Cell biology in support of neurological research: 2018 highlights

A strong basic science foundation is necessary to foster advances in clinical neurology, and 2018 has indeed deepened relevant foundational work in cell biology and neuroscience. This exceedingly brief summary of 2018 highlights will necessarily exclude not only a great deal of deserving bioscience research, but also major advances in artificial intelligence and robotics that use large amounts of patient data and engineering innovations to improve care for people with cognitive impairment.

In a tectonic shift over the past few years, the cell biology of proteostasis has been shown to be central to mechanisms of neurodegeneration. Although crucial details concerning autophagy, the lysosome, and the proteasome continue to emerge, proteostasis is increasingly linked to a process known as liquid–liquid phase separation or demixing of protein complexes into membraneless organelles, such as stress granules and a wide panoply of related organelles called RNA granules. This tendency of proteins to self-associate into condensed complexes through electrostatic interactions has deep evolutionary roots: early in evolution, life forms evolved a means to segregate themselves as metabolic units from the surrounding environment even in the absence of a membrane partition. These phase-separated compartments are under intense study as vehicles in which proteins involved in neurodegeneration become vulnerable to aggregation. Understanding of the composition and formation of these organelles progressed this year with the recognition by Roy Parker and colleagues[1] that RNA homopolymers as well as RNA binding protein–protein interactions contribute to stress-granule formation. The importance of this finding is highlighted by the discovery of a role for neurotoxic arginine-containing dipeptides, which are among the translation products derived from the *C9orf72* expansion that is associated with amyotrophic lateral sclerosis and frontotemporal dementia. These dipeptides stabilise the RNA–RNA interactions and thereby reveal a possible answer to a longstanding question: what initiates aggregation? Additional insight was gained from tracking the RNA binding protein TAR DNA-binding protein 43 (TARDBP, also known as TDP43), which forms aggregates in amyotrophic lateral sclerosis and frontotemporal dementia. As it exits the nucleus, TDP43 damages the nuclear pore and potentially opens a highly deleterious leak between the nucleus and the cytoplasm.[2]

Protein synthesis necessarily operates in partnership with protein degradation and, in the past year, RNA translation has surprisingly been shown to have relevance to the problem of neurodegeneration. In an exceptionally elegant study, Susan Ackerman and colleagues[3] reported that an editing-defective tRNA synthetase can cause degeneration in mouse Purkinje cells and the defect can be rescued by a vertebrate-specific ankyrin. These results identify a novel mechanism of neurodegeneration. By further investigating RNA translation, a therapeutic opportunity was revealed within the pathway that controls the integrated stress response, a widely shared pathway used to downregulate protein synthesis and upregulate some transcripts that allow cells to survive stress. RNA translation and the integrated stress response converge on the phosphorylation of translation initiation factor eIF2 (EIF2). Peter Walter and colleagues[4] have discovered a small-molecule EIF2B activator called ISRIB, which reverses the effects of EIF2 phosphorylation and corrects cognitive deficits after brain injury in rodents. This fundamental discovery introduces a potential wealth of modulatory components that might act as therapeutic

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targets in pathways that control translation. Indeed, the next step is to move these findings to the clinic.

A second shift in the past few years has been a turn to the role of inflammation in neurodegeneration. In two papers, the groups of Junying Yuan[5] and Don Cleveland[6] have independently moved forward the numerous descriptive observations of inflammation in neurodegeneration by showing a mechanism by which serine/threonine-protein kinase TBK1 (already genetically implicated in amyotrophic lateral sclerosis and frontotemporal dementia) inhibits receptor-interacting serine/threonine-protein kinase 1 (RIPK1) and thereby suppresses neuroinflammation and apoptosis by a pathway that links ageing and genetic susceptibility with neuroinflammation. This work moves RIPK1 to prominence in amyotrophic lateral sclerosis and frontotemporal dementia pathogenesis. Detailed microscopy revealed a novel route to the brain for the infiltration of inflammatory cells in mice: microscopic vascular channels cross the inner skull cortex for direct myeloid migration between the brain and the skull bone marrow via the meninges.[7]

Advances in methods are the basis for new insights. Brain organoids derived from human induced pluripotent stem cells hold the powerful potential to model human disease, a sorely needed development as we have come to the seemingly obvious conclusion that rats and mice are not humans, and the conclusions we can draw from animal studies are limited. In 2018, organoids that undergo myelination and myelin compaction were produced, enabling recapitulation of a genetic myelin disorder.[8]

2018 highlights would not be complete without touching upon the progress in a renewed understanding of memory units as engrams. Memory disruption is a common symptom of neurodegenerative diseases, and the specific cellular substrates of memory clusters might reveal selectively vulnerable biochemical pathways in these cells. Episodic memory is particularly vulnerable, and the finding that a hippocampal engram can map experiences points directly to a cell population that might mediate a very common symptom.[9]

To finish, in his 2017 Round-up,[10] John Hardy noted that the octopus generates most of its protein diversity by RNA editing rather than splicing, as humans do. In the same cephalopod wonderment category, 2018 brought us the finding that the octopus, separated by 500 million years of evolution, shares with humans a gene that responds to the drug ecstasy by increasing serotonin levels, thereby inducing a display of physical affection for their fellow octopuses.[11]

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