Decoding PLD3: Structural and functional discoveries with therapeutic potential for Alzheimer's Disease

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In 2024 approximately 421,000 Australians were affected by dementia; without any medical advancements by 2054 this number will double (Dementia Australia, 2023, Dementia Prevalence Data 2024-2054). One emerging target in Alzheimer's disease (AD) pathology, particularly in late-onset AD which is the most common dementia form, is human phospholipase D3 (PLD3)[1]. Certain PLD3 variants are linked with increased vulnerability to neurodegeneration and amyloid pathology[2], with recent studies establishing a direct association between the enzyme and the disease. PLD3 is one of the six members of Phospholipase D family (PLD) and a type II transmembrane protein with a short cytosolic N-terminus, an α-helical single transmembrane domain and a luminal C-terminal domain[1, 3]. When the protein reaches acidic compartments, a cleavage action takes place releasing the soluble domain[4], while there are no indication so far of any membrane signal transduction abilities[1].

Our research aims to shed light on the PLD3 biology and provide groundwork for the development of novel AD therapeutics. Focusing on the soluble domain of PLD3, we successfully expressed and purified it. Extended protein characterisation revealed a dynamic equilibrium between monomers, dimers and high order oligomers. Concentration, pH and post-translational modifications seem to be critical factors in driving the preference for difference species. Enzymatic assays confirmed that our protein has a 5' exonuclease activity and no sign of phospholipase activity. Our structural studies resulted in crystals diffracting at 2.3 Å resolution, which allowed us to computationally compare our structure with other available published structures, as well as PLD3 AD risk variants and other members of the PLD family. I'll be sharing insights into the functional and structural findings from our experiments, along with updates on a structured-based drug design approach aiming to identify small molecule modulators of PLD3 to support the development of novel treatments for AD.

References

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