Asbestos activates NLRP3 inflammasome in mesothelial cells by multiple mechanisms:

Malignant Mesothelioma (MM) is a devastating tumor of mesothelial cells caused by exposure to asbestos with no effective therapeutic approach. Our goal is to better understand the mechanisms behind asbestos-induced MM development so as to design better treatment strategies. We have previously shown that asbestos can prime and activate NLRP3 (Nod-like Receptor protein3) inflammasomes in macrophages as well as in mesothelial cells. Our present project focuses on studying the mechanisms of asbestos-induced NLRP3 activation. Using telomerase immortalized human peritoneal mesothelial cells (LP9), here we demonstrate that asbestos-induced activation of NLRP3 is an oxidant and actin polymerization dependent process and lysosomal degradation, KCl efflux and ATP receptors do not play a significant role. We also show that two signaling pathways - cAMP response element binding protein (CREB) and NF-κB play important roles in this process. In conclusion, our findings demonstrate that asbestos-induced inflammasome activation in mesothelial cells is multifaceted. This work is supported by NIH RO1 ES 021110 and a fellowship from Pathology Department, UVM.