nature neuroscience

Focus on neurodegeneration

Every year, neurodegenerative diseases take a steep toll on millions of people, affecting individuals, their caregivers, families and communities. Most neurodegenerative diseases share a common course: uncontrolled neuronal death that leads to progressive decline in brain functions, such as cognition or locomotor control. We are proud to present this special focus issue on neurodegeneration, with five Perspectives and Reviews discussing recent advances in our understanding of neurodegenerative diseases, particularly those affecting the forebrain (Alzheimer's disease), basal ganglia (Parkinson's disease and Huntington's disease) and motor neurons (spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis). Many of these articles also critically discuss current therapeutic approaches and how recent technological advances and improved understanding of specific disease mechanisms may help to make the future search for therapies more tractable.

In some neurodegenerative disorders (such as Alzheimer's or amyotrophic lateral sclerosis), the diseases can be sporadic (striking people at random in the general population, without any clear genetic cause) or familial, in which case there are specific genetic defect(s) that are identifiable and heritable. Although the familial forms of the disease are far rarer than the sporadic forms, the mechanisms that mediate both forms are thought to be similar. As a result, genetic linkage studies have been invaluable in narrowing the search for candidate genes and proteins that are involved in the disease process and have spawned several useful animal models for these diseases. More recently, advances in the methodologies for robust genome-wide association studies (GWASs) have allowed the identification of genetic loci for sporadic forms of neurodegenerative disorders. On page 789, Sonia Gandhi and Nick Wood discuss the recent results of GWASs of Alzheimer's disease and Parkinson's disease. In their critical perspective, they describe the underlying principles and potential caveats of GWASs and the challenges that neurobiologists face in interpreting GWAS results.

Not all neurodegenerative diseases, however, have multiple genetic causes. SMA is a classic example of a monogenic genetic disease, in which the degeneration of spinal and bulbar motor neurons is attributed to defect(s) in a single genetic locus. In principle, this genetic homogeneity makes SMA more tractable from a therapeutic point of view, but devising an effective treatment for SMA has not been easy. In his perspective on page 795, Michael Sendtner critically evaluates earlier efforts in SMA drug discovery and translational research and describes how current attempts at devising potential therapies may benefit from emerging technologies, such as antisense oligonucleotide and induced pluripotent stem cell technologies.

Pluripotent stem cell technologies are an especially attractive avenue of research because, unlike some vertebrate cells (such as hepatic cells in the liver or epithelial cells in skin), most CNS cells do not usually retain the regenerative capability to divide and replace cells lost as a result of injury and disease. Given this, induced pluripotent stem cell technology may, in theory, be used to replace dead or dying neurons. However, many questions remain as to whether newly transplanted neurons can functionally integrate into the existing architecture of the diseased brain. Regardless of their therapeutic potential, stem cells can be useful in other aspects of disease research, such as examining specific aspects of disease mechanism and devising *in vitro* drug screens in the context of individual-specific genetic landscapes. On page 800, Hynek Wichterle and Serge Przedborski discuss these critical issues and highlight the effective applications of pluripotent stem cells.

Another issue with broad applicability to neurodegenerative diseases is protein aggregation, which is a common cellular hallmark of Alzheimer's disease, Parkinson's disease and Huntington's disease. When uncontrolled, these aggregates can act as a pathogenic species that cause cellular dysfunction and eventually cell death. Neurons normally use a process called autophagy (which relies on lysosomes for the final degradation step) to rid themselves of unwanted cytosolic proteins and damaged organelles. Signs of defective neuronal autophagy have recently been observed in several neurodegenerative conditions, and animal models with deficient autophagic processes recapitulate many aspects of neurodegenerative diseases. However, autophagy is not a single-step process. On page 805, Esther Wong and Ana Maria Cuervo review the specific steps of autophagy that may contribute to different neurodegenerative diseases. They describe the different processes that cells can use to load and deliver proteins to the lysosome and critically evaluate the growing evidence that each neurodegenerative disease may be associated with a specific defect at a specific step during autophagy. They also discuss the therapeutic implications of different types of autophagic failure and how the potential overlap between autophagy and other mechanisms of protein/cellular degradation can inform translational research.

Finally, on page 812, Jorge Palop and Lennart Mucke draw from recent mechanistic studies on molecular, cellular and functional consequences of amyloid-β peptide to review the mechanisms by which various forms of amyloid-β can lead to neuronal dysfunction in Alzheimer's disease. They discuss the implications for synaptic transmission, synaptic plasticity, neural circuits and regional brain networks and offer a synthetic view of how these changes may eventually lead to cognitive decline and neuronal death. In addition, they discuss the potential endogenous functions of amyloid-β in regulating synaptic activity and cell type–specific ways in which oligomeric amyloid-β may affect neural circuit activity.

We hope that this collection of Reviews and Perspectives will offer our readers a stimulating and up-to-date guide on some of the major advances in our understanding of the mechanisms that underlie different neurodegenerative disorders and the challenges that face us as we try and translate this information into therapy. Many of the innovative ideas discussed here will likely require more empirical support, but we hope that these ideas will inspire research in both neurodegeneration and other neurological disorders. We are very grateful to our authors, reviewers and advisors for their help with this collection. ■

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Associate Editor