strong coupling of the electrons to antiferromagnetic spin fluctuations at the critical point, and that high-T_c superconductivity is the most likely consequence.

Hashimoto *et al*. show a clear new signature of this tug-of-war between antiferromagnetism and superconductivity. T_c is at a maximum close to the antiferromagnetic quantum critical point, signaling that antiferromagnetic quantum critical fluctuations do indeed enhance Cooper pair formation. On the other hand, their measurements of the extent to which a magnetic field can penetrate the superconductor at zero temperature show, surprisingly, that this length is also a maximum at the quantum critical point. A large penetration depth implies that the ability of the electrons to a carry a supercurrent is actually at a minimum at the quantum critical point. One possible explanation is that the electrons, and so the Cooper pairs, have an average effective mass that is larger at the critical point, and this impedes their motion. Such an enhancement in the mass of the electrons is a natural consequence of the strong scattering by the antiferromagnetic spin fluctuations. Thus, the maximum in T_c—and the concomitant maximum in the penetration depth—constitute evidence for the opposing tendencies in the influence of the antiferromagnetic quantum critical point on high-T_c superconductivity. These observations will be valuable in the ongoing theoretical effort to unravel the quantum interplay between antiferromagnetism and superconductivity.

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CELL BIOLOGY

A Unifying Role for Prions in Neurodegenerative Diseases

A profound change in thinking about the etiologies of many neurodegenerative diseases has far-reaching implications for developing therapeutics.

Stanley B. Prusiner

Many neurodegenerative diseases—including Creutzfeldt-Jakob disease, Alzheimer's disease (AD), Parkinson's disease, and amyotrophic lateral sclerosis (ALS)—share two remarkable characteristics. The first is that more than 80% of cases are sporadic. The second is that although many of the disease-specific mutant proteins are expressed in embryogenesis, the inherited forms of these neurodegenerative diseases are late-onset. This suggests that some event occurs with aging that renders a disease-specific protein pathogenic. More than 20 years ago, I argued that this event involves a stochastic refolding of the etiologic protein into a misfolded infectious state known as a prion. In the past decade, there has been renewed interest in the possibility that the proteins causing neurodegeneration are all prions, which would profoundly influence the development of diagnostics and effective therapies.

Many diverse explanations for the late onset of neurodegenerative diseases have been offered, including oxidative modifications of DNA, lipids, and/or proteins; somatic mutations; modified innate immunity; exogenous toxins; RNA-DNA differences; chaperone malfunction; and haploinsufficiency. An alternative unifying explanation is that a diverse group of proteins can form prions. Although small numbers of prions could be cleared by protein degradation pathways, accumulation above a certain threshold over time would enable the prions to self-propagate (see the figure), resulting in central nervous system (CNS) dysfunction (*1*).

Fungal prions have been invaluable in defining the spectrum of prions. Although yeast prions are not infectious in the sense of being released into the culture medium and infecting other yeast, they are transmissible from mother to daughter cells and thus can readily multiply. Interestingly, many of the mutant proteins causing heritable neurodegenerative diseases are found in insoluble disease-specific aggregates known as amyloid deposits, such as plaques, neurofibrillary tangles (NFTs), and Lewy bodies (see the figure and table S1). Similarly, most fungal prions have a high β-sheet content and can polymerize into amyloid fibrils. That said, it is important to distinguish between prions and amyloids: Prions need not polymerize into amyloid fibrils and can undergo self-propagation as oligomers. The self-propagation of alternative conformations is a key feature of all prions.

Substantial experimental evidence has now accumulated to support a unifying role for prions in neurodegenerative diseases. In AD, for example, which is characterized by the deposition of Aβ amyloid plaques (see the figure), Ridley and Baker performed a set of heroic experiments in which they inoculated human AD brain homogenates intracerebrally into marmosets. The marmosets developed Aβ amyloid plaques with incubation periods exceeding 3.5 years (*2*), demonstrating for the first time that the disease is transmissible and thus supporting the existence of a disease-causing prion. Similar results have been shown by Walker and Jucker and others using transgenic AD mice (*3*, *4*). Importantly, the disease agent has been identified as consisting solely of Aβ prions using synthetic Aβ peptides (*5*).

The tauopathies are a group of neurodegenerative diseases characterized by tau protein aggregation. Mutant tau has also been shown to be transmissible using transgenic mice (*6*), with tau aggregates being observed 1 year after inoculation. In addition, an aggregated segment of the tau protein initiated tau prion formation after being introduced into cultured cells (*7*). Among the tauopathies, the frontotemporal dementias (FTDs) are particularly interesting because they sit at the interface between psychiatry and neurology. Often, psychiatrists see FTD patients for years before recognizing subtle but progressive deterioration and referring them to neurologists. Aggregates of tau prions in the frontal lobes can produce inappropriate social interactions, depression, and diminished executive function as well as insomnia; later, drug abuse, alcoholism, and suicide may occur. The discovery that some contact-sport athletes, as

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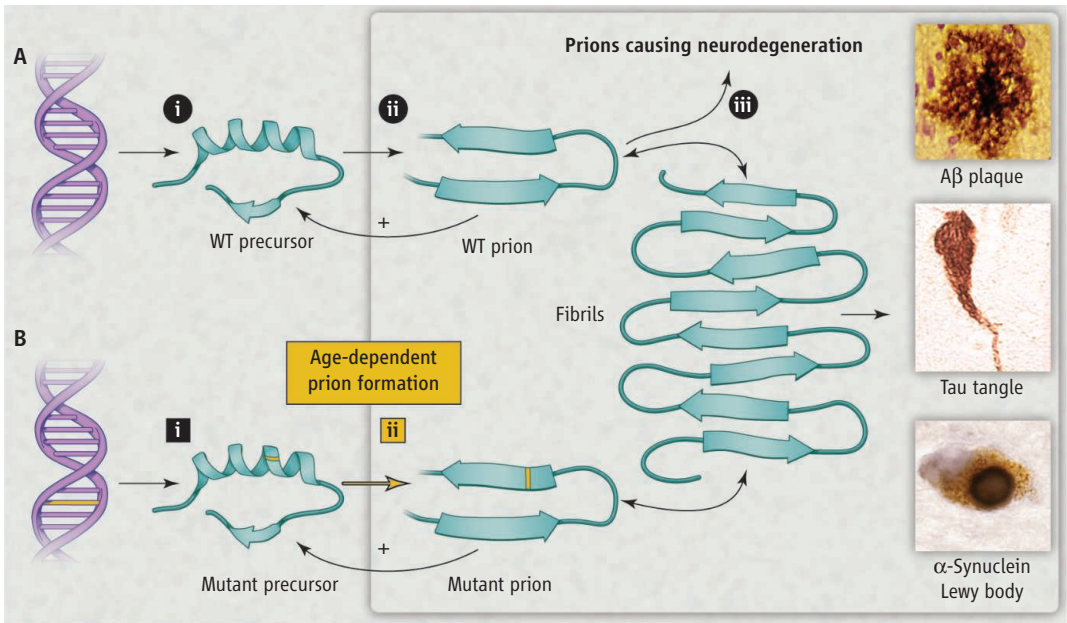

Modeling neurodegeneration caused by prions. (**A**) Wild-type (WT) prions multiply through self-propagating cycles of post-translational modification; generally, an increase in β-sheet content accompanies prion formation. Pathogenic prions are most toxic as oligomers and less toxic after polymerization into amyloid fibrils. Depending on the protein, the fibrils coalesce into amyloid plaques, neurofibrillary tangles, or intracellular inclusions such as Lewy or Pick bodies. Drug targets for the development of therapeutics (black circles): (i) lowering precursor protein, (ii) inhibiting prion formation, and (iii) enhancing prion clearance. (**B**) Late-onset heritable neurodegeneration argues for two discrete events (squares): (i) mutant protein synthesis and (ii) prion formation.

well as soldiers from the Iraq and Afghanistan wars, develop posttraumatic FTDs with psychiatric symptoms—often called posttraumatic stress disorders or PTSD initially—has begun to clarify how diverse neurological insults can all produce NFTs composed of tau prions (*8*, *9*). Some of the variations in the clinical presentations of the tauopathies may be due to different prion strains, which represent distinct conformations (*10*).

Classical scrapie prions in ovines and rodents have been shown to spread throughout the peripheral nervous system and CNS. Consistent with the concept that other neurodegenerative disease–causing proteins are also prions, Heiko Braak and colleagues demonstrated the spreading of Aβ amyloid plaques and NFTs in AD from the entorhinal cortex to many regions of the cerebrum (*11*). Presumably, the Aβ prions spread through the extracellular space, whereas tau prions seem more likely to move between neurons transsynaptically (*12*). Recent studies have traced the spread of tau prions using functional magnetic resonance imaging intrinsic connectivity analysis in several tauopathies (*13*).

Parkinson's disease is characterized by the accumulation of α-synuclein into so-called Lewy bodies in neurons. The finding of Lewy bodies in grafted fetal brain cells a decade after transplantation into Parkinson's patients raised the possibility that α-synuclein proteins can also become prions that were synthesized in these grafted cells (*14*). The surface of Lewy bodies is covered with fibrils composed of β sheet–rich α-synuclein proteins (see the figure). The normal form of α-synuclein seems to be either unstructured or high in α-helical structure, but like other prion proteins, α-synuclein can adopt a β sheet–rich conformation. Although unproven, it seems likely that β sheet–rich α-synuclein prions crossed from the transplanted patient's own neurons into the grafted cells and induced a change in the structure of α-synuclein (*15*). Once established, this process became self-propagating, as with all pathogenic prions. Further evidence for α-synuclein prions comes from studies with recombinant α-synuclein assembled into fibrils that induced α-synuclein prions to multiply in both cultured cells and transgenic mice (*16*, *17*).

Increasing evidence argues that prions cause some forms of ALS and may feature in the pathogenesis of Huntington's disease. More than 60 different mutations in superoxide dismutase (SOD1) have been found to cause familial ALS. Aggregates of mutant human SOD1 have been shown to be self-propagating in cultured cells and, as such, are prions (*18*, *19*). Studies of expanded polyglutamine repeats in a huntingtin protein fragment demonstrated self-propagation of spontaneous aggregates in cultured cells; that is, they are prions (*20*). Huntingtin prions explain why people with 5 to 10 additional glutamines do not become ill until they are 40 to 60 years of age even though the mutant protein is synthesized in embryogenesis.

Not all animal prions cause disease. Some mammalian prions, such as cytoplasmic polyadenylation element-binding (CPEB) protein, mitochondrial antiviral-signaling protein (MAVS), and T cell–restricted intracellular antigen 1 (TIA-1), perform important cellular functions (*21*–*23*), including regulating gene transcription and the immune response. Unexpectedly, the biologically active forms of CPEB and MAVS are the oligomeric prion states and not the monomeric precursor proteins.

The convergence of studies demonstrating prions in the pathogenesis of common neurodegenerative maladies has been remarkable (table S1). Many mysteries are now explicable within the framework of the prion concept. Most important, strategies for developing informative molecular diagnostics and effective therapeutics for these elusive disorders emerge from our knowledge of prions (see the figure). Early diagnosis will require reporters such as positron emission tomography ligands to identify prions long before symptoms appear. Meaningful treatments are likely to require cocktails of drugs that diminish the precursor protein, interfere with the conversion of precursors into prions, and/or enhance the clearance of prions.

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Supplementary Materials
www.sciencemag.org/cgi/content/full/336/6088/1511/DC1
Table S1

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MOLECULAR BIOLOGY

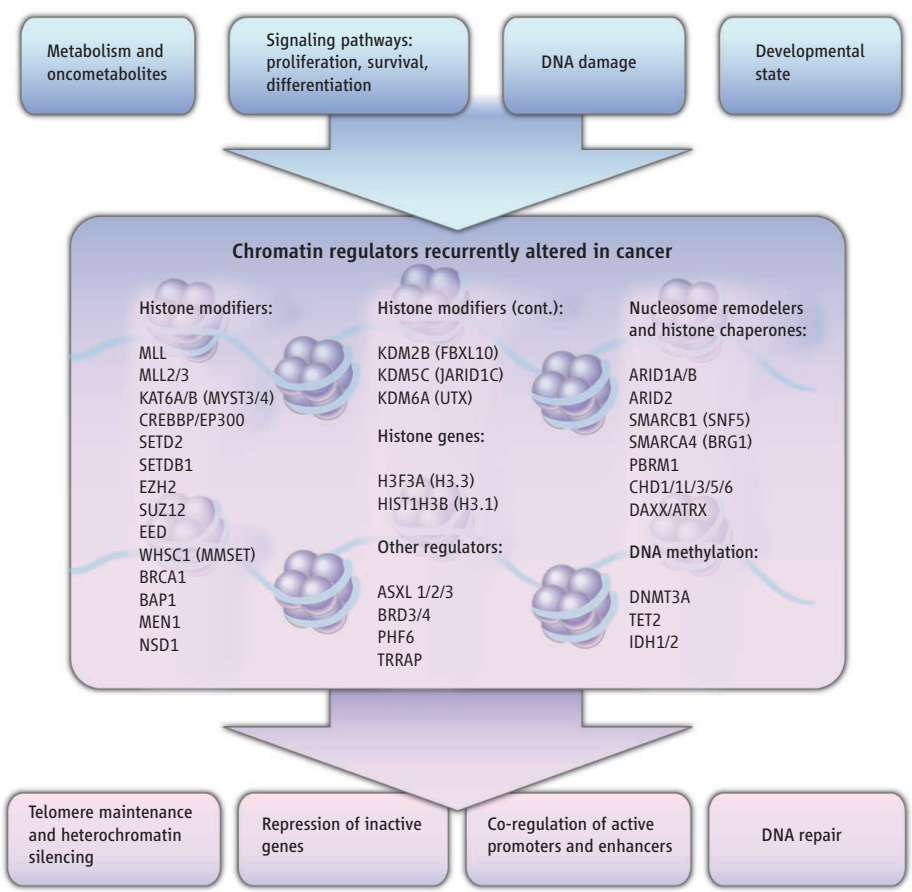
Genetic Events That Shape the Cancer Epigenome

Russell J. H. Ryan[1,2] and Bradley E. Bernstein[1,2]

Mutations in chromatin-related genes in human tumors support a role for epigenetic mechanisms in driving cancer.

Since the discovery of the first recurrent mutations in oncogenes and tumor suppressor genes, it has been clear that cancer is, in large part, a genetic disease. Yet nearly every human neoplasm retains a phenotype reflective of its tissue of origin, thus underscoring the centrality of epigenetics in cancer biology. Indeed, there is increasing recognition that transmissible epigenetic changes—chemical modifications to the genome or its scaffold that do not involve a change in the nucleotide sequence—may be acquired de novo, and that these "epimutations" may also contribute to carcinogenesis. Aberrations of DNA methylation have epitomized this concept, largely because of the direct mechanism by which hypermethylation of a DNA locus can be faithfully transmitted through cell division. Localized hypermethylation of silenced gene promoters and global DNA hypomethylation are characteristic features of many human tumors (*1*, *2*). However, the idea that histone modifications and other chromatin features also mediate epimutations in tumors has been more controversial, in part due to the obscurity of models for direct epigenetic transmission (*3*). The recent flurry of reported mutations in chromatin-related genes in human tumors indicates the need to reassess the perceived roles for chromatin and epigenetic mechanisms in cancer biology.

Histones and associated chromatin proteins control the accessibility of genes and genomic elements and thereby influence their targeting by protein machinery. Regulatory elements in the genome are exposed when chromatin is in a permissive conformation that is conducive to transcription factor binding, whereas inactive loci, regions of repeated DNA sequence, and telomeres (repeated sequences at the ends of chromosomes) are organized into more compact structures. Much progress has been made in understanding how histone-modifying enzymes and other chromatin regulators (CRs) collaborate with transcription factors to translate cell signaling inputs into appropriate transcriptional outputs, playing roles in initiation, elongation, splicing, and repression. Chromatin also affects global genome architecture in a dynamic fashion. Although the epigenome—the totality of chemical changes to DNA and histones—is plastic in embryonic cells, large swaths of DNA become sequestered within compact heterochromatin and nuclear lamina-associated domains during cell differentiation and commitment (*4*). These structures can be further modulated by cellular events, such as epithelial-mesenchymal transition, metabolic changes, and aging (*2*, *5*, *6*). For example, the oncometabolite 2-hydroxyglutarate, generated by mutant isocitrate



Chromatin, mutations, and cancer. Cancer genome studies have uncovered recurrent mutations in numerous chromatin regulatory genes. An important goal will be to understand how the resulting chromatin alterations affect transcriptional regulation, genome stability, telomere maintenance, and other aspects of cell physiology, and to determine which of these effects drive cancer fitness.

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