The law of mass action applied to neurodegenerative disease: a hypothesis concerning the etiology and pathogenesis of complex diseases

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Loci underlying autosomal dominant forms of most neurodegenerative disease have been identified: prion mutations cause Gerstmann Straussler syndrome and hereditary Creutzfeld–Jakob disease, tau mutations cause autosomal dominant frontal temporal dementia, and α-synuclein mutations cause autosomal dominant Parkinson’s disease. In all these cases, the pathogenic mutation is in the protein that is deposited in the diseased tissue and in these cases the whole protein is deposited. In Alzheimer’s disease, mutations in APP or presenilin 1 or 2 cause autosomal dominant disease and these are the substrate and proteases, respectively, which are responsible for the production of the deposited peptide, Aβ. Thus, in all cases, the mutations lead to the disease by a mechanism that involves the deposition process. We briefly review this remarkably predictable biology, but also point out that it seems sporadic forms of all these diseases are predisposed to by genetic variability at the same loci, strongly suggesting that the quantity of the normal protein produced influences risk for the sporadic forms of the disease. The evidence for this assertion is strongest in Parkinson’s disease (PD), where genetic variability in α-synuclein expression affects risk of developing disease, although the oldest evidence for the notion that increased expression of normal sequence protein can lead to disease comes from the observation of Alzheimer’s disease in trisomy 21 cases. From these observations, we make predictions concerning the etiology and pathogenesis of neurodegenerative diseases in general.

INTRODUCTION

In the last 15 years there has been remarkable progress in our understanding of the etiology of the autosomal dominant neurodegenerative diseases. The loci underlying the autosomal dominant forms of Creuzfeldt–Jakob disease (1), frontal temporal dementia (2) and Parkinson’s disease have been identified (3). In each case, the underlying locus has encoded the protein that is often deposited in the disease. In Creuzfeldt–Jakob disease, this is the prion protein: in frontal temporal dementia, it is tau, and in Parkinson’s disease it is α-synuclein. In Alzheimer’s disease, the situation is a little more complex in that the deposited peptide, Aβ, is derived from a fragment of the APP protein when metabolized by the γ-secretase complex: a key component of this complex are the presenilins and mutations in either APP or presenilin 1 or 2 can lead to disease (4–6).

These findings are well established and have driven therapeutics research, especially because they have allowed the development of animal models of these diseases as well as defined therapeutic targets (7). In each of these examples, the precise ‘pathologic species’ of protein is obscure, if there is one, and it is debated whether the deposits themselves, or some intermediate species such as an oligomer, are responsible. This has been extensively investigated, with the balance of recent data favoring smaller intermediate species as the toxic entities (8); however, the generality of the fact that the mutated protein in each example can be deposited suggests that the process of pathogenicity is related to, although perhaps separable from, the process of deposition.

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By studying the autosomal dominant forms of these and other diseases, researchers hope to gain insight into the more common, sporadic forms, and from a mechanistic perspective, this has certainly been the case. However, perhaps more surprisingly, over this last 4 years, it has become clear that, in the case of many of these diseases at least, the haplotype of the Mendelian pathogenic locus influences the disease risk for sporadic disease.

In this review, we briefly summarise these data, and then make predictions concerning the etiology and pathogenesis of these and other neurodegenerative diseases. First, though, it is worth noting what a ‘haplotypic association’ means from a mechanistic perspective: in the absence of coding changes, a haplotypic association implies there is genetic variability either in the amount of expression of the protein, or in the alternate splicing of the protein, and that this contributes to disease risk.

THE DISEASES

Prion diseases

The prion gene has two common coding variants in Caucasian populations: one with prion M129 the other with prion V129 (9,10). It has long been recognized that homozygosity at codon 129 predisposes to sporadic disease, presumably because of the necessity of prion–prion interactions and symmetry considerations (9,10). However, in addition to this well-established risk, recent genetic data have shown that the prion haplotype confers additional risk to idiopathic disease (11), clearly suggesting that genetic variability in prion expression contributes to disease risk. While these genetic data do not establish whether high expressors or low expressors are more susceptible, and since prion knockout mice are completely resistant to disease (12), it is most parsimonious to expect that those who express high levels of prion protein, and are homozygotes at codon 129, are most susceptible to disease.

Alzheimer’s disease

Extensive sequencing of the APP gene in late-onset Alzheimer’s disease has failed to identify mutations (13). However, analysis of data from sibpairs affected with late-onset Alzheimer’s disease has consistently suggested that APP is a locus for this form of disease (14,15). This suggests that genetic variability at the APP locus contributes to disease risk, although the precise variability has not been identified. Such a finding is consistent with the longstanding observation that individuals with trisomy 21 inevitably develop Alzheimer pathology by their fifth decade (16); however, those few cases of Down syndrome caused by triplication of chromosome 21 distal to the APP gene do not develop Alzheimer’s disease (17). Thus, having three copies of the APP gene leads to Alzheimer pathology in the fifth decade and as yet unidentified genetic variability at the APP locus appears to contribute to disease risk.

Frontal temporal dementia: tangle diseases

Mutations in the tau gene cause many cases of autosomal dominant frontal temporal dementia in which there is tau pathology. There are many sporadic diseases in which tau pathology occurs, usually as tangles, but also as Pick bodies or Argyrophilic grains (18). There are two genetic haplotype clades in Caucasian populations, designated H1 and H2, which differ in intron sizes, promoter sequence and wobble bases (19). The H1 haplotype has a frequency of ~75% in Caucasians, and thus the H1 homozygotes constitute ~60% of such populations. However, individuals with one of the three sporadic tau diseases, progressive supranuclear palsy (19), corticobasal degeneration (20) and argyrophilic grain disease (21), although not Pick’s disease (22) or Guam disease (23), show a robust association with H1 homozygosity, with a frequency of H1 homozygotes being ~95%. These data show clearly that variability in either tau expression or tau splicing variability (or both) contribute to disease risk. In this case, it is difficult to determine whether it is control of splicing or control of expression which is the key variable because it is indeed clear that many mutations which lead to Mendelian disease do so through altering alternate splicing (2,24).

Parkinson’s disease/Lewy body dementia

Mutations in the α-synuclein gene cause autosomal dominant Parkinson’s disease, and α-synuclein is the primary component of Lewy bodies, the pathognomonic feature of Parkinson’s disease (25). Genetic variability in the α-synuclein promoter contributes to the risk of sporadic Parkinson’s disease (26,27) with the ‘associated’ promoter allele being a stronger promoter (28). Perhaps most convincingly, triplication of the whole α-synuclein locus causes autosomal dominant Parkinson’s disease/Lewy body dementia with an onset age in the fourth decade (29) and duplication of the locus leads to disease in the fifth decade (30). Thus, with Parkinson’s disease, there is a clear dose relationship between synuclein expression and disease occurrence, with normal genetic variability in the promoter contributing to the risk of typical idiopathic disease and with multiplications of the locus causing Mendelian disease with an onset age determined by the precise ‘dose’. Protein studies in cell lines from affected individuals in these kindreds reveal that the amount of α-synuclein produced correlates with disease (A. Singleton et al., unpublished data; 31).

METHODOLOGICAL CONSIDERATIONS

The problems of the assessment of haplotypic expression

Rigorous assessment of the impact of haplotypic variation on quantitative gene expression and splicing is a surprisingly difficult problem (32). The usual method to test variability in the control of expression is to tie an artificial and arbitrary reporter construct to a bacterially-derived reporter gene and measure its transient effect on expression in a tumor-derived cell line. Clearly such experiments are unlikely to yield data of direct relevance to subtle effects of variation on gene expression. The development of allele-specific gene expression
CONCLUSIONS AND PREDICTIONS

In all the diseases referred to above, there is thus strong evidence that, while frank mutations in the pathologic locus cause autosomal dominant disease and protein deposition, genetic variability in expression of the normal protein contributes to the risk of idiopathic disease. In Alzheimer’s disease, where the deposited protein is a peptide fragment of the primary locus, mutations in the cleaving enzyme also lead to disease. These simple observations lead to some predictions:

1. The mutant and wild-type proteins are quantitatively different, not qualitatively different in their properties in all cases;
2. In other diseases where protein deposition is part of the process, such as the polyglutamine diseases and ALS, genetic variability in the promoter of the gene should be considered as a factor influencing, where applicable, risk of sporadic disease or age of onset of familial disease (see 35 for suggestions that this might also be the case in Huntington’s disease);
3. In polyglutamine diseases in which the deposited fragment is cleaved from a precursor molecule, genetic variability in the cleaving proteases or other interactors which influence stability should be assessed as a risk factor loci;
4. Other loci which impact on risk for these diseases in general, may merely cause their effect through altering the levels of the primary proteins, either because they are transcription factors, or because they are responsible for protein breakdown.

While these findings were unexpected, perhaps they should not have been. All chemists know the power of the law of mass action, and perhaps it should not have surprised us that it may have profound implications in determining our risks of neurodegenerative disease (36). Of course, one therapeutic approach in all cases, therefore, would be to aim to reduce the concentrations of the toxic proteins in the relevant tissue compartment either through decreased production, increased breakdown, or both.

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