31st August 2023

To,
Selection Committee
Sun Pharma Scholar Awards 2023

Brief Summary of Research

Lipids play important role in overall normal functioning of cells and are known to be involved in innumerable biological processes, the most important being the biological membrane formation, energy storage in form of lipid droplets and as chemical messengers in cellular signalling. And due to their critical roles in these processes, any imbalance/deregulation in the levels of these lipids, especially those involved in signalling could lead to various (patho)physiological disorders. Although the roles of signalling lipids in such disorders are known, there is a lack of complete understanding regarding the downstream signalling pathways and the proteins these lipids interact with. The research worked submitted for the consideration of Sun Pharma Science Foundation Science Scholars Awards-2023 was aimed at mapping and annotating the novel protein interactors of one such signalling lipid, monoacylglycerol (MAG). This class of signalling lipids have never been explored in great detail for its involvement in cellular signalling, with 2-arachidonylglycerol (2-AG) being an only exception. However, recent studies have indicated that other MAGs may be involved crucial signalling pathways within the cells that have been neglected thus far. Therefore, we have used a chemoproteomic approach, ligand affinity-based protein profiling (LAPP) where synthesised lipid probes are used to map the protein interactome of MAGs. Our recent finding suggests that a neuron specific protein called Hippocalcin (HPCA) is an interactor of MAGs, which was not known to bind to MAGs or any other lipid previously. Prior studies have shown that HPCA is involved in endocytosis of AMPA receptors in hippocampal and hypothalamic neurons. And yet another study regarding ABHD6, a prominent MAG hydrolysing enzyme has also shown a similar phenotype, wherein overexpression of ABHD6 leads to the internalisation of AMPA receptors in the neurons. This has led us to believe that there exists an as of yet unknown HPCA-MAG-ABHD6 axis that regulate the normal functioning of AMPA receptors in brain. Apart from the proteomic experiments, the lipid probes can also be used to map the dynamics of the respective lipid via microscopy which further could be helpful in performing co-localization experiments of MAGs with selected target protein interactors.

Overall, the submitted work demonstrates how the synthesised MAG probe can be used in mapping the protein interactome of MAGs and delineate novel lipid-protein interactions. Further, with this standardised platform, we would be able to map the protein interactors of other signalling lipids such as lysophosphatidylserines, oxidised lipids that are again, known to be involved in various pathophysiological conditions and disorders. And since the lipid-protein interactions have been exploited as druggable targets for treating several symptoms and diseases, this kind of study could potentially open up new avenues for developing novel drugs and possibilities of therapeutic interventions.

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