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The emerging link between IP₃ receptor turnover and Hereditary Spastic Paraplegia

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Abstract

IP₃ receptor turnover is mediated by the ubiquitin ligase RNF170, which is recruited to active IP₃ receptors by the erlin1/2 complex. A new study by Wagner et al (Nat Commun, 2019) links four cases of Hereditary Spastic Paraplegia to inactivating mutations in RNF170. This increases the number of examples of mutations to the erlin1/2 complex-RNF170 module underlying neurodegenerative disorders.

Hereditary Spastic Paraplegias (HSPs) are a class of inherited neurodegenerative disorders characterized by progressive gait abnormalities due to muscle weakness and stiffness in the lower limbs, usually associated with degeneration of corticospinal tract motor neurons [1,2]. HSPs can be classified as either “uncomplicated” or “complicated”: characteristic symptoms of uncomplicated HSPs are lower limb spastic weakness and urinary urgency, while complicated HSPs have additional features, such as ataxia and seizures [1,2]. These additional features often makes it difficult to differentiate complicated HSPs from other neurological diseases. Interestingly, most uncomplicated HSPs are autosomal dominant, while most complicated HSPs are autosomal recessive, and often linked to inbreeding [1]. Currently, there are more than 80 known HSP-linked genes, but still many HSP cases are without a defined genetic cause [1,2]. This situation is currently being resolved by WGS - whole genome sequencing [2].

The recent article by Wagner et al. [2] uses WGS to link four unrelated cases of autosomal recessive HSP to mutations in RNF170, the ubiquitin ligase (E3) enzyme responsible for the ubiquitination of activated inositol 1,4,5-trisphosphate (IP₃) receptors (IP₃Rs) and their subsequent proteasomal degradation (Fig. 1) [3,4]. RNF170 is typical of most other E3s in that it contains a critical RING domain that helps enlist a ubiquitin-conjugating (E2) enzyme that transfers ubiquitin to substrates, which in turn leads to recognition and degradation of those substrates by the proteasome [5]. For IP₃Rs (of which there are three isoforms, IP₃R1, IP₃R2 and IP₃R3) [6], this ubiquitination and degradation is most clearly seen when IP₃-dependent cell signaling is activated, and seems to be triggered by the conformational change associated with co-agonist (IP₃ and Ca²⁺) binding and channel opening [6]. RNF170 also mediates basal IP₃ receptor turnover, since when RNF170 is deleted, IP₃ receptor levels increase [4,6]. RNF170 is recruited to activated IP₃ receptors by the erlin1/2 complex, to

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which it is constitutively bound (Fig. 1) [6,7]. In each of the four HSP cases [2], the mutation in RNF170 is likely inactivating, due to either a premature stop codon-mediated truncation, or a cysteine to arginine point mutation in the RING domain, C102R (Fig. 1). In fibroblasts from two of the patients, an increase in basal IP₃R3 levels is seen and bradykinin-induced IP₃R3 degradation is impaired [2]. Likewise, IP₃R1 levels are increased by CRISPR/Cas9-mediated RNF170 deletion from cultured human neuroblastoma SH-SY5Y [2] and mouse anterior pituitary α T3–1 cells [4], and in the cerebellum and spinal cord of RNF170 knockout mice [8], indicating that IP₃R1, the predominant IP₃R isoform in neurons, is similarly modified by RNF170. Such increases in IP₃R1 levels could alter Ca²⁺ signaling and impair neuronal viability, although that remains to be demonstrated. Likewise, whether neuronal IP₃R1 levels are altered in the HSP patients with RNF170 mutations has yet to be examined [2]. Zebrafish were used as a model system to study RNF170 in vivo, and while RNF170 knockdown caused neurodevelopmental defects, reintroduction of RNF170 mutants was not very informative, beyond indicating that they were non-functional [2]. It seems that using mice as a testbed for introduction of mutants would be much more fruitful, particularly as RNF170 knockout mice show progressive gait abnormalities resembling human HSP symptoms [2,8].

Besides the four mutations reported by Wagner et al. [2], another mutation in RNF170 (arginine to cysteine in the second transmembrane domain, R199C, Fig. 1) is also found to cause a neurodegenerative disorder, termed autosomal-dominant sensory ataxia [9]. This mutation reduces the stability and abundance of RNF170 and likely affects the overall ubiquitin ligase activity of RNF170 and IP₃R processing [4]. Additionally, several mutations to erlin1 and erlin2, the components of the erlin1/2 complex, have been linked to various neurological disorders, including uncomplicated and complicated HSPs, as well as lateral sclerosis [2,6]. For example, an erlin2 mutation (threonine to isoleucine at amino acid 65), which inhibits erlin1/2 complex recruitment to activated IP₃ receptors and thus IP₃R1 processing, is linked to a HSP case [7]. Just like for RNF170, deletion of either erlin1 and erlin2 increases basal IP₃R1 levels [7], indicating that any mutation that significantly impairs the function of the erlin1/2 complex-RNF170 module will affect normal IP₃R1 processing and may thus cause neurodegeneration [2,6,8]. Interestingly, several IP₃R1 mutations have been identified that appear to be the cause of neurological disorders [2], but these tend to be spinocerebellar ataxias rather than HSPs [2], and whether any of these mutations affect IP₃R receptor turnover remains to be determined.

Overall, since IP₃Rs are the only well-established substrate for RNF170, the new data [2] fit well with the notion that dysregulation of IP₃R-dependent Ca²⁺ signaling pathways contributes to neurodegenerative diseases [10]. It seems highly likely that future WGS will identify additional mutations that affect IP₃R turnover, with corresponding changes in IP₃R levels and Ca²⁺ signaling. Targeting IP₃R-dependent Ca²⁺ signaling may be of therapeutic benefit to those suffering from HSPs, as has been proposed for other disorders, including Alzheimer's, Huntington's and Parkinson's diseases [10].

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Fig. 1.

IP₃R processing and RNF170 mutations. IP₃Rs form tetramers that act as ligand-gated Ca²⁺ channels in the ER membrane [6]. The conformational change associated with channel opening triggers the binding of the erlin1/2 complex-RNF170 module (arrow) and, consequently, RNF170-mediated IP₃R ubiquitination and proteasomal degradation [6,7]. The erlin1/2 complex is composed of ~40 erlin1 and erlin2 molecules and RNF170 is constitutively associated [6,7]. The sites of the newly-described RNF170 mutations are indicated with an asterisk for the C102R point mutation, and with double lines for the truncations starting at amino acids ~ 72, 109 and 173 [2]. Also shown with a triangle is the previously described R199C point mutation in RNF170 that causes autosomal-dominant sensory ataxia [9].