Toxin-Like Microproteins: A Novel Approach to Unveil the Intricacies of Acetylcholine Receptors

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Over 50 million people are diagnosed with neurodegenerative diseases worldwide, however the fundamental molecular mechanisms for the development of these diseases are not well-researched. Understanding these mechanisms is vital to discover disease pathways and supports drug discovery. Research shows that conotoxins are able to interact with nicotinic acetylcholine receptors (nAChRs), which mediates the transduction of chemo-electric signals throughout the nervous system. My work is to investigate toxin-like microproteins, which are non-coding RNAs in the human genome similar to conotoxins, to examine if these microproteins are able to bind and interact with the nAChR subunit α4β2. I selected a toxin-like microprotein (TXM-3092) by blasting a human genome database against a natural conotoxin database, analyzed protein models and ligand-binding sites, synthesized TXM-3092, labeled TXM-3092 with Cyanine-5 NHS Ester fluorescence, and utilized murine brain tissue slices to verify the localization and specificity on α4β2 nAChRs. I performed similar database testing on conotoxin mr5.1a which showed similarity to TXM-3092. T-test results comparing the protein model energy scores revealed that TXM-3092 had a significantly higher binding affinity to the α4β2 nAChR, showing agreement with fluorescence imaging results. Additionally, with comparison to the Allen Brain Atlas, TXM-3092 showed the expected localization of binding. Future work includes performing a dose response of TXM-3092 and testing an additional toxin-like microprotein for further confirmation of toxin-like microprotein specificity on the α4β2 nAChR.