CHAPTER 31

Recent Progress in Understanding the Inherited Motor Neuron Diseases

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Over the last 10 years there has been substantial progress in understanding the genetic and molecular basis for several inherited motor neuron diseases (Table 1). An understanding of the range of genetic defects that cause diverse forms of motor neuron degeneration both illuminates the pathogenesis of the diseases and provides insight into the biologic properties of motor neurons. Ultimately, such studies should lead both to new diagnostic approaches to these diseases and ultimately to suggest new strategies for their treatment. This review briefly summarizes recent research advances in this field.

DOMINANT (ADULT-ONSET) AMYTROPHIC LATERAL SCLEROSIS

About 10% of amyotrophic lateral sclerosis (ALS) cases are inherited as an autosomal dominant trait (familial ALS—autosomal dominant [FALS-AD]). FALS-AD is clinically and pathologically indistinguishable from sporadic ALS and thus appears to share important pathogenic mechanisms with sporadic ALS. Both sporadic and FALS are almost invariably lethal, with a median survival of less than 5 years (1). Pathologic findings in FALS include degeneration and loss of large motor neurons in the cerebral cortex, brainstem, and cervical and lumbar spinal cord. Occasionally, there is subclinical involvement of nonmotor cells and tracts in the central nervous system. These include the posterior columns, Clarke’s column, and the spinocerebellar tracts (2–4). In 1993, a multicenter collaborative study identified several mutations in the gene for Cu/Zn superoxide dismutase in FALS-AD (5).

Cu/Zn superoxide dismutase 1 (SOD1) is a protein of 153 amino acids encoded by five exons within the SOD1 locus (6). The SOD1 gene has been highly conserved during evolution; it is expressed in multiple cell types in many species (7). Its primary function is to detoxify the superoxide free radical \( \text{O}_2^- \), converting it to \( \text{H}_2\text{O}_2 \). In turn, peroxide is converted to water through the action of either catalase or glutathione peroxidase (7,8). As a free radical, the superoxide anion can interact with numerous cellular constituents (e.g., DNA, lipid, carbohydrate, protein) to be cytotoxic. It is important to note that there are mechanisms whereby \( \text{H}_2\text{O}_2 \) can also generate free radicals. For example, in the Fenton reaction, transition metals such as iron or copper interact with superoxide anion to form the hydroxyl radical \( \text{OH}^- \). This species of free radical interacts on formation with any cellular constituent at hand (9,10). Taken broadly, these data suggest that FALS-AD occurs because motor neurons are unusually sensitive to disturbances of free radical homeostasis. A corollary premise is that sporadic ALS is also a free radical disorder. Indeed, experimental studies of ALS tissues support this contention; levels of two markers of oxidative molecular injury, carbonyl proteins and oxidatively modified DNA, are abundant in ALS spinal cord (11).

The mechanisms whereby mutations in the SOD1 gene trigger ALS are not clear. Some ALS tissues bearing some mutant forms of ALS have reduced SOD1 activity, as do the red cell lysates in some cases (12,13). However, this loss of activity is not uniform. Especially in light of the dominant mode of inheritance of FALS, these facts argue strongly that the neurotoxic properties of mutant SOD1 protein are acquired, adverse, and directly a consequence of the mutation. Two additional findings corroborate this view. First, mice generated with inactivation of the SOD1 gene do not demonstrate exaggerated motor neuronal cell death, although their neurons have a sub-
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<td>Adrenoleukodystrophy ATP binding protein</td>
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SMA, spinal muscular atrophy.

normal capacity to resist physical and metabolic stress (14). Second, it is striking that mice expressing high levels of mutant SOD1, with normal or greater than normal total SOD1 activity, develop a phenotype that is clinically and pathologically stunningly like human FALS (15).

The nature of the adverse property of the mutant SOD1 protein has been elusive, although possible explanations arise. Several are predicated on the observation that the mutations seem to diminish the stability of the SOD1 protein, shortening its half-life (16,17) and potentially opening up the folded structure of the protein. One consequence of this change might be either release of copper and zinc into the cytosol or enhanced exposure of molecules in the cytosol to the bound copper and zinc. Another consequence of aberrant SOD1 folding might be enhanced access of atypical substrates to the active channel of the protein. Thus, it has been proposed that the mutations enhance the interaction of peroxynitrite with SOD1, increasing formation of nitrotyrosine groups (18–20). Depending on the particular tyrosine residues that are nitrated, this process may be injurious. Examples might include tyrosines in neurotrophic factor receptors functioning as tyrosine kinases. Recent studies document that nitration of tyrosines on neurofilament subunits can impair neurofilament maturation (21). Over the last year, reports have documented that free nitrotyrosine levels are increased in both human and murine ALS (22–24). The significance of these findings has not been defined.

Another proposed mechanism for neurotoxicity of mutant SOD1 invokes enhanced ability of the mutant protein to act as a peroxidase, using substrates like H₂O₂ to generate hydroxyl radicals (25–27). Yet another mechanism invokes abnormal protein binding and aggregation as the primary source of toxicity. Thus, one report indicates that mutant SOD1 protein binds proteins not normally bound by wild-type SOD1 (28); an alternate possibility is that SOD1 itself may aggregate and precipitate (29). Consistent with this is the finding that cytoskeletal aggregates in motor neurons in ALS may contain SOD1 protein (30–33). However, the specificity of this finding is unclear because such SOD1-positive deposits are seen in both sporadic and FALS.

Regardless of the specific chemistry implicated, several lines of inquiry demonstrate that one consequence of the presence of mutant SOD1 protein is activation of one or more apoptotic cell death pathways. In neurons in vitro, forced expression of mutant SOD1 is clearly proapoptotic (34–36), whereas the wild-type SOD1 molecule is distinctly antiapoptotic (37–40). In the ALS mice in vivo, inactivation of caspase 1 (interleukin-converting enzyme 1) produces a modest but statistically significant increase in disease duration (41); overexpression of Bcl-2 significantly delays disease onset (42). These observations are consistent with a role for apoptotic death as one element in the pathogenesis of motor neuron degeneration in these mice but by no means can be interpreted to
exclude neuronal death via other nonapoptotic pathways. Clear data have not emerged confirming evidence of apoptosis in ALS autopsy tissues, although two initial reports are consistent with this possibility (43,44).

RECESSIVE (JUVENILE-ONSET) AMYTROPHIC LATERAL SCLEROSIS

Ben Hamida et al. (45) described a form of motor neuron disease characterized by chronic slow degeneration of both upper and lower motor neurons. This juvenile-onset disease is inherited as an autosomal recessive trait; survival may be decades. Clinically, the lower motor neuron findings resemble those in denervating polynuropathy. Nonetheless, some affected individuals are also markedly spastic and may demonstrate pseudobulbar disturbances of affect. Cognition is normal in affected individuals. Autopsy tissue has not yet been examined in these cases. A genetic locus for a form of this disease has been defined, but the underlying gene defect is not yet known (46).

ADULT-ONSET TAY-SACHS DISEASE

Although GM2 gangliosidosis usually is evident in early childhood, there are variant forms (adult-onset Tay-Sachs disease) that have a clinical phenotype resembling a lower motor neuropathy (47). Patients with this illness usually offer a history of lifelong motor incoordination. As young adults, they note the subtle onset of progressive proximal muscle weakness with features indicating lower motor neuron dysfunction (fasciculations, mild denervation atrophy, and electromyographic abnormalities). This may then evolve to frank leg weakness, sometimes with dysarthria. Some patients also show psychiatric manifestations (e.g., anxiety, subnormal attention span, or even psychotic episodes) (48). Some patients may reveal spasticity and Babinski signs as the illness progresses. Involvement of the central nervous system is indicated not only by the corticospinal signs but also some atrophy, particularly in the cerebellum. A salient pathologic finding is the presence of distended neurons with periodic acid-Schiff-positive inclusions (49).

The underlying defect in this disease is an accumulation of GM2 ganglioside, which is normally metabolized by N-acetyl-hexosaminidases A and B (Hex A and B); these are dimeric enzymes made up of two polypeptides. An alpha and beta subunit are combined in HEX A, and HEX B has two beta subunits. The activity of both enzymes is augmented by GM2 activator protein, which enhances access of substrate to the enzyme. The genes for the alpha and beta subunits are encoded on chromosomes 15q and 5q (50). The GM2 activator protein may be encoded on chromosome 5 (51). Patient DNA analysis reveals mutations in the alpha and beta subunits and the GM2 activator protein (52,53).

X-LINKED SPINAL BULBAR ATROPHY

The hallmark of this disorder is a slowly progressive lower motor neuropathy arising in adult males (54). Unlike the situation in ALS, pathology in X-linked spinal bulbar atrophy is confined to lower motor neurons. Moreover, the time course is slower than in ALS. In X-linked spinal bulbar atrophy, there may be gynecomasia and testicular atrophy with reduced fertility. LaSpada et al. (55) discovered that the molecular defect in X-linked spinal bulbar atrophy is an expansion of a CAG repeat in the first exon of the androgen receptor gene. This expands a polyglutamine tract within the receptor. It is apparent that as the length of the tract of CAGs increases, the illness becomes more severe (56). It is not clear how this molecular lesion causes motor neuron disease. However, important insights have come from the discoveries that there are diverse inherited neurodegenerative diseases associated with CAG repeat expansions, including Huntington’s disease and several of the spinocerebellar ataxias; in each of these, there is a predicted polyglutamine expansion; and in each, careful ultramicroscopy and analysis with antibodies to expanded glutamine tracts document the presence of intranuclear inclusions of protein consisting in part of polyglutamine (57). That these are abnormal is indicated in part by their aggregation within nuclei and in part by the fact that they are ubiquitinated (57).

SPINAL MUSCULAR ATROPHY

The spinal muscular atrophies are discussed in detail in Chapter 30. Briefly, this family of disorders characterized by progressive degeneration of motor neurons in the brainstem and spinal cord is caused by deficiencies of a survival motor neuron or SMN protein. Recent studies indicate that SMN is important in the formation and function of spliceosomes and thus is important in the processes of splicing of nuclear and nucleolar RNA (58,59).

FAMILIAL SPASTIC PARAPLEGIA

Familial spastic paraplegia (FSP) is an autosomal dominant disorder characterized by slowly worsening spastic weakness that typically starts in the distal legs (60,61). Although the age at onset is variable, in a large preponderance of families the disease begins in the third or fourth decade. Many patients live several decades with this illness. Sphincter disturbance and weakness of the upper extremities are uncommon but may be seen late in the course. By the same token, minor sensory loss may be evident in late-stage FSP. The most prominent pathologic feature in FSP is degeneration of the corticospinal tracts (62). Rarely, FSP is associated with involvement of other regions of the nervous system (63) and thus may entail
amytrophic, mental retardation, optic atrophy, and sensory neuropathy. Although these complex forms of the disease attest to the difficulty in classifying subtypes of FSP, it seems likely that genetic and molecular studies will clarify these nosologic issues. For example, in only the last 5 years, loci for FSP have been identified on chromosomes 2p (64), 14q (65), and 15q (66). X-linked and recessive forms of FSP are also encountered; the latter is more common in regions with consanguinity (67). Atypical FSP has been associated with mutations in genes encoding the proteolipid protein (68) and the cell adhesion protein LICAM (69). A form of adrenoleukodystrophy (adrenomyeloneuropathy) can resemble FSP (70,71).

REFERENCES


