bioenergetic and metabolism, which occurs in mitochondriopathies, cancer, or other metabolic diseases, such as type 2 diabetes mellitus, obesity, or nonalcoholic fatty liver disease.

[1]Institute of Functional Biology and Genomics, University of Salamanca, 37007 Salamanca, Spain

[2]Institute of Biomedical Research of Salamanca, University Hospital of Salamanca, University of Salamanca, CSIC, 37007 Salamanca, Spain

[3]Department of Biochemistry and Molecular Biology, University of Salamanca, 37007 Salamanca, Spain

[4]CIBERFES, Institute of Health Carlos III, 28029 Madrid, Spain

[5]Department of Biology, University of Padova, Via U. Bassi 58/B, Padova 35121, Italy

*Correspondence:
mariaeugenia.soriano@unipd.it

https://doi.org/10.1016/j.tem.2019.08.003

References

1. Rainbolt, T.K. *et al.* (2014) Stress-responsive regulation of mitochondria through the ER unfolded protein response. *Trends Endocrinol. Metab.* 25, 528–537
2. Balsa, E. *et al.* (2019) ER and nutrient stress promote assembly of respiratory chain supercomplexes through the PERK-eIF2alpha axis. *Mol. Cell* 74, 877–890 e876
3. Patten, D.A. *et al.* (2014) OPA1-dependent cristae modulation is essential for cellular adaptation to metabolic demand. *EMBO J.* 33, 2676–2691
4. Cogliati, S. *et al.* (2016) Mechanism of super-assembly of respiratory complexes III and IV. *Nature* 539, 579–582
5. Carreras-Sureda, A. *et al.* (2019) Non-canonical function of IRE1alpha determines mitochondria-associated endoplasmic reticulum composition to control calcium transfer and bioenergetics. *Nat. Cell Biol.* 21, 755–767
6. Cogliati, S. *et al.* (2013) Mitochondrial cristae shape determines respiratory chain supercomplexes assembly and respiratory efficiency. *Cell* 155, 160–171
7. Quintana-Cabrera, R. *et al.* (2018) The cristae modulator Optic atrophy 1 requires mitochondrial ATP synthase oligomers to safeguard mitochondrial function. *Nat. Commun.* 9, 3399
8. Glytsou, C. *et al.* (2016) Optic atrophy 1 Is epistatic to the core MICOS component MIC60 in mitochondrial cristae shape control. *Cell Rep.* 17, 3024–3034
9. Civiletto, G. *et al.* (2015) Opa1 overexpression ameliorates the phenotype of two mitochondrial disease mouse models. *Cell Metab.* 21, 845–854
10. Lebeau, J. *et al.* (2018) The PERK arm of the unfolded protein response regulates mitochondrial morphology during acute endoplasmic reticulum stress. *Cell Rep.* 22, 2827–2836
11. Wai, T. *et al.* (2016) The membrane scaffold SLP2 anchors a proteolytic hub in mitochondria containing PARL and the i-AAA protease YME1L. *EMBO Rep.* 17, 1844–1856
12. Davies, K.M. *et al.* (2014) Visualization of ATP synthase dimers in mitochondria by electron cryo-tomography. *J. Vis. Exp.* 91, 51228

Spotlight

Lots of Movement in Gut and Parkinson's Research

Gabriela Mercado[1] and Patrik Brundin[1,*]

A new mouse model of Parkinson's disease (PD) demonstrates α-synuclein pathology spreading from the gut to the brain via the vagus nerve (Kim *et al.*, *Neuron*, 2019). The pathology is associated with motor and non-motor behavioral deficits in wild-type mice. These findings support the idea that the gut could be a starting point for PD.

An important feature of PD is the progressive accumulation of intraneuronal inclusions, termed Lewy pathology, which are partly composed of misfolded α-synuclein fibrils. The notion that Lewy pathology is first initiated in peripheral tissues outside the brain, for example in the enteric nervous system, and then progressively spreads to different interconnected brain areas was proposed by Braak and collaborators about 15 years ago. Based on the analysis of post-mortem tissue from PD patients, they suggested that Lewy pathology is present in the enteric nerves and the olfactory bulb, several years before the appearance of motor symptoms [1]. They also proposed that the anatomical distribution of α-synuclein pathology can be categorized into defined disease stages that correlate with the progression of symptoms. Thus, autonomic (e.g., constipation) and olfactory disturbances are frequently apparent in the prodromal phase (in the absence of classical motor deficits), and these disturbances are associated with Lewy pathology in the dorsal motor nucleus of the vagus and the olfactory bulb, respectively. It is suggested that, once the pathology reaches the midbrain, it is coupled with degeneration of dopaminergic neurons in the substantia nigra, resulting in the characteristic motor symptoms. In the latter stages of the disease, emotional and cognitive disturbances develop, concomitant with Lewy pathology reaching the cerebral cortex [1]. Around a decade ago, following the observation of Lewy pathology inside fetal neurons transplanted into PD patient brains, it was suggested that the progression of Lewy pathology in accordance with Braak's model is due to α-synuclein fibrils transferring between neurons, even between interconnected brain regions, seeding further aggregation of soluble α-synuclein [2].

Even though Braak's work transformed PD research, the ideas that the disease can start in the periphery and that misfolded α-synuclein acts in a prion-like fashion to cause pathology propagation are still widely debated. The absence of tools that allow the imaging of Lewy pathology longitudinally in living people is a limitation, necessitating the development of animal models to test these ideas *in vivo*. Previous studies inoculating recombinant preformed fibrils of α-synuclein into the gut have demonstrated propagation of α-synuclein pathology to the brain in rodents [3,4]. However, these initial models failed to display further spreading of pathology in the brain,

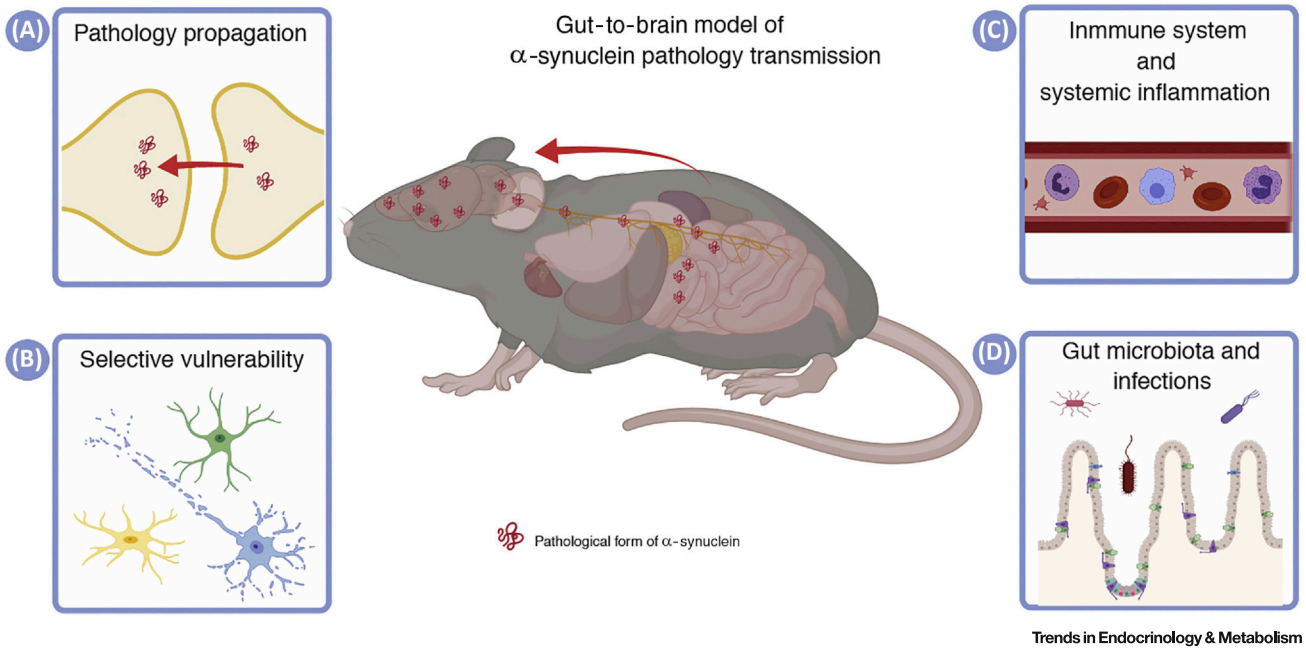

Figure 1. Potential Topics for Future Studies Using the New Gut-to-Brain Model of α-Synuclein Transmission.
(A) Mechanism of α-synuclein pathology transmission between neurons, from the periphery to the brain, and between interconnected brain areas. (B) Selective vulnerability of dopaminergic neurons and potential involvement of glial cells. (C) The role of the immune response and systemic inflammation in pathology transmission and neurodegeneration. (D) Triggering factor(s) for α-synuclein misfolding and aggregation in the gut, such as gut microbiota dysbiosis and infections. Figure created with BioRender.

and they did not reveal degeneration of nigral dopaminergic neurons. In a very recent study, Kim and coworkers developed a new model of PD that provides more compelling support for gut-to-brain propagation of α-synuclein pathology, and most importantly demonstrated that the Lewy-like pathology then spreads throughout the brain, including into the substantia nigra [5]. Seven months after multiple injections of α-synuclein fibrils into the duodenum and pyloric stomach of wild-type mice, α-synuclein aggregates were observed in several brain areas including the midbrain, amygdala, hippocampus, and striatum. Strikingly, the mice also displayed significant loss of nigral dopaminergic neurons and deficits in several tests of motor function. Remarkably, these animals exhibited severe impairment in a battery of cognitive and psychological behavior tests. After 9–10 months, the mice also displayed olfactory dysfunction and α-synuclein pathology in the olfactory bulb and prefrontal cortex. Notably, important control experiments were conducted in α-synuclein knockout mice that showed no propagation of α-synuclein pathology following injection of fibrils into the gut. Two other recent papers support similar gut-to-brain spreading of α-synuclein pathology in rodents, but both use transgenic animals that overexpress α-synuclein and behavioral changes were not systematically addressed [6,7]. Thus, a growing body of work supports gut-to-brain propagation of α-synuclein pathology in animal models. Collectively, this body of work indicates that the exact structural features of the injected α-synuclein fibrils, the precise location of injection site(s) in the gut, the total amount of fibrils injected, and the genetic background of the host all greatly influence the resulting pathology and behavioral deficits.

Although there are intrinsic limitations to any animal model of disease, the study by Kim *et al.* describes the first model that features such a broad constellation of PD-like motor and non-motor deficits that are associated with α-synuclein pathology transmission from the gut to the brain. Interestingly, the development of multiple PD-like features in these mice was prevented by truncal vagotomy, a procedure previously reported to be associated with reduced risk of developing PD [8]. Another recent study has also pinpointed a potential crucial role for the vagus nerve in the propagation of α-synuclein pathology, reporting that oxidative stress can enhance α-synuclein pathology transmission in the vagus of mice [9]. The new PD model reported by Kim *et al.* opens the possibility to elucidate the molecular mechanisms that underlie the propagation of α-synuclein pathology from the

gut to the brain, as well as the selective vulnerability of dopaminergic neurons, including the involvement of the gut microbiota and the immune system (Figure 1). More research will be necessary to address the triggering event(s) leading to the misfolding of α-synuclein in the gut and how they interact with genetic and other factors that can act as facilitators of the disease (Figure 1) [10]. In inflammatory bowel disease, which is both epidemiologically and genetically linked to elevated PD risk, increased levels of α-synuclein have been found in the gut [8]. In addition, the normal human appendix, that is rich in lymphatic tissue, contains an abundance of α-synuclein, including truncated forms similar to those found in Lewy pathology in PD [8]. Possibly, α-synuclein has a functional role in the gut immune system, and under some pathological conditions this goes awry, leading to pathological forms of α-synuclein escaping the gut and traveling along the vagus nerve to the brain. Other mechanisms might also be at play (Figure 1). Mutations in PINK1 cause rare early-onset PD, and a new study showed that PINK1-deficient mice develop PD-like motor impairment after bacterial infections in the gut [11]. Although this study suggests that systemic inflammation and autoimmunity are involved, with no involvement of α-synuclein in the process, it provides a further link between the gut and PD-like neurodegeneration in the brain. Given a remarkable number of studies linking the gut and PD in different ways, these are exciting times for research into the causes and mechanisms of this elusive disease. We envisage that the continued development of relevant and valid animal models of PD will allow us to identify both triggers and facilitators of the disease process, which should enable the development of novel therapies.

Disclaimer Statement

P.B. has received commercial support as a consultant from Renovo Neural, Inc., AbbVie, Neuroderm, Fujifilm-Cellular Dynamics International, Axial Biotherapeutics, and IOS Press Partners. He has received commercial support for grants/research from Lundbeck A/S, Renovo, and Roche. He has ownership interests in Acousort AB and Axial Biotherapeutics, and is on the steering committee of the NILO-PD trial.

[1]Center for Neurodegenerative Sciences, Van Andel Research Institute, 333 Bostwick Avenue NE, Grand Rapids, MI 49503, USA

*Correspondence:
Patrik.Brundin@vai.org

https://doi.org/10.1016/j.tem.2019.08.001

References

1. Braak, H. *et al.* (2003) Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *J. Neural Transm.* 110, 517–536
2. Kordower, J.H. and Brundin, P. (2009) Lewy body pathology in long-term fetal nigral transplants: is Parkinson's disease transmitted from one neural system to another? *Neuropsychopharmacology* 34, 254
3. Manfredsson, F.P. *et al.* (2018) Induction of alpha-synuclein pathology in the enteric nervous system of the rat and non-human primate results in gastrointestinal dysmotility and transient CNS pathology. *Neurobiol. Dis.* 112, 106–118
4. Uemura, N. *et al.* (2018) Inoculation of alpha-synuclein preformed fibrils into the mouse gastrointestinal tract induces Lewy body-like aggregates in the brainstem via the vagus nerve. *Mol. Neurodegener.* 13, 21
5. Kim, S. *et al.* (2019) Transneuronal propagation of pathologic α-synuclein from the gut to the brain models Parkinson's disease. *Neuron* 103, 627–641.e7
6. Van Den Berge, N. *et al.* (2019) Evidence for bidirectional and trans-synaptic parasympathetic and sympathetic propagation of alpha-synuclein in rats. *Acta Neuropathol.* Published online June 26, 2019. https://doi.org/10.1007/s00401-019-02040-w
7. Lohmann, S. *et al.* (2019) Oral and intravenous transmission of alpha-synuclein fibrils to mice. *Acta Neuropathol.* Published online June 22, 2019. https://doi.org/10.1007/s00401-019-02037-5
8. Rolli-Derkinderen, M. *et al.* (2019) Is Parkinson's disease a chronic low-grade inflammatory bowel disease? *J. Neurol.* Published online April 12, 2019. https://doi.org/10.1007/s00415-019-09321-0
9. Musgrove, R.E. *et al.* (2019) Oxidative stress in vagal neurons promotes parkinsonian pathology and intercellular α-synuclein transfer. *J. Clin. Invest.* 130, 127330
10. Johnson, M.E. *et al.* (2019) Triggers, facilitators, and aggravators: redefining Parkinson's disease pathogenesis. *Trends Neurosci.* 42, 4–13
11. Matheoud, D. *et al.* (2019) Intestinal infection triggers Parkinson's disease-like symptoms in Pink1$^{-/-}$ mice. *Nature* 571, 565–569

Spotlight

Hypothalamic Heuristics for Survival

Denis Burdakov[1,*] and Daria Peleg-Raibstein[1]

Hypothalamic neurons implicated in energy homeostasis (Agrp, POMC, orexin, MCH) display fast, nutrient-independent dynamics. They do not simply mirror the slowly changing internal nutrient levels, but adapt rapidly to diverse external cues. Moreover, instead of eating, neonatal Agrp cells stimulate mother-attracting vocalisations, illustrating heuristic energy control beyond nutrient sensing or dietary self-control.

Two decades ago, our conceptual understanding of brain control of energy balance seemed simple. Influential reviews (e.g., [1]) summarised it as a basic feedback scheme, where hypothalamic neurons react to direct internal indicators of body energy status and control eating and energy expenditure according to deviations of these indicators from some set point (Figure 1A). This reactive/feedback model of hypothalamic function was thus conceptually similar to models of peripheral organs (e.g., the pancreas), which are usually