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Title: PNPT1 MEDIATES NLRP3 INFLAMMASOME ACTIVATION BY MAVS AND METABOLIC REPROGRAMMING IN MACROPHAGES

Abstract:
Recent data pointed to the important roles of Type I interferon response and NLRP3 inflammasome activation during infection with highly pathogenic coronaviruses. Polyribonucleotide nucleotidyltransferase 1 (Pnpt1) plays critical roles in mitochondrial homeostasis by controlling mitochondrial RNA (mt-RNA) processing, trafficking and degradation. Dhir et. al. showed that Pnpt1 deficiency resulted in mitochondrial dysfunction that triggered a Type I interferon response, suggesting a role in inflammation. However, the role of Pnpt1 in inflammasome activation remains largely unknown. In this study, we generated myeloid-specific Pnpt1-knockout mice, and demonstrated that Pnpt1 depletion enhanced interleukin-1 beta (IL-1β) and interleukin-18 (IL-18) secretion in mouse acute lung injury and sepsis models. Using cultured peritoneal and bone marrow-derived macrophages we demonstrated that Pnpt1 regulated NLRP3 inflammasome dependent IL-1β release in response to lipopolysaccharides (LPS), followed by poly (I:C) treatment, a synthetic analog of double-stranded RNA. Pnpt1 deficiency in macrophages increased glycolysis after LPS, and mt-reactive oxygen species (mt-ROS) after NLRP3 inflammasome activation. Pnpt1 activation of the inflammasome was dependent on both increased glycolysis and expression of the mitochondrial antiviral-signaling protein (MAVS), but not NF-κB signaling. Collectively, these data strengthen the concept that Pnpt1 is an important mediator of inflammation as shown by activation of the NLRP3 inflammasome in mouse acute lung injury and cultured macrophages. Our study has implications both for the understanding of how the mitochondrial protein Pnpt1 contributes to detrimental outcomes of viral infection and for current efforts to define new therapeutic paradigms for more efficient treatment modalities in COVID-19.