Introduction

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The identification of genes that cause dominantly inherited forms of neurodegenerative disease originally led to hope for rapid therapeutic development. However, despite tremendous advances in our understanding about basic disease mechanisms, and the creation of multiple mouse models, we still do not have an effective treatment for any central nervous system (CNS) neurodegenerative disease. This grim outlook is now changing, however. A strong consensus has emerged around the role of protein misfolding and aggregation in the pathogenesis of neurodegeneration. Virtually all major age-dependent neurodegenerative diseases of adults feature accumulation of protein aggregates. Where dominantly inherited forms are identified, in almost all cases they have been linked to the very proteins that deposit within the brain, to the production of those proteins (in the case of the presenilins), or to protein quality control pathways. Consequently, there is an abundance of potential targets, while, at the same time, the means of intervention via small molecules, peptides, and gene therapy has rapidly evolved.

This issue features reviews that cover the major topics related to protein misfolding and neurodegenerative disease. These range from basic biology to recent advances in drug development and delivery. The issue begins with new perspectives on prion-like mechanisms in the propagation of neurodegenerative diseases (Kaufman and Diamond, see pages XX). This model of the pathogenesis of neurodegenerative diseases is useful because it makes specific predictions about the combined roles of intracellular aggregation and the spread of protein aggregates between neurons. The model does not fundamentally alter the interpretation of existing experimental data regarding protein aggregation mechanisms. However, should essential components of this

model be validated, this will suggest new therapeutic approaches that were not previously envisioned based on purely cell autonomous protein aggregation. Similarly, we now understand in increasingly specific terms the role of protein quality control pathways such as autophagy in clearance of misfolded proteins (Weihl, pages XX). Our knowledge about different pathways involved in the clearance of misfolded monomers versus aggregates, and the complexity of protective mechanisms, can provide better insight into new therapeutic strategies. Indeed, multiple existing candidate compounds might be exploited to promote the clearance of pathogenic proteins.

While protein misfolding and aggregation are strongly linked to many neurodegenerative diseases, the formation of very large aggregates themselves is not necessarily the only cause of pathology. Synuclein has now been extensively studied for its role in the pathogenesis of Parkinson disease and other pathologies, such as diffuse Lewy body dementia. As an intracellular membrane-associated protein, pathogenic synuclein may play a key role in destabilizing mitochondria to promote neuronal vulnerability (Nakamura, pages XX). This could suggest new possibilities for therapeutic intervention independent of preventing large aggregate formation.

With models to study basic mechanisms of pathology, we are increasingly in a position to design interventions to modify these mechanisms, to test the underlying hypotheses, and possibly to develop therapeutic leads. As it is not so feasible to screen candidate genes and small molecules in larger organisms, there has been longstanding interest in the development of cellular models of pathology, and their use to identify candidate modifier genes and lead compounds. Unfortunately, multiple screens using simple models of protein-induced cytotoxicity have failed to produce viable clinical leads. However, we are now beginning to develop more sophisticated early models of protein misfolding and neuronal toxicity (Calamini et al., pages XX). These models encompass yeast, mammalian cell models, slice cultures of

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rodent brain, invertebrate, and vertebrate models. Their integrated use provides a much better chance of facilitating the discovery of more effective lead compounds.

We are also beginning to refine screening methods to target specific cellular pathways to inhibit pathogenesis. Given the importance of protein quality control, the chaperone system has become a prime target (Lotz and Van der Putten, pages XX). A diversity of chaperones and protein quality control pathways is now known to modulate misfolding and aggregation of pathogenic proteins. In numerous cases these have been linked directly to neurological diseases. The spectrum of pharmacological targets presented by these factors creates wide range of possible intervention points to block neurodegeneration.

Multiple approaches have now also emerged to target directly the toxic proteins that lead to neurodegeneration. One of the earliest strategies has been to create small molecules that modify the aggregation state of pathogenic proteins (Bieschke, pages XX). While original approaches with compounds that directly inhibit the growth of fibrils have failed to produce viable leads, new knowledge about the mechanisms of protein aggregation has refined our intervention strategies. Specifically, compounds that alter the stability of aggregate intermediates, and even those that stabilize fibrils, are emerging as new candidates. Targeting specific events in the aggregation process may provide new types of therapies, and, at a minimum, will teach us about the role of these steps in pathogenesis of neurodegeneration.

Numerous groups have now proposed to modulate protein aggregation by peptide-based approaches. One strategy derived initially from the design of short peptides that interfere with the self-association of polyglutamine-containing proteins (Popiel et al., pages XX). This exemplifies tool development that can help to investigate the fundamental role of protein aggregation in pathogenesis. In a related approach, it has been possible to design single chain and single domain intrabodies that are active within the cell (Messer and Joshi, pages XX). These proteins may be targeted to specific regions of a pathogenic protein to modify its self-association or interaction with other cellular proteins. Use of these proteins in experimental models of Huntington disease has now begun to validate their therapeutic potential, if not simply their utility as tools to test molecular mechanisms of pathogenesis.

Systemic antibody-based therapies have also emerged (Yu and Watts, pages XX). Consistent with a role for extracellular aggregates in pathogenesis, passive and active immunotherapy has shown promise in experimental models, and is now being widely pursued. While the delivery of complex molecules, such as peptides or antibodies, to the CNS has long vexed drug developers, there are now innovative new strategies to facilitate crossing the blood–brain barrier. Bi-specific antibodies that target the transferrin receptor plus another target have enabled more efficient delivery of an antibody to the CNS by exploiting endogenous transport mechanisms. This innovative approach may be useful for delivery of a variety of biological agents.

Modulation of gene expression in the CNS offers another approach to neurodegenerative diseases. Specific inhibitory RNA molecules and viral delivery vectors have been validated in a variety of mouse models, and human trials may occur soon for CNS diseases (Ramachandran et al., pages XX). If these approaches are safe, there could be enormous potential to intervene in a variety of neurological syndromes for which inhibition of gene expression (e.g., reduction of a gene that causes gain-of-function toxicity) is desirable. Antisense oligonucleotides (ASOs) can modulate gene expression without the need for viral delivery, but require chronic administration (DeVos and Miller). ASOs against SOD1, for which missense mutations cause dominantly inherited forms of amyotrophic lateral sclerosis, have ameliorated pathology in mouse models. One anti-SOD1 ASO has now progressed through human phase I studies. As for inhibitory RNA, if ASOs are safe there could be an enormous effect on the treatment of neurodegenerative diseases. Finally, the ability to replace or enhance gene expression within the brain has advanced considerably (San Sebastian et al., pages XX). There is now much human clinical experience in the use of engineered viruses to express desired genes, such as those involved in growth factor or neurotransmitter production.

Taken together, these reviews encompass a large body of basic and applied research that is directly applicable to study the biology and effect treatment of neurodegenerative diseases related to protein misfolding and aggregation.

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