A relationship between inflammation and various types of diseases clearly exists, however the mechanism of the inflammatory response and temporal events involved in inflammation appear to depend on the exact nature and time of the initial insult. Exposure to cigarette smoke and asbestos have been shown to promote inflammatory responses in the lung with a synergistic increase in lung disease. Asbestos exposure has been shown to activate the inflammasome, an important arm of the innate immune system, while smoke exposure has produced variable inflammasome activation results. The inflammasome is a large multi subunit protein complex that activates caspase 1, caspase 1 in turn cleaves the inflammation signaling molecule pro IL-1ß into the active form which then mediates multiple down stream inflammation cascades. Here we have investigated the combined interaction of cigarette smoke and asbestos to modulate inflammation in the lung using mouse models. C57BL/6 mice were exposed to asbestos 1 day a week for 5 weeks or exposed to cigarette smoke 4 days a week for 5 weeks or in combination exposed to asbestos 1 day a week and cigarette smoke 4 days a week for 5 weeks. On the day after the final smoke exposure, the animals were processed for analyses of lung inflammation. Analyses of bronchoalveolar lavage (BAL) fluid and lung homogenates from exposed animals suggest several changes in inflammasome-dependent responses upon repetitive insult by both of these compounds alone or in combination. Repetitive
exposure to asbestos induced IL-1ß and KC, downstream mediators of inflammasome activation, in both lung BAL fluid and lung homogenates. In addition, several other markers of lung injury and inflammation are present in this model including induction of LDH, MMP-2, MMP-9, and multinucleated macrophages. Interestingly, the combined treatment of smoke and asbestos generated a stark contrast to the asbestos exposed animals with a marked decrease in the inflammasome marker cytokines and LDH, MMP-2, and MMP-9 levels. Taken together, these results suggest that cigarette smoke represses inflammasome activation by asbestos. This immunosuppressive effect may account, at least in part, for the synergy between cigarette smoke and asbestos in lung tumorigenesis.