Impact of maternal cigarette smoke exposure on brain health, lessons learned from a mouse model

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Smoking tobacco cigarettes is the primary preventable cause of morbidity and mortality in humans, resulting in the premature death of over 7 million people annually. The components of cigarette smoke are absorbed through the lungs into the bloodstream to cause potential diseases in almost all human organ systems, and importantly *in utero* effects on foetuses, potentially interrupting organ development.

Over the years, my group has used mouse models to investigate the impact of maternal cigarette smoke exposure on various disorders in the offspring, including brain and respiratory inflammation, metabolic disorders, and kidney disease. Here, the research on brain health is presented. Epidemiological studies have shown that maternal smoking causes long-lasting adverse effects on the structural or functional development of the foetal brain, leading to cognitive disorders, such as memory change and depression. Smoking during pregnancy increases inflammation and oxidative stress in cord blood, both of which are linked to neurological disorders. Therefore, we hypothesized that similar changes may happen to the newborn brain.

Maternal smoking was modelled in Balb/c mice exposed to cigarette smoke (2 cigarettes twice daily) for 6 weeks prior to mating, during gestation and lactation. Brain inflammatory markers (*e.g.* IL-6 and TLR4) were increased in male offspring from those dams at adulthood. Endogenous antioxidant was reduced with higher nitrotyrosine level and altered mitophagy markers suggesting oxidative stress. This was accompanied by increased apoptotic markers in the brain, associated with reduced grip strength and coordination, as well as increased anxiety. In addition, HIF-1α was also increased suggesting hypoxia. Nicotine may play a key role, by reducing placental blood flow leading to hypoxia. Indeed, maternal smoking is one of the prominent risk factors contributing to brain hypoxic-ischemic (HI) injury. Mitochondria are very sensitive to oxidative stress, and mitochondrial integrity plays a critical role in neural injury and repair during HI injury. We further modelled HI injury in offspring at postnatal day 10 using left carotid artery occlusion, followed by exposure to 8% oxygen. By postnatal day 45, HI injury reduced short-term memory and limb coordination, and more so in offspring from the dams exposed to cigarette smoke. HI induced more apoptotic changes in brain regions of offspring due to maternal smoking, and this may be linked to impaired mitophagy. Although smoking cessation is desired to optimize the foetal outcome, we have also shown certain antioxidant supplementation during pregnancy could ameliorate some of the above changes, which may lead to translational applications.