Depletion of CD11b^{+}Alveolar Macrophages Exacerbates Lung Injury and Oxidative Stress following Ozone Inhalation

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Ozone (O_3) is an urban air pollutant known to cause lung inflammation, injury and oxidative stress. CD11b^{+}macrophages accumulate in alveolar and interstitial regions of the lung following O_3 exposure and have been characterized as Ly6C^{hi}proinflammatory and Ly6C^{lo}anti-inflammatory/wound repair. To assess the role of CD11b^{+}macrophages in O_3 toxicity, we used mice with a transgenic diphtheria toxin (DT) receptor under the control of the CD11b promoter (CD11b-DTR). Mice were treated ip with DT (25 µg/kg) to deplete CD11b^{+}monocytes/macrophages. After 1 h, mice were exposed to air or 0.8 ppm O_3 for 3 h in whole body chambers. Mice were euthanized 24 h later and bronchoalveolar lavage fluid and lung collected. Following exposure of DT-treated CD11b-DTR mice to O_3, numbers of CD11b^{+} Ly6C^{hi}proinflammatory alveolar macrophages increased relative to non-DT treated mice, while Ly6C^{lo} anti-inflammatory alveolar macrophages decreased. This correlated with increases in BAL protein levels indicating exacerbation of O_3-induced lung injury in DT-treated CD11b-DTR mice. O_3-induced oxidative stress, as reflected by increases in YM-1 expression, also increased in these mice. O_3 exposure also caused an increase in CD11b^{+}Ly6C^{hi} and Ly6C^{lo} interstitial macrophages in lungs of non-DT treated mice; both inflammatory macrophage subpopulations were significantly reduced after DT administration to the mice. This was associated with decreased expression of inducible nitric oxide synthase in the lung consistent with fewer proinflammatory macrophages migrating into alveolar spaces from the interstitium following O_3 exposure. Conversely, DT administration had no effect on O_3-induced neutrophil accumulation in the lung. These data indicate that inflammatory monocyte-derived macrophages that localize in the alveolar regions of the lung after O_3 exposure are derived from monocyte and interstitial macrophage precursors; moreover, these cells play a key role in dampening O_3-induced oxidative stress and alveolar epithelial barrier dysfunction. Elucidating the role of inflammatory macrophage subpopulations in O_3 toxicity is key to understanding mechanisms of lung injury and developing approaches for mitigating tissue damage. *NIH ES004738, AR055073 ES005022; EUH 778051; MSHEP 3899/H2020/2018/2.*