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Karyopherins in cancer

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Malfunction of nuclear–cytoplasmic transport contributes to many diseases including cancer. Defective nuclear transport leads to changes in both the physiological levels and temporal-spatial location of tumor suppressors, proto-oncogenes and other macromolecules that in turn affect the tumorigenesis process and drug sensitivity of cancer cells. In addition to their nuclear transport functions in interphase, Karyopherin nuclear transport receptors also have important roles in mitosis and chromosomal integrity. Therefore, alterations in the expressions or regular functions of Karyopherins may have substantial effects on the course and outcome of diseases.

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Introduction

Trafficking of macromolecules across the nuclear envelope is essential to signal transduction, in order to regulate and finely tune a multitude of biological pathways. Proper temporal-spatial localization of macromolecules is regulated in a bidirectional manner through the highly selective nuclear pore complex (NPC). While small molecules (such as ATP) and solutes travel through the NPC via passive diffusion, this mode of transport is not feasible with the increased molecular mass of macromolecules [1] Therefore, to achieve nuclear–cytoplasmic transport of macromolecules in physiologically relevant time scales, they are transported through the NPC in transport receptor-dependent and energy-dependent manners. Members of the Karyopherin-β (Kap) family of nuclear transport receptors are responsible for the majority of the shuttling of cargo proteins from cytoplasm to nucleus (β-Importins) and from nucleus to cytoplasm (Exportins) [2–4]. β-Importins and Exportins recognize specific signals within the cargo proteins termed nuclear localization signal (NLS) and the nuclear export signal (NES), respectively. At this time, a few more than 20 Kaps have been reported in human cells (Table 1). β-Importins and Exportins are each composed of ~20 consecutive HEAT repeats (each composed of a pair of antiparallel α-helices) that are arranged to form super-helical or ring-shaped proteins.

Kap-mediated active nuclear transport is regulated by the small Ras related GTPase, Ran, which controls assembly and disassembly of Kap–cargo complexes [5,6]. The direction of nuclear transport is determined by the asymmetric concentrations of the GTP-bound versus GDP-bound forms of Ran in the nucleus and the cytoplasm, respectively. RanGTP and nuclear export cargos bind with positive cooperativity to Exportins leading to formation of ternary Exportin–RanGTP–cargo complexes in the nucleus to begin the nuclear export process [7,8]. Upon translocation to the cytoplasm, RanGTP is hydrolyzed to RanGDP by the actions of RanGAP1 and RanBP1/RanBP2 causing the trimeric complexes to dissociate. The opposite Kap–cargo–Ran reactions occur in nuclear import. NLS-containing cargos and RanGTP bind Importins with negative cooperativity [9,10]. Importins will only bind their cargos in the cytoplasm where RanGTP is absent (due to the actions of RanGAP1 and RanBP1/RanBP2). Once Importin–cargo complexes enter the nucleus, RanGTP binds with high affinity to Importins causing cargo release (Figure 1).

Most Kaps bind directly to their cargo proteins in order to translocate through the NPC. The amphipathic HEAT repeats of Kaps provide multiple hydrophobic patches on their outer surfaces to bind dynamically to Phe-Gly (FG) repeats found in many nucleoporins of the NPC. The highly dynamic and intrinsically disordered FG repeats in FG-nucleoporins form the permeability barrier in the center of NPC, which prevents passage of unaccompanied macromolecules while promoting the selective and efficient transport of Kap–cargo complexes [11–14].

In addition to the β-Importins, adaptor proteins named Importin-αs (Impα, Karyopherin-α) also play important roles in nuclear import. Impα binds directly to both the classical-NLS (cNLS) in cargo proteins and to Impβ [15–17]. Subsequently, Impβ interacts with the NPC to carry the Impβ–Impα–cargo complex into the nucleus. Seven different Impα proteins have been identified in human cells [18]. All Impαs share a highly conserved protein structure of a flexible N-terminal Impβ binding (IBB) domain followed by a central ARM domain (contains 10 ARM repeats) and a short C-terminal disordered

Table 1

Human Importins and Exportins.

Human protein/gene name	Aliases[a]	Example of cargos[b]	Implicated in cancer[c]
Karyopherin-β proteins in nuclear export			
Exportin 1 (XPO1)	CRM1; exp1; emb	ad1, Rio2, CDC7, CPEB4 SNUPN, X11L2, PKIα,p73, STAT-1-3, MEK1, c-Abl, Paxillin, ADAR1, HPV16 E7, APC2, mdm2	Lymphomas, gynecological malignancies glioblastoma, head & neck squamous cell carcinoma, liposarcoma, multiple myeloma, lung, prostate, hepatocellular, cervical cancer
Cellular apoptosis susceptibility (CAS)	CAS; CSE1; CSEL1 XPO2	Impα1, Impα3, Impα4, Impα5, Impα6, Impα7, Impα8	Bladder cancer, osteosarcoma, melanoma, leukemia, breast cancer, hepatocellular carcinoma, gastric cancer, ovarian cancer, colorectal cancer, thyroid cancer
Exportin for tRNA *(XPOT)*	XPO3	Aminoacylated tRNAs	Breast cancer, ovarian cancer, mesothelioma
Exportin 5 *(XPO5)*	exp5	Jaz, pre-microRNA	Colorectal cancer, breast cancer, bladder, thyroid cancer, melanoma, thyroid, liver cancer, larynx cancer, small-cell lung cancer, gastric cancer, renal cell carcinoma, esophageal cancer
Exportin 6 *(XPO6)*	EXP6; RANBP20	Nuclear actin	Prostate cancer, breast cancer
Exportin 7 *(XPO7)*	EXP7; RANBP16	p50RhoGAP, 14-3-3, STRAD	Non-small lung cancer, prostate cancer, ovarian cancer oligodendrogliomas
Karyopherin-β proteins in nuclear import			
Importin subunit beta 1 *(KPNB1)*	Impβ; MB1; IPO1; IPOB; Impnb; NTF97	Snurportin-1, cyclin B1, SREPB2, CREB	Cervical cancer, gastric cancer, breast cancer, hepatocellular cancer, diffuse large B-cell lymphoma, multiple myeloma
Transportin 1 *(TNPO1)*	Kapβ2; MIP; TRN; IPO2; MIP1; KPNB2	FUS, EWS, hnRNA-A1,2,3, -D,-G-H-M, NFX1	n/a
Transportin 2 *(TNPO2)*	IPO3; TRN2; KPNB2B	n/a	n/a
Transportin 3 *(TNPO3)*	TRN-SR; TRN-SR2; IPO12; TRNSR; LGMD1F; MTR10A;	SRSF1, ASF/SF2, SC35HIV integrase	n/a
Importin 4 *(IPO4)*	Imp4	TP2, Vitamin D receptor	n/a
Importin 5 *(IPO5)*	IMB3; Pse1; imp5; KPNB3; RANBP5	HPV-16-E5(16E2), p60TRP, Rag-2, Apolipoprotein A-I PGC7/Stella	Cervical cancer, Kaposi's sarcoma
Importin 7 *(IPO7)*	Imp7; RANBP7	EZI, ERK2, SMAD3, RPL23A, RPS7 and RPL5	Colorectal cancer, prostate cancer, lung cancer, ependymoma
Importin 8 *(IPO8)*	RANBP8	Cap-free eIF4E, SMAD4,	Acute myeloid leukemia
Importin 9 *(IPO9)*	Imp9	Nuclear actin and cofilin	n/a
Importin 11 *(IPO11)*	RanBP11	UbcM2, Ube2e3, Ub-primed PTEN	Bladder cancers, lung cancer, squamous cell carcinoma
Nuclear import adaptors: Importin-α proteins			
Human Impα5/Karyopherin subunit alpha 1 (*KPNA1)*	RCH2; SRP1; IPOA5; NPI-1	ADAR2, LSD1, Arx (NLS1), NF-κB (p50/p65)	n/a
Human Impα1/Karyopherin subunit alpha 2 (*KPNA2)*	QIP2; RCH1; IPOA1; SRP1alpha; SRP1-alpha	BRCA1, NBS1, RAD51, E2F1	Gastric cancer, colon cancer, endometrial cancer, prostate cancer, CRC, bladder cancer, non-small-cell lung cancer and breast cancer
Human Impα4/Karyopherin subunit alpha 3 (*KPNA3)*	SRP1; SRP4; IPOA4; hSRP1; SRP1gamma	RRC1, RanBP3, XPA, NF-κB (p50/p65)	Chronic lymphocytic leukemia and mantle cell lymphoma
Human Impα3/Karyopherin subunit alpha 4 (*KPNA4)*	QIP1; SRP3; IPOA3	RRC1, RanBP3, hMSH2, p53, NF-κB (p50/p65)	Breast cancer, prostate cancer, glioblastoma
Human Impα6/Karyopherin subunit alpha 5 (*KPNA5)*	SRP6; IPOA6	ARHI (DIRAS3), BRMS1, NF-κB (p50/p65)	Colorectal cancer, breast cancers
Human Impα7/Karyopherin subunit alpha 6 (*KPNA6)*	IPOA7; KPNA7	ARHI (DIRAS3), Keap1, pSTAT1	Smooth muscle neoplasm, chronic myeloid leukemia