COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Targeting Spp1-positive Macrophages For Therapeutic Intervention In Pulmonary Infection

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The emergence of global biological threats, including viral pandemics and drug resistant bacterial and fungal infections, underscores the need for innovative therapeutic strategies targeting pulmonary pathogenesis. Although vaccines and other pathogen-directed therapies are effective in combating infections, their development is time-intensive and requires in-depth knowledge of the pathogen in question. Also, these pathogen-directed approaches could contribute to the emergence of drug-resistant strains. Therefore, we need additional therapeutic strategies such as host-targeted therapeutics that are effective in mitigating or reversing symptoms caused by existing and newly emerging pathogens.

With the goal of identifying potential broad-spectrum therapeutic targets for pulmonary infections, we performed comparative analysis of in-house generated and publicly available single-cell RNA sequencing (scRNA-seq) data from SARS-CoV-2 (mouse and human), Influenza A (mouse) and Coccidioides (mouse) infected lungs. Our bioinformatic analysis of these pre-clinical and clinical scRNA-seq datasets has identified a specific macrophage subpopulation expressing high levels of SPP1, or Osteopontin (OPN), as a potential driver of worsened prognosis conserved in viral and fungal infections. Spp1+ macrophages display a fibrotic and immunosuppressive phenotype, and infiltration into the lung has been reported in lung cancer, idiopathic pulmonary fibrosis, and during SARS-CoV-2 infection, primarily during late stages disease. In addition to expressing high levels of Spp1, these macrophages expressed fibrotic genes such as Fn1, extracellular matrix remodeling enzymes such as Mmp14, and hypoxia inducible genes such as Hif1a. Furthermore, SPP1+ macrophage gene expression suggests robust cellular signaling to other immune cell types such as neutrophils in the lung microenvironment and may contribute to the suppression of T cell function.

We hypothesize that SPP1+ macrophages worsen outcomes in various respiratory infections and inactivation of these macrophages could ameliorate fibrosis and enhance immune efficacy, thereby improving clinical outcomes in pulmonary disease. Our ongoing research specifically examines the pathogenic role of SPP1-positive macrophages within the lung environment and assesses the therapeutic benefits of their targeted inactivation using an anti-Spp1 antibody in mouse models of fungal (coccidioidomycosis/Valley fever) and viral (Influenza A) infection. The effects of the inactivation of Spp1+ macrophages will be assessed through survival, changes in viral load, scRNA-seq, and histological analysis for evidence of decreased fibrosis/lung damage. By focusing on a crucial element of the host immune response that contributes to lung disease severity, this work proposes a novel avenue for the development of host-directed therapies in the management of complex pulmonary infections and during outbreaks of new respiratory pathogens.

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