公益財団法人 セコム科学技術振興財団
研究成果報告書

研究課題名

感染症を重篤化させる特異的炎症の活性化機構と炎症記憶の解析およびその応用

Analysis of the activation mechanism of specific inflammation that aggravates infectious diseases and inflammatory memory, and its applications

研究期間

令和３年　１０月　～　令和７年　９月

報告年月

令和７年　１２月

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Abstract

This study aims to generate foundational insights that will support the development of "host-directed therapies" that modulate detrimental host inflammatory responses, rather than directly targeting the pathogen itself, in light of the silent pandemic of antimicrobial-resistant bacteria that is making treatment with conventional antibiotics increasingly difficult. In this study, we focused on inflammasome signaling as a representative inflammatory response induced during infection. In addition to the conventional view that inflammation contributes to host defense, we investigated the possibility that, in certain contexts, inflammasome activation promotes pathogen expansion and tissue injury, thereby exacerbating disease. A major outcome of this research is the establishment of a pathophysiological framework in which pathogen-derived virulence factors do not simply initiate inflammasome activation but can actively amplify it, resulting in worsened infection. By using representative infection models, we systematically delineated the virulence factor determinants responsible for inflammatory amplification and demonstrated that mutation of the critical region abrogates this enhanced response. These findings broaden the functional interpretation of virulence factors beyond traditional roles such as cytotoxicity or facilitation of invasion, and position them as active modulators of host inflammatory responses.

We also investigated ASC speck formation, a key cellular event in the execution phase of inflammasome activation, to clarify host-side regulatory principles that govern amplification of inflammatory signaling. Our results indicate that stimulus-dependent changes in adaptor status and intracellular organization contribute to rapid escalation of inflammasome responses, supporting the concept that inflammasome activation is shaped by spatiotemporal regulation within cells. This perspective provides a framework for identifying upstream regulatory nodes that determine whether inflammasome signaling remains protective or becomes pathogenic. Importantly, this study also organized how the contribution of inflammasome-related inflammation to disease severity differs depending on bacterial type and pathogenic strategy. We proposed an approach for defining "drivers of severity" in which Gram-positive pathogens can aggravate disease through virulence factor-mediated amplification of inflammation, whereas Gram-negative pathogens may exacerbate pathology through distinct inflammasome pathways. This comparative viewpoint supports rational selection of intervention points under a unified inflammasome concept while accounting for pathogen-specific differences.

From a translational perspective, our findings support the feasibility of improving infection outcomes by targeting components of inflammasome signaling that directly drive disease exacerbation, even in settings where antibiotics provide limited benefit. By suppressing host inflammatory amplification circuits exploited by pathogens, such strategies may offer a lower risk of inducing for antimicrobial resistance. In addition, we established experimental platforms suitable for both drug repositioning and the evaluation of novel inhibitory compounds, thereby strengthening the foundation for practical development of host-directed interventions.

Overall, this work defines a conceptual and mechanistic basis for understanding how pathogen factors amplify host inflammasome responses and how resultant inflammation can worsen infectious disease. The outcomes provide a foundation for developing antibiotic-independent therapeutic options for refractory infections, including those caused by antimicrobial-resistant bacteria, and are expected to facilitate future efforts in host-directed therapy design, biomarker development, and translational drug discovery.