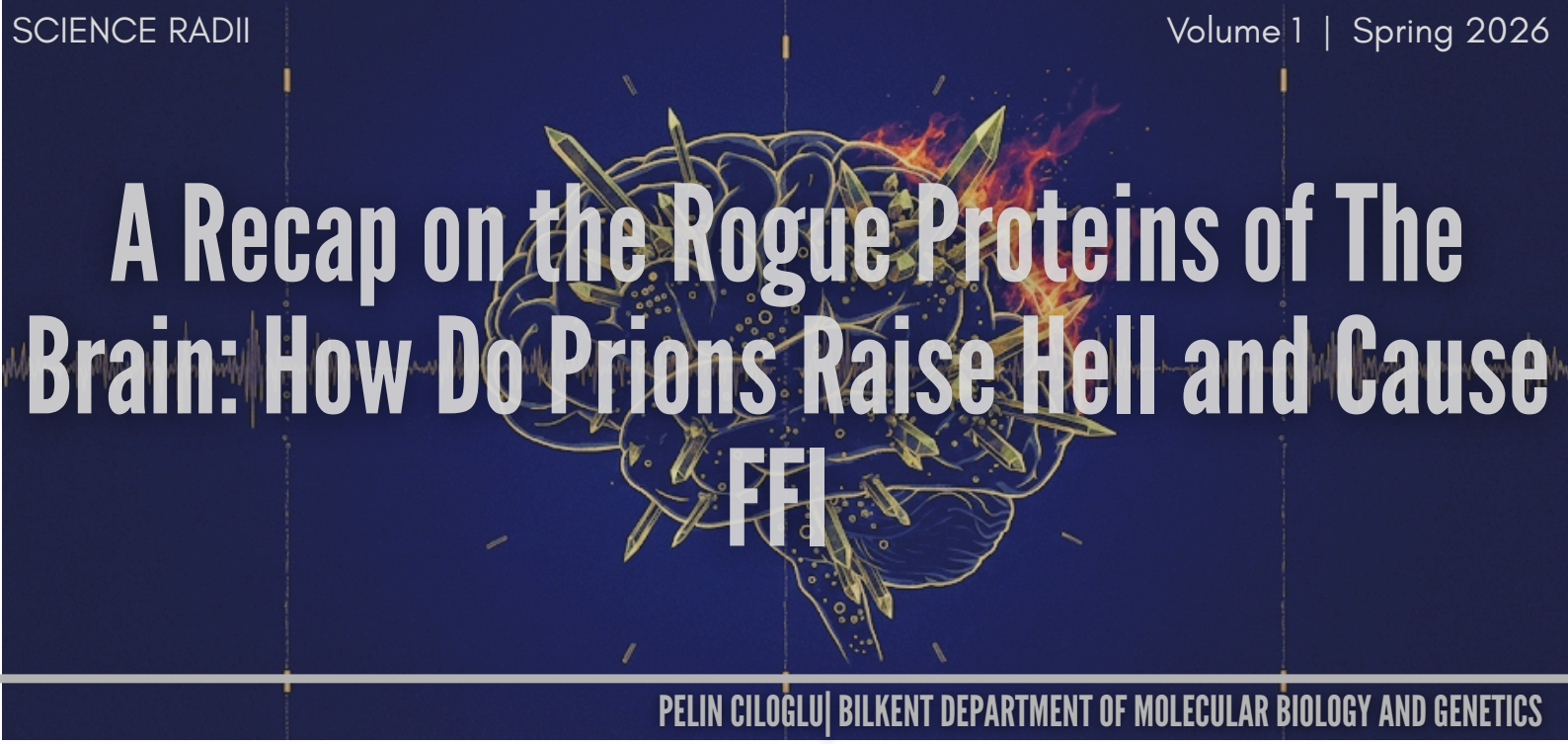

A Recap on the Rogue Proteins of The Brain: How Do Prions Raise Hell and Cause FFI

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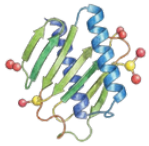
Halloween season is officially over, and yet FFI, which is familial fatal insomnia, is here to petrify any hypochondriac for good. FFI, formerly known as thalamic dementia, is an autosomal dominant disease that is caused by a mutation in the PRNP gene, which is responsible for prion proteins [1]. Prion diseases are also known as transmissible spongiform encephalopathies, or TSEs, and they can be heritable, transmissible, or even sporadic. Moreover, heritable prion diseases are only 10% of the known TSEs, and 1 to 1.5 per million in a population usually report having hereditary or non-hereditary prion diseases [2]. However, certain TSEs can be more prevalent in certain regions of the world, like how kuru disease, another example of a possibly terrifying TSE, was more common in Papua New Guinea in the twentieth century in certain tribes that performed ritualistic cannibalism and contracted infectious prions [3]. TSEs are known for causing medical abnormalities, such as cognitive impairment and the formation of amyloid plaques [4]. The accumulation of plaques usually leads to cellular death, especially in neurons, through vacuole formation, which is why prion diseases are considered lethal [4]. Some prion diseases affect neurons in the central nervous system, whereas some can also affect certain peripheral tissues such as the lymphoid system prior to the propagation of prions in the brain [5]. Recent theories tie vacuolation with prions and propose that the abnormalities in prion function disrupt regular cell membrane functions and form channels that comprise integrity [6]. Vacuoles are membrane-bound lysosome-like organelles that are commonly found in plant cells [7]. However, animal and human cells also do have vacuole-like vesicles that perform the task of disposing of harmful toxins. Moreover, some recent studies have shown that vacuoles can, in fact, begin to form in human cells in vivo after the introduction of bacterial or viral pathogens and various compounds [8]. Cytoplasmic vacuolation is triggered by external stimuli and is a morphological phenomenon that can occur when cytotoxic stimuli exist in the cell [8].

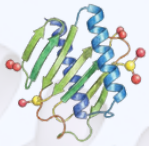
When regular prions, PrPC, aggregate and misfold, they turn into pathogenic proteins, PrPSc. Furthermore, PrPC and PrPSc have different secondary and tertiary tructures, and even though they contain different amounts of beta sheet and alpha-



helical contents, they usually have the same amino acid sequence, which depends on the type of mutation and the disease [1]. Nevertheless, the PrPSc isoform, due to its higher beta sheet content, can be resistant towards degradation and proteinase K, and can be insoluble even in detergent. In the case of FFI, the disease is caused by a 2 single-point highly penetrating mutation where aspartic acid is replaced with asparagine at D178N of the PRNP gene, which is in codon 178 [9]. FFI is highly penetrating due to the visible phenotypical effects of the mutation and therefore the disorder. Nonetheless, since there are many subcategories of prion diseases, another mutation needs to accompany the D178N mutation for FFI, which is the M129V PRNP polymorphism. In this case, the D178 mutation is linked to the methionine of the M129V polymorphism. For instance, if the polymorphism on codon 129 is in valine, the disease is called genetic Creutzfeldt-Jakob Disease (CJD), and it is another example of a TSE [1]. Ergo, polymorphisms can make individuals more susceptible to prion diseases as mutations in the PRNP gene can lead to decreased resistance towards PrPSc formation [10]. Moreover, PrPScs, the abnormal proteins, can recruit PrPC proteins to convert more normally functioning prions into pathogenic prions, which is how prions propagate in the brain [9].

The common clinical characterization of FFI is as follows: insomnia that progresses and worsens over time, which leads to changes in the circadian rhythm, cognitive impairment, and altered hormone secretion [11]. The generally accepted onset for FFI is considered to be between 40 and 60 years, and due to the lethality of the disease, the disease lasts for 7 to 18 months [11]. The thalamus, especially the anteroventral and dorsomedial regions of the thalamic nuclei, is affected by neuron loss and gliosis, which leads to a disrupted circadian rhythm and a disrupted endocrinesystem [11]. At the early stages of the disease, the patients proved to show abnormalities in slow-wave and rapid-eye movement phases in their sleep cycle, and their insomnia progressed over time [12]. FFI has 4 stages. In the first stage of FFI, patients report onset insomnia that worsens over time followed by panic attacks and paranoia. Some patients can claim instances of lucid dreaming [2]. However, patients at the initial stages of FFI usually had minimal memory or attention impairments, even though, through the course of the disease, such deficiencies progressed [12]. As FFI progresses, people with FFI can have hallucinations, and in the last stages of the disease, they can enter coma and stupor, which are different stages of unconsciousness. The third stage of FFI includes total insomnia and complete disruption of the biological clock. Furthermore, FFI patients can have dysautonomia, which can induce hypertension, hyperthermia, and tachycardia. Moreover, difficulty in speaking and ataxia, which is poor muscle control, can be observed in patients [12]. Personality changes and mental health problems such as depression, anxiety, and specific delusions, along with weight loss and involuntary movements, are also some clinical features that are looked for to diagnose FFI [2]. The fourth and final stage of FFI is defined by the patients' inability to talk or move, the eventual comatose phase, and lastly death [2]. Additionally, since methods like MRI and CT are inadequate to fully diagnose FFI, genetic testing and polysomnography, which can a show reduction in overall sleep when utilized [2].

Lastly, since the research about prion diseases is still ongoing, it is evident that there is still a lot to discover about FFI. However, due to the delicate nature of how the disease affects individuals and their families, more people, especially in developing countries, should be aware of prion diseases, and clinicians should offer more genetic testing and care for families who have to experience the horror that is FFI.



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