Macrophage Phenotype and Inflammation in Lung Injury and Resolution: Role of Lipid Metabolism

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Macrophages play a key role in both the initiation of inflammatory responses and the resolution of inflammation and tissue repair. These diverse activities have been attributed to proinflammatory M1 macrophages and anti-inflammatory/wound repair M2 macrophages, which sequentially appear in injured tissues. Key to effective tissue repair is a balance in the activities of M1 and M2 macrophage subpopulations. Thus, whereas overactivation of M1 macrophages or underactivation of M2 macrophages can lead to exacerbation of tissue injury, excessive activation of M2 macrophages can result in chronic inflammation and fibrosis. We have been investigating the role of macrophages in lung injury induced by inhaled toxicants. In previous studies, we showed that both M1 and M2 macrophage subpopulations accumulate in the lung following exposure to pulmonary toxicants such as ozone, particulates, and mustard vesicants. We speculate that toxicant-induced lung injury and disease pathogenesis is due to a failure of M2 macrophages to suppress proinflammatory responses of M1 macrophages. RNA-seq analysis revealed that nuclear transcription factors involved in lipid handling, including PPARγ, LXR, and FXR, are downregulated in the lung after pulmonary toxicant exposure. This is associated with prolonged inflammatory activity of M1 macrophages and reduced anti-inflammatory activity of M2 macrophages. PPARγ agonists induced M2 macrophage activation and reduced lung inflammation and oxidative stress induced by pulmonary toxicants. Conversely, mice deficient in FXR exhibited exacerbated proinflammatory macrophage activity and prolonged oxidative stress. Taken together, these data indicate that lipid handling and metabolism are key to regulating macrophage activation and the resolution of inflammation following lung injury.