The role of the integrated stress response in alveolar epithelial injury following acute ozone exposure in mice.

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Ozone(O_3) is a criteria air pollutant that causes adverse health effects. It is known to disrupt the alveolar epithelial barrier and initiate inflammatory responses in the lung. It is important to understand the biochemical pathways that underlie to these effects. One pathway of interest is the integrated stress response (ISR). This protective pathway is present in eukaryotic cells and becomes active in response to various cellular stressors. A key component of the ISR is the GCN2, a well-established stress sensor that binds to uncharged tRNAs and phosphorylates eukaryotic initiation factor 2 alpha (eIF2α). This activates the ISR, promoting the initiation of apoptosis through differential gene transcription and downregulation of protein translation. Our goal is to assess the role of the ISR in alveolar epithelial cell damage caused by inhaled O_3. Wild-type (WT) mice and mice lacking GCN2 (GCN2KO) were exposed to air or O_3 (800 ppb) for 3 hr. Lungs were processed for histological sectioning and protein isolation for immunohistochemistry (IHC) and western blotting, respectively to assess expression of cleaved caspase-3(cl. cas 3), a key enzyme in apoptosis. Our preliminary data from IHC shows an increased expression of cl. cas 3 over the terminal bronchi and alveoli following O_3 exposure in WT mice ; loss of GCN2 reduced this response. This suggests a link between the ISR and alveolar epithelial apoptosis after O_3 exposure; these findings may lead to the identification of new pathways to target for treatment of oxidant air pollution-induced lung injury. Supported by NIH grants ES04738 and ES005022.