

# Gene Section

## Review

### KPNB1 (karyopherin (importin) beta 1)

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#### Identity

**Other names:** IMB1, IPO1, IPOB, Impnb, NTF97

**HGNC (Hugo):** KPNB1

**Location:** 17q21.32

#### DNA/RNA

##### Description

The KPNB1 gene is constituted of 34163 bp of DNA.

##### Transcription

The transcript variant 1 mRNA (4276 bp) contains 20 exons encoding Importin beta 1 (source: NCBI; nucleotide sequences: GenBank L39793, EMBL-Bank, DDBJ, RefSeq: NM\_002265, CCDS: CCDS11513.1, Vega: OTTHUMG00000036957).

#### Protein

##### Note

**Biological overview:** Importin beta 1 is a prominent member of the karyopherin beta family of transport receptors (reviewed by Ström and Weis, 2001; Mosammaparast and Pemberton, 2004; Chook and Süel, 2011). It was originally identified as an indispensable component for nuclear import

of proteins that function in the nucleus of interphase cells (Moore and Blobel, 1992; Adam and Adam, 1994; Radu et al., 1995; Görlich et al., 1995).

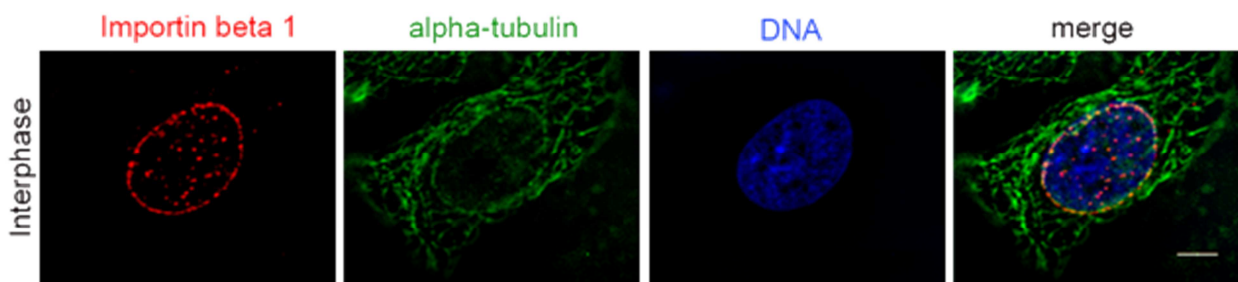
Due to the importance of nuclear transport of proteins (e.g. DNA replication and repair factors, transcription factors, epigenetic regulators, hormone receptors, oncogenes and tumor suppressors; see Fulcher and Jans, 2011), that discovery was awarded the Nobel prize for Biomedicine to Prof. Günter Blobel in 1999 ([www.nobelprize.org/nobel\\_prizes/medicine/laureates/1999/blobel-lecture.html](http://www.nobelprize.org/nobel_prizes/medicine/laureates/1999/blobel-lecture.html)).

The discovery of importin beta 1 as a nuclear import vector overshadowed other functions for some time, but it is now well recognized that importin beta 1 plays multiple roles in cell life and division beyond nucleo-cytoplasmic transport, as will be explained in more depth below:

- at mitotic onset nucleo-cytoplasmic transport ceases and importin beta 1 assumes new functions as an inhibitor of mitotic factors with which it interacts and participating in many mitotic steps (see below). Because these factors are not biologically productive when bound to importin beta 1, the latter is regarded as a negative regulator of mitotic progression (reviewed by Ciciarello et al., 2007; Kalab and Heald, 2008);



Figure 1. Adapted from Cosmic.



**Figure 2. Localization of importin beta 1 by immunofluorescence, in a human HeLa cell in interphase.** Importin beta 1 (red) accumulates in the nucleus and around the nuclear envelope, with a regular, punctuate pattern, typical of the association with nuclear pores. The nucleus is visualized by staining the DNA with 4',6-diamidino-2-phenylindole (DAPI, blue) and the cell shape is depicted by staining the cytoskeleton using an antibody against alpha-tubulin (green). Bar: 5  $\mu$ m.

- Importin beta 1 also regulates the reorganization of the nucleus and the nuclear envelope at mitotic exit prior to the resumption of nucleo-cytoplasmic transport in the next interphase (reviewed by Harel and Forbes, 2004; Güttinger et al., 2009); in this processes it largely operates via nuclear envelope precursors and nucleoporins (NUP), the constituents of nuclear pore complexes (NPCs) that fenestrate the nuclear envelope. Importin beta 1 is therefore a versatile regulator of critical importance to many essential cellular processes and is growingly implicated in the onset of genomic instability in cells in which it is expressed in a deregulated manner.

### Description

The human importin beta 1 protein is composed of 876 aminoacidic residues, with a molecular weight of 97 kDa (Görlich et al., 1995; Chi et al., 1995). It contains 19 HEAT repeats arranged in a superhelical spiral. Each HEAT repeat (about 40-60 aminoacids) consists of A and B helices connected by a short turn, with the A helices localizing to the importin beta 1 outer surface, and the B helices in the inner surface (Cingolani et al., 1999).

Importin beta 1 has a modular flexible structure that enables it to interact with distinct partners in different subcellular compartments in interphase cells, such that each module or domain has a 'topologically' specialized function (reviewed by Ström and Weis, 2001; Conti et al., 2006):

- an extended C-terminal region of importin beta 1 contains sites of interaction with members of the importin alpha subfamily transport receptors (Importin alpha-binding domain, IAB), through which importin beta 1 interacts indirectly with import cargoes (Percipalle et al., 1997; Cingolani et al., 1999). The IAB domain is essential for the formation of import complexes in the cytoplasm, where proteins are synthesized;

- the central region of importin beta 1 contains two major binding sites for phenyl-glycine (FG and FXFG)-rich repeats present in nucleoporins (NUPs), the constituents of nuclear pores (Bayliss et al., 2000; Bayliss et al., 2002; Bednenko et al., 2003); that interaction enables the import complex to traverse the

NPC (Ben-Efraim and Gerace, 2001). Studies with importin beta 1 truncated mutants have mapped the two NUP-binding sites respectively in the N-terminal portion (between HEATs 5 and 7) (Kutay et al., 1997; Chi and Adam, 1997; Bednenko et al., 2003), and near the C-terminal domain (between HEATs repeats 14 and 16; Bednenko et al., 2003) of the central region;

- the N-terminal region of importin beta 1, termed CRIME (for CRM1, Importin beta, etc.), harbours a highly conserved sequence among transport receptors, capable of interacting with the GTP-bound form of the GTPase RAN, which is generated in the nucleus. RANGTP binding to the CRIME domain dissociates the import complex and releases free protein cargoes in the nucleus (Kutay et al., 1997; Vetter et al., 1999).

Importin beta 1 crystals and three-dimensional structures are solved for all domains involved in these interactions (Vetter et al., 1999; Bayliss et al., 2000; Bayliss et al., 2002; Cingolani et al., 1999; Cingolani et al., 2002; Bednenko et al., 2003; Saric et al., 2007; PDB). Structural studies have been essential to clarify that importin beta 1 interacts in a mutually exclusive manner with either importin alpha, or with RANGTP (Moroiaru et al., 1996); this provides the structural basis for the formation of import complex in the cytoplasm (devoid of RANGTP) and for import complex dissociation and cargo release in the nucleus (rich of RANGTP).

### Expression

Although most importin family members are constitutively expressed, emerging evidence shows that expression of at least some importin-coding genes is regulated (Zhang et al., 2000; Hogarth et al., 2006), possibly to adapt to varying requirements for interphase nucleocytoplasmic transport and mitotic division e.g. in development (Vrailas et al., 2006).

The importin beta 1 gene is thought to be expressed in a housekeeping, ubiquitous manner in human tissues, yet has highest expression in actively proliferating tissues, e.g. lymphocytes, tumors, testis and undifferentiated cells (Quan et al., 2008). Elevated importin beta 1 expression in some cancer cell lines has recently been demonstrated to reflect increased transcription due to deregulated activity of the E2F/pRb

pathway, involving the transcriptional factor E2F and the Retinoblastoma tumor suppressor protein (van der Watt et al., 2011).

### Localisation

The localization of importin beta 1 protein is related to its function. In interphase, when it acts in nuclear import of proteins, it is particularly abundant at the nuclear envelope, with a punctuate pattern corresponding to NPCs (figure 2). This localization is particularly evident after treatment with mild detergents that remove soluble importin beta 1.

At mitotic onset, when the nuclear envelope breaks down, importin beta 1 associates with mitotic microtubules, as determined in co-sedimentation assays; importin alpha also co-sediments with mitotic microtubules. The association of both importins alpha and beta 1 with the mitotic spindle microtubules requires the minus end-directed motor dynein (figure 3; Ciciarello et al., 2004). Due to the minus-end directed movement of dynein, the importin alpha/beta dimer can transport NLS-containing spindle regulatory factors to the poles, and thus regulate the mitotic apparatus organization and function.

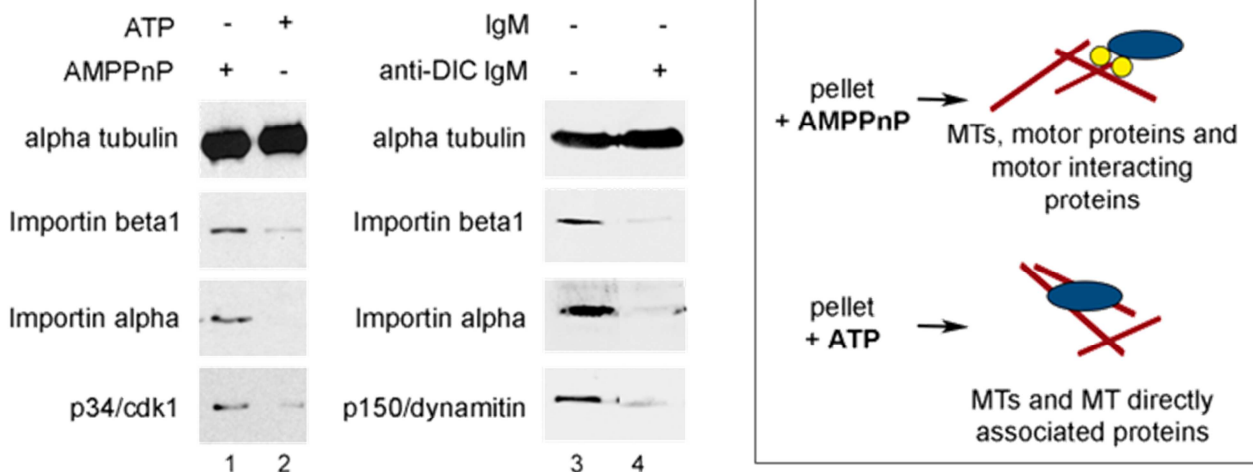
By immunofluorescence staining, importin beta 1 co-localizes with the mitotic spindle and accumulates to the spindle poles (figure 4, top and middle rows), consistent with the microtubule association assay (figure 3). In early telophase, when chromosome segregation is complete, importin beta 1 dissociates from the microtubules and relocalizes around the reforming nuclei (Ciciarello et al., 2010; figure 4 bottom row).

### Function

Importin beta 1 is required for cell survival. RNA interference assays to analyse the requirement for single importin family members in HeLa cells (Quensel et al., 2004) showed that importin beta 1 could not be fully silenced after prolonged RNA interference (seven days), implying that it is very stable at either the mRNA or the protein levels. Moreover, after interference, importin beta 1 showed the weakest reduction in abundance compared to all other tested importins alpha types, suggesting that cells are less tolerant to the loss of importin beta 1 compared to any other member, such that cells in which importin beta 1 was effectively silenced were counterselected. Indeed, importin beta 1 downregulation caused a significant decrease in the number of viable cells, with significant induction of cell death (Quensel et al., 2004).

#### Importin beta 1 as the universal vector for interphase nuclear import

As recalled above, the first identified function of importin beta 1 was protein import in interphase cell nuclei (Görllich and Kutay, 1999). Most proteins that function in the nucleus carry one or more nuclear localization signal (NLS, short stretches of charged aminoacidic residues), recognized by a member of the importin alpha subfamily of transport receptors (adaptors), that interact with importin beta 1 through the IAB domain. Importin beta 1 can heterodimerise with different proteins of the importin alpha subfamily that confer specificity in binding cargoes with subtle NLS sequence variations.



**Figure 3. Sedimentation assay of mitotic microtubules (MTs) after centrifugation through a sucrose gradient; tubulin monomers and dimers remain in the supernatant.** Microtubule-associated proteins were analyzed by Western immunoblotting of the MT pellet, revealed by alpha-tubulin antibody. As schematized on the right, ATP addition recovers proteins that associate with MTs directly: under these circumstances, no importin beta 1 signal is detected in the MT pellet (Western panel, lane 2). The addition of non-hydrolyzable AMPPnP analogue recovers proteins that associate with MTs via motors: under these conditions, both importin beta 1 and importin alpha co-sediment with the MT pellet, as does the mitotic kinase p34/cdk1 (lane 1). To identify the specific motor protein that bridges importin alpha and beta 1 to mitotic MTs, the pellet was incubated with antibody to the dynein intermediate chain (anti-DIC), which sequesters dynein: under these conditions, importin alpha and beta 1 detach from the MT pellet (lanes 4), as does dynamitin, whereas a non-specific IgM has no effect (lane 3). These assays indicate that importin alpha and beta 1 interact with mitotic MTs via dynein. Details in Ciciarello et al., 2004.

This leads to the formation of a trimeric complex (NLS cargo/importin alpha/importin beta) in the cytoplasm (classical nuclear import pathway). Importin beta 1 can also interact with particular cargoes directly, without the mediation of an importin alpha adaptor ("direct" import pathway); the latter is faster yet more uncommon than the classical heterodimer-mediated pathway (Harel and Forbes, 2004; Riddick and Macara, 2007). Most protein cargoes, many of which are relevant to cancer (e.g. c-Myc, pRb, others listed in Marfori et al., 2011), are imported through an importin alpha adaptor, and some through direct interaction with importin beta 1 (e.g. cyclin B1, Smad3, c-Jun, PP2A; other examples in Chook and Süel, 2011). Importin beta 1 also binds Snurportin 1 as an adaptor that binds the m3G-cap of small nuclear RNAs (snRNAs) to import snRNPs (Mitrousis et al., 2008).

Once the classical or direct import complex assembles in the cytoplasm, importin beta 1 drives its translocation across the nuclear pore into the nucleus. Importin beta 1 is thought to traverse the NPC by alternating the binding of its NUP-binding domain to different NUPs, positioned in different NPC regions and endowed with progressively increasing affinity for importin beta 1 from the cytoplasm towards the nucleoplasm (Ben-Efraim and Gerace, 2001).

Upon entry in the nucleus, the GTPase RAN, which is abundant in the nucleus in the GTP-bound form, interacts with the importin beta 1 CRIME domain; this interaction dissociates the import complex and releases free, biologically productive protein cargoes in the nucleoplasm, thus terminating the import process. RANGTP and importin beta 1 exit the nucleus together as a complex and dissociate in the cytoplasm (where RANGTP is hydrolyzed to RANGDP), such that a novel import cycle can restart.

#### **Importin beta 1 as a global regulator of mitosis**

Importin beta 1 plays key roles in mitosis. For clarity, we will separately summarize importin beta 1 roles in a) mitotic spindle assembly and spindle pole formation, b) microtubule/kinetochore interactions and chromosome segregation, c) progression to mitotic completion, and d) mitotic exit.

**a) Regulation of mitotic spindle assembly.** Early indications that importin beta 1 regulates mitotic spindle formation came from studies with *Xenopus* oocyte-derived extract systems, a classical model for spindle assembly due to its high content of spindle assembly factors (SAFs). The simple addition of importin beta 1 to the extract was found to preclude the formation of the mitotic spindle, but RANGTP addition reversed the inhibition (Wiese et al., 2001; Nachury et al., 2001). This led to a simple model, in which importin beta 1 inhibits the SAFs that interact with it, whereas RANGTP releases SAFs in a free, biologically active form with the same mechanisms operating in the classical import pathway. Indeed, two major spindle organizers, i.e. TPX2 (targeting protein for Xklp2;

Gruss et al., 2001) and NuMA (Nuclear and mitotic apparatus protein, Wiese et al., 2001; Nachury et al., 2001), both contain NLS signals and are therefore sensitive to importin beta 1-dependent inhibition.

The spindle inhibitory role of importin beta 1 is conserved across species, in spite of significant biological differences between female germ cell-derived meiotic systems (acentrosomal systems, in which the spindle formation is driven by microtubules originating from a small chromatin volume, standing out as a discrete entity within a large cytoplasm) and mammalian somatic mitotic cells (where the spindle microtubules are predominantly nucleated from centrosomes, with a small contribution from kinetochore-originating microtubules O'Connell and Khodjakov, 2007). Importin beta 1 microinjection in Ptk1 rat-kangaroo cells caused the formation of aberrant, multipolar spindles and defective chromosome alignment, attributable to NuMA inhibition (Nachury et al., 2001). Importin beta 1 overexpression also yielded multipolar spindles with fragmented poles in human HeLa cells, such that chromosome could not congress along a bipolar axis at metaphase (Ciciarello et al., 2004; Kalab et al., 2006). Co-expression of exogenous TXP2, or of any NLS sequence, restored bipolar spindle formation, presumably by "titrating out" the inhibitory effect of importin beta 1 (Ciciarello et al., 2004). Importin beta 1 also suppresses the microtubule-nucleation potential of kinetochores in human cells (Tulu et al., 2006; Torosantucci et al., 2008; O'Connell et al., 2009).

Several more microtubule-regulatory factors involved in spindle formation or function were subsequently found to be inhibited when importin beta 1 binds them, either directly or indirectly, e.g.: the microtubule minus-end binding factor MCRS1 (Meunier and Vernos, 2011); the kinesin XCTK2 (Ems-McClung et al., 2004); the chromokinesin Kid (Trieselmann et al., 2003; Tahara et al., 2008); the CRB3 member of the Crumbs transmembrane protein family, that binds the membrane compartment of cilia and spindle poles (Fan et al., 2007); maskin, a member of the TACC (transforming acidic coiled coil) protein family (Albee et al., 2006); the microtubule-binding proteins NuSAP (Nucleolar and spindle-associated protein; Ribbeck et al., 2006), HURP (hepatoma up-regulated protein; Silljé et al., 2006) and Xnf7 (Maresca et al., 2005); Rae 1, an RNA-binding and mitotic spindle-associated factor (Blower et al., 2005). Many of these factors are implicated in generating genomic instability in cancer cells and the list is growing. These studies indicate that importin beta 1 physiologically inhibits the unscheduled, premature or ectopic activity of mitotic spindle factors until RANGTP reverses the inhibition. Thus, importin beta and RANGTP ensure temporal and spatial control of spindle formation with the same mechanisms operating in protein nuclear import.

**b) Chromosome congression, alignment and segregation.** Once the mitotic spindle is assembled, importin beta 1 regulates kinetochore functions and attachment to microtubules. These functions do not necessarily involve import-type complexes with NLS factors: indeed, assay of importin beta 1 truncated mutants showed that the NUP-binding domain alone can inhibit these processes in a dominant negative manner, while the IAB and NLS-interacting domain is dispensable for these effects (Roscioli et al., 2012).

This role is associated with the regulated delivery of a complex comprising NUP358-RANBP2, a large NUP with SUMO E3 ligase activity, and SUMO-conjugated RANGAP1, to kinetochores (Roscioli et al., 2012). SUMO conjugation to RANGAP1 requires RANBP2 (Joseph et al., 2002; Joseph et al., 2004), with which importin beta 1 interacts along the spindle microtubules (Roscioli et al., 2012). In a normal mitotic progression, a fraction of RANBP2 and SUMO-conjugated RANGAP1 are recruited to kinetochores when the latter attach to microtubules (Joseph et al., 2002; Joseph et al., 2004) in a process requiring CRM1. The process ultimately modifies the RAN status at kinetochores and is important for kinetochore maturation and stable attachment to microtubules during chromosome segregation (Arnaoutov and Dasso, 2003). Importin beta 1 overexpression inhibits the process (Roscioli et al., 2012), suggesting that its physiological role is to prevent premature RANGAP1 delivery, and hence premature RANGTP hydrolysis, to kinetochores. Importin beta 1-dependent negative control also applies to the kinetochore localization of CENP-F, a factor involved in stabilization of microtubule/kinetochore interactions (Roscioli et al., 2012).

**c) Mitotic completion.** When chromosome segregation begins, timely waves of proteolysis eliminate factors required in early mitotic stages, such that the cell can progress towards mitotic completion. Some importin beta 1-interacting proteins required for spindle function and microtubule stabilization, i.e. HURP and NuSAP, are among substrates of the Anaphase-Promoting Complex, an E3 ubiquitin ligase that targets cell cycle proteins for degradation by the 26S proteasome. Their degradation requires release from importin beta 1 by RANGTP: thus, importin beta 1 regulates mitotic progression by regulating the timely degradation of key spindle factors (Song and Rape, 2010).

Additional evidence implicates importin beta 1 in progression through late mitosis: indeed, the Repo-Man protein, which recruits the phosphatase PP1- $\gamma$  onto mitotic chromatin at anaphase and participates to

histone dephosphorylation, targets importin beta 1 as well as other proteins (e.g. NUP153, the most distal NUP on the NPC nuclear side) to anaphase chromatin (Vagnarelli et al., 2011). This binding occurs via direct interaction between Repo-Man and importin beta 1. Repo-Man binding to the chromosome periphery is thought to provide anchoring sites for importin beta 1, potentially marking sites where NPCs will eventually reassemble.

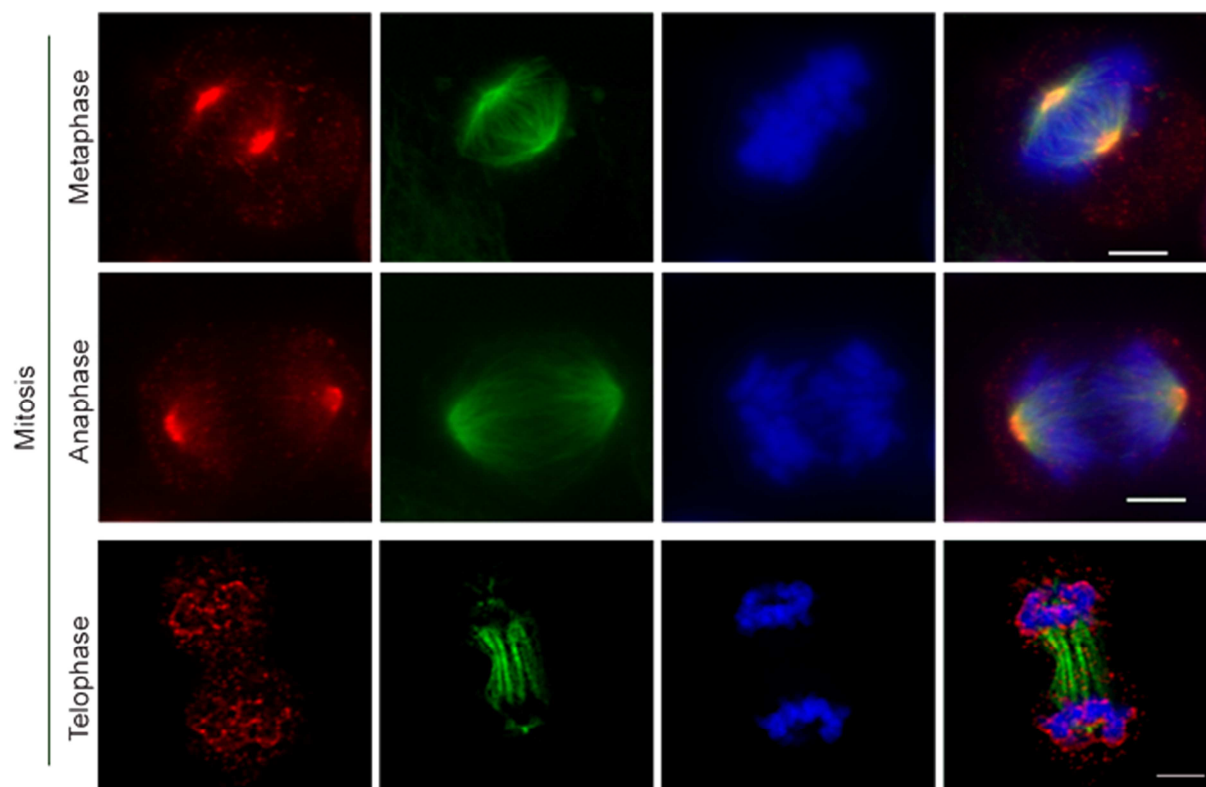
Further evidence indicate an intriguing link between importin beta 1 and protein phosphatases at mitotic completion. A high-throughput RNA interference screening in HeLa cells identified the PP2A phosphatase as a major regulator of mitotic spindle disassembly and nuclear import resumption (Schmitz et al., 2010).

Noteworthy, importin beta 1 is part of a complex with PP2A; importin beta 1 depletion by RNA interference delayed the anaphase-G1 transition and hindered mitotic exit. Thus, PP2A and importin beta 1 cooperate in regulation of post-mitotic processes presumably via regulated dephosphorylation of key substrates in late mitotic stages.

**d) Mitotic exit and nuclear reformation.** When cells exit mitosis, importin beta 1 regulates the reformation of a functional nuclear envelope fenestrated by NPCs in order to reestablish nucleocytoplasmic transport and, hence, nuclear localization of transcription, epigenetic and regulatory factors in the following cell cycle. Importin beta 1 detaches from microtubules in late anaphase/early telophase: at this point, the microtubules reorganize to form the midbody while importin beta 1 relocates around the periphery of the decondensing chromatin (Ciciarello et al., 2010; figure 4) and regulates critical processes therein:

- human importin beta 1 protein addition to a *Xenopus* nuclear reconstitution system negatively regulates both the membrane fusion events required for reorganizing the double-layered nuclear envelope around chromatin (RANGTP-reversible), and the assembly of NPCs into fused nuclear membranes (not reversible by RAN and involving FG-containing NUPs) (Harel et al., 2003).

Using a similar approach Rotem et al. found that importin beta 1 forms a high-molecular-weight complex with NUP107-160 (a subcomplex of the NPC comprising eight NUPs), and ELYS, an adaptor between the NUP107-160 complex and chromatin; when added in excess, importin beta 1 inhibits NUP107-160/ELYS complex binding to chromatin, yielding abnormal nuclei with aberrantly organized, non functional envelopes (Rotem et al., 2009).



**Figure 4. Importin beta 1 localization in human HeLa cells during mitotic progression.** Importin beta 1 (red) accumulates at mitotic spindle microtubules and poles until anaphase; later in telophase it relocalizes around the segregating chromatin, where the nuclear envelope will reform. An antibody against alpha-tubulin (green) stains the spindle microtubules and the midbody in telophase. DAPI stains chromosomes. The merged pictures represent the overlay of all three images. Bars: 5  $\mu$ m.

- importin beta 1 also regulates the repositioning of NUPs around the decondensing chromatin in intact mammalian telophase cells (Ciciarello et al., 2010). Lu et al. reported that in human HeLa cells importin beta 1 interacts with the lamin B receptor, a chromatin- and lamin B-binding protein in the inner nuclear membrane, and that this interaction targets membrane precursor vesicles to chromatin at mitotic exit (Lu et al., 2010).

To sum up, importin beta 1 is a multifunctional regulator, acting at diverse stages of mitosis with specificity:

- in space (at the mitotic spindle microtubules and poles, at the microtubule-kinetochore interface and around the decondensing chromatin);
- in time (spindle formation in early mitosis, microtubule stability and attachment to kinetochores at metaphase, chromosome segregation in late mitosis, mitotic completion and transition to the next interphase);
- in target selectivity (NLS-containing factors, via formation of import-type complexes; NUPs, as well as some microtubule regulators and some protein phosphatases, via direct interaction).

Although we do not yet fully know which specific regulatory switches underlie these diversified functions

of importin beta 1 during mitotic progression, it is clear that a common theme is the intracellular abundance of importin beta 1 over its target factors, which is critical to the correct unfolding of all mitotic processes in which importin beta 1 participates. Through these activities, importin beta 1 can contribute to determine mitotic errors and genomic instability in cells in which it is expressed in a deregulated manner.

### Homology

Human importin beta 1 belongs to the karyopherin beta family of nuclear transport factors, within which 15 evolutionarily derived subfamilies can be distinguished according to their Uniprot gene names (Quan et al., 2008; Chook and Süel, 2011; O'Reilly et al., 2011). Karyopherin beta family members share similar molecular weights (90-150 kDa) and isoelectric points (pI: 4.0-5.0), low sequence identity (10-20%) but all contain helical HEAT repeats.

The karyopherin beta family is highly conserved across Eukaryota, from *Saccharomyces cerevisiae* (14 members) to humans (19 members), suggesting conservation of basic transport mechanisms, though with adaptation to specific cellular / organism contexts (Chook and Süel, 2011; O'Reilly et al., 2011) and

orthologs have been identified in *Caenorhabditis elegans*, *Drosophila melanogaster*, *Danio rerio*, *Xenopus tropicalis*, *Gallus gallus*, and *Mus musculus* (Quan et al., 2008). Remarkably, there is higher homology between orthologues across species than between paralogues in the same species (Quan et al., 2008). In particular, human importin beta 1 belongs to the IMB1 subfamily, named Kap95p in *Saccharomyces cerevisiae* (Chook and Süel, 2011; O'Reilly et al., 2011) and orthologs have been identified in *Caenorhabditis elegans*, *Drosophila melanogaster*, *Danio rerio*, *Xenopus tropicalis*, *Gallus gallus*, and *Mus musculus* (Quan et al., 2008).

## Mutations

### Note

No spontaneous mutations are reported in human cells or tissues. Importin beta 1 mutants (i.e. point mutations or deletion mutants) have been engineered in several laboratories to study the role of different domain in various cellular processes.

## Implicated in

### Cervical cancer

#### Note

Cervical cancer is the second most common cancer among women worldwide. Importin beta 1 is overexpressed in cervical cancer patient specimens and cell lines, often in combination with CRM1, and is critical for cancer cell survival and proliferation (van der Watt et al., 2009).

Gene expression profiling in normal and cervical cancer biopsies by microarray analysis and quantitative RT-PCR revealed highly significant overexpression of importin beta 1 compared to normal cervical tissue ( $p < 0.0005$ ). By immunofluorescence on tissue sections, importin beta 1 protein abundance was confirmed to be higher compared to healthy specimens (p

The same group also demonstrated that elevated importin beta 1 expression in cervical cancer correlates with altered transcriptional regulation, associated with deregulated activity of E2F/pRb (retinoblastoma) pathway (van der Watt et al., 2011). Promoter elements required for high importin beta 1 transcription in transformed and cervical cancer cells map to the -637 to -271 importin beta 1 promoter region.

Bioinformatic analysis of this region identified five putative binding sites for E2F, three of which were proved to be functional in site-directed mutagenesis assays (van der Watt et al., 2011).

E2F activity is well-known to be deregulated in cervical cancer cells due to inactivation of its negative control partner, pRb, by the E7 oncoprotein of HPV, leading to deregulated expression of pRb target genes.

In summary, the E2F sites in the importin beta 1 gene promoter up-regulate importin beta 1 transcription, largely due to E7-dependent inhibition of pRb, and

E2F-dependent promoter activation is more pronounced in transformed and cancer compared to normal cells.

### Ovarian cancer

#### Note

Importin beta 1 mRNA and protein levels are elevated in ovarian cancer cell lines and transformed ovarian cells compared to normal primary ovarian epithelial cells (Smith et al., 2010).

### Transformed fibroblasts

#### Note

Importin beta 1 protein levels are higher in transformed fibroblast cell lines (SVWI38 and CT-1) compared to normal fibroblasts (WI38), suggesting that up-regulation of importin beta 1 is not confined to cervical cancer and may be associated with cellular transformation in general (van der Watt et al., 2009).

### Other cancer types

#### Note

Increased levels of importin beta 1 are found in several transformed cells lines compared to their respective untransformed counterparts, and these increased importin beta 1 levels contribute towards increased rates of nuclear import in transformed cells (Kuusisto et al., 2012).

A genome-wide siRNA screen identified importin beta 1 as a gene necessary for the survival of both lung and head and neck cancer cell lines, highlighting its importance in cancer cells (Martens-de Kemp et al., 2013).

Other instances of cancer tissue profiling of particular cancer types, in which importin beta 1 is differentially expressed (i.e. overexpressed or underexpressed) compared to matched non cancer samples are listed in Rensen et al. 2008. More recent datasets illustrating differential expression in cancer can be found in [www.oncomine.org](http://www.oncomine.org).

## To be noted

#### Note

The association of importin beta 1 with cancer is reviewed in van der Watt et al. 2013, and importin beta 1 is implicated as a potentially useful anti-cancer target (van der Watt et al., 2013).

Moreover, since importin beta 1 inhibition prevents the nuclear localization of its numerous cargo proteins, this could hypothetically be exploited for therapeutic purposes. For example, its inhibition prevents the nuclear translocation of death receptor 5 (DR5), thereby increasing the sensitivity of cancer cells to TRAIL-induced cell death (Kojima et al., 2011).

In synthesis, the potential of importin beta 1 in generating genomic instability in cancer development, and, when dramatically down-regulated, in mislocalizing regulators of cell death, has generated increasing interest in the design of selective inhibitors.

Karyostatin 1A, a small molecule that binds importin beta 1, has been described to specifically inhibit importin  $\alpha/\beta$  nuclear import by disrupting the interaction between importin beta 1 and RAN (Hintersteiner et al., 2010). A more recent study has led to the synthesis of a specific importin beta 1 small molecule inhibitor, called importazole, designed to alter the interaction with RANGTP, with potential for studies of the RAN pathway and for possible therapeutic applications (Soderholm et al., 2011).

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