Discovery of innate immune sensors in viral infections

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Inflammasomes are important sentinels of innate immune defense, sensing pathogens and inducing cell death in infected cells. There are several inflammasome sensors that each detect and respond to a specific pathogen- or damage-associated molecular pattern (PAMP or DAMP), respectively. Influenza A virus (IAV) infection triggers inflammatory responses in the respiratory mucosa, but the mechanisms of inflammasome activation are poorly understood. Using genome-wide high-content shRNA library screening and proteomics analysis, we previously identified MxA as a functional inflammasome sensor in respiratory epithelial cells and MxA inflammasome contributes to IAV resistance by triggering a rapid inflammatory response in infected respiratory epithelial cells (*S. Lee et al., Science Immunology, 2019*). During human herpes simplex virus-1 (HSV1) infection, we found that AIM2 regulates the innate immune sensors Pyrin and ZBP1 to drive inflammatory signaling and a form of inflammatory cell death and provide host protection (*S. Lee et al., Nature, 2021*). Regarding SARS-CoV-2, the cytosolic innate immune sensors that sense SARS-CoV-2 to initiate inflammatory cell death are largely unknown. Using genome-wide CRISPR/CAS9 knockout screening and RNAseq analyses from human patients, we identified NLRPx as an inflammasome sensor that drives inflammatory cell death during SARS-CoV-2 infection (*S. Lee et al., Nature, under the revision*). Overall, our results improve our fundamental understanding of innate immune responses and disease pathogenesis by identifying an innate immune sensor-dependent inflammasome and inflammatory cell death pathway and by defining its contribution to the pathological and life-threatening inflammation.