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Category: Postdoc
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Title: 4-Hydroxynonenal Inhibits Inflammasome Activation by Targeting NLRP3
Abstract: 4-Hydroxynonenal Inhibits Inflammasome Activation by Targeting NLRP3 Chia George Hsu, Camila Lage Chavez, Chongyang Zhang, Mark Sowden, Chen Yan, Bradford C. Berk Department of Medicine, Aab Cardiovascular Research Institute, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA Increasing evidence suggests that NLRP3 inflammasome activation is strongly associated with increased acute lung injury (ALI) mortality. An increase in oxidative stress is a major component of ALI. One important consequence is a chain reaction of lipid peroxidation. Of several reactive aldehydes formed from lipid peroxidation, 4-hydroxynonenal (HNE) is the most abundant end-product from the peroxidation of fatty acids. It has been implicated in both tissue damage and protection, likely dependent on maximum levels. We hypothesized that HNE may be protective by inhibiting the NLRP3 inflammasome. We used oropharyngeal LPS (2mg/kg in 50μ saline) delivery to cause ALI in C57/BL6 mice, and ALI was measured by inflammatory cell infiltration and IL-1β release (a specific product of the inflammasome). There were significant decreases in ALI when co-delivery of HNE (0.3mg/kg) with LPS: a reduction of myeloperoxidase (MPO) positive cell infiltration and IL-1β cleavage in the lung. We used cultured mouse peritoneal macrophages and human peripheral blood mononuclear cells to study the mechanism of HNE protection. Exogenous HNE (3 μM) blocked nigericin and ATP-induced pyroptosis (a specific NLRP3 mediated cell death) and IL-1β secretion. HNE induced the antioxidant Nrf2 transcription factor in a dose dependent manner, but the Nrf2 pathway was not required for the protective effect of HNE measured by nucleic acid stain. HNE did not inhibit NF-kB signaling required for NLRP3 expression. However, it prevented oligomerization of inflammasome components after nigericin treatment in LPS primed macrophages, suggesting that HNE specifically blocked inflammasome activation, not priming. Furthermore, we showed that HNE bound to NLRP3 by using click chemistry followed by streptavidin pulldown. Finally, injection of HNE (2.4mg/kg) or induction of HNE production by inhibiting glutathione peroxidase-4 enzyme activity (RSL3: 2.4mg/kg) reduced IL-1β release in C57/BL6 mice after LPS (10mg/kg) /ATP (200mg/kg) challenge. Our findings indicate that HNE inhibits inflammasome activation by targeting NLRP3, and the generation of endogenous HNE during oxidative stress may be crucial for decreasing inflammasome activation.