. 27 CRM1 structures are now available in the PDB [64]. CRM1 from several organisms (human, mouse, fungi *Chaetomium thermophilum* and *Saccharomyces cerevisiae*) were used in these studies but CRM1 architecture appears conserved across these homologs. Structures of unliganded CRM1, a CRM1-cargo intermediate, CRM1-cargo-Ran export complexes, the post-release yeast CRM1-Ran-RanBP1 complex and several CRM1-inhibitor complexes, all provide snapshots of CRM1 in many steps of the nuclear

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