Impaired proteostasis in rare neurological and nervous system diseases

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Abstract

Rare diseases are classified as such when their prevalence is 1:2,000 or lower, but even if each of them is so infrequent, altogether more than 300 million people in the world suffer one of the ~7,000 diseases considered as rare. Over 1,200 of these disorders are known to affect the brain or other parts of our nervous system, and their symptoms can affect cognition, motor function and/or social interaction of the patients; we refer collectively to them as rare neurological disorders or RNDs. We have focused this review on RNDs known to have compromised protein homeostasis pathways. Proteostasis can be regulated and/or altered by a chain of cellular mechanisms, from protein synthesis and folding, to aggregation and degradation. Here we provide a compilation of 170 proteostasis-related RNDs, deepening on some representative diseases, including as well a clinical view of how those diseases are diagnosed and dealt with. Additionally, we review existing methodologies for diagnosis and treatment, discussing the potential of specific deubiquitinating enzyme inhibition as a future therapeutic avenue for RNDs.

1. Introduction

Rare diseases have a low prevalence and limited pharmaceutical markets, so investment on their research has been historically very low. But, the tide seems to be changing, partly thanks to existing incentives to support orphan drugs [1]. Altogether, rare diseases affect about 7% of the world population, with rare neurological disorders (RNDs) being the largest group (Figure 1). Due to their effect in both cognitive and socializing skills of those affected, RNDs impact heavily in the individuals suffering them, as well as in the society as a whole. In this review we have compiled and classified over 170 RNDs that are caused by a deregulation of the homeostasis of proteins, e.g. caused by mutations in genes involved in protein synthesis, folding, aggregation, autophagy, mitophagy, endoplasmic reticulum (ER) stress or the ubiquitin-proteasome system (UPS). Some of these disorders show partial similarities amongst them, despite different pathways being affected; on the other hand the same gene can be involved in different diseases or a given disease can be caused by more than one proteostasis pathway being disturbed. It is therefore likely that certain proteostatic routes are commonly affected, and we hope this review will bring some light to those common patterns, which could potentially be targeted by influencing the proteostatic balance within the affected neurons.

The main difficulty for diagnosis and treatment of RNDs resides in the genetically heterogeneous nature of these diseases. For instance, so far >50 and >300 genes have been linked to hereditary spastic paraplegia and ataxia, respectively [2]. This complexity leads to the so-called "diagnostic odyssey" where patients typically wait years for a diagnosis and might receive multiple misdiagnoses along the way. Those can lead to inappropriate treatments, or to patients giving up the search for a diagnosis in the false belief they have received the right one [3].

Generation of human induced pluripotent stem cells (hiPSC) [4] from human adult somatic cells has been shown to provide enormous research potential for the field of neurological diseases [5]. In this sense, hiPSC opened an unlimited source of patient-derived cells to be expanded massively *in vitro* and to be differentiated into different types of neurons. In most cases, the differentiated neurons exhibit disease phenotype at different levels (cellular, molecular and functional), thus providing a valuable and

relevant cell model to study the pathophysiology of the disease [6], and thereby overcoming the limitation to work with neurons from patients.

Finally, Deubiquitinating enzymes (DUBs) have been identified as the most likely therapeutic targets within the proteostasis regulatory enzymes [7]. Considering that DUBs could provide a significant degree of pharmacological specificity, we will also discuss DUB inhibition as a plausible approach to tackling proteostasis-linked RNDs.

2. Proteostasis related rare neurological diseases

Maintenance of cellular proteostasis is a prerequisite for optimal cell functioning and survival. It requires precise control of a number of interconnected pathways including protein synthesis, folding, and finally, if required, protein clearance by degradation. Alteration of any of those processes might result in the accumulation of misfolded proteins that interfere in various cellular functions. Hence, it is not surprising that collapse of protein homeostasis is associated in the aetiology of many diseases, including those with very low prevalence and affecting the nervous system.

2.1. Protein synthesis

The production of proteins is initiated in the nucleus of eukaryotic cells where DNA is first transcribed, resulting mRNA is then translocated to the cytoplasm, and finally, mature mRNA is translated into a polypeptide chain by the ribosomes. Mutated versions of chromatin remodelling [8–27] and transcription factors [9,14,28–53] that coordinately drive DNA transcription have been associated with numerous RNDs (Figure 2). Similarly, mutations in distinct molecules playing a role in protein translation, such as tRNAs (*MT-TK, MTTL1*) [54], tRNA loading enzymes (*GARS, YARS, EARS2, DARS2, RARS2*) [55], proteins that regulate ribosome assembly (*SPG7*) [54] or factors directly involved in protein translation that takes place in the cytoplasm or mitochondria (*EIF2B1-5, C12orf65, LRPPRC, MTFMT, TACO1*) [54,56,57], have been linked to several RNDs (Figure 3).

Protein translational machinery is tightly regulated by signalling pathways, including Ras/ERK and PI3K/mTOR pathways, which are orchestrated by a wide variety of proteins. Hence, aberrant forms of some of those effectors underlie the aetiology of a number of RNDs. For example, whereas inactivating mutations in *NF1*

and *PTEN* have been associated with neurofibromatosis 1 and the pathogenesis of autism spectrum disorders (ASD) respectively, mutations is *TSC1* or *TSC2* cause tuberous sclerosis [21]. Additionally, fragile X syndrome is caused upon transcriptional silencing of the *FMR1* gene; its product, the FMRP protein, being responsible for binding and repressing the translation of hundreds of mRNAs [21] (Figure 3).

2.2. Protein folding & aggregation

Progressive accumulation of specific protein aggregates is a hallmark of many neurodegenerative diseases, including some RNDs. Those aggregates are generated from misfolded proteins that should have been removed by cellular quality control mechanisms. In the cellular environment, many proteins require the help of molecular chaperones to stabilize and acquire their 3D native functional state. Consequently, the role of those protein folding factors is essential in the homeostasis of the cellular proteome, and when mutated lead to pathological conditions termed chaperonopathies [58].

Many of the over 100 different heat shock proteins (HSP) encoded by the human genome act as molecular chaperones, including members of the DNAJ, HSPD and HSPB families that have been associated with several RNDs [59] (Figure 3). HSPD1 is a key mitochondrial chaperone system bearing in mind that ~30% of mitochondrial proteins depend on it for folding purposes. A mutation that leads to reduced HSPD1 chaperonin activity has been linked with spastic paraplegia 13 (SPG13), whereas mutations causing premature disassembly of the complex are associated with the recessive mitCHAP-60 disease [59]. Moreover, CCT4 and CCT5, members of the cytosolic CCT chaperonin system that participate in the folding of tubulin and actin, have also been linked with very rare sensory neuropathies [60,61]. Similarly, loss-of-function mutations in *TBCE* gene that encodes a tubulin-specific chaperon cause hypoparathyroidism-retardation-dysmorphism (HRD) [62], an unusual neurodevelopmental syndrome. Mutations on additional HSPs belonging to the DNAJ and HSPB families [59], as well as on the co-chaperones CHIP [63] and SIL1 [64] have also been identified as the genetic cause underlying a diverse array of RNDs.

Nevertheless, not all proteins require chaperones to fold. Protein aggregates can also be generated as a consequence of (i) mutations that cause conformational changes in the native state of a protein [9,18,65–74]; (ii) defects in protein quantity [65,75]; (iii)

elongation of certain protein domains [9,76–78]; or (iv) domain truncations [65–67,79] (Figure 3).

2.3. Protein degradation

Dispensable proteins, proteins that have been synthesized in excess or proteins that, despite the help of chaperones, are unable to fold properly must be eliminated in order to avoid the accumulation of toxic aggregates that may compromise cell function. This is particularly relevant in cells with reduced proliferation capacity such as neurons; structural and functional loss of neurons within the brain and/or spinal cord being the underlying cause of neurodegenerative diseases.

Protein degradation is achieved by two major proteolytic machineries, the ubiquitin proteasome system (UPS) and autophagy [80,81]. UPS mediates the degradation of the majority of misfolded proteins that are targeted by ubiquitination to enter the proteasome where they are cleaved into small peptides. Proteins of the secretory pathway due to fold in the endoplasmic reticulum (ER), when folded incorrectly are retrotranslocated to the cytosol, and also subjected to ubiquitination and proteosomal degradation by a process known as endoplasmic reticulum-associated degradation (ERAD). In turn, autophagy is a self-degradative process in which misfolded or aggregated proteins, as well as defective organelles, are removed by the lysosome. Due to the relevance of protein disposal mechanisms in maintaining cellular proteostasis, it is not surprising that neuronal defects on either of the above mentioned processes are often the underlying cause of RNDs.

2.3.1. The ubiquitin proteasome system (UPS)

UPS-dependent degradation is strictly regulated using ubiquitin, a small and highly conserved protein of 76 amino acids. Covalent attachment of ubiquitin to a target protein is achieved by the sequential action of three distinct classes of enzymes: ubiquitin-activating E1 enzymes, ubiquitin-conjugating E2 enzymes and ubiquitin E3 ligases that provides substrate specificity (Figure 4) [81]. Human genomes are believed to code for at least two E1's, ~ 30 E2 enzymes and above 500 distinct E3 enzymes. Accordingly, few E1 and E2 enzymes, but a large number of E3 ubiquitin ligases have been associated with RNDs [82].

The E1 enzyme UBA1 is implicated in the aetiology of X-linked infantile spinal muscular atrophy (XL-SMA) [83], and mutations in the E2 enzyme UBE2A result in

UBE2A deficiency syndrome [84], whereas the E2 enzyme UBE2K, which can catalyse protein ubiquitination independent of E3 ligases, is a pivotal factor modulating the neurotoxicity of expanded huntingtin in Huntington's disease [85].

Based on structural and mechanistic features, most E3 ubiquitin ligases can be classified as HECT-type, RING-finger-type or U-box type E3s [86]. So far, especially RING-finger-type ligases have been linked with RNDs. While some E3 ligases are monomeric enzymes, many RING-finger E3s work as components of multi-subunit complexes known as cullin-RING E3 ubiquitin ligases (CRL). As shown in Figure 4, not only monomeric RING-finger E3s have been associated with RNDs [82,87–92], but also disparate elements of CRLs [82,93–98] and ubiquitin receptors [99,100]. Additionally, more than 10 distinct RNDs are also known to be originated as a consequence of defective HECT-type E3 ligases [82,101]. The vast majority of RNDs caused by E3s are due to mutations either reducing or disrupting the activity of the ubiquitin ligases, therefore resulting in impaired ubiquitination of their substrates. Nevertheless, it has also been shown that duplication of the HECT-type ubiquitin ligase UBE3A is implicated in autism spectrum disorders (ASD) [102]. While inversely, loss of function mutations of UBE3A are the cause of Angelman Syndrome (AS), a neurodevelopmental disorder that will be described in more detail below (section 4.1).

The U-box domain containing E3 ligase CHIP can cause SCAR16 [103] and is also involved in Gordon Holmes syndrome, a rare neurodegenerative disorder characterized by hypogonadism and ataxia [82]. This disease can also be caused by the combination of mutations in the RING–finger type E3 ligase *RNF216* [88] and the deubiquitinase *OTUD4* [104].

Deubiquitinating enzymes or DUBs are responsible for deconjugating ubiquitin from target proteins and hence, as their counterpart ubiquitin ligases, have a fundamental role in the ubiquitin system and in the aetiology of several RNDs. Indeed, besides the above-mentioned OTUD4, the DUBs USP8, STAMBP and ATXN3 are also known to cause distinct RNDs [9,105,106] (Figure 4).

It should be noted that in a number of RNDs the activity of UPS is altered although disease-causing genes do not code for components of the UPS machinery (Figure 3). For instance, Alexander disease (AxD)-causing mutations in *GFAP* gene result in accumulation of its product, the major astrocyte intermediate filament protein, and consequently, astrocytes suffer many molecular changes, including proteasome inhibition [75]. Similarly, mutant *HTT*, which cause Huntington's disease, impairs the

ability of the UPS to degrade some intracellular protein substrates [107]. By contrast, it has been shown that Cowden syndrome-related mutations in *PTEN* phosphatase associate with enhanced proteasomal activity [108].

The endoplasmic reticulum (ER) is a key organelle for modification and folding of proteins targeted to the transmembrane and secretory pathway. In healthy cellular conditions, misfolded ER proteins are eliminated by ERAD in the cytosol. However, due to proteasome inhibition, overload or ERAD failure, misfolded proteins can accumulate in the ER and unless eradicated, lead to pathogenicity. Indeed, mutations on several components of the ERAD machinery, including *MSK3/TMEM67, ERLIN2, ATX3* and *VCP* have been identified as the genetic cause underlying distinct RNDs (Figure 4) [81,109–111]. Additionally, mutant versions of NPC1, GBA and MLC1 proteins that are associated with distinct RNDs undergo ERAD and are targeted to be degraded at the proteasome [68,112,113].

2.3.2. Autophagy & mitophagy

Autophagy is a process of cellular self-digestion that, despite occurring at low levels under healthy cellular conditions, plays a critical role in protein quality control, especially in neurons. Briefly, the most prevalent form of autophagy named macroautophagy (hereafter referred to as autophagy) consists on a membrane-trafficking system in which membrane compartments, called autophagosomes, engulf cellular components (cargo) that are delivered to lysosomes for degradation (Figure 5) [80].

The serine/threonine kinase mTOR, a master regulator of cellular metabolism, plays a pivotal role in modulating autophagy. In response to environmental stimuli, the mTOR complex 1 (mTORC1) promotes cell growth by simultaneously inducing anabolism and inhibiting catabolic processes such as autophagy. mTORC1-directed blockage of autophagy is achieved by phosphorylation and subsequent inactivation of proteins that are involved in the initiation of autophagy as well as the nucleation of autophagosomes. Additionally, mTORC1 phosphorylates transcription factor EB (TFEB) on Ser142 and Ser211, and consequently the key regulator of lysosomal and autophagy gene expression is sequestered in the cytoplasm [114]. The role of mTOR in modulating autophagy is so critical, that many defects in the autophagic flux that cause RNDs derive from defects in the mTOR pathway [115].

Among others, the serine/threonine kinase ATM and phosphoinositide 3-kinase (PI3K) are upstream effectors of mTORC1 that modulate its activity. Whereas ATM-dependent phosphorylation mediates suppression of mTORC1, PI3K activation results in mTOCR1 activation through AKT-mediated phosphorylation. It has recently been shown that patients affected with Ataxia-Telangiectasia, a rare recessive condition caused by defects in ATM, present abnormal autophagy accompanied with accumulation of autophagic vesicles. It still remains unclear if the dysregulation depends on the absence of ATM-mediated control upstream mTORC1 or defects in DNA repair [116]. By contrast, in patients affected with Duchenne muscular dystrophy, deficient autophagy is accompanied by constant AKT phosphorylation and subsequent mTORC1 activation [117]. Similarly, lamin-A/C (*LMNA*) in Emery-Dreifuss muscular dystrophy, laforin glucan phosphatase in Lafora disease and *PRKAR1A* deficiency in Carney complex induce mTORC1 activity, which results in reduced autophagic flux [118–120]. On the contrary, mTORC1 activity is reduced and concomitantly autophagy is enhanced upon loss of C9orf72 and TDP-43 in ALS [121], as well as upon GLA1 deficiency and GFAP accumulation that cause Fabry's disease [122] and Alexander's disease [123], respectively.

In X-linked myopathy with excessive autophagy (XMEA), decreased expression of *VMA21* gene results in increased lysosomal pH, concomitant reduction of lysosomal activity and autophagy blockage. As a consequence, the concentration of free amino acids is reduced, mTORC1 pathway is downregulated and finally, autophagy is activated in excess in a mechanism known as autophagic overcompensation [124]. It should be noted that besides mTORC1, further kinases participate in the regulation of autophagy. In fact, it has been demonstrated that AMPK and AMPK-related kinases NUAK2 and BRSK2 modulate autophagy via WIPI4, a key player that is mutated in beta-propeller protein-associated neurodegeneration (BPAN) [125].

As mentioned above, in autophagy newly formed membranes engulf parts of the cytoplasm while expanding and finally close to form an autophagosome. For the formation of the autophagosome, the activity of the conserved Atg12-Atg5-Atg16 complex is essential and hence, mutation in *ATG5* reduces autophagy and causes ataxia with developmental delay (SCA25) [126]. As indicated in Figure 5, so far more than 20 mutant genes have been linked with over a dozen distinct RNDs in which either formation and/or maturation of autophagosomes is impaired [9,18,69,70,119,121,126–141]. For instance, lysosomal-associated membrane glycoprotein 2 (LAMP2), which is

involved in autophagosome maturation, cause Danon disease, a rare genetic condition characterized by muscle weakening and intellectual disability [127]. It should be noted that LAMP2 acts also as a receptor for substrates in chaperon-mediated autophagy (CMA), a type of autophagy in which the cargo is directly translocated from the cytosol into the lysosome via the heat shock protein HSC70 that interacts with a multiprotein complex which includes LAMP2 [142].

During macroautophagy, autophagosomes mature and fuse with lysosomes to form the so-called autolysosomes, which are in charge of digesting their content. EPG5 is a key autophagic modulator involved in the formation of autolysosomes that is mutated in Vici syndrome, a rare autosomal recessively inherited multisystemic disorder [128]. Nevertheless, the formation of autolysosomes and subsequent cargo degradation require the coordinated action of additional proteins, some of which have been identified as the genetic cause underlying distinct RNDs [121,143,144] (Figure 5).

The causative factors of some RNDs are even found in the final step of autophagy, the autophagic lysosome reformation (ALR), which aims to regenerate functional lysosomes from autolysosomes to maintain lysosome homeostasis. Spastizin and spatacsin are critical proteins for ALR initiation, and mutations that result in the loss of function of spastizin and spatacsin have been associated with SPG15 and SPG11, respectively [145] (Figure 5).

As mentioned before, autophagy serves as a mechanism for removal of not only misfolded or aggregated proteins, but also defective organelles such as mitochondria. The process by which aberrant mitochondria are degraded via autophagy is called mitophagy. Indeed, defects in mitophagy are a major hallmark of some RNDs (Figure 4). For instance, Barth syndrome -caused by defects in *TAZ*- results in defective mitophagosomes as a consequence of deficient mitophagy [146]. By contrast, mutations in *MFN2* that cause Charcot-Marie-Tooth 2A neuropathy lead to a reduction in mitochondria as a consequence of enhanced mitophagy [147]. Similarly, in various Huntington's disease models, mutated huntingtin (mtHtt) binds VCP in the mitochondria, which elicits excessive mitophagy causing neuronal cell death [148]. However, depending on the genetic defects on the *OPA1* gene that cause dominant optic atrophy (DOA), the defect observed in mitophagy is opposed; whereas dominant-negative *OPA1* mutations result in enhanced mitophagy, *OPA1* haploinsufficiency leads to reduction in mitochondrial turnover [129].

3. Clinical view: diagnosis, analysis and therapeutic perspectives

Neurological disorders are a heterogeneous group of disorders that result from the impairment of the central and peripheral nervous system, including monogenic forms of brain malformations, ataxias, encephalopathies, myopathies and muscular dystrophies, neuropathies, movement disorders, intellectual disabilities, behavioral disorders and dementias. RNDs are a subtype of neurological diseases that represent 19% of all rare diseases, and are often overlooked due to lack of understanding their potential causative factors [149–151].

The advent of next-generation sequencing (NGS) holds particular promise for individuals with undiagnosed rare genetic diseases. In fact, even neurological disorders encompass a large array of genetic defects, NGS has enabled researchers to identify the genetic basis for hundreds of RNDs. This way, for example, constituents of the ubiquitin pathway, namely E3 ligases, have been identified as causative factors for, at least, 42 RNDs [82]).

3.1 Next-generation sequencing for RNDs diagnosis

Next-generation sequencing (NGS) refers to massively parallel sequencing that produces many hundreds of thousands to millions of sequence reads simultaneously. There are three NGS strategies that can be employed on a clinical basis: NGS-based panel testing, whole-exome sequencing (WES) and whole-genome sequencing (WGS).

NGS-based panel testing is a common approach where a few to several hundred genes associated with a specific clinical presentation can be sequenced and analyzed concurrently [152]. Genetic testing performed using a gene-panel approach is an advantageous strategy when more than one gene can cause the clinical presentation. Compared to the sequential gene-by-gene approach, a panel of genes can dramatically increase sensitivity and also simplify the diagnostic algorithm [153]. On the other side, when compared to WES and WGS, disease-targeted tests can have a much higher or often complete coverage of the candidate genes for a specific disorder [152] and also a higher depth (number of times a specific nucleotide is read), so it is less likely to miss a mutation.

WES involves analysis of the protein-coding regions of known genes, representing 1–2% of the genome but the location of an estimated 85% of disease

mutations [154]. WES interrogates approximately 95% of the coding region of the genome, comprising ~20,000 genes and has been used with great success in rare disease research for novel gene identification [155–157]. It is not limited to selected candidate genes (whose number can increase as research advances) and its success depends on several factors, as the type of clinical presentation and the sequencing strategy employed. RNDs with a particularly early age-of-onset tends to have a higher diagnostic rate [158].

WGS evaluates the entire genome, including not only the coding regions but also regulatory regions such as promoters and enhancers, structural variants, etc [159]. WGS data can typically be generated in less than a month and, importantly, WGS has a more uniform coverage compared to WES [160,161]. However, the assembly of the genome is computationally laborious and most of the non-coding sequence is difficult to interpret [162]. Both WES and WGS are emerging as comprehensive and valuable clinical strategies to diagnose patients with RNDs [163].

Promising as they are, it will take some time for these technologies to make an impact on everyday clinical practice. In fact, as new technologies evolve, clinical guidelines have become indispensable and clinical and technological recommendations developed [164,165]. We should not forget than once the molecular alteration is found, the patient have to face two impacts: his/her own prognosis and the implication of the disease in the family as genetic testing is performed not only for diagnosis, but also for prediction of recurrence risk within a family. So, first, diagnostic testing is done to determine whether a patient with symptoms has a suspected condition, or to determine what condition they have, if their symptoms are non-specific. This testing can sometimes provide an explanation, predict recurrence risk, or inform clinical management. And then predictive testing is usually performed in siblings or descendants of the patient for a condition they have not yet presented symptoms and whose results imply enhanced clinical screening or be useful in life planning.

Besides, we should also keep in mind that some RNDs are caused by genetic alterations that cannot be covered by sequencing as large expansions/deletions, triplet and other expansion mutations, copy number variants or imprinting defects [162].

3.2. hiPSCs as a tool to study RNDs

hiPSC technology [166] holds the potential to be used as *in vitro* modeling systems for most of the genetic diseases as well as platforms for drug screening and cell-based therapies in regenerative medicine [167–169]. There are currently 52 hiPSC lines reported in the literature for RNDs with affected proteostasis pathways (Supplementary Table 1), providing unprecedented access to patients' relevant nervous-like cells with *in vivo*-like structural and functional properties such as dopaminergic neurons, glutamatergic neurons, spinal motor neurons, GABAergic neurons and also astrocytes and oligodendrocytes to study basic disease mechanisms [170–172]. Indeed, these nervous-like cells re-capitulate disease-related phenotypes that highlight the importance of a tight regulation of quality control mechanisms to reduce cellular toxicity associated with aggregation, misfolding or damaging mutant proteins that is specifically important in neurons since they cannot be efficiently replaced [173]. In addition, hiPSC from monogenic diseases harboring a known mutation can be corrected using editing tools such as CRISPR/Cas-9 to restore the function of the gene and alleviate the disease phenotype [174]. This approach is becoming more relevant to generate isogenic controls which retain all of the other genetic factors that otherwise could induce phenotypic differences due to individual genetic variability when non-related healthy donors are used as controls.

3.3. DUB inhibition as a potential therapeutic approach for RNDs

Inhibition of the UPS is known to efficiently stop the spread of tumours, and is indeed a widely used treatment for several types of cancer [175]. Proteasome inhibition based chemotherapy, however, has a number of side effects [176], as it affects hundreds –if not thousands – of different pathways within all cells that are also targeted by the drug. A more refined approach would be to either hyperactivate the specific ligating pathway (E1, E2, E3) required for a particular ubiquitination event or, alternatively, to inhibit the activity of the specific DUB responsible for modulating a given ubiquitination event. This has already been shown to function efficiently, as inhibition of proteasome-associated DUBs UCHL5 and USP14 by the small molecule b-AP15 displays substantial antitumor activity in human mantle cell lymphoma [177]. Based on those and other findings, several pharmaceutical companies are currently expanding their portfolios on DUB inhibitors, as this is considered to be an expanding field with direct clinical potential. Since it was proposed that USP30 inhibition is capable to

counteract the lack of E3 ligase Parkin activity [178], USP30 inhibitors are being currently developed for their potential therapeutic use on patients with Parkinson disease.

Along the same rational, we envision that a number of proteostasis affecting RNDs might be modulated by inhibiting specific DUBs. The most obvious targets for this strategy would be the diseases that are caused by reduced activity of a given E3 ligase. We would expect a compensation effect to be caused by inhibiting the counteracting DUB enzyme that physiologically modulates ubiquitination by this ligase. Given that the failure of an E3 ligase activity is responsible for at least 42 RNDs (Figure 4), this is for certain a field that upon further exploration is likely to yield very applicable results.

What remains to be tested is whether neurodegenerative RNDs caused by aggregation of proteins that neurons are not capable of eliminating could also be targeted by inhibiting specific DUBs. We predict that DUB inhibition might enhance the degradation of those aggregation-prone proteins that otherwise might just be deubiquitinated, and not eliminated by the cell. If this was to be the case, targeted DUB inhibition therapy could indeed be developed with the aim to treat several RNDs, particularly those neurodegenerative disorders caused by protein aggregation. For this purpose, however, first of all it will be required that the ubiquitome altered on those diseases to be characterized, as well as the identity of the substrates for all human DUBs, a goal we hope to achieve during the next few years.

4. Implication of proteostasis in clinical scenarios

4.1 Angelman syndrome (AS)

AS (OMIM # 105830) is an imprinting disorder affecting protein degradation, caused by loss of function of the E3 ubiquitin ligase UBE3A [179]. A clinical diagnosis of AS demands fulfilment of four major criteria and minimum three of the six minor criteria. The major criteria are severe developmental delay, movement or balance disorder, severe limitations in speech and language and typical abnormal behavior including happy demeanor and excessive laughter. The six minor criteria are postnatal microcephaly, seizures, abnormal electro-encephalogram, sleep disturbance, attraction

to or fascination with water, and drooling [180,181]. The reported causes of the lack of function are: (i) lack of expression of the maternal copy of *UBE3A* due to maternally derived de novo deletion of 15q11-q13 (70–75%); (ii) paternal uniparental disomy of chromosome 15 (3–7%); (iii) imprinting defects (2–3%) leading to lack of expression of maternally expressed 15q11-q13 genes; or (iv) mutations in *UBE3A* (10–15%) [182].

AS has been studied using *in vivo* models and hiPSCs. As epigenetic regulation of human *UBE3A* is conserved in rodents, researchers have generated different AS murine models, including those encompassing one or several exons of *UBE3A* or even longer deletions affecting the imprinted region, to study this disorder [183–186].Additionally, generation of an UBE3A reinstatement model has allowed researchers to define neurodevelopmental windows that may rescue AS-related phenotypes: motor deficits were rescued by Ube3a reinstatement in adolescent mice, whereas anxiety, repetitive behavior, and epilepsy were only rescued when Ube3a was reinstated during early development. In contrast, hippocampal synaptic plasticity could be restored at any age [187]. .

The function of UBE3A has been studied in *Drosophila* through the use of mass spectrometry proteomics in loss or excess of function mutants *in vivo* [188,189]. Interestingly, Ube3a seems to regulate the ubiquitination of several proteasomal components, such are Rpn10, Uch-L5 and Rngo, a homologue of human DDI1 and DDI2. In this way, by modulating the levels of proteasomal proteins, UBE3A regulates the general status of protein degradation, having an enormous impact in cellular proteostasis.

AS patient-derived iPSC lines and neurons derived from those lines have also given important insights on etiology of the disease. For instance, it was found that during neuronal differentiation, *UBE3A* was imprinted and *UBE3A-ATS* (antisense transcript) overexpressed [190]. An iPSC line containing a deletion of three base-pairs in the maternal *UBE3A* allele confirmed that the neuron-specific *UBE3A-ATS,* which silences paternal UBE3A expression, was upregulated during late-stage neuronal differentiation [191]. More recently, a research carried out with 3 distinct iPSC lines concluded that late-term cultured AS-derived neurons were immature and showed reduced synaptic activity and plasticity. Additionally, it was demonstrated that AS neuronal phenotypes could be reverted either by correcting the mutation or pharmacologically using topotecan [192], and it was also proved that it is plausible to correct aberrant imprinting and hence, restore UBE3A expression by UBE3A-ATS

silencing [193]. All the evidences so far accumulated support the idea that neuronal dysfunctions in AS are directly related with the loss of ubiquitin ligase function of UBE3A.

4.2. Machado-Joseph disease/spinocerebellar ataxia type 3

Machado-Joseph disease (OMIM # 109150), also known as spinocerebellar ataxia type 3 (SCA3), is one of the most common dominantly inherited ataxias affecting protein folding and degradation (for a comprehensive recent review see [194]). It is caused by unstable CAG repeat expansion in the *ATXN3* gene, which is translated into a long polyglutamine (polyQ) tract within ataxin-3 protein. The resulting expanded polyQ fragments form insoluble aggregates that in turn form inclusions in neuronal nucleus and cytoplasm leading to elevated neuronal cytotoxicity [195,196].

Proteostasis plays an important role in the etiology of this disease. Ataxin-3 is known to be a DUB enzyme implicated in the regulation of the ubiquitination and ubiquitin-mediated proteolysis. Ataxin-3 contains an N-terminal Josephin domain that contains the catalytic site, two ubiquitin (Ub)-binding domains, and two or three Ub-interacting motifs (UIMs) flanking the polyQ tract [197,198]. One of the identified target proteins is p53 [199]. Interestingly, polyQ expansion in Ataxin-3 increases the interaction and deubiquitination of p53, which is upregulated. Increased p53 causes cell death and neurodegeneration in zebrafish brains and in the substantia nigra pars compacta or striatum of a transgenic mouse model [199]. Other targets of ataxin-3 are Parkin and CHIP, two ubiquitin ligases, placing ataxin-3 as a central regulator of the UPS and cellular proteostasis and opening new opportunities of intervention [200,201]. Furthermore, ataxin-3 is also related to other members of the ubiquitin-like family, such is NEDD8 and SUMO [202,203]. In addition, ataxin-3 has been involved in ERAD based on its interaction with VCP/p97 and homologues of the of yeast protein Rad23 hHR23A and hHR23B [111].

Ataxin-3 aggregation also disrupts the autophagy process. Ataxin-3 DUB activity interacts with and stabilizes beclin-1, a central protein in autophagy, through the polyQ tract. The polyQ expansion reduces its DUB activity leading to an abnormal decrease of beclin-1 [204]. In addition, SCA3 patients accumulate LC3, p62, and Atg16L in the brain, all of them regulators of autophagy [205], and exhibit defective autophagy [206].

The relation of Ataxin-3 with autophagy also increases the possibilities of intervention, as shown by the administration of an inhibitor of mTOR that upregulates autophagy in a mouse model [130].

By the use of hiPSC and functional neurons derived from SCA3 patients, it was demonstrated the key role of Ca^{2+}-dependent calpain proteases in the proteolysis of CAG-expanded ataxin-3 [207]. In line with this, using fibroblast and iPSCs, it has recently been shown that calpain primarily cleaves ATXN3 in two specific sites, and that resulting fragments have distinct aggregation tendency [208]. Nevertheless, Hansen and co-workers could not replicate ATXN3 aggregate formation using their patient iPSC-derived neurons [209]. These opposing results suggest that SCA3 phenotype might be dependent on neuronal subtypes and highlight the importance of optimized protocols that give rise to similar neuronal population.

In parallel, an iPSC line with 81 CAG repeats in the *ATXN3* gene was used to demonstrate that rapamycin-induced autophagy could eliminate mutant ATXN3 during neuronal differentiation. Hence, although restricted to cytoplasmic aggregates, the treatment could serve as a potential therapeutic agent for SCA3 [210]. More recently, using the CRISPR/Cas9 system, the expanded CAG repeats in ATXN3 were corrected in iPSCs derived from SCA3 patients [211]. It should be noted that edited iPSCs maintained the pluripotency, the neural differentiation and the ubiquitin binding capacities, and improved mitochondria respiration.

5. Conclusions

Protein homeostasis is central in the development of RNDs. Diseases related to any aspects of proteostasis have been described, from protein synthesis and folding, to aggregation and degradation by the UPS and autophagy pathways. In some cases, the mutations affect to genes that encode for proteins with a function in protein degradation, which alters profoundly the cellular proteostasis, such is the case of *UBE3A* in AS or *ATXN3* in Machado-Joseph disease/SCA3; in other cases aggregation and compromised ERAD are crucial, as is the case of FTD. The possibility of manipulation of these processes, for instance by altering the function of DUBs by specific inhibitors or activators, opens an interesting venue for the future treatment of these diseases.

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FIGURE LEGEND

Figure 1. Distribution of rare diseases.

Rare diseases affecting the nervous system represent 19 % of all rare diseases. Categories and frequencies shown in the graph were extracted from information provided by the Genetic and Rare Diseases Information Center (GARD, rarediseases.info.nih.gov). Categories with a frequency < 4 % were grouped into the category termed *Other diseases*.

Figure 2. Schematic representation of RND-associated genes involved in the regulation of transcription. The transcription of genes is conditioned by post-translational modification of chromatin, which determines the compaction level of DNA, and consequently the accessibility of DNA to transcription factors and the basic transcriptional machinery. Chromatin remodelling factors modulating acetylation, methylation, phosphorylation and ubiquitination state of proteins involved in gene expression are marked in pink, purple, blue and orange, respectively. In turn, transcription factors that activate and repress transcription are marked in green and red, respectively. Additionally, transcription factors that, depending on the context, can act

either as activators or repressors are coloured in grey. *ATR-X, Alpha-thalassemia X-linked intellectual disability; CADASIL, Cerebral arteriophaty, autosomal dominant, with subcortical infarcts and leukoencephalopathy; ID, Intellectual disability; HSAN, Hereditary sensory and autonomic neuropathy; MRLIAF, Mental retardation with language impairment and autistic features; XLAG, X-linked lissencephaly with abnormal genitalia.* Disease abbreviations were taken from GARD webpage (rarediseases.info.nih.gov)

Figure 3. Schematic diagram of RND-associated genes involved in protein translation and folding.

This diagram shows a simplified version of protein translation and folding process. Failures in translation and/or folding of newly synthesized polypeptides often lead to the generation of misfolded proteins, which need to be re-folded or degraded in order to avoid protein aggregation. In fact, numerous RNDs are caused by mutations on genes that participate either in protein translation or folding. Additionally, mutants that are prone to form protein aggregates are the underlying cause of various RNDs. *ARMSN, Autosomal recessive mutilating sensory neuropathy; CACH/VWM, Childhood ataxia with central nervous system hypomyelination/vanishing white matter; CIPA, Congenital insensitivity to pain with anhidrosis; HRD, Hypoparathyroidism-intellectual disability-dysmorphism; HSAN, Hereditary sensory and autonomic neuropathy; LBSL, Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation; LTBL, Leukoencephalopathy with thalamus and brainstem involvement and high lactate; MELAS, Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MJD, Machado-Joseph disease; MLC, Megalencephalic leukoencephalopathy with subcortical cysts.* Disease abbreviations were taken from GARD webpage (rarediseases.info.nih.gov)

Figure 4. Schematic representation of RND-associated genes involved in the ubiquitin-proteasome system.

Mutation at different levels of the ubiquitin-proteasome system cascade, i.e. mutations in the E1, E2s, E3s, DUBs and ubiquitin receptors, have been linked with RNDs. Similarly, mutations on genes regulating the degradation of misfolded proteins through the Endoplasmic Reticulum Associated Degradation (ERAD) pathway have also been associated with RND. In the case of components of multimeric RING E3s, genes coding for receptor and cullin proteins are coloured in purple and green, respectively. A diagram showing different parts of oligomeric E3s is also shown. In the case of *UBE3A* gene, the diseases caused by the loss of function and overexpression of this gene are coloured in red and green, respectively. *AR, Autosomal recessive; COACH, Cerebellar vermis hypo/aplasia, oligophrenia, ataxia congenital, coloboma, and hepatic fibrosis; IBMPFD, Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia; MJD, Machado-Joseph disease; MLC, Megalencephalic leukoencephalopathy with subcortical cysts; XL-SMA, X-linked infantile spinal*

muscular atrophy. Disease abbreviations were taken from GARD webpage (rarediseases.info.nih.gov).

Figure 5. Schematic representation of RND-associated genes involved in autophagy.

Mutations on genes participating all along the autophagy pathway, from regulation to initiation of autophagosome formation, cargo delivery and degradation in the autolysosomes, have been associated with a number of RNDs. *BPAN, Beta-propeller protein-associated neurodegeneration; CIPA, Congenital insensivity to pain with anhidrosis; HSAN, Hereditary sensory and autonomic neuropathy; IBMPFD, Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia; MJD, Machado-Joseph disease;* Disease abbreviations were taken from GARD webpage (rarediseases.info.nih.gov).

Supplementary Table 1: **RND studies using disease gene-related iPSC lines**