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Particle-Induced Chronic Inflammation is dependent upon Lysosomal Function and Autophagy

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Chronic inflammation drives the development of many debilitating pulmonary diseases. NLRP3 Inflammasome activation following lysosomal membrane permeabilization (LMP) has been identified as a necessary event in the maturation of IL-1β, a critical cytokine in the development of chronic inflammation. LMP and NLRP3 activation are known to occur rapidly following particle uptake by alveolar macrophages, however the longevity of these responses has not been defined. These studies are the first to describe the persistence of the NLRP3 Inflammasome response in relation to autophagy, the primary degradation pathway for NLRP3 components, and lysosomal integrity. Alveolar macrophages were isolated from C57Bl/6 mice 7 days following silica or vehicle exposure and assessed for impaired autophagy. LC3-II and p62 were elevated in cell lysates from alveolar macrophages isolated from silica-exposed mice, as well as Inflammasome protein components NLRP3 and ASC. IL-1β levels were below detection limits in the whole lung lavage fluid at 7 days and alveolar macrophages isolated from silica-treated mice after 7 days secreted negligible amounts of IL-1β after 24 hours of ex vivo culture, suggesting suppressed Inflammasome activity. Addition of low levels of endotoxin to isolated alveolar macrophages was sufficient to cause Inflammasome reactivation, resulting in renewed IL-1β production. Inflammasome reactivation could be suppressed with the Cathepsin B inhibitor Ca-074-Me, linking Inflammasome reactivation by endotoxin with impaired lysosome function. Multi-walled Carbon Nanotubes induced responses relative to silica, indicating that these mechanisms drive most particle-induced chronic inflammation. These studies demonstrate that lysosomal function and autophagy are integral to the development of chronic inflammation, and targeting of these two integrated pathways should be considered in therapeutic approaches to preventing chronic inflammatory disease.