CHARACTERIZATION OF THE INFLAMMATORY RESPONSE IN THE LUNGS OF MICE EXPOSED TO CIGARETTE SMOKE AND/OR ASBESTOS.


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PURPOSE OF STUDY: Both cigarette smoke and asbestos exposure have been shown to promote inflammation in the lung. Humans exposed to both cigarette smoke and asbestos display a multiplicative increase in lung cancer incidence. Since chronic inflammation promotes lung tumorigenesis, we have posed the basic question of what is the inflammatory profile for smoke and/or asbestos.

METHODS USED: Wild type C57BL/6 mice were exposed to cigarette smoke and/or asbestos (four days per week/smoke and one day per week/asbestos for five weeks). Following exposure, bronchoalveolar lavage fluid (BAL) was collected and lungs were fixed and/or frozen for later use.

SUMMARY OF RESULTS: Asbestos exposed animals display an increase in several markers consistent with increased inflammation through NLRP3 inflammasome activation and down stream activation of Th17 pathways. In contrast, mice exposed to either smoke alone or smoke/asbestos displayed attenuation of many of these markers of inflammation. These markers include BAL fluid protein levels, lactate dehydrogenase (LDH), multinucleated macrophages, caspase-1 activity, HMGB-1 levels, and MMP activity. Examination of cytokine levels in BAL fluid by ELISA based approaches indicated that asbestos increased KC, IL-6, IL-1b, IL-23(p40), and IL-18, while smoke alone or smoke/asbestos attenuated expression of these cytokines. Quantitative RT-PCR analyses in an array format displayed general repression of many of the analytes upon smoke and/or asbestos treatment.

CONCLUSIONS: Both smoke and asbestos separately and in combination exert different effects on cytokine profiles in the lung. Cigarette smoke alone appeared to show only modest effects on cytokine levels compared to unexposed animals. Treatment with asbestos alone increased inflammatory profiles consistent with a Th17 response, while addition of smoke repressed this response. A working hypothesis is that the combination of smoke/asbestos leads to repression of the NLRP3 inflammasome that leads to attenuation of the Th17 response and reduced fiber clearance.