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Karyopherins in Cancer

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Abstract

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.

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- 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

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nuclear transport is determined by the asymmetric concentrations of the GTP- 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 tail. The ARM domain of Impα binds cNLS and its IBB domain binds Impβ [19].

The spectrum of cellular functions for Kap cargos is huge and proper nuclear-cytoplasmic localization of these cargos is critical to their abilities to execute normal cellular functions (Table 1). Many nuclear transport cargos have been implicated in enabling characteristics and hallmarks of cancer [20]. Thus, aberrant temporal-spatial localization of these cargos, due to altered behavior and/or expression of Karyopherins, are likely to impact the biology of cancer cells (Figure 2). Aberrant nuclear-cytoplasmic shuttling of key cellular regulator macromolecules, such as oncogenes and tumor suppressor genes, has been reported in variety of cancers and viral infections. The majority of published studies have focused on pathogenic mutations in the cargo proteins rather than on the Kaps that transport them. Although mutational analyses of cargo proteins have helped identification of many NLSs and NESs, the importance of the Karyopherins in cancer causation, progression and treatment has only begun to be highlighted in the past decade. Here, we compile and review studies in cancer biology where Karyopherins were shown to be deregulated and/or mutated.

Kap-mediated nuclear export and cancer

CRM1/Exportin 1 (XPO1)

CRM1/XPO1 is the Exportin that is responsible for nuclear export of hundreds to more than a thousand NES-containing proteins and RNAs. Many protein cargos of CRM1/XPO1 are tumor suppressors and/or regulators of cell proliferation [21]. CRM1/XPO1 has been shown to display high mRNA and protein levels in many types of cancers [22]. Although the molecular mechanisms that lead to CRM1/XPO1 overexpression remain mostly unknown, CRM1/XPO1 gene copy number gain (chromosome 2p16.1-2p15 locus) has been reported in hematological malignancies [23].

Recently, somatic missense mutations were found in codon 571 of CRM1/XPO1, which results in a mutation of residue Glu571 of CRM1/XPO1 to either a glycine or a lysine (p.E571K/G) [23,24]. Glu571 lies within the hydrophobic NES-binding groove of CRM1/XPO1. Recurrent patterns of E571K/G mutations have been reported in both solid and hematologic cancers [23,24]. However, the molecular consequences of these CRM1/XPO1 mutations and how they lead to cancer, remain to be elucidated.

Two recent studies on functional genomic and pharmacologic profiling of rare sarcoma and KRAS-mutant non-small cell lung cancer identified and evaluated CRM1/XPO1 as a native and generic potential therapeutic target [25,26]. In these independent studies, CRM1/XPO1 was shown to be a context-independent cancer dependent or synthetic lethality gene in a number of well-annotated primary cell-lines that were used to represent heterogeneity of tumors.

Atomic level knowledge of how CRM1/XPO1 recognizes the NES [27] allowed *in silico* small molecule docking studies by Karyopharm Therapeutics Inc. (Newton, MA) to develop compounds named Selective inhibitors of Nuclear Export (KPT-SINEs) into potent CRM1/XPO1 inhibitors. KPT-SINEs are orally bioavailable inhibitors that bind covalently, but in a slowly reversible fashion, to the Cys528 residue that is located in the CRM1/XPO1 NES-binding groove. Binding of KPT-SINE to CRM1 blocks binding of NESs of CRM1/XPO1 cargos and therefore efflux of the cargos into the cytoplasm. This ends up concentrating the cargos in the nucleus where they can potentially mediate apoptosis in response to DNA damage, to the cell's microenvironment or to chemotherapy [28,29]. More than 40 pre-clinical studies, reporting on the application and efficacy of KPT-SINE compounds in hematopoietic malignancies and solid tumors were published from 2012 till the present. Broad antitumor activity of the SINE compounds relies on nuclear retention of a variety of CRM1/XPO1 cargos (such as p53, IκB, NPM1, PAR-4, FOXO, p73, p27, topoisomerase IIα, MDM2, mTOR) in a cell context dependent manner. Retention of these regulators in the nucleus led to subsequent activation of cell-cycle arrest, apoptotic-, anti-inflammatory- and stress-related gene expression [30,31]. Three KTP-SINEs, namely Selinexor (KPT-330) (https://ClinicalTrials.gov, NCT01607892, NCT01607905, NCT02025985, NCT01896505, NCT02025985, NCT02606461, NCT02250885, NCT02606461) [32], Verdinexor (KPT-335) (https://ClinicalTrials.gov, NCT02431364) and Eltanexor (KPT-8602) (https://ClinicalTrials.gov, NCT02649790) are being investigated in over fifty clinical trials for wide varieties of both solid and hematologic cancers. The clinical-trials in human patients include

both single agent trials and trials that combine nuclear export inhibition by Selinexor with cell cycle or proteasome inhibitors or monoclonal antibodies for further multi-pathway/multi-dimensional targeting of critical signaling pathways [33–36].

Cellular apoptosis susceptibility (CAS)/Exportin 2 (XPO2)

CAS is the Exportin for the Impα subunits of the classical Impα/β nuclear import system, and is responsible for recycling Impα back to the cytoplasm for additional rounds of nuclear import [37]. CAS was identified as a putative oncogene. Its overexpression was reported in several tumor types and correlated with cancer grades, cancer stages, and poor outcomes of cancer patients [38]. Recently, additional studies have identified a variety of unexpected links between CAS and different non-Impα proteins suggesting that diverse and context-specific functions of CAS that are still incompletely understood [38,39].

Exportin for tRNA (XPO-t)/Exportin 3 (XPO3)

The Exportin for tRNAs or XPO-t is the major nuclear exporter of aminoacylated tRNAs [40,41]. Recently, in an attempt to identify new prognostic markers through comparative expression pattern analysis among tumor tissues and cell-lines, XPO-t overexpression was shown to correlate with poor prognosis in breast, ovarian cancers and mesothelioma [42,43]. These correlations are reasonable considering the findings that tRNA-derived fragments are dysregulated in several cancers [44]. Other than these preliminary correlative observations, the tumorigenic consequence of XPO-t overexpression and the mechanism of how that influences cancer progression remain to be understood.

Exportin 5 (XPO5)

Xpo5 is the Exportin that transports precursor micro-RNAs (pre-miRNAs) from the nucleus to the cytoplasm [45], a key step in miRNA biogenesis [46]. Both overexpression and decreased expression of XPO5 have been observed in cancer. XPO5 overexpression was shown in colorectal, breast, bladder, thyroid carcinomas and melanomas [47,48]. The molecular basis for XPO5 overexpression and for the resulting tumorigenic activity is not yet known, but XPO5 overexpression originating from 6p polyploidy was shown to be associated with gastric cancer [49]. In contrast, lower expression levels of XPO5 due to the recurrent rs11077 single-nucleotide polymorphism (SNP) located in the 3′ UTR of XPO5, was shown to closely associate with thyroid cancer, liver cancer, larynx cancer, colorectal cancer and leukoplakia [50,51]. SNPs related to the miRNA pathway, known as miR-SNPs [52], can influence miRNA functions either by directly perturbing miRNA expression levels or by perturbing miRNA binding sequence in target genes. miR-SNPs can affect cancer development and prognosis by changing the global miRNA profile of cells. The recently identified TG variant (carries T or G allele) of the rs11077 miR-SNPs, which leads to XPO5 downregulation, correlates with distant metastasis and lymphatic invasion in thyroid cancer [50]. On the other hand, the more frequent heterozygous AC genotype of the miR-SNPs rs11077, in which a genotype from one parent carries a specific A mutation and the genotype from the other parent carries a C mutation, is associated with improved chemotherapy response in non-small cell lung cancer and with longer overall survival in chemosensitive multiple myeloma and non-small cell lung cancer patients [53,54]. The AC genotype is also associated with increased risk in esophageal and renal cell cancers [55,56].

XPO5 downregulation can also result from a loss of function mutation, which generates an inactive C-terminally truncated XPO5 protein. This mutation was shown to be present in 11.6% of the primary malignancies with microsatellite instability including colorectal cancer, gastric and endometrial tumors [57]. Besides altered expression level and gene mutations of XPO5, extracellular-signal-regulated kinase (ERK)-driven XPO5 phosphorylation significantly reduces nuclear efflux of pre-miRNA, and was recently shown to correlate with poor prognosis in liver cancer patients [58]. ERK-mediated XPO5 suppression of miR-122 in liver cells leads to increased microtubule dynamics resulting in tumorigenesis along with drug resistance. Although miR-SNP studies of XPO5 are currently still at early stages, further studies in identification of miRNA dysregulation affected by XPO5 mutations should lead to a better understanding of chemotherapy sensitivity, cancer survival and epidemiology of a given cancer type.

Exportin 6 (XPO6) and Exportin 7 (XPO7)

Exportin 6 is key for the nuclear export of nuclear-actin [59], which was proposed to mediate both growth and quiescence in mouse epithelial cells acting though the laminin-111 (LN1)/PI3K/XPO6/N-actin pathway [60]. In the context of normal mammary basal membrane, LN1 impedes PI3K-induced XPO6 activation thus affecting nuclear export nuclear-actin, which is crucial for cells to become quiescent. This proposed mechanism along with statistical analysis of clinical datasets, led to the proposal that XPO6 expression correlates with poor survival in breast cancer patients. On the other hand, gene expression analysis of samples from prostate cancer patients showed that elevated levels of XPO6 can be used a prognostic marker of reoccurrence [61,62].

XPO7 mediates nuclear export of various cytoplasmic cargo proteins such as 14-3-3, p50RhoGAP and STRAD [63]. Proper cytoplasmic localization of these cargo proteins is important for their normal cellular functions, such as 14-3-3-dependent tuning of apoptosis and cell-cycle checkpoint. Thus, it is not surprising that irregularly elevated cytoplasmic levels of XPO7 is strongly associated with poor overall survival in epithelial ovarian cancer patients [64]. A point mutation where residue Asp237 of XPO7 is mutated to asparagine (p.D237N) was recently identified in oligodendrogliomas tumor samples [65]. We performed homology modeling and sequence alignment of XPO7 with crystal structures of CRM1/XPO1 and XPO4, which placed Asp237 in the putative loop between HEAT repeats 4 and 5 in XPO7 (unpublished data). Increased proliferation observed in an overexpression study indicated that D237N mutation affects the functional property of XPO7 in oligodendroglial and HEK293 cell lines, but further studies along with a broader range of samples are needed for proper characterization of the mutation [65].

Nuclear import and cancer

The classical Importin-α•Importin-β system

Importin-β (KPNB1)—Importin-β (Impβ) is part of the heterodimeric Impα/β nuclear importer complex for cNLS-harboring proteins [66]. Impβ also regulates mitotic progression subsequent to nuclear envelope disintegration [67]. Impβ, often coupled with Impα, sequesters many spindle assembly factors (SAFs) in areas distant from the chromatin and

then releases them in a RanGTP-dependent manner near the mitotic chromosomes/spindles to execute the proper order of events in cell division. These SAF proteins include, but are not limited to, tumor suppressor proteins, Ran-dependent microtubule stabilizers, and a subset of nucleoporins [68]. Impβ was reported to be overexpressed in cervical cancer, gastric cancer [69], breast cancer [70], hepatocellular cancer [71], diffuse large B-cell lymphoma [72] and multiple myeloma [73]. Impβ was also implicated in interference with cell survival and proliferation [69,72,73]. Recent cell culture studies identified two small molecule Impβ inhibitors named the inhibitor of Nuclear Import-43 (INI-43) [74] and its 2-aminothiazole derivative 1 [75], both with therapeutic potential for cancer treatment. Both compounds, at nanomolar concentrations, elicited G2-M cell-cycle arrest in cancer cells and induced an intrinsic apoptotic pathway but did not display adverse effects on normal *in vitro* cell culture models [74,75]. INI-43 also showed substantial inhibitory effect on the growth of esophageal and cervical tumor cells in subcutaneously xenografted models [74]. Impβ plays central roles in both cell cycle regulation and Impα-dependent nuclear import. Since many cancer-sustaining pathways share these fundamental cellular processes, selective inhibition of Impβ represents a powerful approach for anticancer therapeutics.

Adaptor proteins for Importin-β: the Importin-α (Impα) proteins—There are a few examples of the involvement of human Impα proteins in malignancies and in cancer biology. In the following sections we compile knowledge on the different Impα proteins that are grouped into three subfamilies defined by their amino acid similarities and evolutional conservations: 1) the α1 subfamily: Impα1 and Impα8, 2) the α2 subfamily: Impα3 and Impα4 and 3) the α3 subfamily: Impα5, Impα6 and Impα7 [66].

The α1 subfamily: Human Impα1 (KNPA2) and Impα8 (KNPA7): Impα1, one of seven known Impα adaptor proteins of Impβ, binds directly to many cNLS-containing protein cargos including cancer associated proteins such as BRCA1, NBS1 and RAD51 and E2F1 [76–78] and the DNA double-strand break repair complex MRN [79]. Elevated levels of Impα1 protein was reported in gastric cancer, colon cancer, endometrial cancer, prostate cancer, colorectal cancer, bladder cancer, non-small cell lung cancer and breast cancer, and were associated with poor prognosis [80–82]. Because of the aberrant and cancer-related high levels of Imp-α1, the protein was recently identified as one of the target oncogenes for the tumor suppressor microRNA miR-26b [83,84]. In these studies, downregulation of miR-26b was highly associated with upregulation of Impα1 mRNA/protein levels and with unfavorable prognosis in gastric and ovarian cancer patients. The cancer cell secretome, which is the collection of extracellular proteins secreted by cancer cells, provides a novel approach for cancer biomarker identification. Surprisingly, in addition to intracellular overexpression of Impα1, elevated levels of serum Impα1 were detected in lung cancer, colorectal cancer and esophageal squamous cell carcinoma [85,86], making the protein a potential cancer biomarker.

Another Impα subtype, Impα8, is virtually absent in most adult tissues. Impα8 is found in very low levels in oocytes, dendric cells and the small intestine [87]. Its expression is also very tightly regulated during development. Overexpression of Imp-α8 has been shown to promote malignant properties of pancreatic cancer [88].

The α2 subfamily: Human Impα3 (KNPA4) and Impα4 (KPNA3): The evolutionary relationship between Impα3 and Impα4 partitions the two proteins into the same Impα subfamily [66]. They share several cargo proteins that are specific to this subfamily, such as RCC1 and RanBP3 [66]. Other than common specialized cargos, both Impα3 and Impα4 have been shown to be required for proper nuclear influx of some important cancer related gene products. While Impα3 recognizes and rapidly transfers both hMSH2 and p53 under stress conditions [89,90], Impα4 facilitates UV-induced nuclear accumulation of a critical sensor of S-phase DNA damage, the Xeroderma pigmentosum Group A (XPA) protein [91].

Impα3 was also identified as a direct target for tumor suppressor micro-RNAs miR-708, miR-181b and Hsa-miR-567 [92–94]. Downregulation of miR-708 and miR-181b levels results in Imp-α3 overexpression associated with skeletal metastasis of prostate cancer and glioblastoma with poor overall survival, respectively. Impα3 overexpression was also reported in the highly aggressive MDA-MB-231 breast cancer cell line and in samples from patients with poor prognosis [93]. Furthermore, ectopic expression of Hsa-miR-567 in a breast cancer cell line strongly inhibits cell proliferation and migration *in vitro* and in mouse xenografts.

Impα4 expression is down-regulated by miR-223, leading to the inhibition of NF-κB signaling in glomerular endothelial cells [95]. Impα4-dependent NF-κB signaling attenuation was also reported in chronic lymphocytic leukemia and mantle cell lymphoma with loss of 13q14.3. The latter chromosomal aberration leads to Impα4 haploinsufficiency (down-regulation), which in turn may associate with tumorigenesis [96].

The α3 subfamily: Human Impα6 (KPNA5) and Impα7 (KPNA6): There are a few reports of involvement of α3 subfamily members in cancer. Through genome-wide somatic mutation analysis, Impα6 was found to be recurrently mutated in breast cancer tumor samples and thus considered to be a candidate cancer gene [97,98]. These recurrent mutations include the p.F48L mutation within its IBB motif, the p.L179V mutation in its 2nd ARM domain and the p.R319S mutation in its 5th ARM domain. Imp-α7 was identified in a study to evaluate differential gene expression in chronic myeloid leukemia (CML) versus healthy volunteers, as one of the overexpressed genes that may be involved in this disease [99]. In addition to overexpression, recurrent Imp-α7 haploinsufficiency due to regional loss of chromosome 1p was reported in smooth muscle neoplasm of the uterus [100]. However, no clear evidence supporting the importance of the loss of Imp-α7 has been published.

Impα proteins are involved in many cellular processes that range from embryonic stem cell fate to normal neuronal function. Therefore, further research is needed to gain a better understanding of how expression patterns and Importin-cargo specificity for the each Impα subtype affect normal and disease states of cells.

Other β-Importin systems: Kapβ2/TNPO1, TNPO3, IPO4, IPO5, IPO7, IPO8, IPO9, IPO11

Karyopherin-β2/Transportin-1, Transportin-3/Transportin-SR, Importin-4 and Importin-9—Many studies of Karyopherin-β2 (Kapβ2; also known as Transportin-1 or TNPO1), Transportin 3 (TNPO3; also known as Transportin-SR), Importin 4 (IPO4) and

Importin 9 (IPO9) have identified nuclear import cargos for each of the Importins [3,4]. Kapβ2/TNPO1 is one of the major players of the nuclear import system and shown to mediate nuclear import of > 30 of cargos harboring the well characterized PY(proline/tyrosine)-NLS [2]. Many of these cargos, such as hnRNP A1, hnRNP M and FUS, are classified as RNA processing proteins [101]. TNPO3 was initially identified as a novel importer for conserved SR-proteins that are involved in RNA splicing family (e.g. ASF/SF2, SC35) [102], but was later shown to be required for several lentiviruses infection [102]. Kapβ2/TNPO1 and TNPO3 have been shown to play important roles in the pathogenesis of diseases such as familial FUS amyotrophic lateral sclerosis [103] and Limb-girdle muscular dystrophy 1F [104], respectively. However, at this time, none of the four Importins (Kapβ2, TNPO3, IPO4 and IPO9) have reported roles in cancer etiology.

Importin 5 (IPO5): IPO5 imports a variety of functionally diverse cargos by binding to IK-NLSs in their polypeptide chains [2,105]. Among its cargos are several viral proteins. IPO5 binds directly to a human papilloma virus (HPV) protein named HPV-16-E5(16E2), which is an important mediator of oncogenic transformation [106]. Interestingly, HPV-16-E5(16E2) does not have an NLS and is not found in the nucleus, thus it is unclear what role IPO5 assumes in this interaction. In a more conventional role, IPO5 imports other HPV proteins such as the NLS-containing L2 proteins of HPV-11 and HPV-16, into the nucleus [107]. Finally, the IPO5 mRNA was found to be the target of a miRNA produced by the human herpesvirus 8 (HHV-8; an oncogenic virus associated with Kaposi sarcoma and primary effusion lymphoma) [108]. In all the examples above, interactions between IPO5 and viral oncogenes were documented but the pathological significance of these interactions as they pertain to cancer needs further investigation.

Importin 7 (IPO7): There is limited information about IPO7 cellular function and its cargo proteins. IPO7 was shown to directly interact with ribosomal proteins RPL23A, RPS7 and RPL5 in order to facilitate their nuclear import [109]. Overexpression of IPO7 was reported and implicated as a notable factor in colorectal cancer, prostate and lung cancers [110–112]. In many cases, IPO7 upregulation is induced at the transcriptional level either by the c-myc oncogene, which is commonly overexpressed in colorectal cancer [109] or by promoter hypomethylation in pediatric malignancy [113]. While being positively upregulated by c-myc, both mRNA and protein levels of IPO7 were shown to be downregulated by p53 [109]. Interestingly, in the same study, it has been proposed that dysregulation of ribosomal biogenesis by IPO7 deletion results in a p53-driven cell growth arrest. This sequence of events hints that IPO7 may be a therapeutic target, a notion that is further supported by the antitumor effect of IPO7 knockdown in a mouse lung cancer model [110].

Importin 8 (IPO8): Few nuclear import cargos are known for IPO8. One of them is the protooncogene eIF4E, a translation initiation factor, which binds the 5′ cap of mRNAs to direct them for translation [114]. IPO8 binds only the unliganded (5′cap-mRNAs-free) form of eIF4E, and IPO8-dependent nuclear import of eIF4E is important for both tumor formation and metastasis. At this time, the connection between IPO8 and cancer is limited to the study of eIF4E [114]. Elevated levels of IPO8 were found in acute myeloid leukemia but

reports on cancer gene expression studies described IPO8 as a housekeeping gene that displays similar levels of expression among tissue types and treatment conditions [115,116].

Importin 11 (IPO11): Importin 11 mediates the import of ubiquitinated protein cargos into the nucleus [117]. It is also the Importin for the E2 ubiquitin-conjugating enzyme UBE2E3 [118]. At this time, only a few studies have indicated links between IPO11 and cancer. In non-muscle-invasive bladder cancer, IPO11 overexpression that results from Chromosome 5 aneuploidy is strongly associated with poor prognosis [119]. IPO11 was also proposed to be a potential biomarker for bladder cancer. In addition, a recent publication revealed that IPO11 selectively binds to the monoubiquinated form of both PTEN (tumor suppressor protein) and UBE2E1 (E2 ubiquitin–conjugating enzyme) to mediate their nuclear import. IPO11-driven removal of PTEN and UBE2E1 from the cytoplasm prevents degradation of PTEN in the cytoplasm. The role of IPO11 in regulation of PTEN tumor suppressor activity is further supported by identification of frequent occurrence of IPO11 loss of heterozygosity along with reduced level of PTEN in many cancer genomic datasets [120].

Bidirectional nuclear transporters and cancer

Bidirectional Kaps display dual functionality – they mediate nuclear import of certain cargos and nuclear export of other cargos. There are only two known human bidirectional Kaps, Exportin 4 (XPO4) and Importin 13 (IPO13).

Exportin 4 mediates nuclear export of eIF5A and SMAD3, and nuclear import of the SOX2 and SRY proteins [121]. XPO4 was identified as a putative tumor suppressor gene in a hepatocellular carcinoma model [122]. XPO4 loss, commonly observed in human hepatocellular carcinoma specimens, contributes to oncogenesis by promoting aberrant nuclear accumulation of it exports cargos eIF5A1, eIF5A2 and SMAD3 [123,124]. It has also been demonstrated that reintroduction of XPO4 into XPO4-deficient tumor cells selectively suppressed tumorigenesis. Similarly, low XPO4 expression correlates with poor prognosis in hepatocellular carcinoma and breast cancer patients.

Importin 13 is another a bidirectional transporter that is responsible for nuclear import of the Mago-Y14 and Ubc9 proteins while facilitating nuclear export of eIF1A [125]. Clinical relevance of IPO13 has been documented in few human disease cases such as asthma and pterygium (corneal abnormality) [126,127]. There is no clear link between IPO13 and cancer other than a correlation study reporting elevated IPO13 mRNA and protein levels in endometriosis and endometrial carcinoma specimens [128].

Summary and perspective

Many studies have connected altered Karyopherin expression, mainly elevated protein levels with occasional lower expression, to cell transformation in many different types of cancer cells. Most studies of aberrant Karyopherin levels in cancer seem to focus on identification of novel diagnostic and prognostic factors for a given cancer. Studies to understand the origin of dysregulated Karyopherin expression/protein levels and the resulting tumorigenic mechanism are rare and badly needed.

Inhibitors are available for only four of the >20 Kap systems: CRM1/XPO1, Kapβ2/TNPO1, the Impα/β heterodimer and Impβ alone [129]. Kap-specific nuclear transport inhibitors are not only beneficial for identification of novel cargos and to gain better understanding for cargo specificity and cellular mechanisms of Kap-dependent nuclear transport systems, but they can also be developed into much needed targeted therapeutic agents. At present, there are very few initial studies focused on small-molecule inhibitors of nuclear import proteins. The only two reported examples are development of INI-43 [74] and its 2-aminothiazole derivative 1 [75] as potential Impβ inhibitors, and aerosol administration of shRNAs for IPO7 knockdown [110]. Specific and well-characterized small-molecule inhibitors of CRM1/XPO1, like the KPT-SINEs, so far are the most successful and potent chemotropic agent that are being tested in clinical trials for a large spectrum of malignancies (https://ClinicalTrials.gov). Evidence of single-agent anti-cancer activity of KPT-SINEs, particularly Selinexor/KPT-330, has been documented in more than 2000 patients across more than 29 privately- and investigator-sponsored clinical trials.

Frequently observed cases of elevated levels of Karyopherins (different molecular origins) suggest that cancer cells may have developed dependence and addiction to the nuclear transport machinery in order to sustain their tumorigenic and increased metabolic needs [130]. This hypothesis is also supported by the synthetic lethality phenotype of CRM1/XPO1 observed in heterogenic tumors and cell lines [26]. Therefore, as more genome-wide cell-based chemical/genetic screens are advanced, it will be important to search for other components of the nuclear transport machinery and cargos that are aberrantly expressed in cancer cells in order to identify novel targets that may be exploited in the development of diagnostic, prognostic markers and therapeutic agents for cancer and other diseases.

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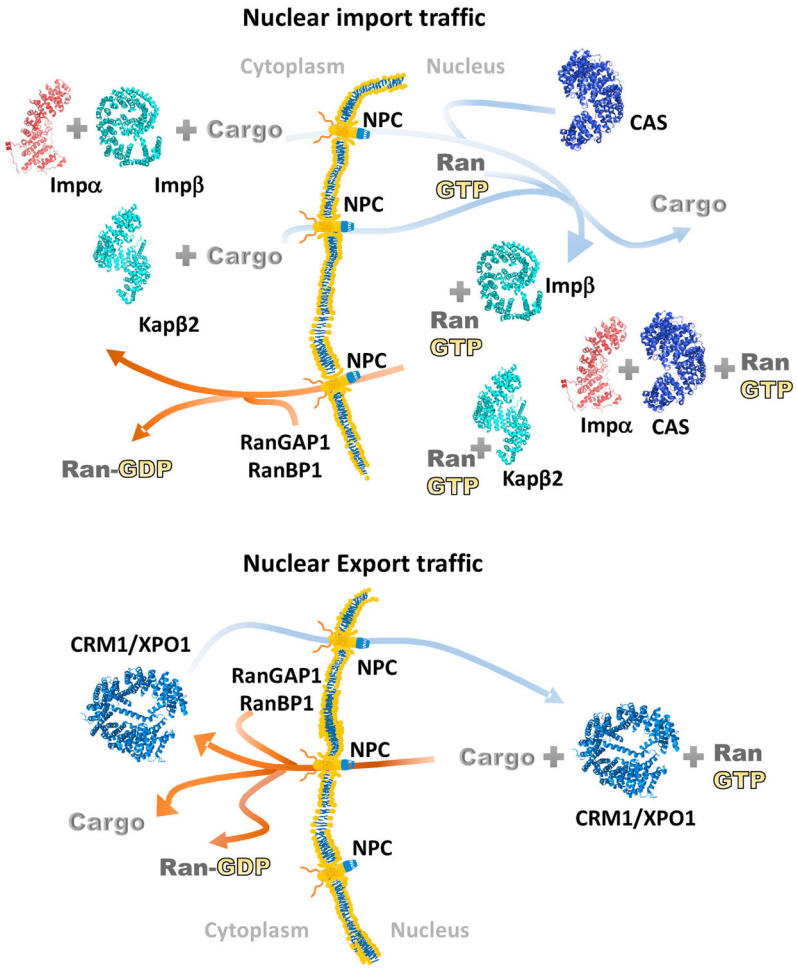

Figure 1. Kap-mediated nuclear import and export

Nuclear import and export of macromolecules occur through the nuclear pore complex (NPC) and are mediated by the Karyopherin family of nuclear transport receptors. Kap-mediated nuclear transport is regulated by the small GTPase Ran, which controls assembly and disassembly of Kap-cargo complexes. The Importins Impβ and Kapβ2 are in cyan, the adaptor protein Impα is in red and the Exportins CRM1/XPO1 and CAS are in blue and dark blue, respectively.

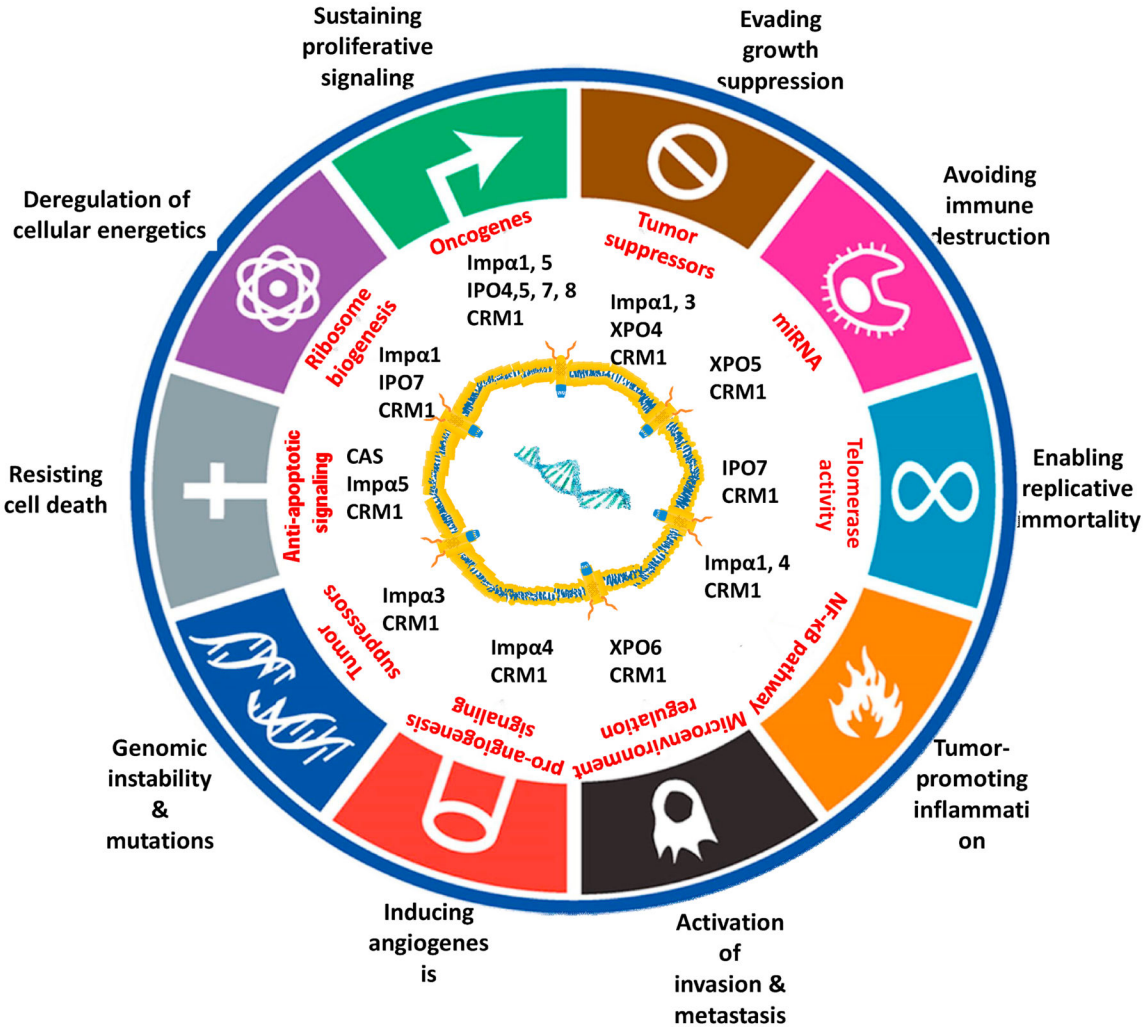

Figure 2. Kap-mediated nuclear transport systems and their impact on the hallmarks of cancer

The ten hallmarks of cancer are shown with associated Kaps that were reported to be involved in cancer onset and progression. The cancer hallmarks diagram is adapted from [20].

Table 1

Human importins and exportins

Karyopherin-β proteins in Nuclear Export			
Human Protein/*Gene Name*	**Aliases***	**Example of cargos****	**Implicated in cancer*****
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-

Karyopherin-β proteins in Nuclear Export			
Human Protein/*Gene Name*	**Aliases***	**Example of cargos****	**Implicated in cancer*****
			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
Human Impα8/Karyopherin subunit alpha 7 (*KPNA7)*	IPOA8	n/a	pancreatic cancer
Bidirectional transporter/Karyopherin beta			
Exportin 4 *(XPO4)*	exp4	Import cargo: Sox2, SRY Export cargo: eIF5A1, eIF5A2, Smad3	hepatocellular carcinoma, breast cancer
Importin 13 *(IPO13*)	IMP13; LGL2; KAP13; RANBP13	Import cargo: Mago-Y14, Ubc9 Export cargo: eIF1A	endometriosis and endometrial carcinoma

*NCBI and HUGO

**Some cargos may have more than one transporter, see detailed lists in [4,66,131]

***Cell culture, *in vivo* or animal/human studies (details in text).