



SVAR COMPLEMENT EXCELLENCE AWARD

Unraveling the Mysteries of Complement Activation in the Lung

An interview with Svar Complement Excellence Award recipient 2023

Understanding the complement system's role in various physiological processes, particularly in lung injury, has been a long-standing passion for Dr. Hrishikesh S. Kulkarni. His research journey began in Mumbai, India and continued under the guidance of Dr. John Atkinson at Washington University in St. Louis in the US. Driven by the desire to unravel the mysteries of the immune system, he focused on the overlooked aspect of the complement system's involvement in lung injury. Moreover, inspired by the mentorship he received, Dr. Kulkarni prioritizes mentoring trainees at all stages.

He is the Associate Program Director for Research for their Divisional fellowship program, where he engages and supports physicians-in-training, allowing them to explore a career in research as a part of an NIH-funded "Principles in Pulmonary Research" training grant. His individual research program aims to create an inclusive and supportive scientific environment by recruiting trainees from diverse backgrounds.

At the heart of Dr. Kulkarni's research group lies the question of reducing the burden of lung injury, with the hypothesis that locally derived immune proteins, such as complement proteins, can be modulated to mitigate disease severity.

In this article, Dr. Kulkarni discusses the role of context-dependent local complement activation in lung injury, specifically in response to infections, lung transplantation, and the role of complement in COVID-19.

Local complement production for lung injury protection against bacteria

The complement system has historically been thought to be a fluid phase derived from the liver, and that is involved in host defense, especially in the context of bacteria.

During his career, Dr. Kulkarni has focused on exploring the role of complement in the airway epithelium. His work has shown that the local production of C3, a central component of the complement cascade, by cells in the lung is protective against bacterial pneumonia-induced lung injury,¹ which was previously attributed to what was derived from the liver and present in the circulation. This creates a precedent to better understand locally-produced and intracellular complement components and for revisiting prior trial studies of complement therapeutics. According to Dr. Kulkarni, "The future of complement therapeutics is bright in the light of developing therapeutics targeting a specific organ." The significant progress in understanding the sources of local complement production in different cells other than hepatocytes has been possible with the advent of new research tools and the ability to study mice and human tissue, explains Dr. Kulkarni.

Importance of early monitoring of complement activation after lung transplantation

Primary graft dysfunction (PGD) remains a significant challenge in lung transplantation and worsens survival after transplantation. It is a form of lung injury where complement is activated early after transplantation, likely in the setting of ischemia-reperfusion injury.

"The Svar Complement Award represents a significant milestone in my career. It is an honor to be recognized for our work in complement and lung diseases. This award not only acknowledges the hard work of our lab members but also provides an opportunity to showcase the vital role of complement in lung diseases. This recognition will allow us to perform daring experiments that are not possible with other funds."

Dr. Hrishikesh S. Kulkarni, MD, MSCI
Assistant Professor of Medicine and Molecular Microbiology; Associate Program Director for Research at Washington University School of Medicine in St. Louis



Dr. Kulkarni acknowledges the ongoing efforts to target specific components of the complement system but cautions that a cure is yet to be found.

His research has revealed that local activation of complement is much higher in those who developed severe PGD. Differences in complement activation products in the lungs are much clearer than those detected in the circulation and are observed within the first 24 hours of transplantation, often within the first 2 hours².

“This is an opportune moment to explore complement inhibition in graft failure as advancements in the field continue to unfold.”

Identifying the specific pathways involved in this ongoing complement activation in the lung is crucial, as well as stratifying the patients that could benefit from a complement-targeted approach, explains Dr. Kulkarni. His work shows components of the alternative pathway are locally upregulated in PGD. Together, these insights suggest that early targeting of the ongoing complement activation in the lungs could lead to more effective targeted therapeutics for mitigating this life-threatening acute injury. Dr. Kulkarni believes that this is an opportune moment to explore complement inhibition in graft failure as advancements in the field continue to unfold.

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Complement implication in COVID-19

The emergence of COVID-19 has further accelerated research on the complement system as scientists from diverse fields recognized its relevance in the course of the disease. This convergence of interests has led to a surge in research and the application of advanced tools, expanding our knowledge of the complement system.

Dr. Kulkarni's work has shown that complement activation in patients with COVID-19 is much higher than is observed in those with other viral illnesses, such as influenza and those with matched-disease severity. They have also shown that patients presenting high levels of complement activation were at higher risk of worse outcomes.

Furthermore, it has shown that, specifically, the alternative pathway activation was higher in patients with severe COVID-19³. His findings have opened the identification of specific targets that may be utilized for risk prognostication, drug discovery, and personalized clinical trials.

Navigating challenges and embracing opportunities for therapeutics targeting the lung

The development of therapeutics targeting local mucosal surface-derived complement proteins would be a great leap towards effective therapeutics with reduced systemic side effects, but it comes with big challenges. The main challenge lies in effectively delivering the drug to the mucosal barrier and maintaining the stability of the therapeutic molecule in that environment. We will need to develop innovative delivery strategies and stability-enhancing techniques to overcome this challenge – Dr. Kulkarni explains.

New avenues in the role of complement in infections

The future areas of research to extend Dr. Kulkarni's work involve exploring the role of complement in other mucosal surfaces, such as the gut or genitourinary tract. Since infections are a major problem in multiple mucosal areas, understanding the local complement activation and its function in these sites is crucial.

“The main challenge lies in effectively delivering the drug to the mucosal barrier and maintaining the stability of the therapeutic molecule in that environment.”

By comprehending the extent of the local complement response, researchers can develop targeted therapies to address infections and related diseases. It is an exciting field with numerous opportunities for the next generation of complement researchers, as the complement system is involved in nearly every biological system, says Dr. Kulkarni. To this effect, he has been collaborating with multiple investigators within and outside Washington University, including Dr. Devesha Kulkarni, who is a gut mucosal immunologist, and Dr. Anuja Java, a transplant nephrologist.

He would also like to thank investigators such as Dr. Claudia Kemper for generating invaluable tools to investigate local complement expression, and sharing them with the scientific community.

ABOUT THE PRIZE

The Svar Complement Excellence Award is handed out annually to individuals that have made great contributions to the complement field.

The awards are intended as grants for two recipients, each worth €20,000. In 2023 the prize was handed out at the International Complement Workshop (ICW) in Newcastle in collaboration with the complement community.

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The future of the complement field is a collaborative quest

Studying the complement system to determine the specificity of the response requires a multifaceted approach, mentions Dr. Kulkarni. One crucial aspect is understanding the temporal dynamics of complement activation. It is important to identify the time when the response transitions from being beneficial to becoming detrimental. This knowledge can guide the development of therapies by targeting the complement system at specific time points.

An important component of his team's approach involves investigating whether the complement system functions through canonical or non-canonical pathways, as well as the role of regulatory proteins in the complement system. Understanding the specific pathways involved will help researchers determine which components of the complement system are best to target for therapeutic interventions.

“It is of great relevance to the complement community develop specific biomarkers and understand how modulators can enter cells to devise effective strategies”

The growing number of researchers studying the complement system from various conditions, such as cancer, metabolic diseases, and infections, holds great promise for finding answers to complex questions. It is of great relevance to the complement community to develop specific biomarkers and understand how modulators can enter cells to devise effective strategies- Dr. Kulkarni emphasizes.

The complement research community is extremely supportive, and the collective efforts of us and others will nurture new investigators and continue to provide new answers that lead to further questions, propelling the field forward.

To read more about Dr. Kulkarni's work:

Selected References

1. Sahu SK, et al. Lung epithelial cell-derived C3 protects against pneumonia-induced lung injury. *Sci Immunol.* 2023
2. Kulkarni HS, et al., Local complement activation is associated with primary graft dysfunction after lung transplantation. *JCI Insight.* 2020
3. Ma L, et al., Increased complement activation is a distinctive feature of severe SARS-CoV-2 infection. *Sci Immunol.* 2021

ABOUT SVAR LIFE SCIENCE

We harness years of experience and deep specialist knowledge in innate immunity, the complement system, and its intricate connections. With synergetic platforms, Svar delivers tailored solutions spanning immunoassay development, cell engineering, and contract research services that address our customer's assessment and testing needs.

The synergy created by our integrated suite of offerings provides customers with a comprehensive approach that not only enhances efficiency but also fosters innovation, enabling seamless transitions from discovery to clinical application.

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