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Endoplasmic reticulum stress induces caspase 8 and 3 activation: Potential involvement of the death receptor Fas

Endoplasmic reticulum stress is characterized by an accumulation of damaged or misfolded proteins in the endoplasmic reticulum (ER). Recently, it has been shown that ER stress can cause damage to lung epithelial cells, leading to idiopathic pulmonary fibrosis. A major mediator of lung fibrosis is Fas induced cell death. Fas is a receptor critical to apoptotic signaling that is activated by ligation of FasL. Once ligation occurs, a cascade of events occurs including activation of caspase 8 and 3. The Janssen-Heininger lab has recently demonstrated that S-glutathionylation of Fas enhances caspase 8 and 3 activity which increases cell death. These events were also shown to be regulated by glutaredoxin-1 (Grx1), a deglutathionylating enzyme in the cell. There are no studies that exist to link these molecular events. Hence, **we hypothesized that upon FasL stimulation, ER stress increases and leads to an increase in S-glutathionylation in lung epithelial cells**. However, our experiments with FasL alone in lung epithelial cells failed to detect ER stress. Thus, we decided to explore the role of Fas in mediating cell death during ER stress using tunicamycin or thapsigargin. When tunicamycin alone was added to the cells, there were increases in ER stress. In addition, tunicamycin activated caspase 3, although not caspase 8, and we saw a decrease in mobility of Fas itself, attributed to deglycosylation of Fas, although further studies are needed to confirm this observation. However, when FasL and tunicamycin were used in combination, ER stress marker CHOP decreased. On the other hand, we found that thapsigargin induced caspase 8 and 3 activation, along with ER stress markers. Testing thapsigargin on Fas deficient cells, we found both caspase 8 and 3 activation had decreased. This indicates that ER stress may induce cell death via Fas activation, but that FasL does not activate ER stress.