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Mutations, protein homeostasis, and epigenetic control of genome integrity

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Abstract

From bacteria to humans, ancient stress responses enable organisms to contend with damage to both the genome and the proteome. These pathways have long been viewed as fundamentally separate responses. Yet recent discoveries from multiple fields have revealed surprising links between the two. Many DNA-damaging agents also target proteins, and mutagenesis induced by DNA damage produces variant proteins that are prone to misfolding, degradation, and aggregation. Likewise, recent studies have observed pervasive engagement of a p53-mediated response, and other factors linked to maintenance of genomic integrity, in response to misfolded protein stress. Perhaps most remarkably, protein aggregation and self-assembly has now been observed in multiple proteins that regulate the DNA damage response. The importance of these connections is highlighted by disease models of both cancer and neurodegeneration, in which compromised DNA repair machinery leads to profound defects in protein quality control, and vice versa.

Keywords

mutagenesis; protein homeostasis; DNA repair; stress response; epigenetics; aging

INTRODUCTION

From bacteria to humankind, organisms employ an ancient cohorts of DNA repair factors to ensure the faithful transmission of genetic information from one generation to the next [1]. Yet it is also clear that evolutionary success requires adaptability. How organisms reconcile these competing demands has been the subject of vigorous debate in evolutionary biology [2, 3]. Extreme examples can be found in nature. ‘Living fossils’ such as the ginkgo tree have similar morphologies today compared to their ancestors that have been preserved in the fossil record. In contrast, some fish species have undergone substantial changes in form and even behavior in only a handful of generations [4, 5]. In clinical settings, rapid evolution

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CONFLICT OF INTEREST STATEMENT

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fueled by mutagenesis can have devastating consequences for human health, as with the acquisition of drug resistance by cancers and infectious pathogens [6]. Recently, some molecular insights into this paradox – how organisms can promote stasis or facilitate changes in response to accumulating genetic variation – have come from a seemingly distant field: protein folding. In particular, the importance of molecular chaperones in facilitating the folding and maturation of unstable protein variants provides a means through which the environment can influence the phenotypic outcome of mutations [7]. Recent findings that proteotoxic stresses can induce a DNA damage response [8], and vice versa [9], provide additional means through which these links can be amplified.

Although there are many conceptual similarities between the quality control responses that govern cellular responses to DNA damage and protein damage, to date these phenomena have largely been considered separately. Here we review the emerging congruence between these fields, pointing to specific links on the molecular, cellular, and organismal scale (Figure 1). Finally, we integrate these findings in the context of cancer and neurodegeneration, which highlight the unexpected fundamental relationship between these two ancient homeostatic responses.

1. Intrinsic connections between mutagenesis and proteostasis

Most proteins, especially signal transducers and gene regulatory factors that control growth and development, are only marginally stable [10]. Many are folded with a free energy of just 1–5 kcal/mol. This is also true of DNA repair and cell cycle proteins, which are enriched in intrinsically disordered sequences – or protein regions that do not adopt a single stable fold. Accumulating mutations are generally destabilizing to protein structure, on average by ~1 kcal/mol. This means that many proteins are only a handful of mutations away from instability, aggregation, or degradation [10]. The conformational versatility inherent to such protein instability is likely central to the function of DNA repair proteins, cell cycle regulators, and factors involved in gene control [11]. However, this flexibility comes with an added cost: mutations can tax the proteostasis network and destabilize even the most robust biological pathways [7, 12, 13].

Prospective studies of protein evolution have extensively characterized the interface between protein stability and mutagenesis [14]. Protein folds must be sufficiently stable to be adopted and exert their functions in the crowded intracellular milieu. In theoretical models of protein evolution, there is a tradeoff between stability and function. That is, it is easier to improve stability while maintaining function than *vice versa*. However, even without imposing a tradeoff, stability provides a fundamental limit on the capacity of the protein to evolve [15]. These inferences have been confirmed experimentally in directed evolution studies using the cytochrome P450 enzyme BM3. Mutants of stabilized parental enzymes are more likely to evolve new or improved functions [14]. Retrospective studies of protein evolution have come to similar conclusions. Throughout life, the best predictor of evolutionary rate is expression level: proteins that are highly expressed tend to evolve at a slower rate [16]. Investigating possible explanations, Drummond and colleagues found that the cost of protein misfolding (often from translational errors) provides a compelling explanation [13, 17]. These examples

underscore the large but often underappreciated impact that DNA mutations can exert on protein homeostasis.

Given that mutations produce proteotoxic stress, how do organisms cope? Species ranging from unicellular bacteria to multicellular eukaryotes employ a conserved cohort of molecular chaperones, disaggregases, and osmolytes to help other proteins to fold. These can act co-translationally, on maturing proteins in the cytosol or ER, and even on protein aggregates that have lost their native folds [18, 19]. This response is critical for survival in the face of proteotoxic stress. Components of the proteostasis network are also critical for an organism's capacity to survive mutagenesis. Both prokaryotes and eukaryotes are remarkably resistant to accumulating mutation burden. Indeed, this property is critical for the survival of many human cancers and highly mutagenic pathogens, such as *Pseudomonas aeruginosa* that infect the lungs of Cystic Fibrosis patients [20]. These pathogens produce levels of mutagenesis that verge on an error catastrophe [21], yet they manage to survive, proliferate, and harness the power of their accumulated mutation burden to rapidly evolve new traits, often with devastating consequences for human health.

Several groups have examined possible mechanisms at play in bacteria by passaging highly mutation-prone strains of either *Escherichia coli* or *Salmonella typhimurium* through single-cell bottlenecks, resulting in the accumulation of a massive mutation burden [22, 23]. These experiments revealed an unexpected relationship between fitness and number of mutations accumulated. An initial sharp decline is followed by a plateau, beyond which additional mutations have little effect on fitness. Even given these strains' increased mutation frequency, the target size for any potential compensatory mutations would need to be much larger than has ever been observed experimentally to quantitatively explain the effect. Instead, the most mutated bacterial strains survived high mutation burden by inducing components of their proteostasis network: the chaperonin GroEL and the Hsp70 DnaK. Both chaperones had previously been known to 'buffer' the cost of mutations in individual proteins [7]. These studies suggest that the relationship between chaperone function and the cost of mutations may be much broader. Indeed, additional overexpression of GroEL further improved the fitness of the highly mutated strains. Directed evolution experiments in *E. coli* provide a final line of evidence linking the activity of this chaperone to the outcome of mutations. Tawfik and Tokuriki attempted to evolve new activities in a collection of metabolic enzymes using serial rounds of mutation and selection under conditions with moderate or high GroEL activity [24]. For GroEL substrates, new activities could be achieved much more rapidly in the presence of high GroEL activity. This was because additional mutational variants were kinetically stabilized at each round of mutation and selection, effectively increasing the number of types that could be subject to selection. In contrast, modulation of GroEL levels had no impact on the evolution of non-substrates.

Many human cancers also mutate at an extraordinarily high rate, owing to defects in DNA repair and checkpoint mechanisms [21]. Yet most can sustain massive numbers of mutations with unexpectedly little impact on their capacity to survive [25]. The activity of a eukaryotic chaperone heat shock protein 90 (Hsp90), and indeed engagement of the heat shock response as a whole [26], may partially explain their apparent robustness [27]. Among protein homeostatic mechanisms that influence cancer biology, Hsp90 is especially

important. Hsp90 is an essential ATP-driven molecular chaperone that catalyzes the folding of kinases, transcription factors, E3 ubiquitin ligases, and DNA repair factors that regulate growth and development. These findings and others have since motivated a flurry of interest in Hsp90 inhibitors as cancer therapeutics [28]. Hsp90 can constitute as much as 5% of total protein in transformed cells, and increased levels of heat shock activation correlate with poor prognosis in breast cancer [29, 30]. Notably, mouse xenograft studies suggest that the greatest benefit of these molecules may lie in their ability to impact the evolution of drug resistance [31–34], a strategy that could be invaluable given that this is the key failure of many oncogene-directed therapies.

2. Chaperone-mediated and proteolytic control of factors critical for DNA repair and mutagenesis

Although the primary role of the proteostasis network is to act on proteins, many of those proteins regulate genome stability. Broadly defined, genome instability encompasses a genome-wide increase in the frequency of point mutations, insertions/deletions, microsatellite slippage events, somatic homologous recombination, and transposon activity. Heat shock proteins have been linked to genome stability – and their loss-of-function has been linked to mutagenesis. In the plant pathogen *Agrobacterium tumefaciens*, the small heat shock protein HspL is critical for assembly of the type IV secretion system that controls horizontal DNA transfer [35]. Loss of beta-crystallin (an eye-specific small heat shock protein) in mice increases genomic instability in lens epithelial cells to a rate that is four orders of magnitude higher than wild-type controls, likely linked to a defective p53 checkpoint [36]. Likewise, Hsp70 deficient mice exhibit telomere instability and a high frequency of spontaneous chromosomal aberrations [37, 38]. In other cases, chaperone inhibition has been linked to improved disease prognosis and sensitivity to chemotherapy, as for Hsp110 [39]. In bacteria, the GroE chaperonin is critical for stress-induced mutagenesis [40]. These findings and others linking proteostasis to DNA damage and other stress responses have led many to place chaperones “at the crossroads of life and death” [12].

The molecular origins of the links between chaperone activity and DNA repair and mutagenesis are often elusive. Most available insight comes from studies of the Hsp90 chaperone, which has been an attractive chemotherapeutic target (many oncogenes require Hsp90 to exert their promiscuous functions) [41, 42]. Hsp90 directly regulates Rev1-mediated mutagenesis [43] as well as the accumulation of DNA polymerase ϵ at replication stalling sites in UV-irradiated cells [44]. A great deal of additional work has investigated the relationship between Hsp90 and genomic instability more generally. In human cells, Hsp90 inhibition increases mutation rates of microsatellites [45], and decreases resistance to ionizing radiation [46]. In yeast, potent Hsp90 inhibition can increase rates of aneuploidy [47], and overproduction of Hsp90 results in modestly reduced DNA repair efficiency [48]. In metazoans, Hsp90 inhibition can increase transposon mobility through the disruption of PIWI-protein function (*D. melanogaster*, *C. elegans*, mice, and human cells) [49–56]. In the plant *Arabidopsis thaliana*, perturbation of Hsp90 levels increases somatic homologous recombination [57] and susceptibility to ionizing radiation [58]. Hsp90 perturbation therefore correlates with and in some cases leads to genome instability. These effects are readily explained by its role in chaperoning many proteins that function in DNA

repair and genome integrity [59] including the sentinel DNA damage kinase Mec1 in yeast [60], telomerase, FANCA in the Fanconi anemia pathway [61], DNA polymerase subunits [44], BRCA proteins [44], and Rad proteins [62], among others (See reference [63] for a database of Hsp90 interactors).

Other arms of the protein quality control network can also impact DNA repair and mutagenesis, notably regulated proteolysis. Indeed, the widespread use of ubiquitin as a signaling molecule in the regulation of DNA repair complexes (although often not as a degradation signal) provides a fundamental link between these cellular processes (reviewed in [64, 65]).

3. An integrated cellular stress response linking PQC and the DDR

DNA damage – whether exogenous or endogenous – usually activates DNA repair pathways and checkpoint responses. This process, referred to as the DNA-damage response (DDR), culminates in recruitment and activation of proteins that trigger checkpoint signaling or directly perform necessary repair steps. When repair is completed, the machinery needs to be disassembled and DDR must be turned off. Hence, the DDR is a tightly controlled process that is regulated at multiple levels and is fine-tuned by a wide array of posttranslational modifications. Key among these is covalent modification with ubiquitin, the central mediator of proteolysis. For example, when DNA damage leads to a block in replication fork progression, the recruitment of translesion DNA polymerase η is specifically mediated by monoubiquitinated but not unmodified PCNA [66]. Similarly, DNA damage induces monoubiquitination of histone H2A, which accumulates at the site of DNA damage and recruits key regulator of DDR ATM [67]. In the DDR response, the function of ubiquitin is typically not to act as a degradation signal, but rather to regulate protein-protein and protein-DNA interactions necessary for DDR. Nonetheless, ubiquitin is a shared substrate that provides a direct link between the DDR and PQC (Figure 1).

PQC also regulates other aspects of the DDR. A notable example is in the orchestrated disassembly of DNA-damage induced repair complexes. For example, the chaperone-like segregase Cdc48/p97 is critical for displacing the DNA-bound Rad51 and Rad52 complex [68], two key recombination/DNA repair enzymes, preventing unnecessary recombination that can promote genome instability. Protein quality control machinery also plays an important role in regulating the processing of DNA double-strand breaks as crossovers during meiosis [69]. Specifically, the proteasome plays a key role in homolog juxtaposition and crossing over, driven by the recruitment of proteasome components to chromosomes by the E3 ubiquitin ligase Zip3 and the synaptonemal complex protein Zip1.

3.1 Engagement of “checkpoints” in response to protein misfolding—

Genotoxic and proteotoxic stresses have largely been treated separately over the many decades that they have been studied. Yet multiple individual studies have uncovered striking connections between the two, often linked to the behavior of intrinsically disordered proteins. We highlight two examples, one from yeast and the other from mammalian cells.

The intrinsically disordered yeast protein Rnq1 can form prion aggregates in the budding yeast *Saccharomyces cerevisiae* [70, 71]. Overexpression of the protein is toxic in cells

harboring such aggregates, but not in cells that do not harbor them [72]. This toxicity does not arise from general proteotoxic stress, but rather from mitotic arrest via the Mad2 cell cycle checkpoint. The mechanism involves Rnq1-mediated sequestration of the yeast centrosome (spindle pole body) component Spc42 [72]. This results in defective centrosome duplication and arrest. Remarkably, Rnq1 does not typically participate in spindle pole dynamics, but rather assembles in a structure known as the insoluble protein deposit (or iPOD) [73]. Thus, this is an instance in which the aggregated protein selectively assembles in a way that promotes mitotic arrest.

In mammalian cells, transient expression of two unrelated proteins that are prone to misfolding – a pathogenic expanded polyglutamine repeat and a mutated cystic fibrosis transmembrane conductance regulator – led to robust inhibition of the ubiquitin proteasome system [74]. Because the proteasome is essential for cell division, this led to a G2/M checkpoint arrest. When these findings were first reported, this was interpreted as a natural consequence of the importance of the ubiquitin proteasome system. But in light of subsequent discoveries also linking the accumulation of protein aggregation to cell cycle arrest, via very different mechanisms in different organisms (e.g. Rnq1 in *S. cerevisiae*), it is tempting to speculate that arresting replication or cell division in response to defects in protein homeostasis – or what might loosely be defined as a protein quality control “checkpoint” – may be a more general property of eukaryotic biology.

4. Adaptation to genotoxic and proteotoxic stress

4.1 Transient genotoxic stress evokes protracted stress response—Thus far, much attention has been focused on the immediate effects of DNA damaging agents, which trigger DDR activation. In a concerted effort to maintain genome integrity, the DDR pathway plays a critical role in sensing DNA damage and orchestrating the repair of ensuing DNA lesions [75–77]. This recovery process typically involves global remodeling of both the transcriptome and the proteome [78–80]. However, an implicit assumption in this thinking is that most cells return to their initial transcriptional and proteomic state following DNA damage and repair, aside from those that may acquire a mutation. Yet there have been limited studies on the physiological state of surviving cells following recovery from genotoxic stress that address this question explicitly.

The limited evidence that is available suggests that genotoxic stresses can induce molecular changes that persist long after the initiating event [81, 82]. In *S. cerevisiae*, Burrill and Silver detected heterogeneous responses in cells exposed to DNA damage using a synthetic memory loop circuit with transcriptional reporters [83]. Whereas weakly responsive cells increased their mutation frequency, strongly responsive cells activated a sustained iron starvation response and upregulated respiration. Notably, this latter response was stably maintained for many generations after the initiating DNA damage [83]. This long-term memory has been proposed to be mediated by the inheritance of damaged mitochondria that are unable to maintain iron homeostasis [84], but the detailed molecular mechanism(s) at play remain to be elucidated.

A second example comes from human stem cells. Following exposure to 2 Gy of gamma radiation, a dose sufficient to induce apoptosis and massive cell death, surviving human

embryonic stem cells remain pluripotent but exhibit changes in the expression of a number of genes involved in cell death, growth, proliferation, and embryonic development [85]. The irradiated cells upregulate growth factor- β and components of the Wnt/ β -catenin signaling pathway, which are implicated in both self-renewal and tumorigenesis [85–88]. Hence, these transcriptional changes could have profound impact on the long-term fate of the surviving stem cells. These results are consistent with the notion that the effects of genotoxic stress on cellular processes is not limited to DNA damage and can persist over many cell divisions in a way that can profoundly impact cell fate.

Although genotoxic stress can impose a heavy burden on the cellular stress response machinery, a few DNA damaging agents induce an adaptive response that protects the surviving cells from similar insults at a later time. Similar to the immune response, which can be primed by vaccination with an inactivated or weakened infectious agent, cellular stress responses can also be primed by exposure to a sublethal dose of some stressors, preconditioning the cells against future insults. Studies have shown that this can result in upregulation of DNA repair genes, and can be maintained for a prolonged period of time. This process has recently been implicated in the emergence of drug resistance in cancer [89, 90]. In melanomas, a single dose of DNA interstrand cross-linkers can lead to robust and long-lasting up-regulation of damaged DNA-binding protein 2 (DDB2) and the nucleotide excision repair gene Xeroderma Pigmentosum complementation group C (XP-C), stimulating DNA repair [90]. Sustained upregulation of DDB2 and XPC, driven by stabilization of p53, likely plays a key role in the suppression of drug-induced apoptosis and the rapid acquisition of chemoresistance in melanoma cells with wild-type p53, dramatically reducing the efficacy of a second dose of the alkylating drugs [90]. Given that the cellular response to the cytotoxicity of DNA damaging agents extends beyond DDR pathways, it is reasonable to suspect that the activation of other stress response pathways could have similar lasting effects on the cells. Indeed, activation of the MAP kinase pathway by ionizing radiation modulates the expression of vascular endothelial growth factor-A, protecting tumor cells from radiation-induced apoptosis [91]. Thus, modulating the magnitude and duration of specific stress response pathway can be a promising therapeutic strategy in desensitizing tumor cells to chemotherapeutics.

Memory of genotoxic insult, and ensuing changes in response to future exposures, can also be recorded within a single protein [92] (Figure 2). Recent studies in our laboratory have uncovered a novel mechanism of DNA damage response that relies on the acquisition of a prion-like protein aggregate as a ‘molecular memory’ of prior genotoxic stress. This prion, termed [*MPH1*⁺], is formed by a self-templating conformational change in the conserved DNA helicase Mph1/FANCM [93, 94]. Acquisition of [*MPH1*⁺] confers increased resistance to many DNA damaging agents such as the lesion inducer 4-nitroquinoline 1-oxide (4NQO) and the intercalating agent doxorubicin [82]. Intriguingly, exposure to hydroxyurea and phosphate starvation each promote [*MPH1*⁺] acquisition. In addition to its effects on DNA damage resistance, [*MPH1*⁺] decreases linkage between neighboring genetic markers in meiotic crosses, suggesting a means through which DNA damage-induced prion can also facilitate increased diversification in times of stress [95].

The non-pathological isoform of the prion protein, PrP^C, also plays a protective role against DNA damage in mammalian cells [96–98]. Exposure to genotoxic stress such as the alkylating agent methyl methanesulfonate (MMS) rapidly induces the expression and nuclear localization of PrP^C in neuronal cells. This in turn stimulates the DNA repair activity of the AP endonuclease APE1 [97]. However, the advantage associated with these adaptive cellular states can come with a cost: elevated expression of wild-type PrP^C is pathogenic [99]. Similar to prion diseases caused by PrP^{Sc}, a protease-resistant conformation of PrP, old mice with increased dosage of PrP^C developed multiple symptoms of neurological illness, including truncal ataxia, hind limb paralysis, and tremors [99]. Overall, these findings and others support the notion that genomic instability can sometimes induce secondary effects in the proteome that outlive the DDR, often with profound effects on cell fate and (dys)function.[117]

4.2 Transient proteotoxic stress triggers a protective cellular response that could involve DDR components—Although protein aggregation is commonly associated with disruptions in the proteostasis network, the functional consequences of protein aggregates remain enigmatic and controversial. The dominant view posits that proteotoxic stress induces aggregation that ultimately results in toxic cellular dysfunction [100]. However, recent work in *S. cerevisiae* and other models has demonstrated that at least some protein aggregation events may be an active and even protective stress response rather than a source of toxicity [101–105]. In a quantitative proteomics analysis, Wallace et al. identified over 170 proteins that aggregate within minutes of a sub-lethal heat shock [102]. Remarkably, these aggregated proteins could also be rapidly solubilized during recovery from the heat stress [102]. Indeed, many of these aggregates can also be generated, and reversed, by thermal fluctuations *in vitro*. In addition, the minimal degradative turnover in these experiments strongly suggests that most proteins in aggregates are not terminally damaged [102].

This type of reversible protein aggregation is now emerging as a novel mechanism of stress adaptation (Figure 2). A notable example is the yeast pyruvate kinase Cdc19, which forms reversible aggregates upon nutrient starvation [101, 106]. Importantly, the dynamic transition between the aggregated and soluble state is critical for Cdc19's function in re-initiating the cell cycle following stress [101]. Cells expressing a mutant form of Cdc19 that is 'locked' in the aggregated state are extremely sensitive to stress and cannot recover from even a mild heat shock [101]. Together, these findings establish that aggregates of endogenous proteins can be beneficial and important for an adaptive stress response.

Decades of work have established that adaptation occurs with proteotoxic stress response. In organisms in which it has been tested, prior exposure to mild heat stress confers increased tolerance to future proteotoxic stresses, a phenomenon known as thermotolerance [107]. Lindquist and Kim further established that the Hsp104 protein disaggregase is alone sufficient to provide thermotolerance, suggesting that memory of heat stress can be retained through sustained expression of Hsp104 [108]. Likewise, activation of the unfolded protein response confers increased tolerance to additional proteotoxic stress [8]. More recent work in astrocytes also demonstrated that prior exposure to MG132, a potent proteasomal degradation inhibitor, preconditions these glial cells to be more resistant to a higher dose of

MG132 in subsequent exposures [109, 110]. Interestingly, although the level of the protein-folding chaperone heat shock protein 70 (Hsp70) is elevated in stressed astrocytes, inhibition of Hsp70 or Hsp32 does not abrogate their resistance to a second challenge with proteotoxic stress [110]. Instead, this stress adaptation is largely dependent on the biosynthesis of the antioxidant molecule glutathione, suggesting that cells have means to protect against proteotoxic stress independent of the proteostasis network [109, 110]. Miyazaki and colleagues recently showed an accumulation of p53, and engagement of an associated transcriptional response, in response to unfolded proteins [8]. It is intriguing to speculate whether preventative activation of the DNA damage response can confer cross-protection against future proteotoxic stress [8].

5. Chronic genotoxic and proteotoxic stress in diseases

Understanding the fundamental interdependence between genomic and proteomic stability is critical for successful therapeutic intervention in a variety of human diseases (Figure 3). In cancer, accumulation of mutation not only drives genomic instability, but also dramatically alters the cellular proteostasis network, culminating in chronic genotoxic and proteotoxic stress [12, 27, 111]. Tumorigenesis often renders mutant oncoproteins and tumor suppressors dependent on chaperones for stability. For example, mutant p53 can be inherently unstable in untransformed tissues [112]. Homozygous p53^{R175H} mice produces undetectable levels of p53, just as wild-type mice do [112]. Instead, mutant p53 becomes stabilized when cells acquire additional mutations associated with malignant transformation [112]. However, mutant p53 is rapidly degraded in transformed cells upon Hsp90 inhibition [113, 114]. Further analysis revealed that in tumor cells, Hsp90 interacts with mutant p53 and the E3 ligase Mdm2, forming a ternary complex that results in Mdm2 activation [115]. Disruption of the Mdm2-p53-Hsp90 complex with Hsp90 inhibitor geldanamycin restores Mdm2 function, re-initiating the ubiquitination and degradation of mutant p53 [115].

Mutations in p53 can also strain the proteostasis network (Figure 2). Certain mutant p53 proteins exhibit prion-like behaviors, aggregating into insoluble amyloid fibrils both *in vitro* and in cancer tissues [116, 119]. Aggregation of mutant p53 is associated with a loss-of-function in DNA-binding capacity and gain-offunction in cytotoxicity [120]. Similar to yeast prions, transient overexpression of mutant, but not wild-type, p53 in tumor cell lines result in the accumulation of p53 aggregates [93, 121]. Mutant p53 aggregates also have the capacity to seed aggregation of wild-type p53 [116]. However, it is unclear whether these aggregates can be transmitted to neighboring cells. De Smet and colleagues further demonstrated that mutant p53 aggregates exert significant pressure on the ubiquitin–proteasome system, leading to the accumulation of unstable proteins that await proteasomal degradation [122]. Furthermore, aggregation of p53 is linked to the hyperactivation of oncogenic heat shock response, suggesting that the demand has greatly exceeded the capacity of the proteostasis network [122].

Another common genetic defect in cancer is karyotype heterogeneity associated with aneuploidy, which can disrupt the steady-state levels of proteins. By imposing unsustainable burdens on the protein quality-control system, aneuploidy sensitizes the cells to additional proteotoxic stress. Studies in yeast and human cells have established that proteins expressed

from additional chromosomes in aneuploid cells destabilize proteostasis [123–125]. Oromendia et al. showed that aneuploid yeast strains are intrinsically more prone to protein aggregation, harboring elevated levels of protein aggregates that require enhanced proteasomal degradation [124]. Additionally, the gain of one extra copy of chromosomes in yeast is sufficient to confer hypersensitivity to inhibition of protein synthesis, folding, and degradation, indicating that the proteostasis network ordinarily operates at full capacity [123, 126]. Studies in tumor cells further demonstrate that activity of the proteostasis network is hampered by aneuploidy [125, 127]. One study showed that available Hsp90 activity is consistently reduced in a panel of human aneuploid cells, while another showed that both Hsf1-dependent heat shock response and Hsp90-dependent protein folding are impaired in trisomic and tetrasomic human cell lines [128, 129]. Together, these findings support the notion that genomic instability is a key contributor to proteostatic dysfunction in tumors.

Given that tumor cells are under chronic proteotoxic stress, exacerbating the strain on the proteostasis network is now being explored as a therapeutic strategy in combination with existing cancer treatments. Many components of the proteostasis network have emerged as promising anti-cancer targets, including the molecular chaperones Hsp70 [130] and Hsp90 [131, 132], the major heat shock transcription factor Hsf1 [133, 134], constituents of the proteasome complex [111, 135–137], and the unfolded protein response in general [138, 139]. Additionally, inhibition of Hsp90 confers sensitivity to radiation-induced DNA damage by interfering with DSB repair and cell cycle checkpoints [46]. Because many protein quality control factors are also key regulators of drug-induced stress responses, targeting components of the proteostasis network not only challenges the tumor cells' capacity to proliferate, but also sensitizes tumors to the cytotoxicity of existing chemotherapeutics [140–144].

Activation of the proteostasis network by genotoxic stress has been well characterized, particularly in the context of cancer, but less is known about the impact of proteotoxic stress on genome integrity. Nonetheless, the accumulation of unfolded proteins due to proteotoxic stress has been shown to promote genome instability in yeast [47, 145, 146]. For example, robust Hsp90 inhibition can potentiate aneuploidy as a mechanism of rapid stress adaptation [47]. Similarly, Shor and colleagues demonstrated that canavanine, a toxic arginine analog that causes the accumulation of non-functional yeast proteins, induces mutagenesis and aneuploidy involving the translesion DNA polymerases Rev1 and Pol ζ and non-homologous end joining factor Ku [145]. Proteotoxic stress can also indirectly affect genome integrity by hindering DNA damage repair. For example, endoplasmic reticulum (ER) stress induced by tunicamycin triggers proteasomal degradation of the DNA repair protein Rad51 and suppresses DNA double-strand break repair, sensitizing tumor cells to ionizing radiation [139]. In contrast, downregulation of Protein kinase RNA-like Endoplasmic Reticulum Kinase (PERK), which activates UPR in response to ER stress, enhances DNA double-strand break repair and desensitizes tumor cells to irradiation [147]. More work is needed to understand whether enhancing the capacity of the proteostasis network could provide cross-protection against future genotoxic stress.

One of the primary risk factors for cancer is aging. The prevailing theory is that the DNA damage repair and protein quality-control machineries naturally deteriorate with age, generating intrinsic genotoxic and proteotoxic stress that promote tumorigenesis [148–151]. Age-related genomic instability can trigger proteotoxic stress that could in principle further destabilize the genome. However, it is possible that the age-dependent decline in proteostasis could itself induce genomic instability, creating favorable conditions for tumorigenesis. A number of yeast proteins involved in protein synthesis, processing, trafficking and degradation are required for tolerating the cytotoxicity of DNA damaging agents [152]. Loss of the Hsp70/Hsp90 co-chaperone Sti1, the sensor of the unfolded protein response (UPR) pathway Ire1, or members of the ubiquitin-mediated proteolytic pathway confers hypersensitivity to the alkylating agent MMS [152].

Aging is also the greatest risk factor for neurodegeneration. Much like the connection between cancer and genomic instability, neurodegenerative diseases are broadly associated with proteomic dysfunction. However, there is now clear evidence that aging and neurodegeneration are accompanied by an increase in somatic mutations in human neurons [153]. An emerging concept is that dysfunction of DNA repair pathways also occurs in neurodegeneration and contributes to cognitive decline [154–156]. Jensen et al recently reported that in Alzheimer's disease (AD) patients, components of the NER pathway are expressed at much higher level in the brain tissue than in the blood [155]. Sepe and colleagues also discovered a link between impaired DNA damage repair capacity and Parkinson's disease (PD): nucleotide excision repair (NER) capacity is crippled in dermal fibroblasts isolated from PD patients, as indicated by persistence of the γ H2AX DNA damage foci 24 hours post-irradiation [156]. Reciprocally, mutant mice lacking the DNA repair *Ercc1* gene exhibit pathological hallmarks of PD, suggesting that defective NER could be a contributing factor in the development of the disease [156]. Remarkably, dietary restriction, which suppresses proteotoxicity diverse animal models of polyglutamine disease and Alzheimer's disease, also reduces the number of γ H2AX foci in *Ercc1*-deficient mice, raising the possibility that effective treatment of neurodegenerative diseases may require attention to dysfunction of the DNA damage response and protein-quality control machinery alike [157, 158].

Conclusion and Future Directions

DNA and protein damage are facts of life, and all organisms maintain a suite of repair proteins to contend with these challenges. In the case of DNA damage, organisms arrest cell cycle progression by inducing a checkpoint and proceed to repair DNA lesions, breaks, and other forms of damage in chromatin [1]. Translesion synthesis can also allow organisms to tolerate DNA damage, allowing replication to proceed, and potentially permitting later repair of the initiating lesions. When these processes go awry the consequences can be severe. In humans, mutations in repair and recombination proteins result in myriad cancer-prone and premature aging syndromes [21, 159]. Yet the (in)fidelity of DNA replication and repair processes is also critical for the generation of genetic variation: the substrate on which natural selection can act. Theoretical and experimental work has hinted that mutation rates are tuned to balance these competing needs, and that this balance can be shifted in times of stress to favor greater diversification [160].

Proteins are also subject to extensive quality control. However, induction of protein quality control pathways cannot always rescue proteins that have lost their native fold in the crowded intracellular milieu, leading to aggregation. A striking number of these aggregation events result in cell cycle arrest. For example, aggregation of Huntingtin expansions leads to inactivation of the anaphase promoting complex and G2/M checkpoint arrest [74] in human cells. In yeast, the Rnq1 prion co-aggregates with the spindle pole body to likewise induce a Mad2-dependent checkpoint [72]. Similarly, responses to unfolded proteins involving the upregulation of many p53 targets in human cells [8] provide a robust link between cellular responses to proteotoxic and genotoxic stress. These results may explain many long enigmatic observations of cross-protection between these two forms of stress.

Perhaps most remarkably, protein aggregates have been directly implicated in a wide variety of transactions related to DNA repair. Examples range from aggregates formed by p53 variants linked to ovarian cancer [118, 161, 162] to PARP scaffolding aggregation of FUS at sites of DNA damage [163]. In some cases, as with the helicase Mph1/FancM [82], aggregation can even be prion-like, providing a means for epigenetic control of DNA repair processes. In this respect, it is remarkable that many DNA repair factors organize into foci in response to damage. It seems likely that at least some such assemblies may resemble the liquid phase separated bodies formed by other nucleic acid binding proteins that harbor prion-like domains [105, 164].

Many differences between damage to proteins and DNA limit parallels that can be drawn. Notably, proteins are reminiscent of the hardware rather than the software that drives the living systems. Yet because protein folding is so sensitive to environmental conditions, it also provides a useful stress sensor that many organisms have integrated into other stress responses, including DDR. In some instances, this crossprotection can also extend to future generations, suggesting that the response can also be endowed with a form of memory. Indeed, molecular memory of genotoxic stress, in the form of adaptation, diminishes the efficacy of existing chemotherapeutics. More broadly, insights from cancer and neurodegeneration point to the central importance of integrating DNA damage responses and proteotoxic stress responses for human health. Rapidly aging populations worldwide necessitate new therapeutic strategies for these plagues of modern civilization. The interface between proteotoxic and genotoxic stress responses may provide fertile ground for finding them.

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ABBREVIATIONS:

PQC	protein quality control
DDR	DNA damage response

HSP

heat shock protein

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Figure 1. The DNA damage response and protein quality control are intimately linked.

(Top panel) Proteomic perturbation disrupts proteostasis, while molecular chaperones and protein quality control factors promote proteostasis, assisting the refolding of misfolded proteins and eliminating aggregated proteins. Likewise, DNA damage threatens genomic stability, whereas DNA replication and repair factors maintain genomic stability. (Bottom Panel) Ubiquitin signaling is a common feature of the DNA damage response and protein quality control. Monoubiquitination of histone H2A in response to DNA damage recruits key regulators of DNA damage repair to the site of DNA damage. In response to proteomic perturbation, molecular chaperones and protein quality control factors are recruited to misfolded proteins, and polyubiquitination targets misfolded protein for proteasomal degradation.

Figure 2. Feedback between protein aggregation and the DNA damage response.

(Top panel) Cancer-associated mutations in p53 drive the formation of toxic p53 aggregates, resulting in the loss of DNA binding activities. (Middle panel) Double-strand breaks induce the formation of [MPH1⁺], a yeast prion that reduces the frequency of spontaneous mutation, likely due to increased homologous recombination. (Bottom panel) Nutrient deprivation triggers the sequestration of Cdc19 into reversible aggregates, which protect Cdc19 from stress-induced degradation and allow for the re-initiation of the cell cycle following stress relief.

Figure 3. Chronic genotoxic stress and proteotoxic stress in the progression of cancer and neurodegenerative disease.

In cancer, the unresolved genotoxic stress can be perpetuated by its strain on the proteostasis network. Similarly, in neurodegeneration the endogenous proteotoxic stress is propagated in part due to its role in promoting genomic instability, which further exacerbates the proteostatic imbalance.