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TITLE: SEQUENTIAL EXPOSURE TO CARBON NANOTUBES AND BACTERIA ENHANCES PULMONARY INFLAMMATION AND INFECTIVITY

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ABSTRACT: Carbon nanotubes (CNT), with their applications in industry and medicine, may lead to new risks to human health. CNT induce a robust pulmonary inflammation and oxidative stress in rodents. Realistic exposures to CNT may occur in conjunction with other pathogenic impacts (microbial infections) and trigger enhanced responses. We evaluated interactions between pharyngeal aspiration of single-walled CNT (SWCNT) and bacterial pulmonary infection of C57BL/6 mice with *Listeria monocytogenes* (LM). Mice were given SWCNT (0, 10, and 40  $\mu\text{g}/\text{mouse}$ ) and 3 days later were exposed to LM (10<sup>3</sup> bacteria/mouse). Sequential exposure to SWCNT/LM amplified lung inflammation and Collagen formation. Despite this robust inflammatory response, SWCNT pre-exposure significantly decreased the pulmonary clearance of LM-exposed mice measured 3 to 7 days after microbial infection versus PBS/LM-treated mice. Decreased bacterial clearance in SWCNT-pre-exposed mice was associated with decreased phagocytosis of bacteria by macrophages and a decrease in nitric oxide production by these phagocytes. Pre-incubation of naive alveolar macrophages with SWCNT in vitro also resulted in decreased nitric oxide generation and suppressed phagocytizing activity toward LM. Failure of SWCNT-exposed mice to clear LM led to a continued elevation in nearly all major chemokines and acute phase cytokines into the later course of infection. In SWCNT/LM-exposed mice, bronchoalveolar lavage neutrophils, alveolar macrophages, and lymphocytes, as well as lactate dehydrogenase level, were increased compared with mice exposed to SWCNT or LM alone. In conclusion, enhanced acute inflammation and pulmonary injury with delayed bacterial clearance after SWCNT exposure may lead to increased susceptibility to lung infection in exposed populations.