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Cigarette smoke and lung injury: mechanism of nSMase2 action

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Cigarette smoke (CS) contains abundant free radical species and reactive oxidants, which have been suggested to play a role in CS-induced adverse health effects in the lungs. Although the connection between smoking and lung disease is clear, the mechanism by which CS leads to lung injury is poorly understood. It has been proposed that absorption of CS-oxidants, such as hydrogen peroxide (H_2O_2), by lung epithelial cells may have direct consequences on cell function.

Consistently, it was recently demonstrated in our laboratory that the neutral sphingomyelinase2 (nSMase2) is involved in the regulation of cell death, i.e. apoptosis, of lung epithelial cells under CS exposure. The ability of activated nSMase2 in inducing apoptosis is due to the fact that it hydrolyzes the membrane sphingolipid sphingomyelin to ceramide and phosphorylcholine; ceramide, in turn, is working as a molecule that triggers apoptosis. Briefly, reactive CS-oxidants affect nSMase2 function. This results in over-activation of the enzyme, thus over accumulation of ceramide and cell death, thereby leading to lung epithelial injury.

Therefore, we will characterize the molecular mechanisms that link CS-oxidants and activation of nSMase2. Our current hypothesis is that CS affects nSMase2 function by modulating its phosphorylation pattern. We will also investigate the effects of CS on nSMase2 expression in cells and in animal models.

Characterization of the pathways involved in lung injury at the molecular and cellular level is crucial not only in understanding how CS leads to lung disease, but also in identifying specific targets for the development of therapeutic and pharmacological strategies to block the deleterious effects of CS-oxidants. These therapies would bring benefits to those who still smoke despite the knowledge of health risks as well as those affected by secondhand smoke.