VIGYAN PATRIKA

Evaluating structure-Activity relationship of an immuno-modulatory signaling lipid, Lysophosphatidylserine

First author: Neha Khandelwal

Work done in Siddhesh Kamat's lab at IISER-Pune

How would you explain your paper's key results to the non-scientific community?

Concerted action of the biomolecules such as carbohydrates, proteins and lipids support the life system through their participation in biological functions in all life forms. Lipids, along with their subclasses consist of a large group of structurally diverse organic compounds that are involved in a diverse array of functions in almost all life processes. Signaling lipids are an important class of biomolecules that control cellullar functions. They recently have gained tremendous attention for their implementation in various pathological conditions including neurological and metabolic disorders. One such bioactive lipid is lysophosphatidylserine (Lyso-PS), present abundantly in the mammalian brain and immune cells.

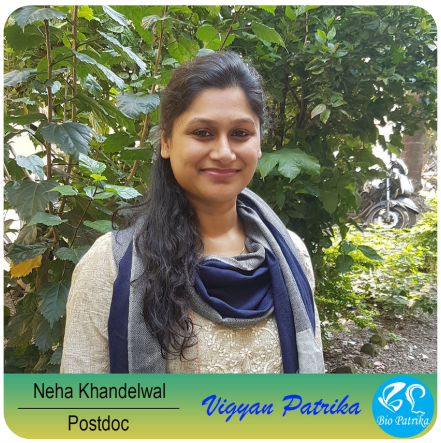
However, owing to its structural diversity and limited commercial availability, we took it upon ourselves to chemically synthesize a library of Lyso-PS with varying lengths of fatty acid chain of medium to very long chains of Lyso-PS. Our research unveiled the distinct role of structurally variant Lyso-PS in immune system function and its underlying molecular mechanism involving immune specific cellular receptors. The study reveals that Lyso-PS exerts it's signaling properties towards the activation of immune cells, such as macrophages and mast cells, by releasing inflammatory cytokines and histamine respectively. Very long-chain lyso-PS which previously found to be associated with the pathology of a neurodegenerative disorder PHARC (Polyneuropathy, Hearing loss, Ataxia, Retinitis pigmentosa, and Cataract) signals through TLR2 (Toll-like Receptor 2) receptors and causes neuroinflammation and microgliosis We proved this by using genetically engineered mice with TLR2 gene deletion where the inflammatory effect were absent upon Lyso-PS treatment.

Our further analysis also revealed the contribution of long-chain Lyso-PS causing mast cell degranulation and histamine release, which is a signal for secondary immune response. Interestingly, we observed that this function was mediated by an, as-of-yet unknown, GPCR (G-protein Coupled Receptors, a class of cell surface receptors), and not TLR2. This indicates a distinct and immune-specific role of long and very long chain Lyso-PS.

In the mice brain, Lyso-PS is majorly regulated by a Lyso-PS lipase enzyme called ABHD12, whose mutation causes PHARC syndrome. For the first time, we have shown that ABHD12 enzyme is also the principal Lyso-PS lipase that regulates its function in mast cell biology.

What are the possible consequences of these findings for your research area?

To begin with, studying a critical biomolecule such as Lyso-PS has been hampered due to its commercial paucity. Our study overcomes that hurdle and provides a chemical synthesis route to synthesize a library of Lyso-PS in order to study their function in the mammalian system. Over and above, we have successfully established that the differential role of lyso-PS is structure driven. Our study showed for the firsttime, that the immuno-modulatory functions exerted by Lyso-PS are driven by the length of the fatty acid chain. This study sets a potential platform in understanding the molecular signaling pathways activated by specific Lyso-PS isoforms under normal or diseased conditions. Our findings pose a significant biomedical



Dr. Neha Khandelwal completed Masters in Biotechnology from Rajiv Gandhi College in 2007 (Now Deemed University) and received her Doctorate from National Chemical Laboratory, Pune under the supervision of Dr. Ashok Giri. In 2018, she joined Dr. Siddhesh Kamat's lab at IISER-Pune as a SERB-National Postdoctoral Fellow and has been a postdoctoral research associate since 2020. Dr. Khandelwal's research work at IISER involves understanding the immunomodulatory activities of an important lipid mediator called lysophosphatidylserine. Apart from research, she enjoys exploring new places, playing badminton and dancing.

relevance and hint towards developing therapeutics using specific Lyso-PS mediated pathway.

What was the exciting moment (eureka moment) during your research?

The eureka moment of my research was when I first discovered, through biochemical investigations, that a small change in lyso-PS structure can initiate differential physiological responses. In turn, these responses are mediated by distinct molecular pathways. Moreover, revealing the structure-activity relationship of chemically divergent Lyso-PSs in the mammalian system, for the first time was an exciting moment.

What do you hope to do next?

The present study utilizes a chemical synthesis route to create a library of lyso-PS with saturated fatty acid chain length. The study presents a potential scope to further dissect the structure-activity relationship of Lyso-PS bearing polyunsaturated fatty acid chain. We have shown the specific contribution of lyso-PSs in brain and immune cells functions. However, currentlynot much information is known about it's role in other mammalian organs. Hence, understanding the role of lyso-PS and its underlying mechanism under various physiological or pathological conditions in specific tissues/organs will be intriguing.

Where do you seek scientific inspiration?

I was always inclined towards Biology and interested to know how complex and intricate life functions are. However, it was during my Masters when I got fascinated with the Immunology subject by attending Dr. P. Sahai's lectures from National Institute of Immunology, who was then a visiting faculty. Since then, I drawn to immunology research and to be a part of important discoveries. I was fortunate enough to work with Dr. Siddhesh Kamat, my Postdoctoral advisor, from whom I seek and receive tremendous inspiration. I admire him not only for his great scientific skills and incredible knowledge, but also for his excellent mentoring and lab managerial skills along with his supportive and generous personality. Working with him always inspires me to do great science and create innovative breakthroughs.

How do you intend to help Indian science improve?

To do great science, it is important to ask significant and relevant questions that are for the betterment of nature and society. Furthermore, the advancement experimental tools has opened new avenues in the area of biological and biomedical research. I am eager in applying these high throughput and advanced technologies to carry out cutting edge research. In this process, I desire to collaborate with other excellent Indian scientists and successfully translate research findings from bench to clinic.

Reference

Khandelwal N, Shaikh M, Mhetre A, Singh S, Sajeevan T, Joshi A, Balaji KN, Chakrapani H, Kamat SS. Fatty acid chain length drives lysophosphatidylserine-dependent immunological outputs. Cell Chem Biol. 2021 Jan 21:S2451-9456(21)00008-8. doi: 10.1016/j.chembiol.2021.01.008.

> "Our findings pose a significant biomedical relevance and hint towards developing therapeutics using specific Lyso-PS mediated pathway."

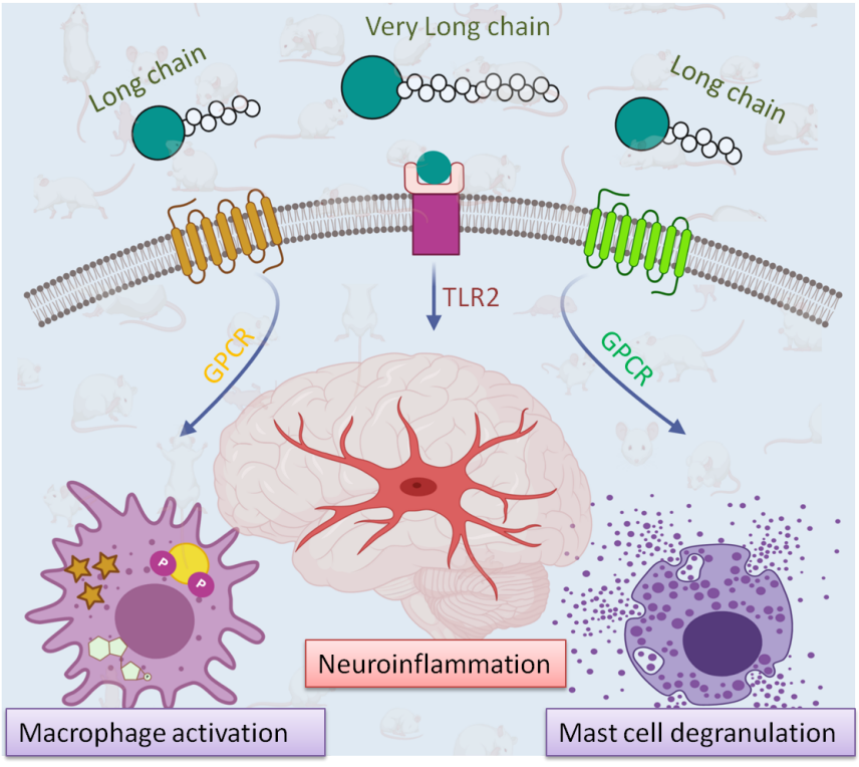


Figure1: Very long chain and long chain Lyso-PS exert their signaling properties via different receptors leading to specific neuroimmunological function.