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The ubiquitin-proteasome system in spongiform degenerative disorders

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Summary

Spongiform degeneration is characterized by vacuolation in nervous tissue accompanied by neuronal death and gliosis. Although spongiform degeneration is a hallmark of prion diseases, this pathology is also present in the brains of patients suffering from Alzheimer's disease, diffuse Lewy body disease, human immunodeficiency virus (HIV) infection, and Canavan's spongiform leukodystrophy. The shared outcome of spongiform degeneration in these diverse diseases suggests that common cellular mechanisms must underlie the processes of spongiform change and neurodegeneration in the central nervous system. Immunohistochemical analysis of brain tissues reveals increased ubiquitin immunoreactivity in and around areas of spongiform change, suggesting the involvement of ubiquitin-proteasome system dysfunction in the pathogenesis of spongiform neurodegeneration. The link between aberrant ubiquitination and spongiform neurodegeneration has been strengthened by the discovery that a null mutation in the E3 ubiquitin-protein ligase mahogunin ring finger-1 (Mgrn1) causes an autosomal recessively inherited form of spongiform neurodegeneration in animals. Recent studies have begun to suggest that abnormal ubiquitination may alter intracellular signaling and cell functions via proteasome-dependent and proteasome-independent mechanisms, leading to spongiform degeneration and neuronal cell death. Further elucidation of the pathogenic pathways involved in spongiform neurodegeneration should facilitate the development of novel rational therapies for treating prion diseases, HIV infection, and other spongiform degenerative disorders.

Keywords

transmissible spongiform encephalopathy (TSE); retroviral infection; mahogunin ring finger-1 (Mgrn1); oxidative stress; autophagy; endocytic trafficking

1. Introduction

Spongiform, or vacuolar, change describes tissue that contains numerous vacuoles that are round or oval in appearance at the light microscopic level and up to 50 μm in diameter [1-3]. These vacuoles can be either extracellular or intracellular, often displacing large organelles such as the nucleus and mitochondria. By electron microscopy (EM), vacuoles can contain curled fragments of membranes and sometimes a fluffy or granular electron-dense material (Figure 1B) [1,4,5]. Intramyelinic vacuoles within white matter correspond with splitting of

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the myelin layers [6-8]. In addition to vacuolar change, neural tissue may also exhibit microvacuolation, in which the neuropil is disrupted by numerous small vacuoles of 2 to 10 μm in diameter [2,3], or status spongiosus, where irregular cavities appear surrounded by a meshwork of glia [2,3]. Spongiform encephalopathy describes a group of diseases that exhibit vacuolar change accompanied by neural and/or glial cell death in the central nervous system. The vacuoles observed in spongiform degeneration are the result of a specific disease process and not merely the product of cell loss.

Spongiform pathology is most commonly associated with prion diseases (Figure 1A) [1], but also occurs in the brains of patients suffering from neurodegenerative diseases (Figure 1A) [3, 4, 9, 10], human immunodeficiency virus (HIV) infection [11-16], and metabolic disease [17]. The extent and localization of spongiform change varies depending on the specific disease, yet each disorder shares common pathological features (Table I). In animals, spongiform degeneration has been observed in prion disease [1], retrovirus infection (Figure 1B) [18-20], and as a consequence of mutation in several different genes (Figure 1B) [6, 7, 21-25]. The vacuolar change observed in animals shares pathological features with human spongiform encephalopathies, and the degree and localization of spongiform change varies by infectious agent or gene mutated (Table II). Histological comparisons of disease versus control tissue from both human and animal spongiform encephalopathies reveals increases in ubiquitinated proteins near areas of spongiform change [4, 9, 20, 26, 27], indicating that aberrant ubiquitination may be involved in the pathogenesis of spongiform degeneration.

Ubiquitination of proteins serves as a signal for a variety of cellular functions (reviewed in [28]). Ubiquitination of a substrate protein occurs via a cascade of three enzymes (an E1 ubiquitin-activating enzyme, an E2 ubiquitin-conjugating enzyme, and an E3 ubiquitin-protein ligase) and is reversible by the action of a deubiquitinating enzyme (DUB). Additional rounds of ubiquitination can result in the formation of a polyubiquitin chain through one of the seven internal lysine residues of ubiquitin. The number and location of attachment sites of mono- or polyubiquitin on a substrate protein comprises the ubiquitin signal [28,29]. A major proteolytic system in the cell is the ubiquitin-proteasome system (UPS), which degrades a majority of cytoplasmic proteins. Substrate proteins processed by the UPS are typically tagged with a polyubiquitin chain linked through Lys 48; four ubiquitins linked via K48 is the minimal signal recognized by the proteasome for substrate degradation [30]. In addition to substrate proteins, the UPS also regulates levels of the ubiquitinating enzymes. A number of E3 ligases are degraded via the UPS [31-33], thus modulating levels of ubiquitination in the cell. Since the ubiquitinating machinery is regulated by the proteasome, proteasomal impairment can result in aberrant ubiquitination of proteins in addition to accumulation of ubiquitinated proteasome substrates [34-39]. Proteasome-independent ubiquitin signals, such as monoubiquitination and K29- and K63-linked polyubiquitination, regulate endocytic trafficking, lysosomal protein degradation, DNA repair, protein aggregation and autophagic degradation, and protein localization [29,35,40-46].

Because of its versatility as a signal, changes in the ubiquitination of proteins can affect a wide range of cellular processes. This suggests that the pathogenesis of spongiform degeneration may result from dysfunction of common pathways regulated by ubiquitination in spongiform disorders with different etiologies. This review will examine the evidence implicating several cellular pathways in spongiform degeneration and explore how these processes are connected and maintained via ubiquitination of proteins. Recent studies indicate that aberrant ubiquitination mediates the pathogenesis of spongiform change and cell death by altering normal cell function and intracellular signaling.