News from the powerhouses

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The disastrous 2011 Fukushima earthquake and its sequelae have sparked intense public discussions around a set of very fundamental questions such as whether our society should go on to maintain nuclear powerhouses in the future and if yes, which quality control mechanisms would have to be in place to guarantee the highest level of safety, how their efficiency and obedience themselves could reliably be controlled, and finally, at what costs a potential nuclear power phase-out would come.

This scenario is quite reminiscent of the situation on the cellular level, where mitochondria, serving the traditional cliché of “cellular powerhouses”, work to satisfy the cells’ energy demands by producing ATP through oxidative phosphorylation and glycolysis. This essential organelle function is, however, invariably coupled to the threat of intracellular damage that—when exceeding the capacity of existing molecular control systems—may easily wreak havoc up to killing the cell from within. On the molecular level, the main perpetrators, reactive oxygen species, leak out of the mitochondrial electron transport chain. Once released, this toxic spill then acts by oxidizing membrane lipids and proteins—including, of course, mitochondrial ones—as well as mitochondrial DNA (mtDNA). Importantly, primarily due to its intron- and histone-less structure as well as due to insufficient repair mechanisms, the latter is much more susceptible to mutational damage than the genomic DNA of the nucleus. As a result, in addition to occurring at much higher frequencies in comparison to genomic DNA mutations, mtDNA mutations also accumulate in postmitotic cells such as neurons in an age-

dependent manner, as reflected clinically by the age-dependent manifestation of a number of classical neurodegenerative conditions.

To prevent potential damage through leakage of toxic reactive oxygen species from the cellular powerhouses resulting in an age-dependent decline in mitochondrial functions, various quality control mechanisms are in place at the cellular level. One of these mechanisms—dynamic changes in mitochondrial morphology through continuous fission and fusion processes—allows to control the level of mutated mtDNA within cells, keeping thresholds of respiration-deficient mitochondria at bay. In addition, protein turnover pathways as well as degradation of entire damaged or dysfunctional mitochondria represent essential protective mechanisms intimately integrated into cellular physiology.

These mechanisms, which have only recently begun to be discovered, are currently the subject of intense research efforts. This is reflected by an impressive increase in the number of respective publications: searching the Web of KnowledgeTM database (Thomson Reuters) for publications using “mitochondria” and “neurodegeneration” as general search terms currently produces more than 1,900 hits, with publication numbers having climbed continuously from less than 75 papers in 2000 to more than 250 yearly publications at present. With dysregulated mitochondrial dynamics having appeared as a new theme in neurodegeneration just a few years ago [1], research on mitochondrial quality control mechanisms has since continued to produce surprising, fundamental new insights into the pathogenesis of certain neurodegenerative disorders.

While the interested reader is referred to excellent comprehensive reviews on the general role of mitochondria in neurodegeneration [2], with this mini-cluster of reviews we intend to shed a flashlight on selected, most exciting current developments in the field.

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In their article, Karbowski and Neutzner [3] illuminate the relevance of specific mitochondria-based protein quality control mechanisms which mediate the turnover of mitochondrial proteins, some of them playing crucial roles in neuronal (patho)physiology. For example, mitofusin-2, mutations of which cause hereditary Charcot-Marie-Tooth disease type 2A (a hereditary axonal peripheral neuropathy which may occasionally occur as a “plus phenotype” including optic atrophy) has recently been postulated to be one of these respective turnover substrates, raising the question in how far dysregulated mitochondrial protein turnover may potentially represent a contributing factor in the pathogenesis of certain neurodegenerative conditions.

In the second contribution of this review cluster, Pils and Winklhofer [4] focus on the newly discovered PINK-Parkin pathway, which is essential for the removal of dysfunctional or damaged mitochondria via mitophagy, a specialized form of autophagy. This mechanism seems to be pathogenically important in PARK2-linked autosomal-recessive juvenile Parkinson’s disease. In this rapidly developing field, it is now already well appreciated that in addition to the E3 ubiquitin ligase Parkin, at least one additional protein well known to neuropathologists, PTEN-inducible kinase 1 (PINK1), also contributes to Parkin-mediated neurodegeneration. Thus, it will be interesting to see in the future, in how far the PINK-Parkin connection is involved in the pathogenesis of additional neurodegenerative (and potentially, other) conditions as well.

Finally, Oettinghaus et al. [5] explore the pathophysiological consequences of dysregulated mitochondrial fission in the context of neurodegeneration. Implicated for the first time in 2007 with a lethal syndromic birth defect involving severe CNS manifestations, the mitochondrial fission mediator Drp1 has recently turned out to be essential for neuronal health. In addition, observations from two independently developed CNS-specific Drp1 knockout models

have since then further substantiated the importance of Drp1-mediated mitochondrial fission for neuronal development. Moreover, from a therapeutic point of view, recently developed small molecule inhibitors capable of interfering with the mitochondrial fission process hold great therapeutic promise as potential neuroprotective agents, especially for acute conditions such as ischemic stroke.

We hope that this cluster of reviews on selected aspects of mitochondria-associated neurodegeneration will be helpful for neuropathologists and our colleagues from neighboring neuroscience disciplines in keeping pace with the rapidly accumulating insights into the molecular pathophysiology of several emerging pathways leading to neurodegeneration. Such knowledge will undoubtedly also be crucial in our efforts aimed at developing novel therapeutic avenues to inhibit acute neuronal damage or to successfully interfere with the progression of certain relentlessly progressing neurodegenerative conditions.

References

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