Myelin modulates macrophage inflammatory responses after spinal cord injury

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Spinal cord injury (SCI) produces chronic inflammation largely mediated by resident microglia and infiltrating monocytes (here, collectively referred to as macrophages). These activated SCI macrophages eventually adopt a pro-inflammatory, pathological state that continues long after the initial injury. Pro-inflammatory macrophages potentiate secondary damage and impair SCI recovery, yet the mechanisms driving chronic pathological SCI macrophage activation are poorly understood. After SCI, macrophages clear and accumulate extensive myelin debris. Published data demonstrates that myelin debris can directly stimulate macrophages to adopt different activation states. We hypothesize that myelin, in combination with inflammatory stimuli within the SCI lesion environment, increases pro-inflammatory macrophage activation. To test this hypothesis we stimulated bone marrow derived macrophage with pro-inflammatory stimuli (LPS+INF-gamma) in vitro in the presence or absence of myelin. Myelin co-stimulation significantly increased pro-inflammatory IL-12 cytokine production, decreased anti-inflammatory IL-10 production, and increased reactive oxygen species production relative to unstimulated or LPS+INF-gamma treated controls. One potential mechanism for the myelin-mediated pro-inflammatory potentiation is increased activation of the enzyme cytosolic phospholipase A2 (cPLA2) within macrophages. This enzyme has the potential to modify membrane lipids into direct and indirect pro-inflammatory stimuli. Indeed, through immunohistochemical analyses of spinal cord tissue sections after T9 contusion SCI in female C57BL/6 mice we observed cPLA2 activation in myelin-laden macrophages at both 7 and 28 days post injury. Ongoing studies aim to link this continued cPLA2 activity to potentiated pro-inflammatory macrophage activation and explore potential therapeutics to block these pathways after SCI.