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Commentary Article

Cellular RA Binding Proteins (CRABPs) Signalosomes: Targeting Dynamic Signal Regulation in Managing Neurodegeneration

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Vitamin A (retinol) and its derivatives, collectively referred to as retinoids, are gaining increasing appreciation in managing neurodegenerative diseases such as Alzheimer's Disease (AD), Amyotrophic Lateral Sclerosis (ALS), Huntington Disease (HD) and Parkinson's Disease (PD) [1-12]. Retinoic Acid (RA) is the principal active metabolite of vitamin A and has profound roles in numerous biological processes and organ systems, including differentiation, proliferation, cell death programs, development, immunity, the Central Nervous System (CNS) and the visual system, etc [13]. RA exerts its effects by two major mechanisms, binding nuclear RA Receptors (RARs) to regulate gene expression in the nucleus (canonical mechanism) and binding its cytosolic receptors, Cellular RA Binding Proteins (CRABPs) for metabolism or cytosolic signaling [14]. In addition, RA has also been reported to directly modulate kinases such as PKC or certain activity of extranuclear RARs (reviewed in-depth elsewhere) [15]. In the cytoplasm, CRABP2 binds RA to facilitate its metabolism, whereas CRABP1 binds RA to elicit its regulatory activities in multiple cytosolic signaling pathways [16-18]. These CRABP1-targeted cytosolic signaling complexes are named CRABP1-signalosomes and are referred to as the main non-canonical mediators of RA. This commentary focuses on the CRABP1-mediated non-canonical activities of RA, which are characterized by three features - independence from RARs, cytosolic localization and rapid (minutes) actions [17].

As a therapeutic agent, RA and its analogs have been proposed to act through the canonical mechanism mediated by nuclear RARs - inducing changes in the expression of genes that are generally neuroprotective and/or neuro-regenerative. These genomic changes can facilitate neurogenesis, dampen neuroinflammation and oxidative stress and modulate proteostasis [5,6]. However, one serious concern about this RAR-centric approach is its extreme toxicities (retinoic acid/differentiation syndrome), severely hindering its clinical application for decades [18,19]. Importantly, RA-mimetic compounds can be designed to specifically bind CRABP1 without engaging RARs. This CRABP1-mediated, non-canonical mechanism offers a unique opportunity to develop new retinoid therapeutics without eliciting serious adverse effects such as retinoic acid syndrome.

CRABP1 can form protein complexes (named CRABP1-signalosomes) with certain components of multiple signaling pathways to modulate specific signal propagation in the cytoplasm [18]. Several CRABP1-signalosomes have been implicated in maintaining neuronal health/function, thereby preventing/halting degeneration. Maintaining the health and function of neurons depends on proper and timely modulation of multiple rapid and dynamic signaling pathways that govern essential neuronal processes, in particular, excitability and stress responses [20-25]. Through molecular and *in-vivo* studies of *Crabp1* Knockout (CKO) models (mice and primary cultures), we have identified multiple CRABP1-signalosomes that can regulate neuronal excitability and stress responses or modulate neuroinflammation and neural stem cell proliferation [26].

Firstly, the CRABP1-CaMKII signalosome dampens over-excited CaMKII activity, thereby protecting neurons from excitotoxic insults and axonal degeneration and preserving neuromuscular junction integrity and motor function in mice [27]. Secondly, the CRABP1-IRE1α signalosome can modulate stress-response, particularly the unfolded protein response in the Endoplasmic Reticulum (ER-UPR), which was first demonstrated in thyrocytes. We then identified a potential neuronal CRABP1-eIF2α signalosome which can regulate the Integrated Stress Response (ISR) [28]. In CKO mouse spinal cord tissues, failure of eIF2α activation retards the engagement of mitochondrial UPR and compromises oxidative stress management, which is essential for maintaining cellular homeostasis under sustained stress and critical for neuronal health and function [24,29]. Consistently, dysfunction of IRE1α and eIF2α-mediated stress signaling has been implicated in neurodegeneration [22,30,31]. Thirdly, CRABP1-MAPK signalosome modulates neural stem cell proliferation, thereby impacting memory function. Finally, based on our unbiased proteomic profiling of CRABP1-containing protein complexes, CRABP1-signalosomes can also directly involve many kinases [32]. Regulating kinase has emerged as an attractive approach in managing neurodegeneration [33,34]. Based on these findings, we propose that targeting CRABP1 signalosomes offers a potentially more effective strategy to address the multifactorial nature of neurodegeneration. In particular, it can be very attractive to exploit novel RA-mimetic and signaling pathway-selective (or biased) specific CRABP1-binding compounds, such as those we have characterized in the past [26]. Because of their CRABP1-specificity and signaling pathway-selectivity, these RA-mimetic compounds are less likely to elicit RA toxicities mediated, mainly, by RARs that are almost ubiquitously present.

Mining human disease datasets have revealed that CRABP1 expression is significantly reduced in several Motor Neuron (MN) degeneration diseases including ALS and Spinal Muscular Atrophy (SMA) [18]. Given the vastly different disease pathogenesis of ALS and SMA, the loss of CRABP1 expression in these diseases suggests that proper expression of CRABP1 is important for the maintenance of MN health in general [34,35]. To this end, our bioinformatic studies also revealed several Single Nucleotide Polymorphisms (SNPs) present in the promoter region of CRABP1 gene in ALS patients, which validates the relevance and significance of controlling *CRABP1* gene expression, particularly for the health/function of MNs [18]. It is tempting to speculate that maintaining a proper level of *CRABP1* gene expression, thus providing enough CRABP1-signalosomes, is an essential process required for the integrity and function of neurons, at least for spinal MNs. Coincidentally, age is a known risk factor for ALS in human patients, CKO mice develop ALS-like phenotype in an age-dependent manner and bioinformatic data have revealed that CRABP1 expression decreases with age in human spinal cord tissues [18,34,36].

In conclusion, recent studies have established CRABP1 as a major mediator of non-canonical activities of RA which acts to modulate cell-context specific signaling pathways through CRABP1-signalosomes in the cytoplasm. The physiological basis of these CRABP1-signalosomes has been uncovered mostly by studying CKO mice/tissues. These findings have prompted the search for new avenues in developing novel retinoid therapeutics without RAR-mediated retinoid toxicities, particularly in managing neurodegeneration that most likely requires extended periods of intervention. This can be a promising strategy, as supported by the success in a) our structural studies revealing essential residues of CRABP1 protein that preferentially engages certain specific signaling pathways and b) identifying specific CRABP1-binding (without engaging RARs) compounds that target specific signaling pathways in a cell context-dependent manner. It will be of great interest to further characterize and develop novel RA-mimetic compounds that can more specifically and potently modulate the exact signaling pathways crucial to specific defects in certain neurodegenerative processes. This type of signaling pathway-targeting, "tailored" approach is more likely to deliver the desired therapeutic effects with minimal toxicity.

Keywords: Amyotrophic Lateral Sclerosis; Huntington Disease; Alzheimer's Disease; Central Nervous System; Integrated Stress Response

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability Statement
No new data were created or analyzed in this study.

Ethical Statement
The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Informed Consent Statement
Informed consent was taken for this study.

Authors' Contributions
JN and LNW: conceptualization, writing-original draft preparation, writing-review and editing. LNW: supervision, project administration, funding acquisition. All authors have read and agreed to the published version of the manuscript.

References
1. Alsharief M. How do retinoids affect Alzheimer's disease and can they be novel drug candidates? Cureus. 2024;16:e57548.
2. Behl T. Therapeutic insights elaborating the potential of retinoids in Alzheimer's disease. Front Pharmacol. 2022;13:976799.
3. Beheshti S. All-trans retinoic acid in Alzheimer's disease. In: diagnosis and management in dementia: the neuroscience of dementia. 2020;559-72.
4. Das B, Dasgupta S, Ray S. Potential therapeutic roles of retinoids for prevention of neuroinflammation and neurodegeneration in Alzheimer's disease. Neural Regen Res. 2019;14:1880.
5. Clark JN, Whiting A, McCaffery P. Retinoic acid receptor-targeted drugs in neurodegenerative disease. Expert Opin Drug Metab Toxicol. 2020;16:1097-108.
6. Riancho J. Retinoids and motor neuron disease: Potential role in amyotrophic lateral sclerosis. J Neurol Sci. 2015;360:115.
7. Escudier O, Zhang Y, Whiting A, Chazot P. Evaluation of a synthetic retinoid, ellorarxine, in the NSC-34 cell model of motor neuron disease. Int J Mol Sci. 2024;25:9764.
8. Ciancia M. Retinoic acid receptor beta protects striatopallidal medium spiny neurons from mitochondrial dysfunction and neurodegeneration. Prog Neurobiol. 2022;212:102246.
9. Sharma S. Retinoid X receptor: Cellular and biochemical roles of nuclear receptor with a focus on neuropathological involvement. Mol Neurobiol. 2022;59:2027-50.
10. Pareek A. Retinoic acid in Parkinson's disease: Molecular insights, therapeutic advances, and future prospects. Life Sci. 2024;355:123010.
11. Marie A, Darricau M, Touyarot K, Parr-Brownlie LC, Bosch-Bouju C. Role and mechanism of vitamin A metabolism in the pathophysiology of Parkinson's disease. J Parkinsons Dis. 2021;11:949-70.
12. Sanders M, Chandraratna R, Marek K, Jennings D. A phase 1 clinical study of the retinoid X receptor selective agonist IRX4204 in patients with early Parkinson's disease. Neurology. 2016;86:P2.342.
13. Duester G. Retinoic acid synthesis and signaling during early organogenesis. Cell. 2008;134:921-31.
14. Cunningham TJ, Duester G. Mechanisms of retinoic acid signalling and its roles in organ and limb development. Nat Rev Mol Cell Biol. 2015;16:110-23.
15. Piazza A, Carlone R, Spencer GE. Non-canonical retinoid signaling in neural development, regeneration and synaptic function. Front Mol Neurosci. 2024;17.
16. Napoli JL. Cellular retinoid binding-proteins CRBP, CRABP, FABP5: Effects on retinoid metabolism, function and related diseases. Pharmacol Ther. 2017;173:19-33.
17. Nagpal I, Wei LN. All-trans retinoic acid as a versatile cytosolic signal modulator mediated by CRABP1. Int J Mol Sci. 2019;20:3610.
18. Nhieu J, Lin YL, Wei LN. CRABP1 in non-canonical activities of retinoic acid in health and diseases. Nutrients. 2022;14:1528.
19. Montesinos P, Sanz MA. The differentiation syndrome in patients with acute promyelocytic leukemia. Mediterr J Hematol

Infect Dis. 2011;3:e2011059.
20. Szydlowska K, Tymianski M. Calcium, ischemia and excitotoxicity. Cell Calcium. 2010;47:122-9.
21. Van Den Bosch L, Van Damme P, Bogaert E, Robberecht W. The role of excitotoxicity in the pathogenesis of amyotrophic lateral sclerosis. Biochim Biophys Acta Mol Basis Dis. 2006;1762:1068-82.
22. Costa-Mattioli M, Walter P. The integrated stress response: From mechanism to disease. Science. 2020;368.
23. Gandhi S, Abramov AY. Mechanism of oxidative stress in neurodegeneration. Oxid Med Cell Longev. 2012;2012:428010.
24. Lindholm D, Wootz H, Korhonen L. ER stress and neurodegenerative diseases. Cell Death Differ. 2006;13:385-92.
25. Doyle KM. Unfolded proteins and endoplasmic reticulum stress in neurodegenerative disorders. J Cell Mol Med. 2011;15:2025-39.
26. Nhieu J, Wei LN. Targeting CRABP1 signalosomes in managing neurodegeneration. Biomolecules. 2025;15:1428.
27. Lin YL. CRABP1-CaMKII-Agrn regulates the maintenance of neuromuscular junction in spinal motor neurons. Cell Death Differ. 2022;29:1-13.
28. Wei CW, Lerdall T, Najjar F, Wei LN. Depleting cellular retinoic acid binding protein 1 impairs UPRmt. J Cell Signal. 2023;4:151-62.
29. Gao J, et al. Abnormalities of mitochondrial dynamics in neurodegenerative diseases. Antioxidants. 2017;6:25.
30. English AM, Green KM, Moon SL. A disintegrated stress response: Genetic diseases of eIF2α regulators. Wiley Interdiscip Rev RNA. 2022;13.
31. Chen L. The functions of IRE1α in neurodegenerative diseases: Beyond ER stress. Ageing Res Rev. 2022;82:101774.
32. Nhieu J, Wei CW, Ludwig M, Drake JM, Wei LN. CRABP1-complexes in exosome secretion. Cell Commun Signal. 2024;22:1-17.
33. Naim A. The role of kinases in neurodegenerative diseases: From pathogenesis to treatment. Eur J Neurosci. 2025;61.
34. Masrori P, Van Damme P. Amyotrophic lateral sclerosis: A clinical review. Eur J Neurol. 2020;27:1918-29.
35. D'Amico A, Mercuri E, Tiziano FD, Bertini E. Spinal muscular atrophy. Orphanet J Rare Dis. 2011;6:71.
36. Nhieu J, Najjar F, Wei LN. CRABP1 signalosomes in non-canonical actions of retinoic acid-maintaining health and preventing thyroid dysfunction in aging. Endocrines. 2025;6:26.

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