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Protein quality control in the nucleus

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The nucleus is the repository for the eukaryotic cell's genetic blueprint, which must be protected from harm to ensure survival. Multiple quality control (QC) pathways operate in the nucleus to maintain the integrity of the DNA, the fidelity of the DNA code during replication, its transcription into mRNA, and the functional structure of the proteins that are required for DNA maintenance, mRNA transcription, and other important nuclear processes. Although we understand a great deal about DNA and RNA QC mechanisms, we know far less about nuclear protein quality control (PQC) mechanisms despite that fact that many human diseases are causally linked to protein misfolding in the nucleus. In this review, we discuss what is known about nuclear PQC and we highlight new questions that have emerged from recent developments in nuclear PQC studies.

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Introduction

The misfolding of proteins is an unavoidable problem that every eukaryotic organelle encounters. Protein misfolding occurs via numerous mechanisms: genetic mutations, errors in transcription or translation, problems during nascent peptide folding, and stressors that damage structures of normally folded proteins. The devastating issue of protein misfolding is highlighted by the human pathologies that are causally linked to misfolded protein aggregation such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis (ALS) [1]. To prevent aggregation, eukaryotic cells have evolved robust and often interconnected compartmental protein quality control (PQC) pathways that manage misfolded proteins by either refolding them into functional proteins through chaperones [2], sequestering them into large inclusions via small heat shock proteins or chaperones [2], or degrading them through the ubiquitin-proteasome system [3] or autophagy [4,5] (Figure 1). From a historical view, much of what we have learned about eukaryotic PQC systems and their role in maintaining proteostasis has largely come from studies in the cytoplasm and endoplasmic reticulum (ER) [6]. By contrast, much less is known about PQC mechanisms in the nucleus. However, at least 15 human diseases are associated with misfolded protein aggregation in the nucleus and include Huntington's, many spinal cerebellar ataxias (SCAs), and spinal bulbar muscular atrophy (SBMA) [7].

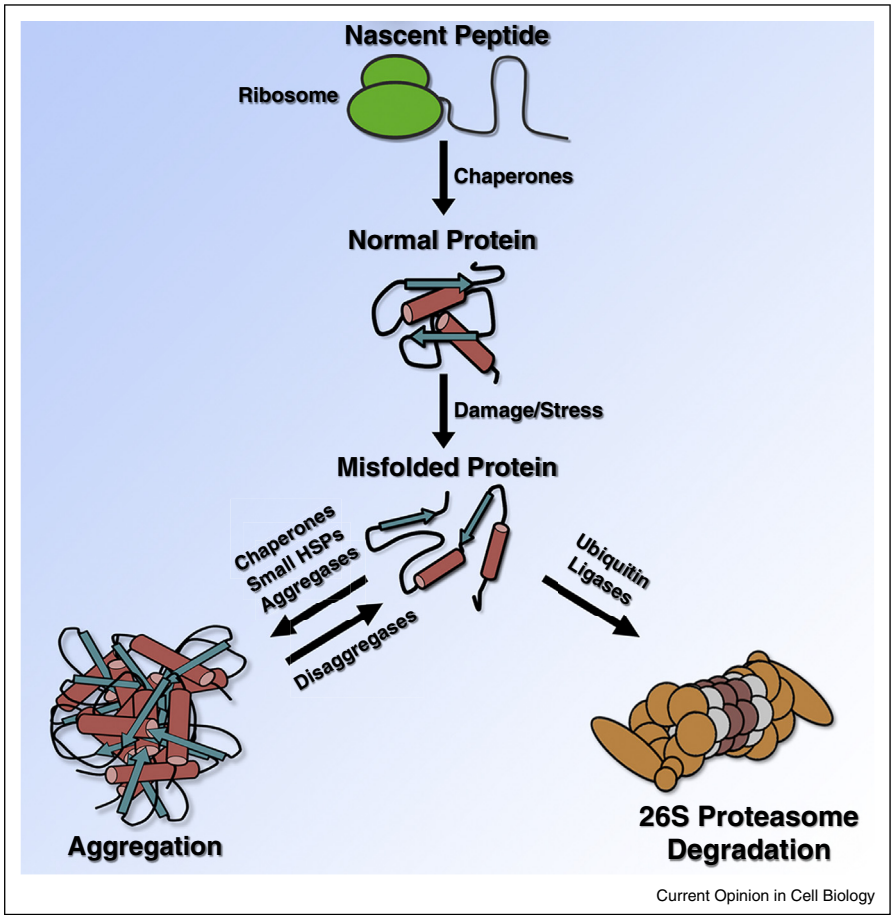
Overall nuclear protein quality control

Quality control studies in the nucleus have traditionally focused on how the cell maintains the integrity of the nuclear genome and the quality of mRNA before export from the nucleus [8,9]. By contrast, our understanding of how the cell maintains the quality of nuclear proteins has lagged behind. The protein aspect of overall nuclear quality control is exceptionally important to consider because an escalating failure to remove or repair misfolded nuclear proteins can lead to a deterioration in the integrity of the nuclear genome and the quality of the mRNA produced. This in turn can impact overall cellular proteostasis due to a reduction in the translational fidelity of the genetic code into its functional complement of proteins. Over the last decade, studies of misfolded nuclear proteins have revealed some of the folding and degradative PQC systems that function in the nucleus and these appear to operate on similar overarching principles as PQC systems in the cytoplasm with chaperones, small heat-shock proteins, and ubiquitin ligases generally managing misfolded nuclear proteins [10••,11••,12••,13••,14•,15•,16••,17••,18•,19••,20••,21].

One unique aspect of the nucleus is that it contains a high concentration of DNA, which is organized into chromatin. Because of the negative charge of DNA, many structural chromatin proteins have a considerable positive charge, such as histones. In addition, the nuclear proteome is enriched for proteins that possess low complexity, intrinsically disordered regions [22], suggesting these proteins have a broad capacity for conformational flexibility. Furthermore, chromatin is dynamic and there is ongoing remodeling that involves continuous assembly and disassembly of DNA–RNA–protein complexes [23]. These factors are potentially a considerable source for protein misfolding and aggregation specific to the nucleus.

Unlike the cytoplasm, one key PQC challenge the nucleus does not face to any considerable extent is the need to balance the robustness of PQC in the misfolding of damaged proteins with the PQC in the folding of nascent proteins. That is because nuclear proteins are synthesized in the cytoplasm and are imported into the nucleus through the nuclear pore [24]. Thus, nuclear PQC can

Figure 1



Overall summary of general PQC. General stages of PQC in the cell from nascent peptide synthesis to degradation.

be primarily focused on proteins that have become misfolded via damage during or after nuclear import, and nuclear PQC pathways may have evolved to target specific features of damage-induced misfolding that are particularly harmful in the nuclear environment. However, we note there is a possibility that the nucleus engages in limited translation [25], and may have to manage a low level of translational products. Furthermore, failures in cytoplasmic PQC can reduce the amount of correctly folded nuclear proteins, which can subsequently burden nuclear PQC pathways by decreasing the levels of functional nuclear proteins.

PQC degradation in the nucleus

The majority of proteasomes are nuclear localized [26], and the ubiquitin–proteasome system is the main route for misfolded protein degradation in the nucleus [3]. However, a recent study has suggested that nuclear proteins destined for proteasome degradation are first exported from the nucleus and destroyed by cytoplasmic proteasomes [27]. It is not clear if this is specific to a class of proteins that contain nuclear export signals or general for all nuclear proteins. However, it is clear that a number of nuclear-localized ubiquitin ligases have been implicated in the PQC degradation of misfolded nuclear proteins (Table 1). For this review, we will limit our discussion to the major yeast ubiquitin ligases involved in the degradation of misfolded nuclear proteins (Figure 2), as yeast has been the most extensively used organism for studies of nuclear PQC degradation.

The best understood yeast ubiquitin ligase involved in nuclear PQC degradation is San1. Originally discovered as a gene that, when mutated, suppressed the temperature-sensitive mutant phenotypes of *sir4-9* and *cdc68-1* cells [28,29], San1 was later found to be a ubiquitin ligase [10••,30] that is nucleoplasmic localized and specific in targeting misfolded nuclear proteins for ubiquitination and proteasome degradation [10••,12••]. Since the discovery that San1 is a nuclear PQC ubiquitin ligase [10••], additional genetic screens have revealed that loss of San1 leads to the stability of many other temperature-sensitive

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