A common theme for axonopathies? The dependency cycle of local axon homeostasis

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Funding information
Biotechnology and Biological Sciences Research Council. Grant/Award Numbers: BB/I002448/1, BB/L000717/1, BB/M007553/1, BB/P020151/1

Abstract

The number of acquired or inherited conditions leading to axon degeneration (from now on referred to as axonopathies) is vast. To diagnose patients, clinicians use a range of indicators including physiology, morphology, family and patient history, as well as genetics, with the specific location of the lesion within the nervous system being a prominent feature. For the neurobiologist, these criteria are often unsatisfactory, and key questions remain unanswered. For example, does it make sense that different axonopathies affect distinct neuron groups through distinct mechanisms? Would it not be more likely that there are common routes to axon degeneration? In this opinion piece, I shall pose this fundamental question and try to find answers that are hopefully thought-provoking and trigger some conceptual rethinking in the field. I will conclude by describing the ‘dependency cycle of axon homeostasis’ as a new approach to make sense of the intricate connections of axon biology and physiology, also suggesting that different axonopathies might share common paths to axon degeneration.

KEYWORDS
axonal transport, axonopathies, axons, cytoskeleton, microtubules, neurodegeneration

1 | AXONOPATHIES—CAN WE SEE THE FOREST FOR THE TREES?

Axons are the cable-like cellular processes of neurons that wire the nervous system. Their morphology is truly unique: in humans, neuronal cell bodies that are not larger than 100 μm can give rise to up-to-two-meter-long axons (between green arrow heads in Figure 1) with diameters of only ≤15 μm (Prokop, 2020); in blue whales, axons are believed to achieve length of up to 30 m (Smith, 2009; Wedel, 2012). In spite of their delicate morphology, most axons have to survive for an organism’s lifetime, that is, up to a century in humans. Unsurprisingly, mammals lose ~40% of axons during healthy ageing (Adalbert & Coleman, 2012; Calkins, 2013; Marner, Nyengaard, Tang, & Pakkenberg, 2003); they are key lesion sites in trauma, and many acquired or inherited conditions can trigger premature axon decay (from now on referred to as axonopathy). In certain cases, axonopathy can be an early symptom or even a key driver of neurodegenerative pathology, in others it is the primary feature of the disease (Adalbert & Coleman, 2012; Burgess & Crish, 2018; Medana & Esiri, 2003; Salvadores, Sanhueza, Manque, & Court, 2017).

Axonopathies can be acquired (Box 1) or inherited (Box 2), and the different forms are often not trivial to tell apart. They are usually classified based on clinical and post-mortem criteria (Chung, Prasad, & Lloyd, 2014; Garg et al., 2017; Katona & Weis, 2018; Klein, 2005; Verschuere, 2017) including the patient and family history (e.g., onset and progress of functional symptoms, other family members affected), the location of symptoms (e.g., sensory neurons, upper/lower motorneurons; Figure 1), the quality of symptoms (e.g., weakness, spasticity, electrophysiological indicators of demyelination), the presence of associated symptoms (e.g., scoliosis, cognitive...
deficits), subcellular features (e.g., protein aggregates, axon swellings) and, where appropriate, genetic sequencing results.

For an ever-increasing number of axonopathy-associated disorders, genetic links are being identified (Table S1), providing us with concrete molecular tools to study the mechanistic basis of axon decay. However, even with this knowledge, it remains a challenge to explain how identified gene functions cause specific disease symptoms. When comparing functions of genes linked to these disorders (Table S1), several observations can be made:

- Vitamin E deficiency; dying back pathology, axonal swellings (Kohlschütter, 2009; Lampert, 1967)
- Diabetic peripheral neuropathy/DPN; stocking-glove pathology (Juster-Switlyk & Smith, 2016)

(c) Metabolic neuropathies (Minagar, 2010)

- Chemotherapy-induced peripheral neuropathies/CIPN; dying back pathology (Fukuda, Li, & Segal, 2017; Malacrida, Meregalli, Rodriguez-Menendez, & Nicolini, 2019; Zajączkowska et al., 2019)
- Alcoholic neuropathy; dying back pathology (Chopra, 2012 #10812)
- Organophosphorus compound-induced delayed neurotoxicity/OPIDN; dying back pathology (Stassart, 2018 #10765)
- Neurotoxic hexacarbon-induced; dying back pathology, axonal swellings (Spencer & Schaumburg, 1977a, 1977b)
- Heavy metal-induced; stocking-glove pathology (Jang & Hoffman, 2011)

(d) Toxic neuropathies (Brandner, 2014)

- Multiple sclerosis; dying back pathology (Cotsapas, Mitrovic, & Hafler, 2018; Dutta & Trapp, 2011; van den Berg, Hoogenraad, & Hintzen, 2017)
- Carcinoma-associated paraneoplastic peripheral neuropathy; proximal-distal pathology (Dalmu, 1999)

(e) Upon inflammation or infectious diseases

- Neurotoxic hexacarbon-induced; dying back pathology, axonal swellings (Spencer & Schaumburg, 1977a, 1977b)
- Heavy metal-induced; stocking-glove pathology (Jang & Hoffman, 2011)

First, apart from spinal muscular atrophies (SMA), which is predominantly linked to the small ribonucleoprotein regulators survival of motor neuron 1 and 2 (SMN1 and 2) and was recently shown to also display a neurodevelopmental component (Kong et al., 2021), the other disease classes are usually caused by mutations in a variety of genes associated with a wide range of cellular functions (see colour code in Table S1A–C).

Second, different disorder classes seem to have prevalence for genes that relate to specific aspects of cell function; for example,
Some examples of rare hereditary axonopathy-related disorders

- **Giant axonal neuropathy (GAN)** (OMIM® #256850); dying back polyneuropathy displaying large axonal swellings filled with neurofilaments; fatal (~three decades); starting during infancy as severe peripheral motor and sensory neuropathy, evolving into central nervous system impairment (intellectual disability/dementia, seizures, cerebellar signs/ataxia, and pyramidal tract signs); linked to gigaxonin required for ubiquitin-proteasomal degradation of NFs (Kuhlenbäumer, Timmerman, & Bomont, 2014; R. Prior et al., 2017; Stassart et al., 2018).

- **Adrenomyeloneuropathy (AMN)** (OMIM® #300100); dying back pathology; progressive ataxic gait and spastic paraparesis most probably reflecting the degeneration of long spinal cord axons; linked to ABCD1, a peroxisomal adenosine triphosphate binding cassette transporter (Raymond, Moser, & Fatemi, 2018; Stassart et al., 2018).

- **Krabbe disease/globoid cell leukodystrophy (GLD/GCL)** (OMIM® #245200); affecting the white matter of the central and peripheral nervous system. Most patients present within the first 6 months of life with ‘infantile’ or ‘classic’ disease manifest as extreme irritability, spasticity, and developmental delay; absence of galactosylceramidase (GALC) causes neuronal accumulation of psychosine, a highly cytotoxic lipid that affects lipid rafts, endocytosis, transport and MT acetylation/polyglutamylation; causes axon swellings/transactions and dying back pathology (Nogueira-Rodrigues, Brites, & Sousa, 2016; Wenger, Rafi, Luzi, Datto, & Costantino-Ceccarini, 2000).
across different classes of axonopathy-related disorders including CMT, distal hereditary motor neuropathy (dHMN), HSP, amyotrophic lateral sclerosis (ALS) and hereditary cerebellar ataxias (HCA); for example, Bis-Brewer, Danzi, Wuchty, & Züchner, 2019; d’Ydewalle et al., 2011; Fridman & Murphy, 2014; Gentile et al., 2019; Katz et al., 2020; Liu, Duan, Zhang, Sun, & Fan, 2020; Ma, Chen, Raskind, & Bird, 2020; Scarlino et al., 2020; Tian et al., 2020).

2 | IS THERE A COMMON GENETIC EXPLANATION FOR AXONOPATHIES?

The last notion might indicate that the different classes of axonopathies may, to a degree, root in a common fundamental cell biology upheld by comparable genetic networks (see also Züchner & Vance, 2005). Therefore, the observed bias of specific axonopathies linking to certain gene functions, may have to be interpreted within the specific context of the neurons affected in each case, as will be briefly discussed in the following.

Thus, different neuron types have different developmental histories, and their genetic programs specified during early neurogenesis, trigger distinct gene expression profiles translating into distinct gene expression patterns across nervous tissues (Jessell, 2000). For example, dystonin is expressed in sensory and central neurons, whereas its close parologue MACF1 is mainly confined to the CNS (Voelzmann et al., 2017); loss of dystonin function causes HSAN6 (type 6 hereditary sensory and autonomic neuropathy) with little impact on central neurons (Edvardson et al., 2012; Lynch-Godrei & Kothary, 2020); dystonin loss is likely compensated for by MACF1 in the CNS. Similarly, loss of the glial proteins myelin protein zero (MPZ) and peripheral myelin protein 2 (PMP2) cause CMT by affecting myelination in the peripheral nerves but not CNS because they are specifically expressed only in peripheral myelin (Stassart, Möbius, Nave, & Edgar, 2018). Based on this thinking, one might be able to predict novel gene linkages: for example, microtubule crosslinking factor 1 (MTCL1) is an organiser of the axon initial segment specifically expressed in Purkinje cells (Satake et al., 2017) and might therefore turn out to be linked to HCAs in the future.

Furthermore, different neuron types display distinct properties that make them differentially dependent on specific aspects of their cell biology. Axons of different neuron classes display significant differences in lengths, diameters, neurofilament contents and arborisations, and they can be non-myelinated, myelinated or grouped in Remak bundles (Gardiner, 2011; Prokop, 2020). For example, the very specific dendritic morphology and physiology of cerebellar Purkinje cells makes them prime targets for specific genetic links to cerebellar ataxias (Hoxha, Balbo, Miniaci, & Tempia, 2018). As another example, nigrostriatal dopaminergic neurons have an unusually high number of axonal projections and presynaptic endings, thus displaying elevated levels of metabolic activity demand that likely renders these cells vulnerable in Parkinson’s disease (Bolam & Pissadaki, 2012; Spaulding & Burgess, 2017). Finally, myelinated axons are selectively vulnerable to the non-autonomous impacts of demyelination which can trigger harmful changes in energy demand, inflammation and signalling homeostasis (Stassart et al., 2018).

Furthermore, the axonopathies discussed here preferentially affect motor- and sensory axons which tend to be very long projection neurons connecting to distant targets (Figure 1); distal dying-back or stocking-glove pathologies (see next section) would indeed suggest that the longer the axons, the higher their risk to degenerate, usually starting from distal. This said, ALS has close links to frontotemporal dementia (FTD; Table S1C), of which the latter disorder affects much shorter axons through the same genetic defects.

With respect to diameter, one could argue that thinner axons have less content and therefore stochastically a lower likelihood of biological accidents that could start a degeneration process; vice versa, thinner axons might have less buffer to compensate for accidents which therefore display with much higher penetrance. For example, breaking endoplasmic reticulum (ER) tubules might have drastic consequences in a thin axon by interrupting the physiologically relevant continuous smooth ER network (Burton & Laveri, 1985; Gonzalez & Couve, 2014), whereas larger diameter axons might better tolerate tubule breakages because they contain more tubules running in parallel that can sustain continuity of the network.

Finally, we need to consider the complications of human genetics. It is the most refined genetics we have, but it also raises two fundamental challenges. First, heterozygous constellations are naturally the most frequent mutant conditions in human populations which cause symptoms only if alleles are of dominant nature: they either display haploinsufficiency or gain of function. In agreement with this notion, many disease-linked genes are of dominant nature (third column in Table S1A–C). In those cases, focussing on the endogenous function of the linked gene may be little informative or even misleading (Kim, Gautier, Tassoni-Tsuchida, Ma, & Gitter, 2020). For example, several mutant forms of the microtubule (MT)-associating protein TAU/MAPT (linked to a range of neurological conditions; OMIM® #157140) become hyper-phosphorylated and/or cleaved, affecting its association with MTs (Iqbal, Liu, Gong, Alonso Adel, & Grundke-Iqbal, 2009; Noble, Hanger, Miller, & Lovestone, 2013). This causes a loss-of-function impact on MT networks (Baas & Qiang, 2019; Morris, Maeda, Vossel, & Mucke, 2011; Voelzmann et al., 2016). In parallel, the aberrant pools of TAU accumulating in the cytoplasm express a wide range of de novo functions (Noble et al., 2013): for example, they interfere with mitochondrial fission (Duboff, Gotz, & Feany, 2012), structurally change axons in ways that affect neuronal excitability (Hatch, Wei, Xia, & Gotz, 2017), or cause the formation of pathological neurofibrillary tangles (Bamburg & Bloom, 2009) or actin-rich rods (Fulga et al., 2007). Pinpointing which of the loss- or gain-of-function mechanisms, or combination thereof, causes the axonal decay can be a challenging task and may involve aspects of cellular function that are not related to endogenous roles of the affected gene locus (Kim et al., 2020).

Second, the disease-associated mutations listed in Table S1 usually allow individuals to survive for long enough to be identified and sequenced by clinicians; they are selected for restricted functional
impacts, and this could be one potential explanation as to why they often cause symptoms restricted to specific neuron types. Complete loss-of-function conditions (also eliminating genetic redundancy) or stronger gain-of-function conditions are more likely to give us profound genetic insights into axonopathies. However, such conditions likely have a strong bias to cause embryonic or early postnatal lethality. These would therefore be discovered primarily through foetal sequencing in missed abortions (Fu et al., 2018) or through work in model organisms, which provide powerful strategies to complement human genetics and gain more profound genetic, conceptual and mechanistic understanding of axonopathies.

3 | IS THERE A COMMON PATHOLOGY?

Apart from genetic considerations, we need better knowledge of the cell biology of axon pathology as an important further source of information to clarify commonalities and differences between axonopathies. However, as stated by Vallat and colleagues: ‘The characteristic microscopic lesions can only be identified by ultrastructural analysis of a nerve biopsy, which is nowadays only carried out in rare cases’ (Vallat et al., 2016). Even if more biopsies were available, their interpretation remains a challenging task. Axon degeneration occurs over an extended time period, and key traits of pathology are likely to change from early to late stages of an axon’s degenerative process; any sample taken will only provide us with a narrow time window of a long process. Furthermore, axonopathies are unlikely to synchronously affect all axons in a nerve, and they may initiate in varying proximo-distal positions, thus making it difficult to stage disease progression of individual axons in biopsies. To really understand the origin and progression of decay, we would need pathological timelines of events—but such systematic descriptions are rare (e.g., Spencer & Schaumburg, 1977a, 1977b).

This said, there are various features frequently reported that show a certain degree of commonality across different forms of axonopathies. They comprise the ‘dying-back’ pathology, that is, the degeneration of axons starting at their distal ends; this can be observed in hereditary diseases including CMT and hereditary motor sensory neuropathy (HMSN), HSP, giant axonal neuropathy (GAN), adrenomyeloneuropathy (AMN) and in most forms of acquired axonopathies (Boxes 1 and 2). A further common observation is the occurrence of blocked transport as a key feature of axonopathy (Brady & Morfini, 2017; De Vos, Grierson, Ackerley, & Miller, 2008; Guo, Stoklund Dittlau, & Van Den Bosch, 2020; Millecamps & Julien, 2013; Prior et al., 2017; Sleigh, Rossor, Fellows, Tosolini, & Schiavo, 2019), which is also considered a hallmark of ageing neurons (Mattedi & Vagnoni, 2019). Furthermore, there are many reports of axon swellings; as pointed out by Mike Coleman: ‘axon spheroids, or smaller varicosities, which can be broadly termed axonal dystrophy, are almost universal in neurodegenerative diseases of the CNS,

![Figure 2](https://wileyonlinelibrary.com)
probably as manifestations of a major pathway of CNS axonal death’ (Coleman, 2005). Usually, these swellings are characterised by the accumulation of organelles and disorganisation or even disappearance of the cytoskeleton (Figure 2b, top; e.g., Berard-Badier, Gambarelli, Pinsard, Hassoun, & Toga, 1971; Bridge et al., 2009; Fassier et al., 2013; Fiala, Feinberg, Peters, & Barbash, 2007; Havlicek et al., 2014; Jellinger & Jirasek, 1971; Probst et al., 2000; Seitelberger, 1971; Tarrade et al., 2006; Yang et al., 1999); they are known to interfere with active potential propagation (Gu, 2021).

Finally, there is little indication that chronic damage to axons has known to interfere with action potential propagation (Gu, 2021).

So far, we identified several mechanisms of MT bundle maintenance. First, spectraplakin- and Eb1-dependent mechanisms guide the extension of polymerising MTs along the axonal cortex into parallel bundles; this mechanism might explain severe disorganisation of axonal MTs observed in sensory neurons upon loss of the spectraplakin DYSTONIN in mouse models of human HSN6 (Alves-Silva et al., 2012; Voelzmann et al., 2017). Consistent with the dependence of this guidance mechanism on MT polymerisation, the functional deficiency of polymerisation-promoting factors (we identified a functional trio of Eb1/Eb3, Msps/XMAP215 and tau/TAU in fly and frog neurons) causes not only a reduction in MTs but also their curled disorganisation (Hahn et al., 2019; Lam et al., 2016). This may explain our astonishing finding that a whole range of mutant constellations removing very different classes of MT-binding and -regulating proteins (MTBPs) causes almost identical MT curling phenotypes (Figure 2b, top; summarised in Hahn et al., 2019); we propose that the kinesin-rich axonal environment imposes a default bias for MTs to curl and become disorganised, whereas MTBPs play major roles in preventing this from happening and maintaining orderly bundles (‘4’ in Figure 2a).

The second mechanism is provided by cortical collapse factors, able to eliminate any MTs that leave the bundle and project towards the surface; lack of this surface elimination causes a gradual build-up of curled MT disorganisation (Qu et al., 2019), a mechanism that might explain congenital fibrosis of extraocular muscles (CFEOM1; 135700) linked to the cortical collapse factor KIF21A (van der Vaart et al., 2013).

Further important roles are played by the axonal cortex which provides architectural support and also influences MT polymerisation behaviours (‘4’ in Figure 2a; Datar et al., 2019; Dubey et al., 2020; Qu, Hahn, Webb, Pearce, & Prokop, 2017; Wang et al., 2020). These cortical properties might explain brain disorders linked to gene mutations of cortical actin or actin regulators: adducin 3 (ADD3) is linked to type 3 spastic quadriplegic cerebral palsy (CPSQ3; #617008; Krueer et al., 2013), nonerythrocytic β-spectrin 2 (SPTBN2) to spinocerebellar ataxias (SCA5 and SCA14; #600224, #615386), ankyrin 3 (ANK3) to autosomal recessive mental retardation (MRT37; #615493), and β-actin (ACTB) to Baraitser-Winter syndrome 1 (BRWS1; #243310) and juvenile-onset dystonia (DJO; #607371). Any of these pathologies could potentially relate to gradual MT bundle decay in axons through damage or a reduction in MT polymerisation and turnover.

This scenario where MT bundle-damage due to life-sustaining axonal transport is counterbalanced by bundle-maintaining actions of MTBPs and the cortex, could be an essential pillar of axon
maintenance and has originally been formulated in our model of ‘local axon homeostasis’ (Hahn et al., 2019).

5 | EXPANDING THE MODEL

However, we since realised that our model of ‘local axon homeostasis’ was incomplete, as suggested by our studies of motor protein loss. Based on our model, we would have predicted that deficiencies of transport motor proteins should relieve MT bundles of damage, hence be beneficial for their maintenance. However, we found the opposite: when functionally deleting five independent axonal motor proteins, three of them (Khc/KIF5A-C, Unc-104/KIF1A/Bδ and dynein), caused MT curling indistinguishable from phenotypes associated with other MTBPs (Hahn et al., 2019 and our unpublished data); of these, knockdown of dynein heavy chain was similarly shown to cause MT curling phenotypes in rat superior cervical ganglia neurons (Myers et al., 2006). Interestingly, these exact three proteins have human homologues linked to axonopathies: dynactin 1 (ALS1; #105400), dynein heavy chain 1 (CMT2A1; #614228), KIF1B (CMT20; #118210), KIF1A (SPG30; #610357) and KIF5A (SPG10; #604187; all listed in Table S1). This might be a co-incidence, or it might hint at specific roles of these particular motor proteins during axon biology.

Our further investigations dedicated to kinesin-1 or –3 deficient neurons revealed that the patho-mechanisms leading to MT curling involved oxidative stress in form of harmful reactive oxygen species (ROS; our unpublished data). How this harmful ROS is generated upon loss of these kinesins, and whether it involves aberrant organelle dynamics (e.g., Fransen, Lismont, & Walton, 2017; Pascual-Ahuir, Manzanares-Estreder, & Proft, 2017), remains to be explored; but our finding is consistent with previous reports that the actin cytoskeleton is modified by ROS (Wilson, Terman, Gonzalez-Billault, & Ahmed, 2016; Wioland et al., 2021), that oxidative stress leads to the oxidation and damage of MTs in cardiac myocytes (Goldblum et al., 2020 preprint), and that it explains axon swellings in models of Parkinson’s disease and multiple sclerosis (Czaniecki et al., 2019; Nikić et al., 2011). Importantly, our findings triggered new ways of thinking: loss of motor proteins might potentially relieve the MT bundles from mechanical damage, but such an effect appears to be outweighed by pathomechanisms triggered by loss of transport: transport deficiencies seem to trigger changes in axonal physiology that become severely harmful to MT bundles through alternative routes (‘S’ in Figure 2).

This idea is gaining momentum through various independent publications (Guo et al., 2020). The most striking case was the recent report depletion of JNK-interacting protein 3 (JIP3), a kinesin-1 linker protein associated with the neurodevelopmental disease neuromuscular disorder with or without variable brain abnormalities (NEDBA; #618443). JIP3-depleted human iPSCs (inducible pluripotent stem cells) displayed lysosome-filled axonal swellings in which the actin cortex was disturbed and MTs showed the exact same curling as described in our work (Rafiq, Lyons, Gowrishankar, De Camilli, & Ferguson, 2020 preprint); upon JIP3 knock-down, TAU is less likely to associate with MTs as suggested by hyperphosphorylation at several assessed sites (T181, S202/T205, S396), and TAU depletion from MTs could be one cause for their curling (Hahn et al., 2020 preprint). In another example it was shown that the RNA-binding protein SFPQ (SPLICING FACTOR PROLINE/GLUTAMINE-RICH) is an axonal survival factor and specifically transported by KIF5A and KLC; in its absence, MT bundles become disrupted and this effect is also observed when introducing the CMT2-associated KIF5A<sup>β280H</sup> mutation (Cosker, Fenstermacher, Pazyra-Murphy, Elliott, & Segal, 2016; Fukuda et al., 2020). Another example of axonal physiology impacting on MT bundles is the CMT2F mouse model: it carries mutations in heat shock protein β1 (HSPB1) that cause decreased acetylation of α-tubulin impacting on axonal transport (d’Yde et al., 2011). Finally, the DBA/2 J mouse model for glaucoma carries two mutations in the glycoprotein nonmetastatic melanoma protein B (GPNNMB) gene coding for a transmembrane glycoprotein and tyrosinase related protein 1 (TYRP1) involved in melanin biosynthesis (McKinnon, Schlamp, & Nickells, 2009); prime events of axon degeneration in this mouse model is the deterioration of the cytoskeleton including MTs (Wilson, Smith, Inman, Dengler-Crish, & Crish, 2016).

6 | WHAT ARE THE IMPLICATIONS?

The notion that axonal physiology downstream of axon transport might be a key factor involved in MT bundle maintenance, changes the model substantially in that it becomes a ‘dependency cycle of axon homeostasis’ where all aspects of axon biology and physiology are up- and downstream of each other (Figure 2a). This means that lesions in any position would break the axonal homeostasis cycle and cause a chain reaction of auto-destruction. Various examples of such lesions were listed above. They include mutations of motor proteins (‘a’ in Figure 2b; e.g., axonopathies linked to dynactin, KIF1A, KIF5A/ B), lesions to the MT bundles themselves (‘b’ in Figure 2b; e.g., chemotherapy-induced peripheral neuropathies, Box 1, with vincristine leading to MT disorganisation; Tanner, Levine, & Topp, 1998; TUBA4A mutations linking to ALS22, Box 2), genetic lesions to the axon cortex or MTBPs involved in bundle maintenance (‘c’ in Figure 2b; e.g., spinocerebellar ataxias linking to β-spectrin, loss of spectraplakins in HSAN6) and, eventually, direct or indirect impacts on axonal physiology (‘d’ in Figure 2b; e.g., links of ER-regulators in SPGs, of tRNA regulators in CMTs, of heat shock protein β1 in CMT2F, or the impact of demyelination on axonal physiology).

Obviously, the sequence of events will differ depending on the site of lesion. However, the model would predict that the outcome should be very similar. Unfortunately, the existing descriptions of axonal pathology are too scarce to validate our predictions, and substantial work would be required to compensate for this lack, ideally using standardised approaches in animal models and patient biopsies that cover a broader set of readouts. For example, as argued earlier (Hahn et al., 2019), MTs are too often neglected in axon analyses, with more emphasis being given to the staining with less relevant neurofilaments; or in ultrastructural analyses resolutions are kept too low to properly visualise MTs.
Taken together, I strongly believe that all the arguments listed above, including genetics, pathological observations and the ‘dependency cycle of axon homeostasis’, build an increasingly strong case for a common concept of axonopathies. I predict that axonopathies will have their individual variations but also share a fundamental common pathway of auto-destruction. Clearly, we require more pathological analyses to validate or disprove this point. Whatever the outcome, such an effort will pay off through providing us with essential new understanding of the essential patho-mechanisms that lead to the tragic occurrence of axonopathies.

ACKNOWLEDGMENTS

Work underpinning this article was made possible through support by the BBSC to A.P. (BB/I002448/1, BB/P020151/1, BB/L000717/1, BB/M007553/1). I am grateful to Cahir O’Kane for encouraging feedback and thoughts on axon length and the ER in axonopathy. I am indebted to my fantastic team that has driven our research into the axonal cytoskeleton for the last 15 years; they are in alphabetic order: Juliana Alves-Silva, Robin Beaven, Wolfgang Bottenberg, Beatriz Costa-Gomes, Abigail Elliott, Judith Fülle, Ines Hahn, Meredith Lees, Yu-Ting Liew, Robert Lühr, Cristina Melero, Michael Mende, Jill Parkin, Sanjai Patel, Simon Pearce, Yue Qu, Natalia Sánchez-Soriano, Mark Travis and André Voelzmann. Furthermore, I would like to thank the teams of GeneCards® and OMIM® for their outstanding work in making genes and diseases transparent and accessible. The author has no conflict of interests and no sharable data were generated.

DATA AVAILABILITY STATEMENT

No sharable data were generated.

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How to cite this article: Prokop A. A common theme for axonopathies? The dependency cycle of local axon homeostasis. Cytoskeleton. 2021;78:52–63. https://doi.org/10.1002/cm.21657