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The importance of neutrophil extracellular traps and vascular leakage in pneumonia caused by influenza virus and *pneumococcus*

Vincent TK Chow
National University of Singapore, Singapore

Excessive host inflammatory responses negatively impact disease outcomes of pneumonia. To better understand host-pathogen interactions during the critical inflammatory and repair phases of pneumonia, we investigated the role of neutrophils, neutrophil extracellular traps (NETs) and c-angiopoietin-like 4 (cANGPTL4) in the pathogenesis of influenza and pneumococcal pneumonia. The presence of NETs and the effects of cANGPTL4 were studied in mouse models of primary infection with influenza virus H1N1 and/or H3N2, and secondary pneumococcal pneumonia. Excessive infiltration of neutrophils and significant formation of NETs were associated with severe influenza and pneumococcal pneumonia. Intense pulmonary NETs generation, elevated myeloperoxidase activity, cytokine dysregulation, pneumococcal capsule thickness determined the disease severity. Influenza infection stimulated the expression of cANGPTL4 via a direct mechanism mediated by interleukin-6 and STAT3. cANGPTL4 enhanced pulmonary tissue leakiness and exacerbated inflammation-induced lung injury. Treatment of infected mice with neutralizing anti-cANGPTL4 antibody significantly accelerated lung recovery and enhanced lung tissue integrity. The cANGPTL4-deficient mice also displayed diminished lung damage and recovered more rapidly from influenza pneumonia compared to their wild-type counterparts. Retrospective examination of lung biopsies and clinical samples from patients with infection-induced pneumonia with tissue damage revealed elevated expression of cANGPTL4 compared to normal or uninfected samples. These observations highlight the important roles that NETs and cANGPTL4 play in pulmonary infection and damage, and may facilitate the development of novel biomarkers and intervention strategies to improve the management of pneumonia. From the infection control perspective, the research also emphasizes the clinical importance of improving the coverage of influenza and pneumococcal vaccination especially among high-risk individuals.

Biography

Vincent TK Chow is a medical virologist and molecular biologist who graduated with MD, PhD, FRCPath, MBBS, and MSc qualifications. Currently, he serves as an Associate Professor of Microbiology and Principal Investigator of the Host And Pathogen Interactivity Laboratory at the Yong Loo Lin School of Medicine, National University of Singapore (NUS). Since 1996, he established the Human Genome Laboratory in the Department of Microbiology at NUS that has isolated and characterized several novel human genes and proteins. Dr Chow previously served as President of the Asia-Pacific Society for Medical Virology as well as Chair of the Virology Section of the International Society of Chemotherapy. His laboratory has published over 250 articles in international refereed journals. He has received several awards and honors (including the Murex Virologist Award for Rapid Viral Diagnosis, the Special Commendation Award and Faculty Research Excellence Award from NUS, the Singapore Society of Pathology – Becton Dickinson Award, the Chan Yow Cheong Oration at the 6th Asia-Pacific Congress of Medical Virology). His research interests in the past several years have focused on the molecular genetics and infectomics of influenza pneumonia and of hand, foot and mouth disease, specifically on the cellular, molecular, and viral pathogenesis of severe influenza and enterovirus 71 infections.

micctk@nus.edu.sg

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