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Molecular mechanisms of chronic traumatic encephalopathy

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The prevalence of neurodegenerative disorders is rapidly increasing. While Alzheimer's disease and dementia generally correlate with longer lifespans, neurodegenerative disorders like chronic traumatic encephalopathy often affect individuals at young age. Historically, the underlying disease mechanisms of these chronic disorders—the slowly changing biochemical composition during aging and the repeated, rapidly changing biomechanical environment during head impact—have been viewed as distinct events. Recent studies suggest that Alzheimer's disease and chronic traumatic encephalopathy share common degenerative pathways on the molecular and cellular levels. Here we examine this current trend and explore the molecular, cellular, tissue, and organ level mechanisms of neurodegeneration through the lens of biomedical engineering. Understanding the underlying disease mechanisms across the spatio-temporal scales of neurodegeneration provides new opportunities to modulate, slow down, and possibly revert molecular dysfunction, axonal death, tissue atrophy, and loss of brain function.

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A brief history of chronic traumatic encephalopathy

Chronic traumatic encephalopathy is a progressive degenerative disease

Every year, more than 40 million people worldwide experience a mild traumatic brain injury or concussion [1]. Recent studies suggest that even mild concussions, if repetitive, can trigger progressive neurological degeneration, a condition that is now widely recognized as chronic traumatic encephalopathy [2]. The current media hype around chronic traumatic encephalopathy has created a new level of awareness and increasingly more head injuries are now associated with the condition [3]. Yet, to date, the only method to reliably diagnose chronic traumatic encephalopathy is post mortem histopathology, where it manifests itself through an accumulation of hyperphosphorylated tau protein [4], progressive axonal failure, and gradual structural degradation [5]. Strikingly, axonal failure and structural degradation appear to be shared, at least in part, by traumatic brain injury [6] and a number of other neurodegenerative diseases [7] including Parkinsonism [8] and Alzheimer's disease [9]. However, the molecular mechanisms of neurodegeneration remain poorly understood.

Chronic traumatic encephalopathy is more than just a disorder associated with boxing

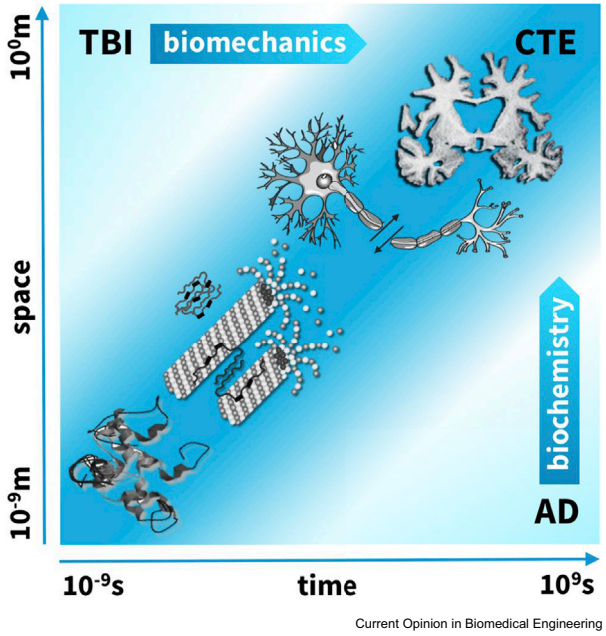
Historically, the impact of repeated head injuries on unsteady gait and mental confusion were first reported in professional boxers in 1928, where the symptoms became collectively known as punch-drunk syndrome [10]. A decade later, upon recognizing that these symptoms were in fact chronic and worsened in time, the term chronic traumatic encephalopathy was coined [11]. Single incidences of chronic traumatic encephalopathy were reported in a soccer player, a circus clown, and a head banger; yet, it was not until the autopsy of a deceased professional football player more than half a century later that the condition became associated with widely popular contact sports [12]. We now know that its symptoms typically do not occur until years, if not decades, after the initial injury [13]. This uncertainty has provoked a growing anxiety amongst affected individuals: Throughout the past decade, dozens of former NFL players have been diagnosed with the condition and hundreds have pledged to donate their brains for scientific studies [14]. With this new insight, the definition of chronic traumatic encephalopathy has rapidly evolved [15] and its clinical symptoms have been collectively summarized as research diagnostic for criteria traumatic encephalopathy syndrome [16]. We now broadly associate chronic traumatic encephalopathy with repeated head impacts in a variety of sports including American football, boxing, wrestling, rugby, hockey, and soccer [17], as well as blast impacts on the battlefield [18]. Although the public awareness of chronic traumatic

encephalopathy has drastically increased throughout the past decade, and we have made important advances in diagnosing the condition, we still know surprisingly little about its prevalence, incidence, and risk factors [4].

Chronic traumatic encephalopathy spans across multiple spatial and temporal scales

From systematic case studies, we now know that chronic traumatic encephalopathy is characterized through a well-defined, ordered, and predictable progression of abnormally phosphorylated tau protein throughout the nervous system [5]. The pathophysiology of chronic traumatic encephalopathy is closely correlated with other abnormally aggregated proteins including transactive response DNA-binding protein 43, amyloid beta, and alpha-synuclein, which are associated with frontotemporal dementia, amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease [8]. This supports the emerging view that chronic traumatic encephalopathy—a condition associated with the deposition of misfolded protein with age—shares several characteristic neuropathological and clinical hallmarks with many other forms of neurodegeneration [19]. Figure 1 highlights the underlying spatial and temporal spectrum of these neurodegenerative diseases: Traumatic brain injury takes place on extremely short temporal scales and manifests itself as biomechanical damage on the larger spatial scales, top left [6]. Alzheimer's disease, by contrast, takes place on extremely long temporal scales and manifests itself as biochemical damage associated with the hyperphosphorylation of tau on the smaller spatial scales, bottom right [20]. Chronic traumatic encephalopathy initially originates in isolated focal perivascular hyperphosphorylated tau lesions at the depths of cortical sulci [4], from where it gradually propagates across the spatial and temporal scales to eventually affect the entire brain [21]. It manifests itself histopathologically through biomechanical and biochemical damage in the form of neurofibrillary tangles, breakdown of the tau-microtubule complex, diffuse axonal injury, and marked gray and white matter atrophy [22]. These observations raise the important questions if and how repeated head injuries affect tau kinase and phosphatase, and how tau lesions gradually propagate across the brain.

Figure 1



Spatial and temporal spectrum of neurodegeneration. Traumatic Brain Injury (TBI) takes place on extremely short temporal scales and manifests itself as biomechanical damage on the larger spatial scales. Alzheimer's Disease (AD) takes place on extremely long temporal scales and manifests itself as biochemical damage on the smaller spatial scales. Chronic Traumatic Encephalopathy (CTE) propagates gradually across the spatial and temporal scales and manifests itself through neurofibrillary tangles, breakdown of the tau-microtubule complex, diffuse axonal injury, and pronounced gray and white matter atrophy.

Spatial and temporal determinants of neurodegeneration

On the molecular level, neurofibrillary tangles are a hallmark of neurodegeneration

Neurofibrillary tangles are aggregates of hyperphosphorylated tau protein. In the healthy axon, tau is an intrinsically disordered protein that is subject to a complex array of posttranslational modifications [23]. By binding to microtubules, tau contributes directly or indirectly to key structural and regulatory function: Within individual microtubules, tau modulates microtubule polymerization, controls microtubule structure, and regulates axonal transport [24]; within the axon, tau promotes the assembly of individual microtubules into well-organized, evenly spaced bundles [25]. Two competing hypotheses have recently emerged to explain the remarkable dense and regular packing of microtubules within the axon: the polymer brush hypothesis and the cross-bridging hypothesis [26]. In the polymer brush hypothesis, dense packing is a result of repulsive forces between tau proteins of neighboring microtubules and compressive forces induced by periodically spaced actin rings underneath the axonal plasma membrane. In the cross-bridging hypothesis, the regular distance between neighboring microtubules is a result of tensile forces induced by the formation of an electrostatic zipper between two tau proteins of neighboring microtubules. Despite its critical importance for axonal stability and intracellular transport, the precise mechanism by which tau regulates microtubules packing remains insufficiently understood [27]. We do know though, that phosphorylation, the site-specific addition of a phosphate group, can modulate tau's affinity to bind to microtubules [23]. Hyperphosphorylation reduces tau's ability to bind to microtubules, which destabilizes microtubules, causes tau to clump together in neurofibrillary tangles, and disrupts intracellular function [7]. Neurofibrillary tangles have long been recognized as the