Testing Valproic Acid and Surfactant Regulation as Potential Therapeutics for Nitrogen Mustard Injury

Gow, James

Tissues were obtained from a previous study in which rats were exposed to NM (.125 mg) or PBS (which was used as a control) through an intratracheal injection; after 30 minutes rats received an intratracheal dose of Valproic acid (300mg per day) which is a class one HDAC inhibitor, while the vehicle control group received a saline solution. Valproic acid suppressed the up-regulation of HDAC2 generally associated with NM injury and an increase in H3K9Acteylase production, which together increase histone acetylation. Valproic acid reduced inflammation and chronic injury as well as recruitment of cells and influx of liquid to the bronchoalveolar lining. This VA treatment resulted in a down regulation of protein synthesis generally associated with innate immune activation. It reduced gene expression in such M1 associated makers as i-NOS, COX2, and MMP 9. Conversely, maturity/M2 associated genes such as CD68 and CD163 were up-regulated. Flow cytometric analysis indicated that generally after NM injury two subpopulations occur in the macrophages, a resident population with generally anti-inflammatory gene expression and an invading population expressing mostly inflammatory genes. Conversely, VA treated macrophages reduced the M2 population at 3 days which caused an increased inflammation of the lung, however after 7 days the resolution phase was seemingly far more effective as the lung appeared less damaged and the population was largely resolution phase macrophages. It can be concluded that the acetylation and deacetylation of histones plays a major role in macrophage phenotypic differentiation in pathogenic NM injury.

Awards Won:

Third Award of $1,000