



Review

Nuclear transport factors in neuronal function

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ABSTRACT

Active nucleocytoplasmic transport of macromolecules requires soluble transport carriers of the importin/karyopherin superfamily. Although the nuclear transport machinery is essential in all eukaryotic cells, neurons must also mobilise importins and associated proteins to overcome unique spatiotemporal challenges. These include switches in importin α subtype expression during neuronal differentiation, localized axonal synthesis of importin β 1 to coordinate a retrograde injury signaling complex on axonal dynein, and trafficking of regulatory and signaling molecules from synaptic terminals to cell bodies. Targeting of RNAs encoding critical components of the importins complex and the Ran system to axons allows sophisticated local regulation of the system for mobilization upon need. Finally, a number of importin family members have been associated with mental or neurodegenerative diseases. The extended roles recently discovered for importins in the nervous system might also be relevant in non-neuronal cells, and the localized modes of importin regulation in neurons offer new avenues to interrogate their cytoplasmic functions.

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1. Introduction

Active nucleocytoplasmic transport of macromolecules across the double lipid bilayer of the nuclear membrane occurs through channels formed by nuclear pore complexes (NPC) [1].

This process involves the specific recognition of cargoes by soluble transport carriers of the importin/karyopherin superfamily, that bind nuclear localization signals (NLS) in cargoes either directly or through an adaptor protein and escort them through the NPC [2,3]. In the best understood ("classical") nuclear import pathway, an importin α binds the NLS within the cargo protein directly. Its affinity for NLS is increased by interaction with an importin β , which then facilitates transport of the complex through the nuclear pore (Fig. 1). Formation and dissociation of the importin α/β complex is

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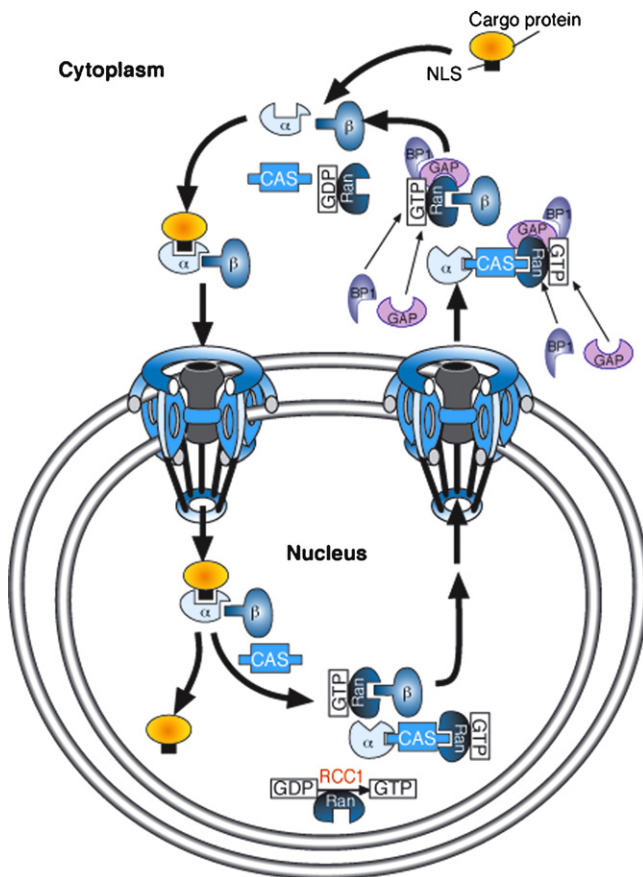


Fig. 1. Schematic model of the classical nucleocytoplasmic transport mechanism. Importin-mediated nucleocytoplasmic transport is regulated by a gradient of RanGTP in the nucleus versus RanGDP in the cytoplasm, defined by nuclear localization of the RanGEF RCC1, and cytoplasmic localization of RanBP1 and RanGAP, the RanGTP displacing and hydrolyzing facilitators. RanGTP exits the nucleus in complex with importin β or with CAS and importin α , and encounters RanBP1 and RanGAP, which catalyze its dissociation and hydrolysis to the GDP-bound form. The importins are then free to associate with each other to form a high affinity carrier for NLS-containing cargo proteins for import to the nucleus.

regulated by the small GTPase Ran, which controls the directionality of transport [4,5]. A number of additional import pathways have been identified for transport substrates with NLS' that are distinct from the "classical" sequence, and that bind directly and specifically to different importin β 1 homologs (e.g. [6]). Although the nuclear transport machinery is essential in all eukaryotic cells, the unique morphology of neurons highlights additional roles for these molecules that are the focus of this review.

2. Importins in neurons and in neuronal differentiation

The polarized morphology of nerve cells, with processes extending distances that can exceed the diameter of the cell body by many orders of magnitude, imposes a requirement for efficient anterograde and retrograde transport to connect between dendritic and axonal terminals and the cell soma [7]. In addition to 'conventional' roles of nucleocytoplasmic transport systems in regulation of cell body centered processes, neurons mobilise karyopherins and associated proteins to overcome unique spatiotemporal challenges to development, growth, and survival [8,9].

Long-range signaling from axon terminals to the nucleus is critical during development, when the transcriptional profile of a neuron is modified by signals received from distal growth cones as they navigate and contact potential partners [10]. In the adult brain, the requirement for transcription during long-lasting forms

of synaptic plasticity requires signal transport from synapses to the nucleus [9]. Injury and damage activate diverse signaling mechanisms that transmit information from distal compartments to the cell body and nucleus of neurons [11–13]. Finally, perturbations or mutations of nucleocytoplasmic transport molecules have been linked to a range of diseases in the nervous system. Below we detail the involvement of karyopherins and associated molecules in these diverse aspects of neuronal physiology, starting with regulation of importin expression in neural differentiation.

2.1. The effect of importin α subtypes and cargo specificity

Importins α s and β 1 are expressed in a wide range of mammalian tissues and cell lines, with expression levels of individual α isoforms changing during cell differentiation [14]. Kawata and colleagues recently performed in situ hybridization analyses to examine the mRNA expression patterns of importin α isoforms and importin β 1 in the mouse central nervous system (CNS) at adult and early postnatal stages [15]. They found moderate to high expression levels of importins α 3, α 5, α 7 and β 1 throughout the brain and spinal cord. Importin α 4 revealed a more restricted pattern of expression, while importin α 1 was found at low expression levels throughout the brain and spinal cord, and at moderate expression levels in the olfactory bulb and reticular system. In the adult, importin α and β 1 mRNAs were predominantly expressed in neuronal cells of the hippocampus and in the cerebral cortex, while their expression levels in glial cells were relatively low [15]. Yoneda and colleagues showed that mouse embryonic stem cells must abrogate expression of importin α 1 and up-regulate expression of importin α 5 in order to import Brn2, a transcription factor cargo critical for neuronal differentiation in vitro (Fig. 2A) [16]. In addition, the same group reported that importin α 5 was highly expressed in developing and adult mouse brains, whereas the expression of importin α 1 was low, suggesting that their in vitro findings may apply in vivo. Indeed, the prediction would be that a mouse lacking importin α 5 should reveal drastic brain phenotypes. However, importin α 5 knockout mice generated by Bader, Kohler and colleagues were born in normal Mendelian ratios, were viable and fertile, and did not show any obvious morphological or behavioural abnormalities [17]. Following this study, Yasuhara and Yoneda found that importin α 4 and α 7 are also able to import higher concentrations of Brn2, although the import efficiencies were very low [18]. Importin α 1 could not mediate Brn2 import under any of the experimental conditions, whereas importin α 5 efficiently imported Brn2 under all assay conditions. These results raise the possibility that importin α 4 can substitute for depleted importin α 5 and compensate for importin α 5 function during neuronal development [18]. Furthermore, a very recent study has reported changes in importin α 4 protein expression during motor neuron differentiation [19]. Taken together, these findings suggest that changes and switches in importin α subtype expression may be important in development of diverse neuronal populations. The redundancy in the system, along the fact that different importin α subtypes have high specificity for particular cargoes, enables differential modulation of nuclear import efficiencies according to need.

3. Importins in axonal injury signaling

In the peripheral nervous system, regeneration following axonal injury requires new gene transcription in the soma, and this is dependent on the transport of injury signals from the lesion site to the cell body [11–13]. Early work in Aplysia showed that some of the retrograde injury signals were NLS-targeted proteins [20]. Hanz et al. then provided evidence that importins play a crucial role in the transmission of such retrograde injury signals in rodent sciatic

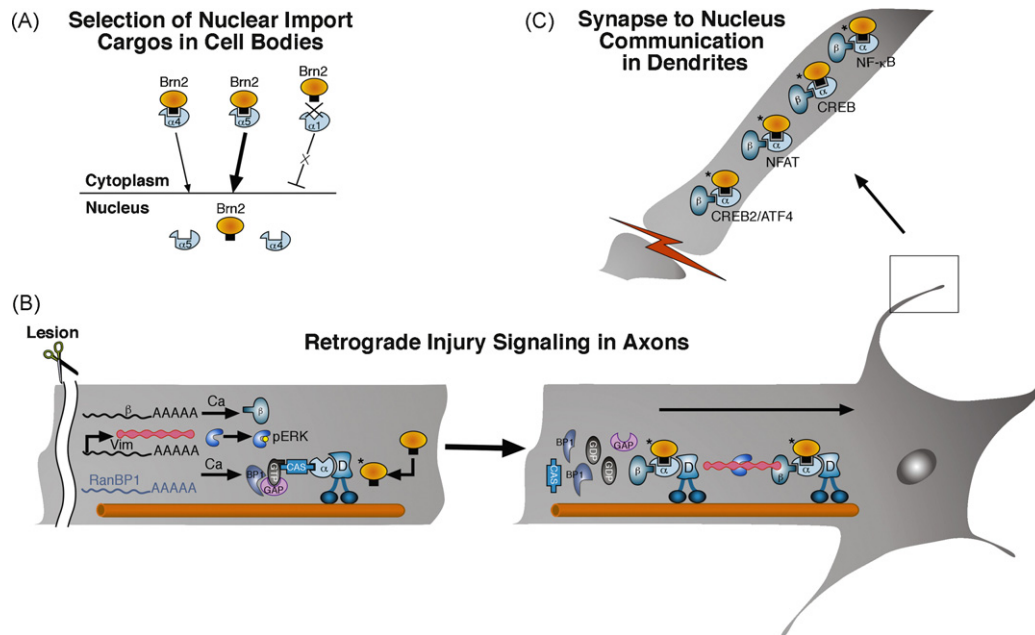


Fig. 2. Diverse roles for importins and associated molecules in neurons. (A) Selection of nuclear import cargos in cell bodies. Abrogated expression of importin α 1 and up-regulation of importin α 5 and/or α 4 during neuronal differentiation switch the cell's capacity to import the transcription factor Brn2 into the nucleus (Refs. [15–17]). (B) Retrograde injury signaling in axons. Importin α protein is constitutively associated with the retrograde motor dynein (D) in axons, whereas importin β 1, vimentin and RanBP1 are normally present in transcript form. Upon lesion, local translation of these mRNAs leads to up-regulation of the corresponding proteins. Newly synthesized RanBP1 stimulates dissociation of RanGTP and RanGAP synergized hydrolysis, thus allowing formation of a cargo-binding complex of importin α with de novo synthesized importin β 1. Vimentin is transported in the retrograde injury-signaling complex via a direct interaction with importin β (Refs. [20–23,53]). (C) Synapse to nucleus communication in dendrites. Assorted signals can be actively transported from terminals to the cell body by importin-mediated transport systems, thus linking synaptic signals to nuclear responses (Refs. [38,39,43–46]).

nerve [21]. A number of importin α s were found in sensory axons in both control and injured sciatic nerve, in constitutive association with dynein motor proteins. In contrast, importin β 1 protein was not detectable under normal conditions in sciatic nerve axoplasm, although transcripts encoding importin β 1 were found intermittently distributed in a granular pattern throughout the axons. Upon lesion, this mRNA was rapidly translated into importin β 1 protein, leading to the formation of importin α/β heterodimers bound to the retrograde motor dynein. Retrograde transport of fluorescently labeled NLS peptides was indeed observed in lesioned sciatic nerve, and introduction of excess NLS peptides into lesioned DRG axons inhibited or delayed both in vitro regenerative and in vivo conditioning lesion responses (Fig. 2B). These data suggest that in parallel with local axonal synthesis of importin β 1, local activation of NLS-bearing signaling proteins creates a signaling cargo that binds to the α/β high affinity NLS binding site, thus accessing the retrograde transport pathway [21].

3.1. Vimentin role in axonal injury

A proteomics-driven search for cargo molecules for the mechanism outlined above identified a number of candidates, most prominently the type III intermediate filament vimentin [22,23]. Vimentin is generated in injured nerve axoplasm by local translation and calpain-mediated cleavage, followed by direct binding of phosphorylated axoplasmic Erk1 and Erk2 to the vimentin cleavage fragment. Vimentin also binds directly to importin β 1, thereby linking activated Erks to importin-mediated retrograde transport [23]. Strikingly, the vimentin–Erk complex protects Erk from dephosphorylation, and since the interaction is calcium dependent the signal generated may provide information both on the injury and on the degree of damage as reflected by sustained calcium elevation [24]. Thus, even though Erk1 and Erk2 do not contain classical NLS sequences, they utilise importins for retrograde transport after

nerve injury via a series of protein–protein interactions linking Erk, vimentin, importin β , importin α , and dynein.

3.2. JAK–STAT3 in retrograde signaling

Other studies have identified a number of transcription factors in peripheral nerve axons, that might be implicated in retrograde signaling [13]. Peripheral nerve injury causes up-regulation of the interleukins LIF and IL-6 and the growth factor ciliary neurotrophic factor (CNTF), all of which activate the JAK–STAT3 signaling pathway. Liu and Snider showed an increase in STAT3 activation in injured sensory neurons, and were able to attenuate the injury response by application of a JAK inhibitor in vitro [25]. A later study by MacLennan and colleagues demonstrated that peripheral nerve lesion leads to a very rapid activation of STAT3 in axons at the lesion site in sciatic nerve in vivo [26]. This response increases during the first 24 h after injury and extends back to neuronal cell bodies over a time course consistent with the possibility that axonal STAT3, activated at the injury site, acts as a retrograde signaling transcription factor [26]. STAT3 has been reported to interact with a number of importins and associated molecules for nucleocytoplasmic transport [27–31], so that it is tempting to speculate that it traffics in axons via importin/dynein-mediated transport as well. This hypothesis still requires experimental confirmation.

3.3. Other modalities for retrograde injury signaling

Finally in this context, one should bear in mind that retrograde injury signals may utilise adaptors other than importins for their retrograde transport. In particular, retrograde signals from the jun kinase (Jnk) network connect to dynein via an endosome carrier regulated by Jnk interacting protein (JIP) scaffolds [32,33]. Also, there are diverse modalities of retrograde signaling that are not necessarily dependent on importins, such as signaling endosomes

for neurotrophic factors [7,34]. Importin-mediated retrograde injury signaling is therefore one of a spectrum of mechanisms for long distance communication within neurons.

4. Importins in neuronal plasticity and pathfinding

In addition to retrograde injury signaling, importin-mediated transport plays a role in connecting neuronal terminals and synapses to the cell body in development, axon guidance, and plasticity [9]. The formation of neuronal circuits during development relies on precise spatial and temporal control of axon guidance and synapse formation. Although a significant fraction of guidance decisions are made locally at the neuronal growth cone, transcription factors are involved in coordinating neuronal responses to guidance cues [35], indicating that communication between terminals and cell bodies is crucial for correct wiring of the nervous system. A genetic screen in the *Drosophila* visual system showed that importin $\alpha 3$ is required to prevent axon terminals of a specific neuronal subtype from overlapping with the terminals of adjacent neurons in the optic lobe. This function requires the activin signaling pathway and is dependent on the transcription factor dSmad2, and on retrograde transport from the growth cone to neuronal nuclei [36]. Earlier studies in the *Drosophila* eye had shown that expression of a truncated importin β , designed to act as a dominant-negative [37], led to extensive guidance errors by photoreceptor neurons [38]. In addition there was a defect in cell adhesion, causing some of the photoreceptors to descend below their designated layer. These axon guidance and cell adhesion defects both arose from disruptions in the function of Ketel, the *Drosophila* ortholog of importin β [38]. Thus, cell adhesion and axon guidance in the fly eye have specific requirements for nucleocytoplasmic transport molecules.

4.1. Retrograde transport from synapse to nucleus during synaptic plasticity

The requirement for transcription during long-lasting synaptic plasticity likewise indicates that signals generated by activity at the synapse must be retrogradely transported to the nucleus. Martin and colleagues investigated the role of importins in this process using two models of learning-related synaptic plasticity: long-term facilitation (LTF) of *Aplysia* sensory–motor synapses and long-term potentiation (LTP) of mouse hippocampal synapses. They found that importins were present in distal synaptic compartments, and that stimuli known to induce transcription triggered their translocation to the nucleus [39]. Specifically, importins accumulated in the *Aplysia* sensory neuron nucleus in response to stimuli producing transcription-dependent LTF, but not in response to stimuli producing transcription-independent short-term facilitation. In cultured hippocampal neurons, it was found that activation of N-methyl-D-aspartate (NMDA) receptors triggered an accumulation of importins in the nucleus, which was accompanied by a decrease in importin immunoreactivity in distal dendrites. Chemical induction of transcription-dependent, late-phase LTP in acutely prepared hippocampal slices produced an accumulation of importins α and β in the nuclei of CA1 pyramidal neurons. To determine whether importin-mediated transport is necessary for transcription-dependent forms of plasticity, anti-nuclear pore antibodies were microinjected into *Aplysia* sensory neurons. These antibodies block active transport but not passive diffusion through the pore. Consistent with an essential role for importin-mediated signaling, injection of these antibodies blocked long-term facilitation without affecting basal synaptic transmission or short-term facilitation. Taken together, these findings indicate that importins function to carry signals from the synapse to the nucleus during

transcription dependent forms of learning related synaptic plasticity [39].

4.2. Potential cargoes of importins in neuronal processes

A number of transcription factors have been implicated in long distance movement in neuronal processes, and might depend on importin-mediated transport systems for their trafficking (Fig. 2C). A recent report suggested that cAMP-responsive element (CRE)-binding protein (CREB) is locally translated and retrogradely transported in sensory neurons in response to nerve growth factor (NGF), but did not determine the transport mechanism [40]. It should however be noted that this observation has not yet been confirmed *in vivo*, and that it does not fit with long-standing work describing cell body activation of CREB in sensory neurons by NGF signaling through other retrograde pathways [41–43]. Nonetheless, the Martin group subsequently showed that CREB2, a transcriptional repressor that modulates long-term synaptic plasticity and memory, is localized to distal dendrites in rodent hippocampal neurons and to neurites of *Aplysia* sensory neurons [44]. They further demonstrated that CREB2 binds to specific importin α isoforms in both systems, and that binding of CREB2 to importin α is required for its transport from distal synaptic sites to the nucleus after LTD-inducing stimuli [44]. Jacob, a caldendrin binding partner, is another newly identified component of the CREB signaling network, which regulates termination of CREB signaling in the nucleus [45]. Activation of NMDA receptors induces nuclear translocation of Jacob from distal dendrites, and this trafficking requires importin α and is antagonized by caldendrin [45]. Another study reported that kainic acid (KA) seizures rapidly induced the translocation of importin $\beta 1$ from distal cytoplasm to the nucleus in pyramidal CA1 neurons, and that this translocation was prevented by an NMDA receptor blocker [46]. In addition to NMDA signaling to CREB, other factors that require NLS mediation for transport in neuronal processes are NF- κ B in hippocampal neurons [47], and *Aplysia* apCAM-associated protein during synapse-specific LTF [48]. Although the authors did not examine direct involvement of importins in the latter two cases, the requirement for NLS for retrograde transport is certainly suggestive. Taken together, these studies show that importin-mediated transport is important in dendritic communication pathways that link synaptic activity to nuclear signaling.

5. Regulation of importin functions in neurons by Ran

The multiple roles for importins in cytoplasmic transport of diverse signals in neuronal processes have directed recent attention to regulation of these functions. The GTPase Ran is the principal regulator of nucleocytoplasmic transport. Ran effects are determined by its guanine-nucleotide state, which is regulated by the nuclear GEF RCC1 and cytoplasmic RanGAP, as well as a number of Ran binding proteins. The asymmetric distribution of Ran effectors and consequently of GTP- and GDP-bound Ran provides directionality to nuclear transport (Fig. 1) [49,50]. Recent studies have reported expanded roles for the Ran system in neurons, including signaling in distal cytoplasm, and functioning as a regulator of cytoskeletal dynamics at sites distant from the nucleus. A genome-wide RNAi screen and RNAi experiments results suggest that Ran has an important role in regulation of embryonic neuronal morphology in *Drosophila* and mouse [51]. The Ran binding protein RanBP9/RanBPM has been shown to interact with the cytoplasmic domains of the neural cell-adhesion molecule L1 and the axon guidance receptor plexin A1, and to regulate neurite outgrowth effects of these signaling pathways. Overexpression of RanBPM in primary neurons reduced neurite outgrowth regulated by both signaling pathways [52,53]. Truncation or suppression of RanBPM reduced

responses to the Plexin A1 ligand Semaphorin 3A [52,53]. Yudin et al. found that Ran and its associated effectors RanBP1 and RanGAP regulate the formation of the retrograde injury signaling complex after peripheral nerve lesion [54]. RanGTP was found in sciatic nerve axoplasm, distant from neuronal cell bodies and nuclei, and in association with dynein and importin α . Following injury, localized translation of RanBP1 stimulated RanGTP dissociation from importins and hydrolysis, thereby allowing binding of newly translated importin β to importin α and dynein. Perturbation of RanGTP hydrolysis or RanBP1 blockade at axonal injury sites reduced the neuronal conditioning lesion response [54]. Localized control of RanGTP levels in axonal cytoplasm is dependent on local translation of RanBP1 [54], and may also require new RanGEF's distinct from RCC1 [55,56]. Thus, tight and local regulation of axonal RanGTP unveils a new function for Ran in regulating importin-dependent cytoplasmic transport, and perhaps also in regulation of cytoskeletal dynamics independently of importins. The implications of such cytoplasmic roles for Ran are discussed more extensively elsewhere [56].

5.1. Local translation of RanBP1 and importin β transcripts in distal axons

Both RanBP1 and importin β are recruited upon need in distal axons by local translation of axonal transcripts [21,54]. Under normal conditions in peripheral nerve, importin β mRNA is found in intermittent concentrations throughout the axon, while the protein is not detectable [21]. RanBP1 distribution is similar, and the localization of axonal RanBP1 transcripts was shown to depend on a specific region in the 3'UTR [54]. The occurrence of these mRNA's in neuronal processes and their localized up-regulation by de novo synthesis provides a highly versatile rapid response mechanism that may regulate different types of long-range signaling in both normal and injured neurons. Intriguingly, local axonal translation of both RanBP1 and importin β is calcium sensitive [54], which might indicate co-regulation of these and other transcripts required for the injury response.

5.2. mRNA localization and translation in axons

Maintenance of a latent signaling complex in the form of specific axonal mRNAs can allow regulated long-range signaling to the cell body by locally translating critical components of the system. Most of the proteins required in axons and synaptic terminals are synthesized in the cell body, but a number of specific mRNAs are transported into axons and dendrites for local protein synthesis, with tight regulation of both delivery and translation [57]. Translocation of transcripts to their correct intracellular destination enables rapid responses to different stimulations and localized generation of required proteins. In multiple cycles of translation, one mRNA molecule can give rise to several protein molecules, meaning that localization of mRNA might be more efficient in this context than protein transport in setting up protein gradients, or to establish and maintain cellular polarity or cell diversification [58]. Only a fraction of the transcripts expressed in neurons are targeted into dendrites or axons [59], and selection of transcripts for such targeting is typically dependent on specific sequences, most often located in the 3'UTR region [60,61]. These cis-acting RNA motifs are thought to give rise to stable secondary stem loop structures, which allow recognition and docking of trans-acting RNA binding proteins (RBP). Consequently, localization signals operate at the level of secondary and tertiary structure, allowing a degree of nucleotide heterogeneity that makes them difficult to predict from sequence information alone. Indeed, the axon-targeting sequence identified in the 3'UTR of RanBP1 is not homologous to known RNA trafficking motifs, and the RBP involved in its targeting is not known [54]. It will be inter-

esting to find out if importin β and RanBP1 share the same RBP, or if their targeting to axons is even more complex. Regardless, targeting of RNAs encoding critical components of the importins complex and of Ran system to axons allows sophisticated local regulation of importin-dependent transport systems for mobilization according to need.

6. Importin links to nervous system disorders

The importance of nucleocytoplasmic transport in general, and of long distance cytoplasmic transport in neurons, and the requirement for importins in both these processes implies that their perturbation could lead to disease. Indeed mutations in importin genes in *Drosophila* [62,63] and in *Caenorhabditis elegans* [64] give rise to embryonic lethality and abnormal oogenesis. A gene trap knockout of importin β in mouse arrested the development of homozygous embryos at blastocyst stage, with death ensuing before embryonic day 5.5 [65]. Thus, importins have essential roles in embryonic development across phyla.

6.1. Importin β 3 and importin α 3 gene association with schizophrenia

Neurodevelopmental disruptions may be involved in the pathogenesis of major mental disorders, such as autism and schizophrenia [66,67]. The latter is a debilitating mental illness that affects ~1% of the population. Despite intensive study, the molecular etiology of schizophrenia remains enigmatic, and it is thought to be of multifactorial origin, with both genetic and environmental contributions. Recent studies associate single nucleotide polymorphisms (SNPs) in importin β 3 and in importin α 3 gene with schizophrenia in British and in Chinese populations [68,69]. The statistical effects are small and there have been conflicting reports on their validity [70,71], but combinations of certain SNPs for both genes may confer increased genetic risk [72]. Moreover, given the strong link between NMDA receptor signaling and mental disorders [73,74], and the involvement of importin regulated pathways in connecting synaptic NMDA signals to nuclear responses [39,44–46], cytoplasmic functions of importins may reward investigation for modulation or treatment of schizophrenia and related disorders.

6.2. Importins involvement in Alzheimer, ALS and MS diseases

At the opposing end of the spectrum, others have investigated involvement of importins in neurodegenerative diseases. Ogawa et al. reported aberrant localization of nuclear proteins in neurons from Alzheimer's disease (AD) patients [75]. Zhu and colleagues then compared the localization of importin α 1 within neurons of AD and non-affected brains and found that importin α 1 abnormally accumulated in Hirano bodies in vulnerable hippocampal neurons in AD [76]. Abnormal distributions of importins might also be implicated in some types of motor neuron degeneration. Zhang et al. examined the subcellular localization of nucleocytoplasmic transport proteins in the lumbar spinal cord in the mutant SOD1 (G93A) transgenic mouse model of Amyotrophic Lateral Sclerosis (ALS) [77]. They found that nucleocytoplasmic partition of importin immunoreactivities were changed in a subset of the surviving anterior horn cells in these transgenic mice, although it is not clear at this stage if this observation reflects disease causation or outcome [77]. Finally, a recent observation suggests that interference to nucleocytoplasmic transport in glia may affect progression of multiple sclerosis (MS) [78]. MS results from destruction of the protective myelin sheath surrounding axons, which prevents the transmission of nerve impulses. Precursors of oligodendrocytes, the cells capable of myelinating axons, are preserved in demyelinating lesions, but an unknown mechanism prevents their differentiation into mature

Table 1
Nucleocytoplasmic transport mechanisms in trauma or disease in neuronal systems.

Disease	Involvement of importins	References
Peripheral nerve injury	Local axonal translation of importin β 1 and linkage to dynein via importin α 's coordinates retrograde injury signaling	[21,23,54]
Schizophrenia	Single nucleotide polymorphisms in importin β 3 and in importin α 3	[68–72]
Alzheimer	Abnormal accumulation of importin α 1	[75,76]
Amyotrophic lateral sclerosis	Abnormal distribution of importins	[77]
Multiple sclerosis	Interference of nucleocytoplasmic transport	[78]

oligodendrocytes. Oligodendrocyte differentiation is dependent on Notch signaling, and Nakahara et al. recently showed in MS lesions that the Notch1 intracellular domain interacts with importin β 1 but does not translocate to the nucleus [78]. This turned out to be due to abnormal expression of TIP30/CC3 [78], a direct inhibitor of importin β s [79], suggesting that blockade of nuclear import in oligodendrocyte precursors contributes to MS pathologies. Thus, perturbations of nucleocytoplasmic transport mechanisms within neurons and/or glial cells may be involved in the pathogenesis of a number of neurodegenerative disorders (Table 1).

7. Summary and perspectives

A PubMed search at the dawn of the new millennium combining the keywords 'importin or karyopherin' with the keywords 'neuron or nerve' would have found a mere three publications. A similar search conducted less than a decade later to cover the literature for this review resulted in over 70 references, clearly reflecting an increased interest in the crossroads between nucleocytoplasmic transport mechanisms and neuronal biology. In certain cases, observations of new functions for importins in neurons have been subsequently replicated in non-neuronal cells, for example dynein-associated transport of NLS-bearing plasmid or viral constructs [80,81]. In other cases it seems (unsurprisingly) that some NLS-targeted molecules require specialized cytoskeleton-based mechanisms for transport within neurons, but can dispense with such mechanisms in certain non-neuronal cells [47,82,83]. Regardless, it is now clear that neurons mobilise importins and associated molecules to participate in dendritic and axonal transport, synapse to nucleus communication, retrograde injury signaling, and control of differentiation. The mechanistic details and physiological significance of these new roles for nucleocytoplasmic transport molecules will require experimental approaches that discriminate between cytoplasmic and nuclear functions, such as selective targeting of transcript species designated for localized translation in distal cytoplasm. It will be especially interesting to see if such experiments establish new roles for nucleocytoplasmic transport molecules in other cell types in addition to neurons.

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