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Huiting, Wouter; Bergink, Steven

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REVIEW ARTICLE

Locked in a vicious cycle: the connection between genomic instability and a loss of protein homeostasis

Wouter Huiting[1] · **Steven Bergink**[1]

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Abstract

Cardiomyopathies, neuropathies, cancer and accelerated ageing are unequivocally distinct diseases, yet they also show overlapping pathological hallmarks, including a gradual loss of genomic integrity and proteotoxic stress. Recent lines of evidence suggest that this overlap could be the result of remarkably interconnected molecular cascades between nuclear genomic instability and a loss of protein homeostasis. In this review, we discuss these complex connections, as well as their possible impact on disease. We focus in particular on the inherent ability of a wide range of genomic alterations to challenge protein homeostasis. In doing so, we provide evidence suggesting that a loss of protein homeostasis could be a far more prevalent consequence of genomic instability than generally believed. In certain cases, such as aneuploidy, a loss of protein homeostasis appears to be a crucial mechanism for pathology, which indicates that enhancing protein quality control systems could be a promising therapeutic strategy in diseases associated with genomic instability.

Keywords Protein homeostasis · Genomic instability · Degeneration · Protein quality control

Introduction

To safeguard nuclear genome integrity, cells rely on an extensive network of cell cycle checkpoints, DNA repair pathways and damage-induced signaling cascades, collectively referred to as the DNA Damage Response (DDR) (reviewed in Giglia-Mari et al. 2011). Although the DDR successfully deals with DNA damage and prevents them from becoming 'locked-in' genomic alterations, DNA lesions can occasionally be repaired improperly, resulting in a tendency of any genome to accumulate changes over time, a phenomenon referred to as genomic instability (Niedernhofer et al. 2018). For example, point mutations (i.e. base substitutions) are the result of stochastic replication errors or DNA lesions that are improperly detected or repaired (Aguilera and Gómez-González 2008). Larger, structural variants—so named because they require a disruption of the DNA sugar backbone—are caused by various mutational processes during DNA recombination, replication or repair (reviewed in Carvalho and Lupski 2016). These different types of 'locked-in' genomic alterations can be inherited, but due the constant pressures of DNA damage and the inherent stochasticity of genome replication and maintenance, they can also occur de novo (i.e. in the germline of the parent). Additionally, they can arise somatically (i.e. acquired during development and life), resulting in distinct and unique genomic alterations in each individual cell (Shendure and Akey 2015). Lastly, genomic instability can also be considered to include the accumulation of unrepaired, persistent DNA lesions, although many of these are thought to eventually result in mutations or chromosomal rearrangements as well (Tubbs and Nussenzweig 2017).

Nuclear genomic instability is a central feature of carcinogenesis (Jeggo et al. 2016; Negrini et al. 2010), but it is also strongly implicated in a range of other pathologies. The impact of genomic instability on tissue homeostasis is underlined by the more than 50 disorders currently known to be caused by mutations in genes that function in DNA repair (Petr et al. 2020). Because of its compelling link to cellular degeneration, genomic instability is widely recognized as one of the primary hallmarks of ageing (Vijg and Suh 2013). However, whereas the role of genomic instability in carcinogenesis is well-documented, how it can drive

✉ Steven Bergink
s.bergink@umcg.nl

[1] Department of Biomedical Sciences of Cells and Systems, University Medical Center Groningen, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands

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degenerative processes is far less understood. In this regard, an often underexposed side of genomic instability is its possible impact on the proteome.

To maintain a balanced proteome (i.e. *protein homeostasis* or proteostasis) inside the complex and crowded intracellular environment, cells rely on the constant surveillance of an elaborate, interlinked system of molecular chaperones, regulators and protein degradation pathways, referred to as the proteostasis- or protein quality control (PQC) network (Hipp et al. 2019). The PQC network ensures that proteins are synthesized at the right time and in the right quantity, that they are folded correctly, and that proteins that are misfolded, aggregated or no longer needed are degraded. Safeguarding protein homeostasis is crucial for any cell, as 'proteome instability' can result in protein aggregation and proteotoxic stress, which drive dysregulation of cellular pathways and functionality impairment, degeneration and cell death (Klaips et al. 2018; Labbadia and Morimoto 2015).

If and how genomic instability challenges protein homeostasis remains incompletely understood, but emerging data suggests that they may indeed be inherently connected. This is illustrated tellingly in cancer cells, which suffer from severe proteotoxic stress, resulting not only from their increased metabolism—elevating the protein folding demand—but also from a high burden of genomic alterations (Anon 2020; Dai et al. 2012; Deshaies 2014; Priestley et al. 2019; Vogelstein et al. 2013). Genomic instability has also been implicated in several (age-related) degenerative disorders believed to be primarily caused by a loss of protein homeostasis, including Alzheimer's (Hou et al. 2017) and Parkinson's (Sepe et al. 2016) disease. Vice versa, several recent studies have reported that proteotoxic stress plays a central role in disorders strongly associated with genomic instability (Hamczyk et al. 2019; Zhu et al. 2019). Although the DDR and the PQC network have long been approached as separate entities, over the last few years it has become clear that they are intricately interwoven with other core cellular signaling pathways, and importantly, with each other as well (Chatzidoukaki et al. 2020; Xie and Jarosz 2018). Together, these findings point at the possibility that genomic instability and proteome instability converge on a path to disease.

In this review we discuss the intricate relationship between genomic instability and protein homeostasis. We start by outlining the functionality of the PQC network in some more detail, and by explaining the concepts of protein aggregation and proteotoxicity. After this, we continue with an overview of the emerging interconnectivity between DDR and PQC network components. Next, we focus on the often complex proteomic impact of distinct genomic alterations—which frequently venture far beyond a simple 'loss of function'—and discuss their molecular links with protein stability, misfolding and aggregation. In the last section, we explore the possibility of augmenting the capacity of the PQC network to mitigate the detrimental consequences of genomic instability.

Protein aggregation and proteotoxicity

Most proteins are thermodynamically only marginally stable in the physiological context of the cell (DePristo et al. 2005), and some are even found to be inherently unstable due to their specific sequence properties (Deller et al. 2016). Up to 30–50% of the human proteome appears to be made up of proteins that contain large regions of low complexity (intrinsically disordered regions, IDRs), most of which are only stabilized upon binding to specific partners (Gsponer et al. 2008; Uversky 2019). A large number of these proteins are expressed at concentrations close to their solubility limit in the cellular environment, forming a 'metastable subproteome' that is highly susceptible to misfolding (Tartaglia et al. 2007). These features likely overlap with the functional use of liquid–liquid phase-separation of biomolecules (proteins and nucleic acids) in cells, a process that needs to be closely regulated to avoid off-pathway phase transitions (Box 1). All of this underlines the extreme complexity of the human proteome, in which thousands of marginally stable protein species are coordinately expressed, the majority of which need to fold into a well-defined three-dimensional structure (i.e. their 'native state') and be maintained at precise abundances to perform their function. In addition, stresses like elevated temperatures (Ghosh and Dill 2010), heavy metals (Tamás et al. 2014) and oxidative stress (Lévy et al. 2019) pose an added burden on the proteome by damaging proteins and impairing protein production.

For most (globular) proteins the native state is a finite ensemble of closely related three-dimensional conformations ('conformers'). Within the native state, a protein can (locally) adapt its structure, for example upon ligand binding and release (including nucleic acids and other proteins) (Janin et al. 2008), or during enzymatic activity (Chiti and Dobson 2017). In the complex environment of the cell, proteins rely on molecular chaperones of the PQC network to guide them into this conformation, prevent them from becoming misfolded, or even refold them when needed (Hartl et al. 2011). Several conserved families of molecular chaperones exist, two core machineries of which are particularly relevant for the topic of this review: HSP70 and HSP90 (Fig. 1).

HSP70 has a strong affinity for hydrophobic stretches, which in the native state of a globular protein are hidden in the core, but become exposed when proteins unfold. HSP70 assists in the (re)folding of these substrates by binding and subsequently releasing them in iterative, ATP-dependent

Box 1.

An expanded view of aggregation: genomic instability affecting biomolecular condensation?

In recent years biomolecular condensation or 'liquid-liquid phase separation' (LLPS) has emerged as a fundamental principle of protein organization that underlies the formation of a wide range of subcellular structures (reviewed in Alberti 2017; Shin and Brangwynne 2017). During biomolecular LLPS, proteins and nucleic acids condense (i.e. 'de-mix' from solution) when it is energetically favorable for them to switch from interacting with water (i.e. soluble) to interacting with other macromolecules (Alberti, Gladfelter, and Mittag 2019). In its simplest form, this results in two distinct phases — a dilute phase and a dense phase. Biomolecular condensation can have a broad impact in cells, for example by locally concentrating certain factors to facilitate reactions or processes (e.g. in gene regulation (Boija et al. 2018), DNA repair (Pessina et al. 2019), autophagy (Fujioka et al. 2020)), or even by sensing and/or exerting direct mechanical force on its surroundings (Shin et al. 2018). A complex interplay of factors determines whether LLPS occurs for a given macromolecule, including its intrinsic properties (e.g. valency, structure), local concentration (i.e. supersaturation), the presence of binding partners or post-translational modifications (e.g. ubiquitylation), and environmental conditions affecting solubility (e.g. temperature, salt, pH) (Banani et al. 2017; Hofweber and Dormann 2019; Martin and Mittag 2018; Ruff et al. 2018; Sun et al. 2018; J. Wang et al. 2018).

Accumulating evidence indicates that protein aggregation can be the result of aberrant phase-separation, in which biomolecular condensates have undergone further transitions to reach an almost irreversible, (fibrillar) solid-like structure (Alberti and Hyman 2016; Verdile, de Paola, and Paronetto 2019). Strikingly, many aggregating proteins are also characterized by the presence of multivalent intrinsically disordered regions (IDRs), which appears to be a particularly important determinant of LLPS occurrence (Harmon et al. 2017). This suggests that genomic alterations may also challenge protein homeostasis by altering LLPS dynamics, either directly (e.g. by changing properties or concentrations) or indirectly (by disrupting PQC network processes dependent on LLPS (Fujioka et al. 2020; Yasuda et al. 2020)). Several recent studies provide support for at least the former. For example, CAG expansion in huntingtin has been shown to catalyze its transition from a reversible liquid-like assembly into a solid-like, fibrillar aggregate (Peskett et al. 2018), and disease-associated mutations in for example tau (Wegmann et al. 2018) and FUS (Patel et al. 2015) have been reported to have a similar impact. Interestingly, recent work has indicated that LLPS may also be used by cells as a 'low-pass filter' to reduce transcriptional noise (Klosin et al. 2020), indicating that LLPS can perhaps also be wielded to safeguard protein homeostasis.

Although it is likely that we have only scraped the surface of its biological importance, LLPS appears to play a pervasive and complex role in mediating the relationship between genome and proteome. Its relevance for protein homeostasis and aggregation is already rapidly materializing, and despite the fact that much has yet to be shown experimentally, the potential impact of global genomic instability on this process appears evident.

cycles, thus preventing aggregation and allowing their folding to take place (Rudiger et al. 1997; Kampinga and Craig 2010; Mayer 2018). The HSP70 cycle is closely regulated by J-domain proteins (JDPs, also called HSP40s) which facilitate client engagement (Kampinga and Craig 2010). HSP70 works in close concert with the chaperone machinery of HSP90, which is thought to take over partially folded clients directly and facilitate their complete (re)folding (Morán Luengo et al. 2019). Besides acting downstream of HSP70 in protein folding, HSP90 also fulfills many crucial roles in cell physiology by facilitating the maturation and conformational stability of client proteins, often assisted by various 'co-chaperones' (reviewed in Biebl and Buchner 2019). Many DNA repair proteins rely extensively on HSP70 often in combination with HSP90 to shape their conformational stability, and control their assembly into multiprotein DNA repair complexes (Knighton and Truman 2019; Sottile and Nadin 2018) (Fig. 1, bottom table).

When proteins fail to reach or hold their native state—i.e. when chaperones are unable to meet the folding demand—they can misfold and lose their function. Misfolded and superfluous proteins are sent for degradation (Fig. 1), or they can aggregate (see below). The two main intracellular proteolytic pathways are the ubiquitin–proteasome system (UPS) and the autophagy–lysosomal system. The UPS is a highly specific pathway that is responsible for most of the individual protein degradation. UPS substrates are recognized and posttranslationally tagged by ubiquitin in a three-step enzymatic cascade to target them for degradation (Amm et al. 2014). The autophagy–lysosomal system is an umbrella

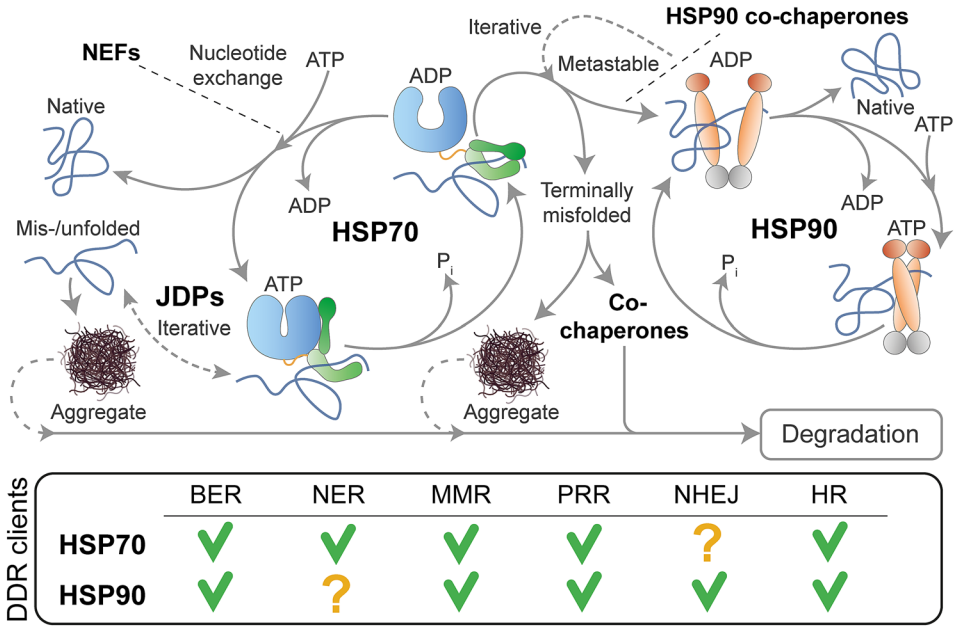

Fig. 1 A simplified overview of the chaperone machinery of the PQC network, responsible for proper protein (re)folding, maturation, and maintenance of conformational stability, all to avoid aggregation and enable protein function; through these functions the PQC network is also of crucial importance for regulating the function of clients in DDR pathways. Interaction of HSP70 with protein substrates is allosterically controlled by ATP and the substrate itself, and co-regulated by different JDPs, which function as 'targeting factors' that further increase substrate affinity. Through iterative cycles of substrate binding and release, where the substrate-binding domain of the HSP70 machinery alternatingly adopts an 'open' or 'closed' conformation, substrate folding is promoted. Substrates can also be handed over—mediated by co-chaperones (e.g. HOP)—to the HSP90 machinery when they are metastable and/or require HSP90 for full maturation. HSP90 exists as a homodimer that assumes an extended conformation when bound to ADP. Its folding activity depends on alternating between this 'open' state and a 'closed' state, which is favored by ATP-binding to the N-terminal domain that subsequently dimerizes. When proteins are terminally misfolded, they can be targeted for degradation, mediated by co-chaperones (e.g. the E3 ubiquitin ligase CHIP). *BER* base excision repair, *NER* nucleotide excision repair, *MMR* mismatch repair, *PRR* post-replication repair, *NHEJ* non-homologous end-joining, *HR* homologous recombination, *JDP* J-domain proteins, *NEF* nucleotide exchange factor

term that describes three major forms of proteolysis: chaperone-mediated autophagy, microautophagy and macroautophagy. Importantly, all three make use of the same general principle of lysosomal degradation, and only differ in how they deliver substrates to the lysosome (Hansen et al. 2018). Autophagy occurs primarily in response to cellular stress, to free up molecules like amino acids or lipids for reuse, or to degrade large unwanted substrates, including damaged organelles like mitochondria (Dikic and Elazar 2018). It starts by the engulfment of sequestered cytosolic cargo by a double-membrane structure known as an autophagosome. This autophagosome then translocates to the lysosome with which it fuses, after which the inner membrane together with the cargo are degraded by the hydrolytic enzymes inside the lysosomal lumen (Bento et al. 2016).

Protein aggregation, proteotoxicity and pathology

When the PQC network is unable to guide or hold proteins in their native state, they can misfold and convert into a non-functional, aggregated state, which is believed to frequently render a protein toxic to its environment (i.e. a 'proteotoxic gain of function') (Fig. 1). Protein aggregates exist in a range of different conformations, but overall, they can be divided into two main classes: disordered/amorphous aggregates, and amyloids. Whereas amorphous aggregates arise typically as a result of off-pathway, hydrophobic interactions (Hipp et al. 2019), amyloids are formed by the self-assembly of β-strand containing proteins into a 'cross-β' filament structure (Dobson 2017). How these protein aggregates can drive pathology through proteotoxicity lies beyond the scope of this review, but is thoroughly reviewed elsewhere in Kampinga and Bergink (2016), and in Klaips et al. (2018). Importantly, metastable or aggregation-prone proteins can also affect the stability of the global proteome, for example by increasing the aggregation propensity of other proteins. This is believed to be mainly the result of a competition for limited chaperone-mediated folding capacity and/or sequestration of chaperones in protein aggregates (Gidalevitz et al. 2010; Hipp et al. 2019). In addition, protein aggregates (in particular amyloids) can directly induce the 'co-aggregation' of other proteins, which likely occurs through various

mechanisms (Bondarev et al. 2018). These and other findings indicate that an initial aggregation event can drive a cascade (or 'snowballing') of subsequent misfolding and aggregation events, which ultimately leads to a complete loss of protein homeostasis.

Protein homeostasis mechanisms are interlinked with genome maintenance

Protein aggregation poses a threat to the integrity of the genome

A growing body of experimental data points at protein aggregation as a possible cause of DNA damage. Aggregation of certain disease-associated proteins, including amyloid-β fragments and α-synuclein, has been associated with elevated levels of DNA strand breaks (Farmer et al. 2020; Illuzzi et al. 2009; Vasquez et al. 2017), indicating that DNA damage can be an ancillary consequence of protein aggregation. Two primary biological cascades have been proposed to underlie this damage. First, aggregated proteins can elicit genotoxic oxidative stress by engaging mitochondria and driving mitochondrial dysfunction (Lévy et al. 2019). One example comes from pathogenic α-synuclein aggregates, which can bind mitochondrial membranes and impair respiratory chain components, hampering oxidative phosphorylation (Ludtmann et al. 2018). This in turn can lead to the dissipation of the mitochondrial membrane potential and to the formation of harmful reactive oxygen species (ROS). Although cause and consequence can sometimes be difficult to disentangle, aggregation of, among others, mutant SOD1 (Vehvilainen et al. 2014), TDP-43 (Wang et al. 2019), Huntingtin(Htt) (Bossy-Wetzel et al. 2008) and amyloid-β (Moreira et al. 2010) fragments have been reported to lead to a similar impairment of mitochondrial function.

Second, aggregating protein species can sequester factors required for DNA repair, thus draining the functional pool of proteins involved in maintaining genome integrity. Although it is not always clear if the sequestration of DNA repair factors is able to completely explain the observed impairment of genome maintenance, this appears to be a general phenomenon in several neurodegenerative disorders associated with protein aggregation (Enokido et al. 2010; Gao et al. 2019; Nakamura et al. 2019; Suberbielle et al. 2015).

Related to this, the native, soluble isoforms of certain disease-associated proteins, including Tau, FUS, SOD1 and α-synuclein, have been directly linked to genome maintenance in vivo, and genomic instability caused by their mutant species has been attributed to their effective loss from the nucleus (Bordoni et al. 2019; Maina et al. 2016; Schaser et al. 2019; Wang et al. 2018). Importantly, it is not always understood if this is a direct consequence of their misfolding, or a result of their accelerated aggregation in the cytoplasm.

Although several studies have investigated the relationship between protein aggregates and reduced genome maintenance, it is still unclear to what extent this connection is limited to aggregation of specific disease-associated proteins. Recent experimental work suggests that it extends to protein aggregation in general, as artificial aggregation of firefly luciferase has also been found to impair genome maintenance in human cells (Ben Yehuda et al. 2017).

The PQC network is crucial to maintain genome integrity

The PQC network safeguards protein homeostasis by carefully regulating protein synthesis, folding, and degradation, and through these functions it also plays a role in coordinating genome maintenance pathways. Many DNA repair proteins rely extensively on PQC network chaperones to shape their conformational stability, and control their assembly into multiprotein DNA repair complexes (Knighton and Truman 2019; Sottile and Nadin 2018). A well-studied example is HSP90, which has emerged as a central player in many DNA repair processes (Dubrez et al. 2020). HSP90 accumulates in DNA damage sites (Oda et al. 2007; Quanz et al. 2012), and its inhibition sensitizes human cells to both UV (Sekimoto et al. 2010) and γ-irradiation (Dote et al. 2006). HSP90 chaperones multiple DNA repair factors in different pathways, including RAD51 (Ko et al. 2012), FANCA (both homologous recombination, HR) (Oda et al. 2007), DNA-PK (non-homologous end-joining, NHEJ) (Solier et al. 2012), Pol eta (translesion synthesis, TLS) (Sekimoto et al. 2010) and XRCC1 (base-excision repair, BER) (Fang et al. 2014). It also has a critical role in the recruitment of the DSB repair machinery by stabilizing the MRN complex and stimulating the activity of ATM (Cheng et al. 2017). HSP90's function complements that of HSP70 in various genome maintenance pathways, including BER, mismatch repair (MMR) and HR (Dubrez et al. 2020). These findings appear to reflect a broad nuclear activity of the HSP90 chaperone machinery, which is further underlined by the conserved role of the HSP90 co-chaperone p23 in several DNA repair pathways (Echtenkamp et al. 2011).

The two main proteolytic pathways of the PQC network, the autophagy–lysosomal system and the UPS, can also impact genome integrity. Not only do they mitigate oxidative DNA damage by controlling mitochondrial quality (Pickles, Vigié, and Youle 2018; Ravanelli et al. 2020), they also influence the dynamics of genome maintenance by controlling the turnover of many key DNA repair proteins (Brinkmann et al. 2015; Guo and Zhao 2020) and the DNA replication machinery (Roseaulin et al. 2013; Walter et al.

2016). Autophagy also appears to play a key role in maintaining nuclear homeostasis by selectively degrading other nuclear components (i.e. 'nucleophagy'), including nucleolar factors and nuclear lamina proteins (Otto and Thumm 2020; Papandreou and Tavernarakis 2019). Although it is not always clear to what extent nucleophagy-substrates constitute damaged nuclear content, or whether it is a reflection of normal turnover, inhibiting autophagy has been shown to result in an aberrant nuclear morphology (Park et al. 2009), which may affect the integrity of the genome as well. Turnover of nuclear components is sometimes mediated by crosstalk between the two systems through the autophagy adaptor protein SQSTM1/p62 (Hewitt et al. 2016). For example, autophagy inhibition results in the nuclear accumulation of p62, which can indirectly alter HR by facilitating the proteasomal degradation of CHK1, FLNA and RAD51 (Hewitt and Korolchuk 2017). The UPS also plays a central role in genome maintenance by orchestrating a vast amount of ubiquitylation events, most of which are however not linked to client degradation (reviewed in Bergink and Jentsch 2009). Interestingly, although impairment of both autophagy and the UPS has been increasingly linked to genomic instability, several studies have also reported decreased DNA repair after inhibition of the proteasome (Arlow et al. 2013; Karpov et al. 2013; Sciascia et al. 2020). Together, this indicates that the autophagy–lysosomal system and the UPS have a complex—and still incompletely understood—role in the context of genome maintenance.

The strong dependency of DNA repair on the PQC network also poses a risk. During chronic proteotoxic stress, an excessive protein folding and degradation demand can overwhelm the capacity of the PQC network, depleting free chaperone pools (Hipp et al. 2019) and disrupting the function of both autophagy (Monaco and Fraldi 2020) and the UPS (Thibaudeau et al. 2018). This could potentially lower their net functional availability for other cellular processes, including genome maintenance. An interesting example of such a possible trade-off between protein homeostasis and genome integrity is proteotoxic stress-induced aneuploidy, which has been shown to result from a reduced availability of the HSP90 machinery for kinetochore assembly, leading to karyotype changes following cell division (Chen et al. 2012). While this mechanism may benefit the population in the long term by increasing genetic variation in the face of changing environments (Chen et al. 2012; Kaya et al. 2020; Rancati et al. 2008), it has substantial consequences for the individual cell. Another example is the widespread use in both contexts of ubiquitin and ubiquitin-like proteins (most notably NEDD8 and SUMO) as posttranslational modifications. These small polypeptides (8–11 kDa) are conjugated to target proteins and act as signaling molecules, often in concert with each other. They perform crucial regulatory roles in genome maintenance as modulators of protein–protein and protein-DNA interactions (reviewed elsewhere in Bergink and Jentsch 2009; Brown and Jackson 2015; Wang et al. 2017), but in the PQC network they function primarily as coordinators of the UPS and the autophagy-lysosomal pathway (Liebelt and Vertegaal 2016; Pohl and Dikic 2019), and as regulators of protein aggregation. The pervasive use of ubiquitin and ubiquitin-like protein modifications in both genome maintenance and protein homeostasis mechanisms has led to the idea that under proteotoxic stress, the PQC network competes for free ubiquitin with other ubiquitin-dependent processes, including genome maintenance and chromatin regulation pathways (Dantuma et al. 2006; Park and Ryu 2014). In line with this, proteasome dysfunction and aggregation of ubiquitin-positive substrates have been shown to specifically deplete the nuclear pool of unconjugated ubiquitin (Farrawell et al. 2018; Mimnaugh et al. 1997), and one recent study reported that DNA repair capacity was hampered as a consequence of this (ben Yehuda et al. 2017). However, mechanistic intervention studies are lacking so far, and although ubiquitin-, NEDD8- and SUMO-conjugated substrates all accumulate in protein aggregates upon proteotoxic stress (Bence 2001; Enchev et al. 2015; Liebelt and Vertegaal 2016), it is still unclear if competition for these posttranslational modifiers can explain increased genomic instability upon a loss of protein homeostasis.

Genome maintenance defects are causally linked to a loss of protein homeostasis

Overall, safeguarding protein homeostasis appears to be important to preserve genomic integrity. Importantly, this relationship between cellular protein homeostasis and genome integrity extends in the both directions. For example, protein misfolding and aggregation can affect genome maintenance, but genome maintenance defects are also causally linked to a loss of protein homeostasis.

A first indication of this is the notion that genome maintenance processes have been picked up in genetic screens designed to identify possible modulators of protein aggregation in various model organisms (van Ham et al.2009). More direct evidence for this connection is provided by heritable defects in several genome maintenance pathways that are causally linked to a loss of protein homeostasis. A well-studied example is ATM, a PI3K-like kinase that functions as a master switch in genome maintenance and cell cycle checkpoint regulation. The absence of functional ATM—which causes the severe neurodegenerative disorder ataxia–telangiectasia (A–T) (McKinnon 2012)—results in a hypersensitivity to double-strand breaks (DSBs) and to oxidative stress-inducing drugs, and leads to higher intracellular ROS levels (Barzilai et al. 2002). This increase in baseline ROS is associated with reduced cellular health, and

in particular with a loss of protein homeostasis, including endoplasmic reticulum (ER) stress and activation of the unfolded protein response (UPR) (Barzilai et al. 2002; Liu et al. 2005; Yan et al. 2008). More recent work has revealed that ATM acts as a central regulator of cellular redox homeostasis, and that this function can, surprisingly, be genetically separated from ATM's role in the response to DNA damage (Guo et al. 2010). In the same study, impaired activation of ATM by either DNA damage or oxidation both resulted in the accumulation of aggregated protein species. Additional oxidative stress further exacerbated protein aggregation only in the latter. This indicates that a loss of ATM can potently affect protein homeostasis via a dysregulated redox homeostasis, but also through impaired genome maintenance. In agreement with this, loss of kinase activity of the yeast ATM/ATR kinase Mec1—or its downstream signaling targets—also causes widespread protein aggregation and confers sensitivity to stresses challenging protein homeostasis (Corcoles-Saez et al. 2018). Considering the notion that in A–T, it is—arguably—the absence of ATM's central role in the response to DNA damage which is responsible for the strong cerebellar degeneration observed (Shiloh 2020), this raises the question if genomic instability-induced loss of protein homeostasis could be an underlying pathogenic mechanism in this context.

Interestingly, a similar destabilization of the proteome has been found after impairments of other genome maintenance pathways, mechanistically largely unrelated to ATM. For example, Werner syndrome (WS) is a progeroid disorder cause by mutations in WRN, a DNA helicase involved NHEJ and HR (Croteau et al. 2014). Fibroblasts from WS patients accumulate protein aggregates and exhibit a dramatic upregulation of autophagy (Talaei et al. 2013). Cockayne syndrome (CS) is another severe progeroid disorder, caused by mutations in the transcription-coupled nucleotide excision repair (TC-NER) genes CSA or CSB (Vessoni et al. 2020). A recent study showed that CS patient-derived cells exhibit increased levels of misfolded proteins and ER stress, postulated to result from a reduced ribosomal translation fidelity (Alupei et al. 2018). Similarly, loss of the central NER protein XPA, which is associated with neurodegeneration (Kraemer 1987), has also been shown to lead to increased levels of polyubiquitylated proteins (Arczewska et al. 2013), impaired UPR function and accelerated protein aggregation (de Sousa Leal et al. 2020). For most of these examples, the molecular chain of events connecting a genome maintenance defect to a loss of protein homeostasis is still far from understood, and different pathological mechanisms have been hypothesized for each of them. However, the notion that impairments of mechanistically distinct genome maintenance pathways all lead to an eventual loss of protein homeostasis suggests that they may also share a common underlying cause: a destabilization of the proteome resulting from genomic instability.

Genomic instability intrinsically challenges protein homeostasis

How can genomic instability affect global protein homeostasis? Over the last two decades, studies focusing on age-related disorders, including Alzheimer's and Parkinson's diseases, have contributed enormously to our appreciation of the broad proteome-destabilizing impact of specific inherited and de novo mutations (Chiti and Dobson 2017; Vendruscolo et al. 2011). Accumulating evidence suggests that this connection between genomic instability and a loss of protein homeostasis may extend to somatically acquired alterations and persistent DNA damage as well. For example, recent advances in single-cell sequencing techniques that enable the profiling of cell-to-cell genomic variation (i.e. mosaicism) in high-throughput have revealed that—in parallel to declining protein homeostasis—genomic instability increases widespread in ageing tissues (Blokzijl et al. 2016; Brazhnik et al. 2020; Laurie et al. 2012; Lodato et al. 2018; Martincorena et al. 2015; Zhang et al. 2019). Moreover, we now appreciate that a large array of different types of genomic alterations, including persistent DNA damage, has the potential to destabilize the proteome, either directly or indirectly (Fig. 2). In the next sections, we will review the main mechanisms linking these genomic alterations to a loss of protein homeostasis.

Single nucleotide alterations: conformational instability and synthesis of aberrant mRNA

The potential of genetic alterations to affect protein homeostasis is first highlighted by the numerous base substitution mutations linked to protein conformational diseases, for example in Parkinson's disease (Chiti and Dobson 2017). Many of these mutations alter the conformation of a single protein, which is believed to drive a cascade of misfolding and aggregation events that ultimately destabilizes the proteome, leading to pathology (Vendruscolo et al. 2011). From a molecular perspective, an intrinsic connection between base-substitutions and protein conformational instability is evident. The marginal thermodynamic stability of proteins leaves the protein folding process highly vulnerable to mutations that result in a change in the amino acid sequence, so-called missense mutations, as most of these are destabilizing (Redler et al. 2016). In certain cases, depending on the stability of the native protein and its folding intermediates, and on the location (e.g. hydrophobic core residues are generally less tolerant than

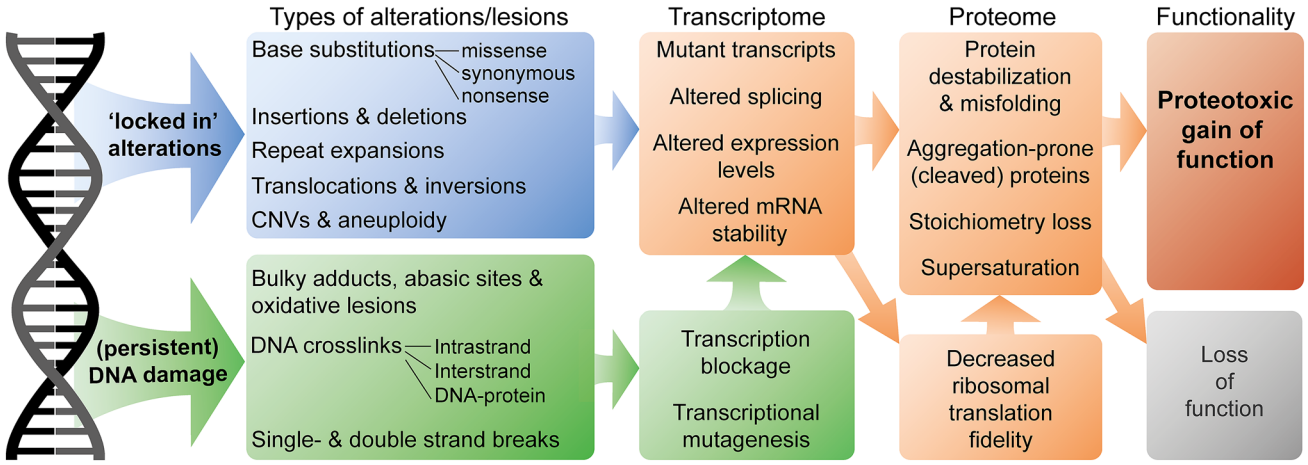

Fig. 2 Schematic overview of the various pathways via which genomic alterations and DNA damage can potentially destabilize the proteome and drive a proteotoxic gain of function

hydrophilic surface residues (Matsui et al. 2017)), even a single missense mutation can completely destabilize a protein, causing it to misfold and/or increase its propensity to aggregate. Examples of this include certain mutations in α-synuclein (Dettmer et al. 2015), PFN1 (Boopathy et al. 2015), p53 (Wilcken et al. 2012), lysozyme (Booth et al. 1997) and transthyretin (Lim et al. 2017), and this list is far from exhaustive. In general, disease-associated mutations appear to occur more frequently at loci vulnerable to substitution-induced protein destabilization and aggregation (de Baets et al. 2015), adding further support to the notion that protein aggregation has a pervasive impact on human disease.

Other mechanisms by which missense mutations can lead to protein aggregation have been reported as well—amino acid substitutions that are not directly destabilizing may still drive a protein into an aggregation-prone conformation. For example, most of the disease-linked mutations in tau reduce its binding affinity for cytoskeletal microtubules, resulting in the accumulation of unbound tau which is highly aggregation-prone (Spillantini and Goedert 2013). A related mechanism has been uncovered for gelsolin, where mutations can impair its ability to bind calcium, leading to the gradual destabilization of the protein. However, unlike tau, the conformational change does not lead to the aggregation of gelsolin itself, but instead exposes a previously buried cleavage site, resulting in the production of small, highly amyloidogenic gelsolin fragments (Solomon et al. 2012). High levels of aggregating amyloid-β and apolipoprotein A-I fragments are the result of a similar mutation-induced dysregulated proteolysis events (Chen et al. 2017; Raimondi et al. 2011).

The incorporation of a different amino acid is not the only mechanism through which point mutations can challenge protein homeostasis. The removal or introduction of a premature stop codon (i.e. 'nonsense' mutation) can prevent a protein from ever being properly synthesized in the first place, as illustrated in the case of Apolipoprotein A-II and PrP, respectively (Benson et al. 2001; Bernardi and Bruni 2019). In both examples, translation is halted at the wrong place of the transcript, leading to the production of (partially) unfolded, aggregation-prone polypeptide fragments. Mutations can also affect protein production by altering splicing patterns, which can result in unstable and/or aggregation-prone polypeptides. In this regard, accumulating evidence suggests that also synonymous (long referred to as 'silent') mutations can profoundly affect both protein expression and conformation. For instance, next to many missense mutations, synonymous mutations in the *MAPT* gene (encoding for tau) can cause altered splicing of the MAPT transcript, resulting in increased synthesis of the disease-associated 4R tau isoform (Niblock and Gallo 2012). Synonymous mutations can even act more subtle, by altering mRNA stability, or by affecting translation rates leading to disrupted co-translational folding (Sauna and Kimchi-Sarfaty 2011). A recent study in *E. coli* showed that synonymous mutations can impair cellular fitness by driving misfolding of the native protein (Walsh et al. 2020), supporting the idea that these mutations can lead to proteotoxicity as well. Although far less studied, mutations located outside of the coding sequence of a gene, including promoter and enhancer regions, introns, and 3′ and 5′ UTRs may all affect protein homeostasis through similar mechanisms (Sauna and Kimchi-Sarfaty 2011).

Of special interest are insertion and deletion mutations ('indels'). Indels spanning a number of nucleotides divisible by three will lead to the incorporation or deletion of one or more amino acids from the polypeptide, which may challenge folding stability. However, indels of any other

size, including single-nucleotide alterations, can dramatically affect protein biogenesis because they change the reading frame of the genetic sequence. For example, frameshift mutations in the transcription factor p63 have been shown to lead to extensions of its C-terminus, resulting in the production of aggregating peptide fragments that display a toxic gain-of-function (Russo et al. 2018). Frameshift mutations in the tumor suppressor protein PTEN were also found to increase aggregation propensity, far stronger than both missense mutations and non-frameshifting indels (Palumbo et al. 2020). The extent to which frameshift mutations, especially those occurring in somatic cells, contribute to a loss of protein homeostasis is still largely unknown—they are difficult to detect in conventional short read sequencing data (Shigemizu et al. 2013) and likely much less frequent than substitutions (Brazhnik et al. 2020). Moreover, their pathological impact has been investigated mainly in the context of carcinogenesis. Nevertheless, their potentially profound impact on the proteome supports the idea that they can play a strong role in disrupting protein homeostasis.

Structural variants and ploidy changes: supersaturation and stoichiometric imbalances

A large, but relatively poorly understood group of genomic alterations is formed by structural variants (SVs), here defined as inversions, translocations, duplications and large indels. SVs typically comprise DNA segments spanning more than 50 basepairs (Baker 2012), leading to either chromosomal rearrangements or changes in absolute DNA content. Although the existence of SVs was initially met with skepticism, a growing body of evidence has shown that SVs are pervasive (Abel et al. 2020), and that they accumulate with age (Forsberg et al. 2012). As a group, SVs are thought to account for most of the interindividual variation among human genomes in terms of total nucleotides involved (Weischenfeldt et al. 2013). Their relationship to pathology and degeneration has been studied mainly in the context of carcinogenesis (Yi and Ju 2018), and although SVs can potentially have a strong proteomic impact—through gene disruption or fusion, or by altering gene expression (Weischenfeldt et al. 2013)—their global effect on protein homeostasis is still largely unexplored.

The proteomic impact of SVs is better characterized in the case of copy number variants (CNVs), resulting from either large duplications or deletions. CNVs are associated with a range of diseases and phenotypic outcomes, including ageing and neurodegeneration (Potter et al. 2019; Shepherd, Yang, and Halliday 2018). Of particular interest here are the CNVs of *SNCA* and *APP* which have been directly linked to an accelerated loss of protein homeostasis and disease progression in Parkinson's (Perez-Rodriguez et al. 2019) and Alzheimer's diseases (Rovelet-Lecrux et al. 2006), respectively. These extra-copy CNVs are thought to increase the expression of aggregation-prone α-synuclein and amyloid-β. Interestingly, Down's syndrome patients, carrying an extra *APP* gene due to trisomy 21, are highly prone to Alzheimer's disease as well (Lott and Head 2019). These findings may reflect the phenomenon of protein supersaturation, where an increased abundance of marginally stable proteins causes them to supersede their in vivo solubility, catalyzing aggregation (Tartaglia et al. 2007). This is supported by findings showing that in yeast, aneuploidy causes widespread proteotoxicity, irrespective of the chromosome involved (Oromendia et al. 2012). Moreover, the proteotoxicity resulting from a single extra chromosome leads to a decrease in yeast replicative lifespan, the extent of which is proportionate to the size of the chromosome (Sunshine et al. 2016). Recent work has uncovered an additional mechanism through which aneuploidy may lead to proteotoxic stress: loss of protein complex stoichiometry. Eukaryotes rely on coordinated protein expression to maintain the proper stoichiometry required for multiprotein complex assembly. The significant expression changes caused by aneuploidy result in a net surplus of protein complex subunits, which have to be dealt with by the PQC network—they are either degraded, or they aggregate (Brennan et al. 2019; Stingele et al. 2012).

Like other SVs, CNVs and aneuploidy can pose a significant threat to the stability of the proteome (Oromendia and Amon 2014), but their contribution to for example the age-related decline in protein homeostasis has not been fully elucidated. One of the reasons for this is that most studies investigating the proteomic consequences of CNVs and aneuploidy have approached it mostly from a germline perspective. Nonetheless, despite at times conflicting data (Bos et al. 2017), many studies have reported that both CNVs, including large megabase variants, and aneuploidy accumulate with age (Revay et al. 2017), also in humans (Forsberg et al. 2012; Villela et al. 2018). Their impact on protein homeostasis may very well depend on the proteins involved, and future studies will therefore have to establish if they have a degenerative role in the general population.

A related class of genomic alterations that can disrupt protein homeostasis is formed by expansions of repetitive DNA sequences. Although such repeat expansions (or 'tandem repeats') can also be considered SVs, underneath we discuss these alterations separately as they can have profoundly distinct proteomic consequences (Spielmann et al. 2018).

Tandem repeats: aggregation-proneness, RAN translation and somatic expansion

Currently, 13 different types of tandem repeats (tri-, tetra-, penta- or hexanucleotide) have been identified, together causing over 40 distinct hereditary disorders (Paulson 2018). In many of these diseases, the expanded tandem repeat leads to the production of a highly aggregation-prone protein that gradually destabilizes the proteome, ultimately leading to a loss of protein homeostasis (Gidalevitz 2006), as is the case for certain polyalanine expansions (Pirone et al. 2019; Polling et al. 2015). One of the most prevalent expansions is the CAG expansion, which occurs in several different proteins. The resulting polyglutamine stretch (i.e. polyQ) causes diseases like Huntington's disease (HD) and most spinocerebellar ataxias (SCAs) (Adegbuyiro et al. 2017). In all known polyglutamine diseases, the size of the expanded CAG tract is inversely correlated to the age of disease onset (Kuiper et al. 2017). This is attributed mainly to the length-dependent ability of polyQ stretches to form stable β-hairpins, resulting in a highly amyloidogenic conformation, although other factors have been shown to affect polyQ aggregation as well (Kuiper et al. 2017). Recently, CAG expansions in huntingtin were also shown to drive its aggregation by altering phase separation dynamics (Box 1).

Although close to half of the repeat expansion disorders are thought be primarily driven by RNA-dependent gain-of-function mechanisms (Ellerby 2019), most of these have been associated with a loss of protein homeostasis as well. One important reason for this is that repeat expansion transcripts can produce proteins in multiple reading frames without the need for a canonical AUG start codon (i.e. repeat-associated non-AUG or RAN translation) (Banez-Coronel and Ranum 2019). Hence, even when an expansion lies outside a protein-coding region, both sense and antisense transcripts can produce different aggregation-prone repetitive polypeptides (Cleary, Pattamatta, and Ranum 2018). This is illustrated by the CTG expansion in junctophilin-3 (*JPH3*) which causes an HD-like syndrome (HDL2). Here, RAN translation of the antisense CAG transcript results in the production of polyglutamine stretches that aggregate, which is thought to be a main driver of HDL2 pathology (Swinnen et al. 2020). A similar mechanism may also play a role in myotonic dystrophy type 1 (DM1), which is caused by a CTG expansion in the 3′ UTR of *DMPK* (Gudde et al. 2017; Zu et al. 2013). RAN translation is also responsible for the production of proteotoxic dipeptide-repeats from the G_4C_2 repeat expansion located in the first intron of C9orf72, which is strongly linked to ALS and frontotemporal dementia (FTD) (Balendra and Isaacs 2018; Zu et al. 2013). Interestingly, RAN translation of both G_4C_2 and CGG (associated with fragile X-associated tremor/ataxia syndrome or FXTAS) repeats has been shown to be activated in a PERK- and eIF2a-dependent manner by the integrated stress response (ISR). This points at the existence of a pathological feed-forward loop, where a gradual destabilization of the proteome favors additional RAN translation of toxic proteins, accelerating the protein homeostasis decline (Green et al. 2017).

Recently, advanced genome profiling techniques like long-read sequencing have unveiled previously unknown neurodegeneration-associated repeat expansions linked to protein aggregation (Cortese et al. 2019; Ishiura et al. 2019), suggesting that pathological tandem repeats may be more common than generally thought. In addition, known tandem repeats may also contribute more to the age-related decline of protein homeostasis than currently believed. Repeat expansions are often highly unstable, expanding further from one generation to the next, a phenomenon referred to as anticipation (Paulson 2018). However, for several tandem repeats, including CAG, CTG, and C9orf72, ongoing expansion has also been observed in somatic cells (Castel et al. 2010; Nordin et al. 2015), in some (but not all, see (Cancel et al. 1998) cases specifically in those tissues most prominently involved in pathology (Kennedy 2003), and correlating with disease progression (Ciosi et al. 2019; Morales et al. 2012; Swami et al. 2009). This supports the idea that in certain situations, somatic expansion can influence disease progression and perhaps even pathogenesis. In line with this, recent work has found that expansion of the only naturally occurring mouse polymorphic CAG repeat (located in the *Tbp* gene) takes place in aged WT mice (Sanchez-Contreras and Cardozo-Pelaez 2017). Although studies investigating ongoing somatic expansion of tandem repeats have so far been largely correlative in nature, it is tempting to speculate about their possible impact on the stability of the proteome. Additional studies combining for example long-read single-cell sequencing with proteomics are therefore needed to address the global effects of expansions on protein homeostasis in the context of both disease and normal ageing.

Persistent DNA damage: transcription blockage and transcriptional mutagenesis

Wrongly repaired DNA damage can lead to mutations and other stable genetic alterations, but importantly, even unrepaired damage can impact protein homeostasis. Although accurately measuring the steady-state levels of such persistent DNA lesions in high-throughput is still difficult, they do appear to accumulate with age, and this has been proposed to be one of the main drivers of the ageing process itself (Lans et al. 2019; Ou and Schumacher 2018; Petr et al. 2020). DNA lesions can affect transcription by impairing or even completely blocking the progression of RNA polymerase II (Pol II), resulting in the reduced production of mRNA which can hamper cellular function. In addition, complete

transcription blockage has been linked to the formation of vulnerable (i.e. unpaired) DNA R-loops that are lesion-prone, which may in turn lead to a vicious cycle of genotoxic events (Lans et al. 2019). Although such a molecular cascade has been associated with increased apoptosis and cellular senescence (Petr et al. 2020), it may also influence the stability of the proteome, for example by altering the stoichiometry of protein engaged in multiprotein complexes. Alternatively, many DNA lesions can also be bypassed by Pol II, but this can severely reduce transcriptional fidelity and lead to transcriptional mutagenesis (Brégeon and Doetsch 2011). In these cases, transcription-coupled repair is not triggered, which can result in a rapid build-up of faulty transcripts (Brégeon et al. 2003), a process that has been hypothesized to contribute to the protein aggregation observed in neurodegenerative diseases (Basu et al. 2015; Brégeon and Doetsch 2011). Although both transcriptional blockage and transcriptional mutagenesis have the potential to drive a destabilization of the proteome, their (relative) contributions on a genome-wide level in vivo remain incompletely understood. Interestingly, persistent DNA damage has recently been found to drive the activation of the integrated stress response (ISR), a signaling network important for maintaining protein homeostasis (Clementi et al. 2020). In this study, activation of the ISR was shown to promote cell survival through increased translation of ATF4, a transcription factor controlling various stress response genes. Although the transcriptional response initiated by ATF4 in this context has yet to be unveiled, notable downstream targets of the ISR and of ATF4 in particular include key PQC network components (Fusakio et al. 2016). Future research should investigate the relative proteomic impact of transcriptional blockage and transcriptional mutagenesis, and determine whether ATF4 dependent stress signaling indeed plays a role in maintaining protein homeostasis upon persistent DNA damage.

Additional factors: transposons, 3D genome organization, and natural variation

Factors that increase the instability of the genome largely independent of conventional DNA damage have in recent years also been brought under attention. Although these processes are likely very important for cellular function and disease, there is still much unknown about them and how they interface with pathology. Importantly, their potential impact on protein homeostasis would likely occur through similar processes as discussed above. For these reasons, we will only touch upon two examples briefly.

The first is dysregulated retrotransposon activity. A substantial fraction of the human genome is made up of transposable elements (TEs), among which retrotransposons, a class of TEs that includes for example the long interspersed nuclear elements (LINEs) (Cordaux and Batzer 2009). Retrotransposons are mobile genetic elements that can be copied and randomly re-inserted (i.e. transposition) into the genome. Not only can this process be highly mutagenic and change coding or regulatory sequences (Muotri et al. 2005; Upton et al. 2015), but transcription of retrotransposons may also result in cytotoxic polypeptides (Li et al. 2015). In healthy cells most of them are thought to be silenced, but a loss of their silencing has been associated with age-related degenerative disorders, most notably Alzheimer's disease and ALS (Jönsson et al. 2020).

A second example is aberrant three-dimensional (3D) genome organization. Instead of floating around freely or being randomly folded inside the nucleus, dynamic genome organization is tightly controlled. Each chromosome occupies a defined territory, and within each chromosome, several layers of organization appear to determine the position of specific chromosomal regions relative to each other, and to the nuclear lamina (reviewed in Yu and Ren 2017). This organization is crucial in DNA replication and gene regulation, underlying the formation of closed and open chromatin and the function of distal *cis*-regulatory elements, but also larger processes like X-chromosome inactivation in humans. Aberrant 3D genome organization has been linked to increased genomic instability and disease, for example in Hutchinson–Gilford progeria syndrome (HGPS) (Evans et al. 2019). Interestingly, a recent study found that proteotoxic stress plays is a crucial driver of atherosclerosis in HGPS, arguably the most debilitating symptom of this disease (Hamczyk et al. 2019).

Both examples reflect a growing awareness that our genomes are far from static, but that they are instead shaped by numerous internal and external factors, many of which are active throughout life. Together with the more established sources of genomic instability discussed above, they illustrate the vastly complex relation between genome and proteome. Although it is still unclear whether specifically dysregulated TE activity and aberrant 3D genome organization can challenge protein homeostasis, each has the potential to profoundly shape this relation.

Finally, the broad potential of genomic alterations to impact protein homeostasis also raises the question to what extent 'naturally' occurring genetic variation (e.g. single-nucleotide polymorphisms, SNPs) may contribute to a loss of protein homeostasis. Importantly, such variation is generally not considered as the outcome of genomic instability, but as a result of the inherent stochasticity of genome maintenance processes coupled to neutral and adaptive genetic processes, the main driving forces of evolution in a population (Prohaska et al. 2019). The impact of this variation on disease and lifespan is still far from

understood, but it is thought to contribute substantially to the variation observed in protein homeostasis decline with age as well (Gidalevitz et al. 2013; Gidalevitz, Prahlad, and Morimoto 2011).

Proteome instability as a targetable pathological mechanism of genomic instability

Although genome alterations—in particular single nucleotide alterations—can lead to loss of protein function, it is clear that many (if not all) types of DNA changes and lesions also have the potential to disrupt proteome stability and drive protein aggregation through a proteotoxic gain of function in many different ways (Fig. 2). Importantly, this is not restricted to specific disease-associated proteins, but extends to a large fraction of the proteome, and as a consequence, it does not necessarily take specific or large genomic changes to challenge protein homeostasis (Gidalevitz 2006; Gidalevitz et al. 2009). From the inherent metastability of the proteome (Gidalevitz et al. 2011), the pervasive aggregation-prone characteristics (Ciryam et al. 2016; Goldschmidt et al. 2010), and possible feed-forward loops in place (Green et al. 2017), it can thus be inferred that even a seemingly small amount of random genetic alterations—mutations or SVs; either inherited, arisen in the germline, or acquired somatically—may at some point in time (when the PQC network is unable or no longer able to deal with it) set off a cascade of aggregation events (Vendruscolo et al. 2011), driving a loss of protein homeostasis.

How pervasive the link between genomic instability and proteome instability really is, and what role it plays in disease, is a crucial question that has so far been largely left unanswered. As a loss of protein homeostasis can profoundly impact cellular function, and potently drive pathology, could a loss of protein homeostasis then also contribute to the degeneration resulting from genomic instability? Intriguingly, emerging data suggest that, at least in certain situations, a loss of protein homeostasis is not only a consequence of genomic instability, but could even be one of the primary mechanisms underlying downstream pathology, as we will discuss below. First, we need to briefly outline how the PQC network can be used to control the consequences of genomic alterations.

The PQC network can modulate the degenerative consequences of genomic instability

For almost two decades it is known that the PQC network plays an important role in shaping the consequences of genomic alterations. Early work from the field of evolutionary biology found that bacterial strains engineered to accumulate a large amount of mutations survive by upregulating the expression of the chaperonin GroEL and the molecular chaperone DnaK, the bacterial HSP70 (Fares et al. 2002; Maisnier-Patin et al. 2005). Normally, these heat shock proteins collaborate in the folding and assembly of proteins, and prevent them from becoming misfolded (Gragerov et al. 1992). During increased genomic instability, they buffer the effects of mutations by similarly engaging mutated client proteins and kinetically stabilizing them so that they remain functionally active (Jarosz, Taipale, and Lindquist 2010; Tokuriki and Tawfik 2009; Zhao et al. 2019).

This role of the PQC network appears to be highly conserved. To sustain their inherent proteotoxic stress and even thrive under it, cancer cells hijack the PQC network, including the UPS and chaperone systems (Calderwood and Gong 2016; Deshaies 2014). The abundant heat shock protein HSP90 (Borkovich et al. 1989) has emerged as a particularly interesting chaperone in eukaryotes in this regard. Like GroEL and DnaK in bacteria, HSP90 can bind and stabilize genetically altered proteins, allowing them to explore new functions, thus potentiating genetic variation (Jarosz et al. 2010). Cancer cells make extensive use of HSP90's ability as a potentiator as a means of stabilizing oncogenic proteins (Whitesell and Lindquist 2005), including mutant p53 (Nagata et al. 1999) (often in concert with HSP70 (Boysen et al. 2019)).

Importantly, this modulatory role of the PQC network is not just limited to cancer. In a recent study by Karras and colleagues, HSP90 was shown to act as a pervasive buffer against mutations, mitigating their detrimental effects on protein function (Karras et al. 2017). The buffering of HSP90 comes at the price of rendering the manifestation of detrimental genetic variation vulnerable to cellular stresses—e.g. upon heat stress, Hps90's ability to potentiate genetic alterations is compromised (Karras et al. 2017)—which could be highly relevant in situations of chronic stress like ageing.

A loss of protein homeostasis may be a major link between genomic instability and pathology

As HSP90 can mitigate the loss of function of individual proteins, this raises the question whether the PQC network can also dampen the phenotypic consequences of increased genomic instability. Recent studies indicate that this may be the case. Overexpression of the transcription factor HSF1 (the major transcriptional regulator of the PQC network) is able to counteract not only the global proteotoxicity caused by aneuploidy in human cells, but also rescue the associated growth defects (Donnelly et al. 2014). More recently, a loss

of protein homeostasis was found to play a crucial role in the etiology of Down syndrome (DS) and Hutchinson–Gilford progeria syndrome (HGPS), two disorders for which, respectively, a large genomic alteration (trisomy) or global genomic instability has been well-established as a primary underlying cause (Antonarakis et al. 2020; Gonzalo and Kreienkamp 2015; Musich and Zou 2009). In cell culture and mouse models of both syndromes, increased ER stress and UPR activation have been observed (Aivazidis et al. 2017; Hamczyk et al. 2019; Lanzillotta et al. 2018), along with an elevated sensitivity to either induction of ER stress or heat shock (Paradisi et al. 2005). Importantly, the use of chemical chaperones was shown to reduce protein aggregation, and in addition prevent cell degeneration and death in DS (Hirata et al. 2020; Nawa et al. 2019). A similar strategy in an HGPS mouse model was able to diminish vascular pathology, and extend lifespan (Hamczyk et al. 2019).

In a particularly insightful study, Zhu et al. inferred that the proteome instability in DS may even be responsible for a substantial part of the DS cognitive phenotype (Zhu et al. 2019). They discovered that the DS-associated defects in long-term memory and synaptic plasticity are driven by a maladapted downregulation of protein synthesis by the ISR, repressing transcriptional programs that are crucial for memory formation. Suppression of the ISR reversed these transcriptional changes, and restored synaptic plasticity and cognitive function (Zhu et al. 2019). This poses the interesting hypothesis that proteome instability may also affect cellular function by triggering a transcriptional rewiring at the expense of normal cellular functioning. Future studies should determine how intervening in this rewiring affects long-term pathological outcomes, as restoring transcription would be expected to also increase the protein folding burden, potentially further destabilizing the proteome.

Together, these findings show that the PQC network plays an important role in shaping the downstream consequences of genomic instability in these disorders, suggesting that a loss of proteome instability is—either directly or indirectly—a key intermediate event leading to disease. Whether a loss of protein homeostasis is a general pathological consequence of genomic instability remains unknown, but it represents a very promising avenue for future research, as it could help explain the substantial overlap between pathologies associated with a loss of protein homeostasis and genomic instability, including cancer and neurodegeneration, and may provide an answer as to why many genome maintenance disorders exhibit strong (neuro) degenerative symptoms (Jeppesen et al. 2011).

Targeting proteome instability to break a vicious cycle of degeneration?

The data discussed in this review indicate that genomic instability and proteome instability are closely interconnected phenomena, similar to what has been proposed by others (Xie and Jarosz 2018). Importantly, the fact that defects in one can result in impairments of the other points at the possibility of a vicious cycle of events (Fig. 3), which could be important for disease. Genomic alterations also increase widespread in somatic cells over time (Blokzijl et al. 2016; Brazhnik et al. 2020; Martincorena et al. 2015; Martincorena and Campbell 2015; Zhang et al. 2019), and the cumulative impact of these changes on the proteome is still largely unknown. Considering that this increase in

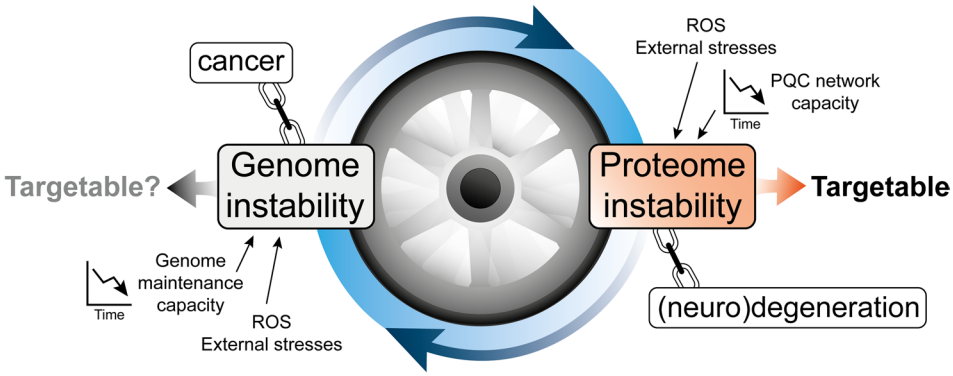

Fig. 3 Genomic instability and proteome instability locked in a vicious cycle. Proteome instability is closely associated with (neuro) degenerative phenotypes, and genomic instability is strongly linked to cancer. However, significant overlap between pathologies associated with each of them exists as well, which may be explained by a vicious cycle of events. Proteome instability can result in genomic instability through the formation of protein aggregates which either drive oxidative stress or sequester genome maintenance components. In addition, it can cause a reduction in the availability of PQC network components involved in genome maintenance. Vice versa, genomic instability may further increase proteome instability through the accumulation of genomic alterations that, either directly or indirectly, challenge protein homeostasis. Auxiliary stresses like ROS or heavy metals, as well as declining capacities of genome maintenance systems and the PQC network can add additional momentum to this cycle

genomic instability frequently correlates with the progression of degenerative pathologies associated with a loss of protein homeostasis (Ciosi et al. 2019; Lodato et al. 2018; Park et al. 2019; Vijg and Dong 2020), this indicates that this cycle may even play a fundamental role in ageing.

Dissipating momentum from this cycle could be a very interesting opportunity to mitigate pathologies associated with both a loss of protein homeostasis and genomic instability. It seems unlikely that this can be achieved by targeting genomic instability, as several crucial issues would need to be overcome. Although over the last few years several studies have reported that DNA repair can be selectively improved (Georgiadis et al. 2016; Gioia et al. 2019; Mason et al. 2014), this can be a dangerous endeavor, as it is often dysregulated DNA repair (Curtin 2012)—instead of absent repair—that leads to genomic instability, and hyperactive DNA repair has been linked to carcinogenesis as well (Bryant et al. 2019; Herrero et al. 2015; Sy et al. 2020). Moreover, DNA damage occurs largely stochastic, both in its nature and in genomic location, and through a range of different processes, and so the spectrum of lesions will be different from cell to cell. Even though protein aggregates can sequester DNA repair factors, it would therefore be impossible to precisely restore DNA repair capacity without the risk of adverse effects. Complicating this problem even further is the fact that, for this strategy to be effective (i.e. to repair lesions and prevent them from becoming 'locked-in' alterations), DNA repair would not only need to be boosted precisely, but also continuously, from an early age onwards. Enhancing DNA repair capacity sufficiently to prevent or even alleviate global genomic instability may therefore not be possible.

In contrast, attenuating proteome instability by enhancing the capacity of the PQC network is likely a far more feasible strategy (Balch et al. 2008; Labbadia and Morimoto 2015). Nature frequently relies on activation and broad transcriptional upregulation of the PQC network to maintain protein homeostasis upon stress situations, for example during elevated temperatures or starvation (Åkerfelt et al. 2010). In addition, the PQC network has been shown to be able to dampen the detrimental consequences of genomic alterations (this review). It would be highly insightful to investigate whether PQC network components can be used to mitigate degenerative phenotypes associated with genomic instability, for example in DNA repair syndromes. There are several particularly interesting targets in this regard, including the core PQC network machinery of HSP90, but other chaperones, specifically those with broad substrate ranges like small heat shock proteins, may be interesting too, as these have been shown to form a first line of defense against protein aggregation under a range of cellular stresses (Haslbeck and Vierling 2015). Stimulation of the two proteolytic systems, autophagy and the UPS, via drug-mediated manipulation of specific components in these pathways could also be an attractive strategy to safeguard protein homeostasis upon genomic instability (Njomen and Tepe 2019; Rubinsztein et al. 2012). Importantly, much more work is needed to investigate the value of each of these approaches in this context. As many PQC network components are intricately involved genome maintenance, altering their capacity might not always be beneficial, and may in some cases even lead to increased genomic instability (Poletto et al. 2017). Future studies should determine how and when modulation of the PQC network could abate the pathological consequences of genomic instability.

Concluding remarks

Genomic integrity and proteome stability rely on intricately connected regulatory pathways. As a result, the relationship between these two is highly complex, with disruptions in either one often affecting the other. Together with the notion that the PQC network can be wielded to mitigate the degenerative consequences of genomic alterations, this suggests that a loss of protein homeostasis could be an important consequence of genomic instability. This may be highly relevant for disorders such as DNA repair syndromes, and could help explain the overall overlap in pathology associated with genomic instability and proteotoxicity.

For now, uncovering whether the relationship between genomic instability and a loss of protein homeostasis plays an important role in vivo, and if so, which of these phenomena contributes the most to the associated disease phenotypes still stands as a major future goalpost. Nevertheless, the data reviewed here already indicates that targeting proteome instability may be a promising therapeutic strategy to mitigate the degenerative consequences of genomic instability.

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