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Concept Paper

Acquired Piezo2 Channelopathy is the Gateway to Condensopathies of Stress Granules, Like in Amyotrophic Lateral

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Abstract

Recent amyotrophic lateral sclerosis (ALS) related paper raised the possibility of a common underlying mechanism that impairs membrane organelle function, like the one leading to the toxicity of C9orf72-derived arginine-rich dipeptide repeats in the affected cells. The current opinion piece proposes that the principally affected cells are glutamatergic fibers on which cell-autonomous neuron-specific processes may prevail leading to neurodegeneration, as an ALS-based genome-like association study revealed it. Moreover, these glutamatergic fibers are suggested to be Type Ia proprioceptive neurons in the case of ALS and the gateway to pathophysiology is proposed to be the irreversible Piezo2 channelopathy of these terminals. These Piezo2-containing glutamatergic fibers in a given compartment, like the Type Ia proprioceptive one in the muscle spindle, may regulate neighboring Piezo1-containing cells through Piezo2-Piezo1 crosstalk, not only functionally, but metabolically as well. Finally, the underlying gateway to pathophysiology, leading to acquired Piezo2 channelopathy is suggested to be a proton affinity switch or proton reversal on Piezo2, as the current paper proposes that this proton reversal impairs membrane organelle function downstream. Similar pathogenic derailment of liquid-liquid phase separation with possible underlying linked mechanism could be experienced in several diseases, like cancer, inflammation, virus infection and neurodegeneration, collectively coined as “condensopathies”. Accordingly, the current author proposes that acquired chronic or irreversible Piezo2 channelopathy-induced proton reversal of glutamatergic somatosensory terminals may constitute the common underlying initiating switch mechanism, leading to the pathogenic derailment of liquid-liquid phase separation of condensopathies, like is proposed in ALS.

Keywords: condensopathy; stress granule; liquid-liquid phase separation; acquired Piezo2 channelopathy; amyotrophic lateral sclerosis

Introduction

Recent amyotrophic lateral sclerosis (ALS) related paper raised the possibility of a common underlying mechanism that impairs membrane organelle function, like the one leading to the toxicity of C9orf72-derived arginine-rich dipeptide repeats (R-DPR) in the affected cells [1]. The current opinion piece proposes that the principally affected cells are glutamatergic fibers on which cell-autonomous neuron-specific processes may prevail leading to neurodegeneration, as an ALS-based genome-like association study (GWAS) revealed it [2]. Moreover, these glutamatergic fibers are suggested to be Type Ia proprioceptive neurons in the case of ALS and the gateway to pathophysiology is proposed to be the irreversible Piezo2 channelopathy (Piezo2c) of these terminals

[3, 4]. These Piezo2-containing glutamatergic fibers in a given compartment, like the Type Ia proprioceptive one in the muscle spindle, may regulate neighboring Piezo1-containing cells through Piezo2-Piezo1 crosstalk, not only functionally, but metabolically as well [5]. Finally, the underlying gateway to pathophysiology, leading to acquired Piezo2c is suggested to be a proton affinity switch or proton reversal on Piezo2 [6], as the current paper proposes that this proton reversal impairs membrane organelle function downstream.

Acquired Piezo channelopathy

Inherited Piezo1 and Piezo2 mutations and variants in diseases are well known from the scientific literature. Nevertheless, Piezo channelopathy was put forward only in 2021 (had not been used even in regard to inherited Piezo mutations and variants) by introducing the feasibility of the acquired microdamage of Piezo ion channels with system-wide implications [7]. More specifically acquired Piezo2c was proposed first in perineal muscles derived delayed-onset muscle soreness (DOMS) associated strange sexual disfunction [7]. It was even put forward a year later in 2022 that acquired Piezo2c may not only be the gateway to pathophysiology in DOMS, but in ALS as well in an acute transient and irreversible manner respectively [4]. The first indirect research-based verification of intrafusal acquired Piezo2c theory came also in 2022 in a DOMS-related research where the medium-latency response (MLR) of the stretch reflex was shown to be significantly delayed [8]. This study highlighted the neurocentric initiating microdamage and the muscle spindle origin in DOMS with a working hypothesis that this primary damage was an acquired Piezo2c [8]. This working hypothesis was supported by the finding that Piezo2 is the principal mechanosensory ion channel responsible for proprioception, as the team of Nobel laureate Ardem Patapoutian claimed it [9]. Authors, including Ardem Patapoutian, indeed confirmed two years later in 2023, that perineal mechanosensation and PIEZO2 were essential in sexual function [10], further substantiating the first acquired Piezo2c paper [7].

The direct research-based verification of the existence of acquired Piezo2c came through a neurogenetic disorder, called Angelman syndrome (AS) without known PIEZO2 mutations or variants, also published in 2023 [11]. Interestingly, supplementation of linoleic acid ameliorated acquired Piezo2c in AS [11]. The same research team found in 2025 that cofilin inhibition also improved acquired Piezo channelopathy in AS [12]. It was already highlighted in 2022 that acquired Piezo channelopathy could arise from both direction, hence from the direction of Piezo2 and Piezo1, due to the underlying Piezo2-Piezo1 crosstalk, but neural Piezo2c is a more complex mechanism, not to mention if it evolves on glutamatergic neuron terminals contributing to proprioception [5]. Interesting recent research from 2025 introduced inherited Piezo1 channelopathy causing point mutation PIEZO1 and successfully mimicked acquired Piezo1 channelopathy in Alzheimer's disease (AD) brain microcirculation model [13]. Moreover, the initiating pathophysiology of AD was put forward to be acquired irreversible Piezo2c on glutamatergic terminals too, like in ALS[3], but at the prefrontal cortex [14].

Stress Granule Formation and Impaired G3BP1 Phase Separation

PIEZO's evolutionarily conserved role in stress buffering is achieved through the modulation of intracellular calcium handling even in *Drosophila* [15]. Noteworthy that theorized loss of Piezo2-initiated proton handling to ASIC2 in ALS due to irreversible Piezo2c of Type Ia proprioceptive terminals is translated to cause the feed-forward upregulation of ASIC2 on motoneurons [3]. The theorized Piezo2c-induced significant delay of MLR due to DOMS effect does not cease the static phase firing sensory encoding of the stretch reflex, but conveyed exclusively on Type II proprioceptive fibers from there on, probably through secondary proprioceptive ASIC3, in a polysynaptic way [5, 8]. However, the loss of monosynaptic static phase firing sensory encoding, or the equivalent of lost Piezo2-initiated ultrafast proton-based long-distance non-synaptic signaling, might wear out the neuromuscular junction of motoneurons, leading to their accelerated aging and

degeneration, or even to motoneuron death, as experienced in ALS [3, 6] and as one mouse-model ALS-related research may show [16]. This impairment and wearing-out of neuromuscular junctions are suggested by the current author to be associated with stress granule (SG) assembly and its dysregulation in the below manner.

SGs evolve by liquid-liquid phase separation (LLPS) as a result of an RNA-derived switch from a closed inactive state to an open activated state of Ras GTPase-activating protein-binding protein 1 (G3BP1) [1]. However, R-DPRs of cellular SGs in ALS disadvantage RNA in the binding to G3BP1 and induce LLPS preferentially [1]. As a result of this pathogenic dysregulation, R-DPR-G3BP1 droplets aggregate, leading eventually to TDP-43 formation [1]. G3BP1 has three intrinsically disordered regions, of which IDR1 is highly negatively charged, while IDR3 is positively charged [1]. When RNA binds to IDR3 then the closed inactive state of G3BP1 opens and activates [1]. Short RNAs are not able to induce G3BP1 LLPS, moreover even long RNAs needs a crowding effect in order to facilitate LLPS promotion [1]. Further consideration that the proposed initiating cell autonomous Piezo2 microdamaging event on Type Ia proprioceptive terminals in ALS is prolonged eccentric contractions under allostatic stress [5, 7]. Important feature of muscle contractions that they increase regulatory non-coding RNAs. Amongst contractions, the proprioception damaging eccentric contractions[17] especially promote myogenesis and skeletal muscle regeneration (suggested to be the consequence of Piezo2c-induced transcription activation and impaired Piezo2-Piezo1 crosstalk within intrafusal and extrafusal compartments [5]), in which process long non-coding RNAs (lncRNAs) play a pivotal role [18].

Nevertheless, fibroblasts and ultradian rhythms should be considered in this stress response, as a result of impaired Piezo2-Piezo2 and Piezo2-Piezo1 crosstalks [19]. Accordingly, Piezo2 is theorized to be an ultrafast ultradian sensor and ultradian fine rhythm modulator [19, 20] with verified role of evolutionarily conserved Piezo and Piezo2 in acute stress response [15, 21]. Impaired Piezo2-Piezo2 crosstalk (due to Piezo2c) not only theorized to elevate sympathetic tone [22] with resultant elevated β 2 adrenergic-driven nerve growth factor (NGF) production from activated fibroblasts, but directly activates fibroblast through Piezo1 [19]. Stress granules of fibroblasts are shown temporal regulation due to alternative oscillatory mechanism than circadian rhythm[23] and this alternative mechanism is devoted by the current author to ultradian rhythms, that is proposed to be finetuned by Piezo2 and Piezo2-Piezo1 crosstalk within an affected compartment. However, acquired Piezo2c may impair this crosstalk, leading to the aforementioned exaggerated Piezo1-induced NGF production by activated fibroblasts [19], as an indication of neural microdamage.

One more consideration that should be contemplated in this mechanism is gravity. Notable that Piezo2 is theorized to be the principal ultrafast gravity sensor and fine modulator of anti-gravity force production [24]. Indeed, altered gravity (like microgravity and hypergravity) modifies fibroblasts' response to wound-healing by delaying cellular migration and mechanosensitive cell structures[25]. This delay is translated by the current author to be the result of altered Piezo2-initiated anti-gravity modulation, mimicking acquired Piezo2c and impaired Piezo2-Piezo1 crosstalk. This is why the author of this paper is in agreement of earlier hypothesis that gravity could be a possible etiological factor in ALS [26], with underlying irreversible Piezo2c that is reflected in pathological remodeling [3, 5]. In support, evolutionarily conserved Piezo ion channel indeed shows pathological remodeling in the absence of PIEZO even in *Drosophila*[15]. While Piezo is shown to exert a transient molecular break on wound closure to promote effective inflammation, maintaining homeostatic integrity[27]. Correspondingly, the inducement of inflammatory reflex by Piezo2 under allostatic stress is theorized to be homeostatic, while the inducement of the gateway reflex could be the consequence of transient acquired Piezo2c, as DOMS may reflects [5, 7].

Returning back to the aforementioned disadvantaged position of RNA arises when highly positively charged R-DPRs bind to highly negatively charged IDR3 of G3BP1 thousand time stronger in ALS [1]. This R-DPR-derived toxicity further dysregulate crucial cellular processes, like axon development and branching, axonal transport, nucleocytoplasmic transport, protein translation,

mRNA splicing, proteasomal function and the response to endoplasmic reticulum stress, as hallmarks of ALS pathomechanism [1].

Similar pathogenic derailment of LLPS with possible underlying linked mechanism could be experienced in several diseases, like cancer, inflammation, virus infection and neurodegeneration, collectively coined as “condensopathies” [1]. Accordingly, the current author proposes that acquired chronic or irreversible Piezo2c induced proton reversal may constitute the common underlying initiating switch leading to the pathogenic derailment of LLPS, such as in cancer[5, 19], inflammation[3, 5], virus infection[28] and neurodegeneration [5, 6], in an analogous mechanism, like is proposed in ALS [3].

Proton affinity switch may impair ultradian sensing

The critical depletion of PIP₂'s functional role was highlighted in 2022 a gateway to irreversible Piezo2c in ALS [4] in which process the dissociation of auxiliary proteins (like TACAN and MyoD) from Piezo2 is suspected, leading to proton reversal [3]. Even the therapeutic administration of PIP₂ was proposed in 2022 as a remedy for chronic Piezo2c [29]. Correspondingly, it was shown in 2025 that PIP₂ indeed improves endothelial Piezo1 channelopathy [13].

However, it is worth considering that PIP₂ plays a pivotal electrostatic role in the interaction with intrinsically disordered proteins (IDP) and their disordered regions (DIR), especially in the co-functioning of intrinsically disordered intracellular domain of Piezo2 and the intrinsically disordered ectodomain of syndecan-3 [20]. Consequently, the current author proposes that prolonged forced-lengthening under allostatic stress not only could deplete PIP₂, leading to Piezo2c, but inhibits the co-functioning of Piezo2 and syndecan-3 on cellular membranes. Moreover, depleted PIP₂ may translocate intracellularly, in order to associate with IDPs in an RNA-dependent manner to contribute to nuclear compartmentalization [30]. However, this RNA-dependent electrostatic mechanism is not only important in nuclear compartment formation, but in the cytosol as well to form SGs by LLPS. Nonetheless, R-DPRs derails this process pathologically in ALS [1].

Additionally, DOMS-induced HRV findings showed non-linear alterations, including sample entropy, that were devoted to the impaired stochastic non-linear functioning of Piezo2, or acquired Piezo2c [22]. Indeed, later research established the stochastic entropic spring-like mechanics of Piezo ion channels and this article even theorized that this mechanics exist in other ion channels as well [31]. In agreement, the current author proposes that Piezo2 stand out as the principal ion channel initiating this stochastic entropic spring-like mechanics on glutamatergic terminals, especially the ones contributing to proprioception. Moreover, the author of this paper suggests that these Piezo2 containing glutamatergic terminals could initiate reflex mechanisms, like the Type Ia proprioceptive terminals initiate the monosynaptic stretch reflex, due to this Piezo2-initiated concerted stochastic entropic spring-like mechanics, supported by the Piezo2-initiated ultrafast long-distance non-synaptic proton motive force-based signaling [6]. The impairment of this mechanics due to irreversible Piezo2c on Type Ia terminals may cause reflex alterations in ALS, as was put forward first in 2022[4] and shown later [32]. Additionally, the stochastic entropic spring-like mechanics, propelled by OXPHOS-induced proton motive force and ATP, has been theorized recently that it serves anti-gravity modulation [24]. Moreover, this anti-gravity stochastic entropic spring-like mechanics is suggested to entail the co-functioning of intrinsically disordered intracellular domain of Piezo2 and the intrinsically disordered ectodomain of syndecan-3 [20], with the aforementioned PIP₂ support. Consequently, the current author proposes that IDPs provide the stochastic non-linear, or ultrafast ultradian mechanosensation on glutamatergic terminals contributing to proprioception of which Piezo2 stand out as the principle initiating one.

Conclusion

After all the acquired Piezo2c of glutamatergic somatosensory terminals, as a common switch mechanism, may impair the ultrafast regulation of anti-gravity, may induce proton reversal,

electrostatic and metabolic switch, PIP₂ intracellular translocation, transcription activation, SG formation that could be further dysregulated by chronic stress, aging, and underlying environmental and genetic risk factors, leading to condensopathies, like in ALS.

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