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Mini review

Quality control of cytoplasmic proteins inside the nucleus

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ABSTRACT

A complex network of molecular chaperones and proteolytic machinery safeguards the proteins which comprise the proteome, from the time they are synthesized on ribosomes to their destruction via proteolysis. Impaired protein quality control results in the accumulation of aberrant proteins, which may undergo unwanted spurious interactions with other proteins, thereby interfering with a broad range of cellular functions. To protect the cellular environment, such proteins are degraded or sequestered into inclusions in different subcellular compartments. Recent findings demonstrate that aberrant or mistargeted proteins from different cytoplasmic compartments are removed from their environment by transporting them into the nucleus. These proteins are degraded by the nuclear ubiquitin–proteasome system or sequestered into intra-nuclear inclusions. Here, we discuss the emerging role of the nucleus as a cellular quality compartment based on recent findings in the yeast *Saccharomyces cerevisiae*. We describe the current knowledge on cytoplasmic substrates of nuclear protein quality control, the mechanism of nuclear import of such proteins, as well as possible advantages and risks of nuclear sequestration of aberrant proteins.

Contents

1. Introduction

The nuclear compartment is part of a complex and intricately organized internal membrane system inside the eukaryotic cell harboring the vast majority of genetic material required for life. Essential processes like DNA-replication, DNA-repair, gene regulation, transcription, ribosome biogenesis, and mRNA splicing occur in this compartment. The nucleoplasm is bound by two membranes, the nuclear envelope, which is continuous with the endoplasmic reticulum (ER) [1]. The transport of RNAs and proteins between the nucleus and the cytoplasm occurs through nuclear pore complexes spanning both lipid bilayers of the nuclear envelope. An emerging function of the nucleus is its role in the turnover and sequestration of proteins imported from different cytoplasmic compartments. The import of mistargeted or aberrant proteins into

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the nucleus might pose a risk to the integrity of the nuclear proteome and nuclear function. Thus, an intact nuclear protein homeostasis (or proteostasis) is indispensable to maintain cellular function when cytoplasmic proteins are imported for quality control.

A complex network of proteolytic systems and molecular chaperones, collectively termed the proteostasis network ensures the fidelity of the nuclear proteome [2,3]. The correct folding of proteins can be perturbed by genetic mutations, defects in protein synthesis, thermal stress, or conditions that cause abnormal protein modification such as oxidative stress. Especially metastable proteins with disordered regions are susceptible to undergo unwanted interactions and tend to form toxic aggregates, which are associated with neurodegenerative diseases. In mammals, for instance, such metastable proteins account for approximately 30 % of the proteome [4]. Failure in protein quality control is usually visible by the accumulation of proteins in aggregates, a hallmark of many neurodegenerative diseases, where the formation of protein inclusions is often observed along with an age-dependent decline of the capacity of the cellular proteostasis network [5–7]. Many of these diseases such as Huntington's disease, dentatorubral-pallidoluysian atrophy, spinal-bulbar muscular atrophy, and several forms of spinocerebellar ataxia, show protein aggregation inside the nucleus [8,9]. These observations highlight the involvement of the nucleus in the quality control of proteins accumulating in such pathologies. It is becoming increasingly clear that not only nuclear but also cytoplasmic proteins are subjected to quality control inside the nucleus. Misfolded cytosolic proteins, as well as proteins normally targeted to mitochondria or other organelles, are targeted to the nucleus, where they are either degraded or sequestered into intra-nuclear inclusions [10–15]. Here, we discuss recent evidence from the yeast *Saccharomyces cerevisiae* on how the nuclear proteostasis network is employed in the quality control of cytoplasmic proteins.

2. Mechanisms of protein quality control

An elaborate proteostasis network ensures proper protein folding and targeting, or if this fails, efficient degradation of non-native proteins [16]. At the center of this network are molecular chaperones, which assist in protein folding and prevent aggregation, refold stress-denatured proteins and cooperate with both, the ubiquitin proteasome system (UPS) as well as the autophagy pathway, to degrade terminally misfolded proteins. The main proteolytic machinery degrading proteins in the cytosol and the nucleus is the 26S proteasome [17–19]. This large multi-subunit complex consists of a 19S cap required for substrate recognition and unfolding, and a 20S core particle harboring the proteolytic activity inside its ring-like structure. In most cases, proteasomal turnover of proteins is mediated by post-translational modification with ubiquitin, a process known as ubiquitylation. Predominantly, ubiquitin is attached to lysine residues, but also ubiquitylation of other amino acids has been observed [20–22]. Especially chains of several ubiquitin moieties, built on internal lysine residues at positions K11 and K48 of ubiquitin, destine proteins for degradation [23,24]. Substrate ubiquitylation is mediated by an enzymatic cascade, involving a ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin-ligases (E3) [25]. Specificity towards individual substrates is usually determined by the last step depending on target recognition by the ubiquitin-ligase [26,27]. The proteasome targets soluble unfolded proteins or small soluble oligomers for degradation. Thus, in protein quality control, degradation is often supported by molecular chaperones, which maintain substrates in a soluble state or mediate disaggregation to allow for proteasomal turnover [6]. Here chaperones of the Hsp70 family in conjunction with their Hsp40 co-chaperones and nucleotide exchange factors (NEF) are of central importance [28,29]. Hsp70 chaperones bind to short hydrophobic peptides, usually exposed by proteins that are not in their native conformation [4,30,31]. Thereby, aggregation and misfolding of proteins are prevented, which in the context of protein turnover supports degradation by the proteasome. Hsp70 contains a substrate binding and a nucleotide binding domain. ATP hydrolysis by the nucleotide binding domain results in the binding of the substrate, while the exchange of ADP with ATP allows for substrate release. A large family of Hsp40 co-chaperones (also called J-proteins) stimulates the ATPase activity of Hsp70 and is responsible for the great diversity of functions supported by Hsp70 [30,31]. Hsp40 chaperones can function as substrate recognition factors or guide Hsp70 to different subcellular locations. Moreover, Hsp70 mediates disaggregation in conjunction with specific Hsp40s and NEFs in metazoa [32–34]. In yeast, efficient disaggregation, in addition requires the disaggregase Hsp104, which is only present in lower eukaryotes [35,36].

Another central component of the proteostasis network is the conserved AAA-ATPase Cdc48 (p97/VCP in mammals), which can extract proteins from membranes, multi-protein complexes, translocation channels, or protein aggregates [37–41]. Cdc48 forms a hexameric complex with a central pore, through which substrates are pulled using the force generated by the activity of two ATPase domains [42,43]. In protein quality control, Cdc48 is critical in proteasomal degradation of proteins that require extraction out of or across membranes, as in ER associated-degradation (ERAD) and mitochondria-associated degradation (MAD), or from ribosomes as in ribosome-associated quality control (RQC) [40,44,45]. When protein degradation fails, sequestration of proteins into cellular inclusions or different organelles is a common strategy to limit the burden of damaged proteins on the proteostasis network [46,47]. This includes the formation of cytoplasmic and nuclear protein aggregates, as well as the transport of proteins into mitochondria or the nucleus [10,11,48–51].

3. Protein turnover in the nucleus

The 26S proteasome is the sole proteolytic machinery present inside the nucleus and is thus at the center of nuclear protein quality control (Fig. 1). The proteasome is present in the cytosol and nucleus but has been shown to be enriched inside the nucleus in most conditions and cell types [52–54]. The nucleus contains several soluble and membrane-bound ubiquitin-ligases that recognize and ubiquitylate damaged proteins to mediate proteasomal turnover [55]. The main soluble ubiquitin-ligases functioning in nuclear protein quality control are San1 and Ubr1 [2,15]. San1 has been identified as a nucleoplasmic ubiquitin-ligase, which targets mutant variants of many nuclear proteins, but not the respective wildtype versions [2,56]. Multiple regions of disorder within San1 facilitate the recognition of exposed hydrophobic regions in other proteins, thereby achieving substrate specificity [57–59]. A stretch of at least five hydrophobic residues, as it is often exposed when proteins are not correctly folded, is sufficient for recognition by San1 [57]. In the absence of San1, proteins containing such exposed hydrophobic stretches accumulate in aggregates and are toxic to the cell [57].

The ubiquitin-ligase Ubr1 was first described to function in the degradation of misfolded cytosolic proteins but was later shown to be mainly localized inside the nucleus [13–15]. However, while Ubr1 is conserved between yeast and mammals, its nuclear localization has only been observed in yeast [15,60]. Originally, Ubr1 was identified as a ubiquitin-ligase of the *N*-end rule pathway, where protein stability is determined by the *N*-terminal amino acid

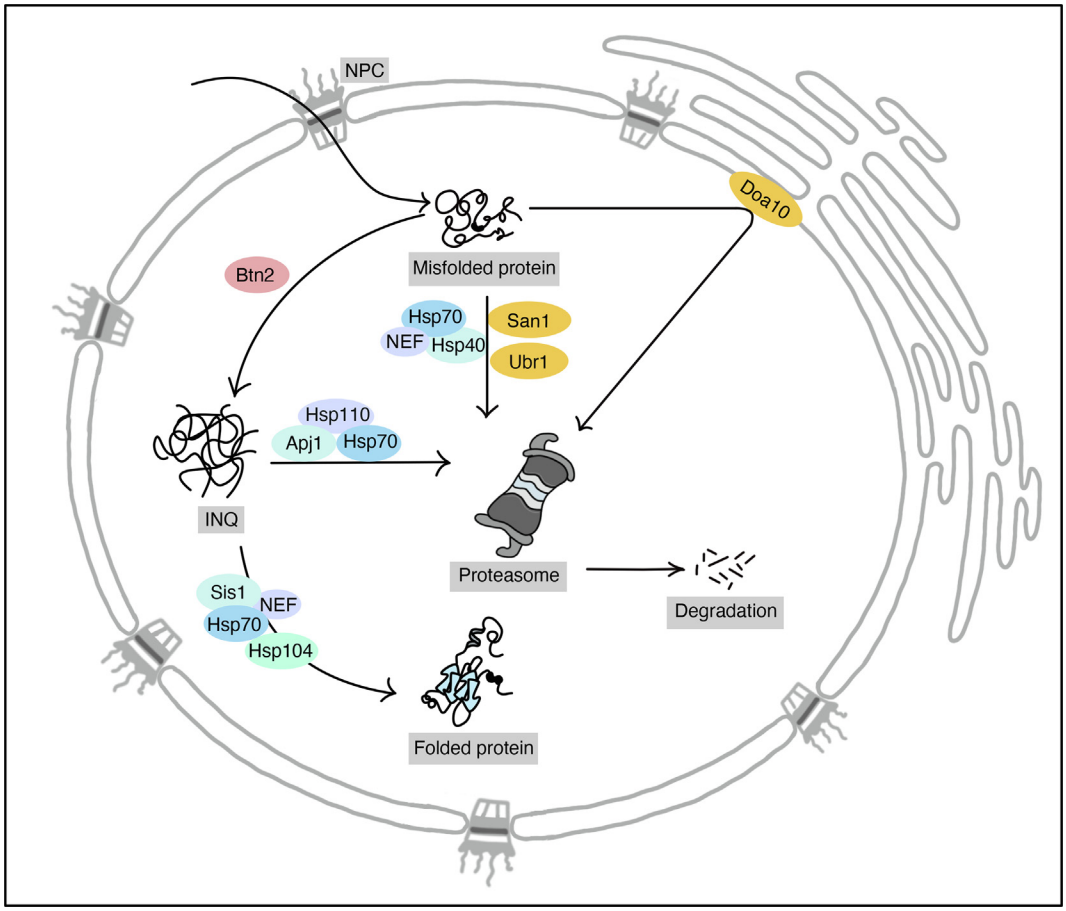

Fig. 1. Nuclear protein quality control pathways. Misfolded proteins can be targeted for proteasomal degradation inside the nucleus by the action of different ubiquitin ligases residing in the nucleoplasm (San1 and Ubr1) or inner nuclear envelope (Doa10). INQ (intranuclear quality control compartment) formation is mediated by Btn2. Proteins from INQ can be either disaggregated by Apj1, Hsp70, and Hsp110 or Sis1, Hsp70, Hsp104, and nuclear exchange factors (NEF) for Hsp70. After disaggregation proteins can be refolded or degraded by the proteasome.

[61]. Ubr1 can directly interact with basic or bulky hydrophobic amino acids at the *N*-terminus of a protein and mediate its ubiquitylation and turnover. In protein quality control, substrate recognition by Ubr1 is largely independent of the identity of *N*-terminal amino acid [14,62–65]. Instead, Ubr1 requires Hsp70 with its Hsp40 co-factors Ydj1 and Sis1 as well as the NEFs Fes1 and Sse1 for substrate ubiquitylation [13,14,62,66–68]. Sis1 directly supports substrate recognition through physical interaction with Ubr1 [67]. Ydj1 interacts with substrates of Ubr1 and is required for their ubiquitylation, which might be due to the requirement of Ydj1 to maintain substrates in a soluble state [66,67] Ubr1 and San1 often show an overlap in substrate specificity [13,14]. This might be explained by the fact that hydrophobic stretches as recognized by San1 can also be bound by chaperones co-operating with Ubr1 [30,57]. Another determinant for specificity between those two ligases might be the size of a substrate as an increase in molecular mass rendered San1 substrates Ubr1-dependent [69]. It should be noted that here Ubr1 dependent degradation is rather dependent on the cytoplasmic fraction of Ubr1 and likewise it has been shown that some San1 substrates become Ubr1 dependent when targeted to the cytoplasm.

A special class of ubiquitin-ligase involved in quality control within the nucleoplasm is the heterodimeric protein Slx5/Slx8. This ligase contains several SUMO-interacting motifs, which allow binding to proteins that are modified with the ubiquitin-like protein SUMO (small ubiquitin-like modifier) [70]. While SUMOylation in most cases has regulatory, non-proteolytic functions, SUMO-mediated proteolysis by the ubiquitin proteasome system can serve to terminate nuclear processes regulated through SUMOylation [71]. In addition, Slx5/Slx8 mediates the turnover of mutant variants of some transcription factors, suggesting a role in protein quality control [72].

Ubiquitin-dependent turnover of nuclear proteins is also mediated by ubiquitin-ligases residing on the inner side of the nuclear envelope. Doa10 is localized to the nuclear envelope and the ER and can therefore target soluble proteins from the nucleoplasm and cytosol as well as membrane-bound proteins from the nuclear envelope and the ER membrane [73–75]. Doa10 targets proteins containing an amphipathic helix with a hydrophobic surface [76–78]. In some cases Doa10-dependent turnover requires Hsp70 together with Ydj1 or Sis1 [76,79,80]. Due to its ability to target soluble proteins, Doa10 also displays overlapping substrate specificity with the soluble ubiquitin ligases San1 and Ubr1 [81,82]. In addition to Doa10, the nuclear envelope resident Asi-complex targets misfolded or mislocalized membrane proteins for proteasomal degradation [83,84]. This complex consisting of Asi1, Asi2, and Asi3 is a branch of ERAD that localizes exclusively to the inner nuclear membrane.

The ligases San1, Ubr1, Slx5/Slx8 and Doa10 promote the formation of K48-linked ubiquitin chains [85–87]. In addition, Doa10 can also mediate the formation of K11-linked ubiquitin chains, due to its interaction with different ubiquitin-conjugating enzymes [87,88]. Inside the nucleus K48-linked ubiquitin chains are sufficient to achieve efficient turnover, while it was shown that

degradation of some proteins in the cytosol requires the formation of mixed K48- and K11-linked chains [89].

Taken together, a diverse set of ubiquitin-ligases with distinct but also overlapping modes of substrate recognition provide a robust nuclear quality control network.

4. Formation and clearance of nuclear protein inclusions

Despite the presence of multiple ubiquitin-ligases and the high abundance of proteasomes, timely degradation of proteins might fail due to acute stress, overloading of the proteolytic capacity of the nuclear proteostasis network, or impairment of the nuclear ubiquitin proteasome system. Under such conditions, proteins are sequestered into intra nuclear inclusions [49,50,90]. The formation of this intranuclear quality control compartment, termed INQ, depends on the nuclear aggregase Btn2 [49]. INQ formation is triggered upon expression of misfolded model substrates or in response to proteotoxic or genotoxic stress [49,91]. Btn2-dependent INQ formation maintains proteostasis under conditions of limited chaperone capacity, demonstrating the protective role of protein sequestration into inclusions [92]. Nuclear, as well as cytoplasmic proteins, are found in INQ, depending on the conditions analyzed [10,91]. In particular proteasomal inhibition results in an increased abundance of cytoplasmic proteins in intra-nuclear inclusions [10].

Proteolytic turnover of intra-nuclear protein aggregates requires a preceding disaggregation step, to facilitate degradation by the proteasome. In the nucleus, disaggregation by Hsp104 in conjunction with Hsp40/Hsp70 mainly targets proteins for Hsp70 dependent refolding [92–94]. However, Hsp104 has also been shown to support Doa10-dependent degradation by the proteasome [95]. Efficient disaggregation of nuclear inclusions is supported by the physical interaction of Btn2 with the Hsp40 Sis1, which mediates disaggregation in conjunction with Hsp70 and Hsp104 [90,92]. In addition, the Hsp40 Apj1 localizes to INQ and mediates disaggregation together with Hsp70 and its NEF Sse1 (Hsp110) [10]. While Hsp104 allows for complete disaggregation and refolding, Apj1 appears to rather solubilize proteins for proteasomal turnover [10,92]. In addition, Cdc48 was shown to extract specific proteins from INQ [96]. In line with this, it has been shown that Cdc48 is required for targeting insoluble proteins for San1-dependent turnover [97]. Collectively, these data demonstrate that nuclear inclusions present a reversible storage compartment for proteins under stress conditions.

5. Sequestration of cytoplasmic proteins into the nucleus

Although, each cellular compartment contains a designated protein quality control machinery, extensive crosstalk between different compartments has been observed, where damaged proteins are rerouted within the cell [46]. The role of the nucleus in the quality control of cytoplasmic proteins has been initially observed in studies analyzing the behavior of different model substrates of misfolded cytosol-localized proteins [12–15]. In particular deletion of San1 often results in nuclear accumulation of such proteins [2,12,13,49]. A substrate widely used is ΔssCPY*, a mutant version of carboxypeptidase Y, which lacks the signal sequence required for ER targeting and is therefore present in the cytoplasm as a terminally misfolded protein [80,98]. This protein is targeted to the nucleus and degraded depending on the ubiquitin-ligase San1 [12–14,80]. Recent studies also identified endogenous cytoplasmic proteins as substrates of nuclear protein quality control [10,11]. The nuclear-specific Hsp40 Apj1 binds to aggregated proteins in the nucleus and the substrates of Apj1 have been identified by mass-spectrometry [10]. Upon proteasome inhibition, more than half of the proteins co-precipitating with Apj1 were of cytoplasmic origin, with mitochondrial proteins as the predominant group. Using the mitochondrial ribosomal proteins Mrpl7 as a model, it was shown that interaction with Apj1 indeed occurred inside the nucleus. Nuclear aggregation of Mrpl7 occurs following inhibition of the proteasome and is further increased upon arrest of mitochondrial protein import (Fig. 2). Collectively these data show that INQ contains cytoplasmic proteins, in particular when proteasomal degradation is blocked [10]. This is in line with a report that found the GFP-tagged respiratory chain complex III subunit Qcr6 to co-localize with INQ [91]. Similar observations were made in a screen for the localization of more than 500 distinct GFP-tagged mitochondrial proteins upon inhibition of mitochondrial import [11]. Under this condition, extensive rerouting of these tagged mitochondrial proteins to different compartments was observed, including a fraction of 6.4 % of the proteins which were observed in the nucleus. Consistent with a nuclear role in the clearance of mitochondrial precursor proteins, their proteasomal turnover was blocked by simultaneous deletion of the three nuclear E3 ubiquitin-ligases San1, Ubr1, and Doa10 [11]. Consistently, San1 and Ubr1 have also been implicated in the degradation of mutant variants of mitochondrial outer membrane proteins, which might also imply a contribution of nuclear quality control in the turnover of such proteins [99]. Importantly, the exclusion of a mitochondrial protein from the nucleus abolished its proteasomal degradation [11]. Likewise, it was shown that exclusion of ΔssCPY* from the nucleus results in strong stabilization, suggesting that nuclear import can be a prerequisite for the efficient turnover of some proteins [12]. Collectively these data led to the conclusion that misfolded cytosolic and non-imported mitochondrial proteins can be targeted for degradation inside the nucleus.

6. Transport of misfolded proteins into the nucleus

While an increasing body of evidence shows that cytoplasmic proteins are targeted to the nucleus especially under conditions of impaired protein homeostasis, little is known about the mechanistic details of this process. Critical factors for nuclear targeting of misfolded proteins are heat shock proteins (Hsp) such as Hsp70 chaperones with specific Hsp40 co-chaperones and nucleotide exchange factors [12,15,80,100] (Fig. 2). Here, the two Hsp40 co-chaperones Sis1 and Ydj1 in conjunction with Hsp70 and the Sse1 were shown to play an important role [12,15]. Depletion of Sis1 blocks nuclear import and thereby turnover of ΔssCPY* [12]. Sis1 shuttles between the cytosol and the nucleus, where it accumulates upon proteasome inhibition. The shuttling function of Sis1 is required for nuclear targeting and San1-dependent degradation of ΔssCPY*, as Sis1 variants artificially localized to just the nucleus or just the cytoplasm do not support the turnover of ΔssCPY*. While Sis1 is only required for a subset of substrates, Ydj1 seems to be generally involved in the transport of cytoplasmic proteins [12,15]. Mechanistically, Ydj1 appears to be required for nuclear targeting by keeping the substrates in a soluble state and preventing their aggregation. In line with this, it was shown that the nuclear import of proteins from cytoplasmic aggregates is blocked when Hsp104 is inhibited [49]. Classically, the nuclear import of most proteins is mediated by nuclear transport receptors of the karyopherin family [101]. For ΔssCPY* it has been shown that turnover is impaired in cells deficient in the karyopherin/importin-α Srp1 [12]. However, nuclear import inhibition might also impair the nuclear localization of quality control components, such as Sis1 which is imported into the nucleus in an Srp1 independent manner [90]. If classical import receptors are generally required for the nuclear import of misfolded proteins remains to be investigated. One possibility is that chaperones co-operate with

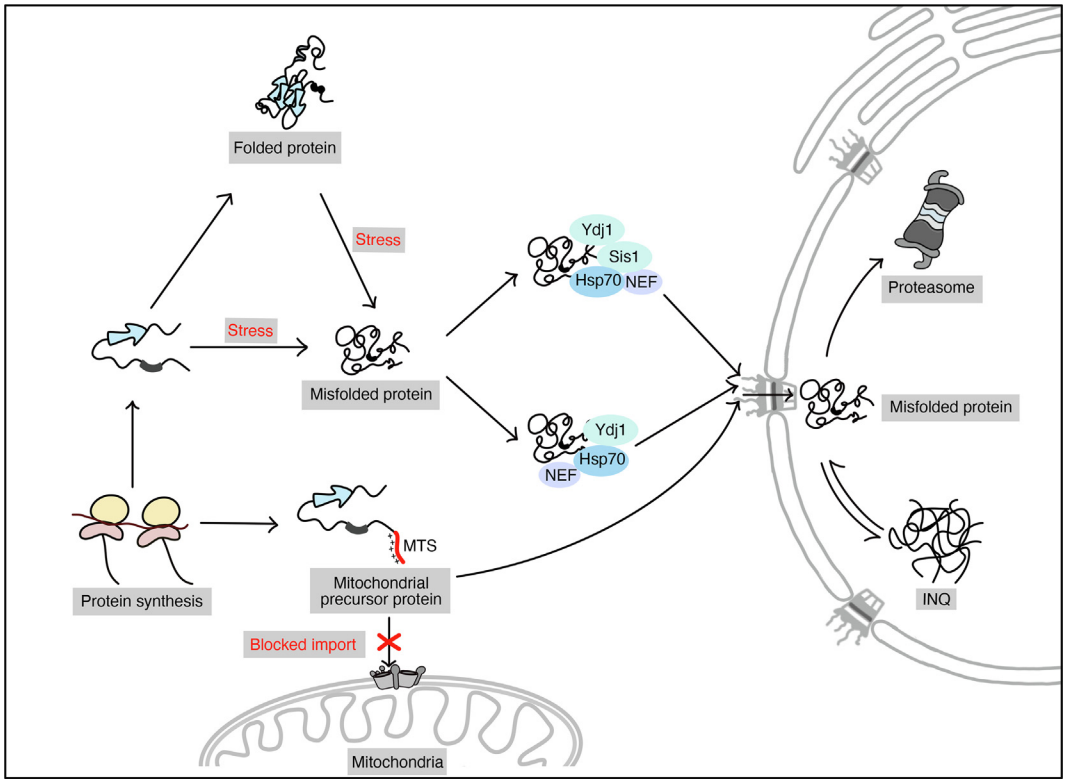

Fig. 2. Targeting of cytoplasmic proteins for quality control inside the nucleus. Misfolded cytosolic proteins are transported into the nucleus by the action of Hsp70, Hsp40 (Sis1 and Ydj1), and nuclear exchange factors (NEF). Upon failed mitochondrial import mitochondrial precursor proteins are transported into the nucleus. Inside the nucleus, cytoplasmic proteins are subjected to degradation by the ubiquitin–proteasome system or sequestered into INQ (intranuclear quality control compartment) sites.

karyopherins in the transport of proteins into the nucleus. The Hsp70 Ssa2 has been shown to mediate the transport of tRNAs to the nucleus in conjunction with Sis1 and Ydj1 [102]. In this study, it was shown that Ssa2 can mediate transport through the nuclear pore complex, which is facilitated by interaction with the nucleoporin Nup116. Transport of misfolded proteins through the nuclear pore complex was also abolished when the non-essential nuclear pore complex subunit Nup42 was deleted [49]. However, it is unclear if Nup42 or Nup116 are directly involved in the transport of misfolded proteins through the nuclear pore complex. Interestingly, proteasomes bind to the nucleoplasmic side of nuclear pore complexes, raising the question if these are directly involved in the degradation of proteins imported for turnover [103,104].

7. Conclusion and perspective

The transport of cytoplasmic proteins into the nucleus for degradation has been observed for a variety of substrates. Inside the nucleus, these proteins are ubiquitylated by multiple ubiquitin ligases, which thereby facilitate proteasomal turnover. However, it should be noted that the nuclear import of cytoplasmic proteins per se does not infer that this occurs solely for protein degradation. For instance, several enzymes of the mitochondrial tricarboxylic acid cycle can move into the nucleus, where they exert regulatory functions [105,106]. Likewise, impaired mitochondrial import of the protein ATFS1 results in nuclear localization, where it drives the mitochondrial unfolded protein response [107]. Also, the ubiquitin ligases San1, Ubr1, and Doa10 with established roles in nuclear protein quality control have been shown to regulate the stability of a few transcriptional regulators, assigning a regulatory role to these ligases [108–110]. Thus, a clear distinction between nuclear function versus nuclear quality control of normally cytoplasmic proteins remains to be investigated in many cases. However, the large number of cytoplasmic proteins targeted inside the nucleus upon proteotoxic stress, such as proteasome or mitochondrial import inhibition, is consistent with a role of the nucleus in the quality control of such proteins. Moreover, the observation that well-characterized terminally mis-folded model substrates like ΔssCPY* are transported into the nucleus for degradation further supports this hypothesis.

The potential role of the nucleus as a compartment for protein degradation could explain the enrichment of proteasomes inside the nucleus. To date, it is unclear to what extent cytoplasmic proteins are targeted to the nucleus for protein quality control which might preferentially occur under severe stress conditions when cytoplasmic protein quality control is overloaded. The physiological advantage of nuclear sequestration of damaged proteins is not fully understood as it can be expected to pose a substantial risk to the functionality of the nuclear proteome. Accumulation of misfolded cytoplasmic proteins inside the nucleus can potentially overload the nuclear proteostasis network, which in turn would cause the accumulation of aberrant nuclear proteins. Indeed, proteotoxic stress and impaired protein quality control, for instance, due to depletion of nuclear ubiquitin, result in impaired DNA repair and genomic instability in yeast and mammals [111–113]. It is conceivable that the trafficking of damaged proteins has a role in buffering proteotoxic stress between different compartments. The elimination of mistargeted or damaged proteins from the cytosol may serve to protect newly synthesized proteins from unwanted interactions. In addition, it has been hypothesized that spatial separation of protein synthesis and turnover prevents premature degradation of newly synthesized proteins [16]. In line with this, some cytoplasmic proteins are only efficiently degraded when targeted into the nucleus [11,12]. How the nuclear proteome

is protected from potential damage caused by imported aberrant cytoplasmic proteins remains to be investigated.

The transport of damaged proteins for quality control inside the nucleus is not well understood. For some substrates, the involvement of Hsp40/Hsp70 chaperones has been demonstrated [15]. However, it remains unclear what determines the nuclear import of such proteins and how this process is regulated to prevent the nuclear targeting of proteins that might still reach their native folding or subcellular compartment. In particular, the possible involvement of classical nuclear import pathways is still unknown. Moreover, it has not been addressed if misfolded cytoplasmic proteins might get re-exported into the cytosol upon refolding.

Nuclear targeting of cytoplasmic proteins has mainly been described in yeast, however, some findings indicate that this process may be conserved in mammalian cells. As in yeast, the misfolded cytosolic protein ΔssCPY* as well as a mutant variant of firefly luciferase accumulate in nuclear inclusions upon proteasome inhibition [12]. Moreover, aberrant proteins resulting from the translation of non-stop mRNAs are targeted to the nucleolus and PML bodies, which serve as protein quality control compartments in the mammalian nucleus [111,114,115]. Also, several forms of the mainly cytosolic localized protein Ataxin are found in nuclear aggregates upon pathogenic extension of the proteins polyglutamine tracts [116]. The reason for this nuclear localization remains to be identified. One possibility is that such proteins are normally targeted for degradation by nuclear proteasomes, which is prevented by aggregation caused by the polyglutamine extension. Conversely, polyglutamine proteins can sequester chaperones, thereby inhibiting the nuclear import of misfolded proteins [12]. Thus, nuclear sequestration of cytoplasmic proteins might not only contribute to the severity of pathologic nuclear protein aggregation but also represent a protein quality control pathway impaired in such disease conditions. Thus, understanding the contribution of the nucleus in the quality control of cytoplasmic proteins is central for a comprehensive view on the cellular proteostasis network.

CRediT authorship contribution statement

Lion Borgert: Writing – original draft, Writing – review & editing. **Swadha Mishra:** Writing – review & editing, Visualization. **Fabian den Brave:** Conceptualization, Writing – original draft, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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