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Nuclear Trafficking in Health and Disease

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In eukaryotic cells, the cytoplasm and the nucleus are separated by a double-membraned nuclear envelope (NE). Thus, transport of molecules between the nucleus and the cytoplasm occurs via gateways termed the nuclear pore complexes (NPCs), which are the largest intracellular channels in nature. While small molecules can passively translocate through the NPC, large molecules are actively imported into the nucleus by interacting with receptors that bind nuclear pore complex proteins (Nups). Regulatory factors then function in assembly and disassembly of transport complexes. Signaling pathways, cell cycle, pathogens, and other physiopathological conditions regulate various constituents of the nuclear transport machinery. Here, we will discuss several findings related to modulation of nuclear transport during physiological and pathological conditions, including tumorigenesis, viral infection, and congenital syndrome. We will also explore chemical biological approaches that are being used as probes to reveal new mechanisms that regulate nucleocytoplasmic trafficking and that are serving as starting points for drug development.

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Nuclear transport in health

Transport of molecules of less than 50 kDa can passively occur through the NPC. However large molecules, including proteins, require receptors for trafficking through the NPC. Proteins usually contain specific motifs termed nuclear localization sequences (NLSs) and nuclear export sequences (NESs) that are recognized by transport receptors termed karyopherins, importins (α and β transportin, snurportin, etc.), or exportins (Crm1/XPO/exportin 1, etc.). The receptor–cargo complexes interact with nuclear pore complex proteins (nucleoporins or Nups) and are translocated through the NPC. Once import complexes reach the nucleoplasmic side of the NPC, the GTPase Ran binds the transport receptor and the cargo is released to exert its function in the nucleus. In contrast, RanGTP enhances the interaction of transport receptors with cargos destined for nuclear export. The export complex is then translocated through the NPC and dissociated at the cytoplasmic side by the actions of the GTPase-activating protein RanGAP and other factors [1].

Regarding transport of RNA, a subset of mRNAs, miRNAs, and tRNAs can also bind export receptors that utilize RanGTP in a similar manner as transport of proteins [2]. On the other hand, bulk mRNA nuclear export is mediated by transport receptors that do not belong to the karyopherin family of proteins and do not require Ran. Bulk mRNA export is driven by the heterodimer NXF1(TAP)–NXT1(p15) (Mex67 and Mtr2 respectively in yeast) that is recruited to the mRNA by the TREX complex [3]. Once the mRNP reaches the cytoplasmic side, the ATP-dependent RNA helicase Dbp5 promotes the release of the mRNP into the cytoplasm. This step is regulated by the mRNA export factor Gle1 and inositol hexakisphosphate (IP_6) [3]. NXF1(TAP)–NXT1(p15) heterodimer has structure similarity to the transport factor NTF2 [4], which imports RanGDP into the nucleus [1]. This NTF2-like domain of the NXF1–NXT1 heterodimer, together with another domain at the C-terminus of NXF1, interact with FG repeats on nucleoporins to mediate nuclear export of mRNAs [4].

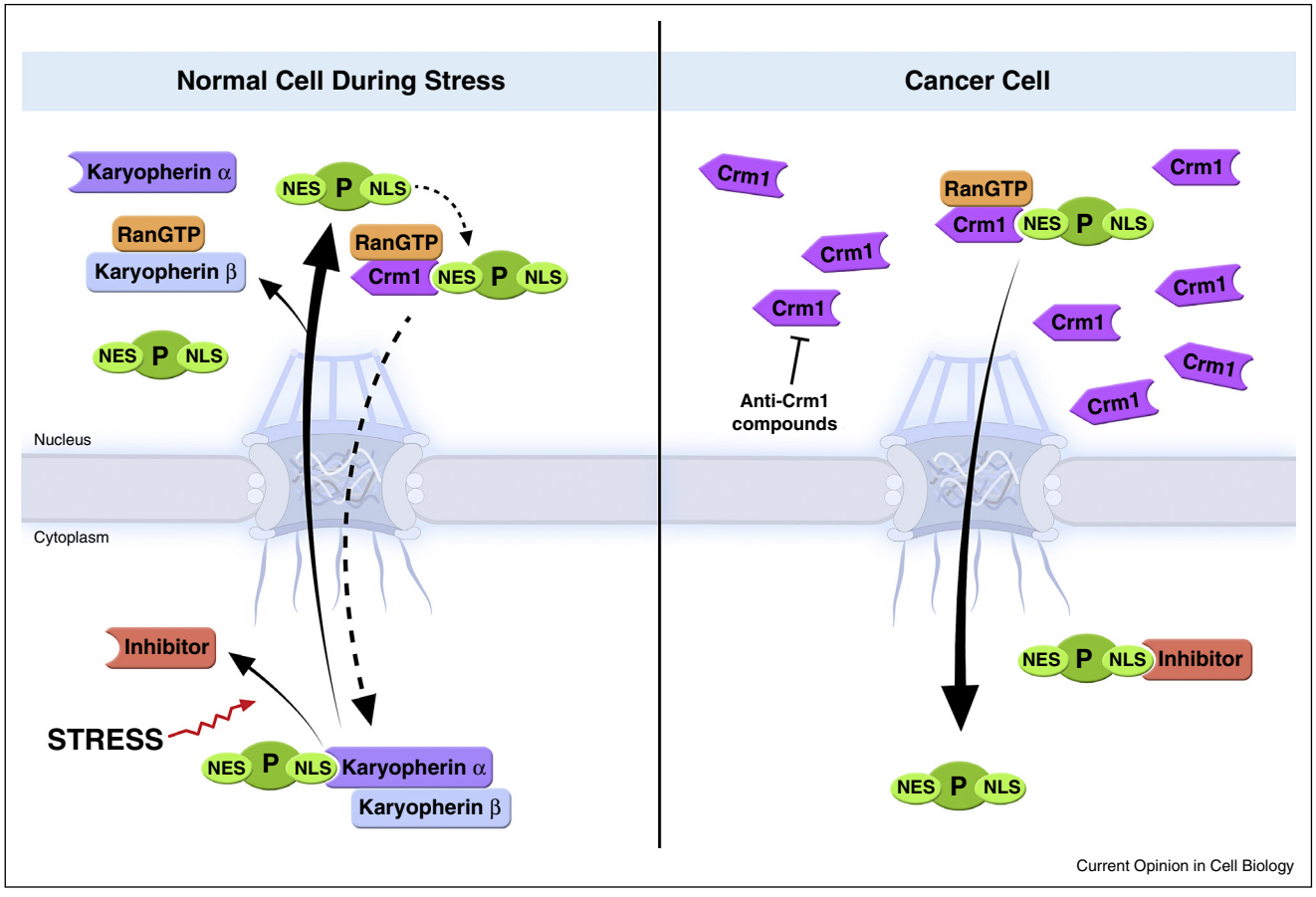
Nucleocytoplasmic trafficking in cell proliferation and tumorigenesis

An elegant mode for regulation of nuclear transport is achieved by post-translation modifications [5]. An example of such regulation can be found in the NF-κB signaling pathway, a major regulator of immunity and cell proliferation, which is involved in tumorigenesis and response to viral infection [6]. Briefly, in basal conditions, NF-κB binds to its inhibitory protein IκB. Since IκB masks the NF-κB NLS, this heterodimer is mostly cytoplasmic. As a response to stress or extracellular cues sensed by plasma membrane receptors, IκB is phosphorylated and targeted for degradation. The exposed NF-κB NLS will then interact with karyopherins leading to rapid import of NF-κB into the nucleus where it will regulate transcription of various genes. This allows a rapid response to stress conditions and emphasizes the importance of regulated nucleocytoplasmic trafficking in health and disease. Other regulated nuclear import and export mechanisms are used by various key signaling pathways such as the p53 pathway [7], interferon (IFN) response pathway [8], and hormone activated pathways [9]. Since there are ~20 karyopherins in humans that can

differentially recognize cargos, nuclear transport regulation may serve as an efficient and specific way to control different pathways upon activation by diverse stimuli. Thus, regulated transport is important to signaling and cellular response to environment and stress. In turn, disruptions of transport can lead to disease.

Since key oncogenes and tumor suppressors function in the nucleus and have NLSs and NESs, unbalanced nucleocytoplasmic shuttling of these factors are correlated with tumorigenesis. Examples include p53, FoxO, topo-IIα and the NF-κB inhibitor IκB, which interact with karyopherins/importins as they enter the nucleus and bind Crm1 (exportin-1 or XPO1) when they exit the nucleus (Figure 1). It has been shown that Crm1 is highly overexpressed in many different types of malignancies including gliomas, osteosarcomas, and leukemias [10–13]. Various findings have led to the model that overexpression of Crm1 enhances nuclear export of tumor suppressors and therefore prevents their accumulation and function in the nucleus. This outcome was specifically demonstrated in certain cases of acute myeloid leukemia (AML) where a mutation was found in the tumor suppressor nucleophosmin (NPM1) [14]. This mutation creates a novel NES that enhances Crm1 binding. Abnormal Crm1-mediated nuclear export of NPM1 removes it from the nucleus and prevents its suppression function on cell proliferation [14–16]. Given the putative pivotal role of Crm1 in a broad spectrum of malignancies, there is an ongoing effort to specifically inhibit this export factor. In fact, Crm1 inhibitors such as leptomycin B (LMB) and derivatives were shown to preferentially induce apoptosis of malignant cells when compared to normal cells, at specific concentrations [17]. However, these inhibitors

Figure 1



Abnormal nuclear export of proteins in cancer cells. Upon genotoxic stress, various proteins (P) including tumor suppressors, such as p53, accumulate in the nucleus to regulate intranuclear processes. The translocation of these proteins into the nucleus involves recognition of the protein's nuclear localization sequence (NLS) by a karyopherin or importin, which in some cases bind a second karyopherin. In the nucleus, the karyopherin(s) is dissociated from the cargo through the action of RanGTP. Certain proteins involved in cell proliferation have their NLS masked by inhibitors, which are dissociated upon various stimuli. This effect allows recognition of the NLS by karyopherins and protein import into the nucleus. Some of these proteins also have a nuclear export sequence (NES), which interacts with the export receptor Crm1 (XPO1). This interaction is enhanced by RanGTP, which is followed by subsequent translocation of the export complex to the cytoplasm. In certain types of cancer, Crm1 is overexpressed and promotes nuclear export of proteins, including tumor suppressors, inducing cell proliferation. Anti-Crm1 compounds are being tested for cancer therapeutics.