Tobacco smoke affects early human embryonic development

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(Medical Xpress) -- Scientists have gained insight into how second-hand tobacco smoke damages the earliest stages of human embryonic development.

The UCSF-led team made its discovery by studying the impact of smoke on human embryonic stem cells as they differentiated, or specialized into various cell types, in the culture dish.

They determined that both nicotine and non-nicotine components of tobacco smoke impede the cells from specializing into a broad range of cell types, including those of the blood, heart, musculoskeletal systems and brain.

They also established that at least some of the impact was mediated through several molecular pathways known to play a role in differentiation.In one of the pathways, the toxins dramatically increased the activity of a key gene that keeps embryonic stem cells in an undifferentiated state, suggesting that its disruption might be responsible for much of the delay seen in embryonic development.

Scientists already know that in utero exposure to tobacco smoke increases the risk of a child being born pre-term and underweight, conditions associated with an increased risk of respiratory distress syndrome, cardiovascular defects, cleft lip and palate, immunodeficiency and Sudden Infant Death Syndrome. They also know that exposure is associated with increased risk of childhood leukemia,

lymphoma and brain tumors, and, later in life, attention deficit and hyperactivity disorders, as well as other behavioral and psychological problems.

However, until now, they've known little about the underlying molecular mechanisms responsible for these pathologies. The study, reported in the April issue of *Differentiation*, provides some of the first hard evidence.

"We know second-hand smoke exposure is bad for the developing fetus, causing everything from heart defects to childhood cancer, but we haven't understood why," said senior author Harold S. Bernstein, MD, PhD, who is a UCSF professor of pediatrics and a member of the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at UCSF. "We hope the findings will be a launching pad for further investigations on the impact on fetal development at the cellular level."

In the study, led by Water Liszewski, who was at the time a technician in the Bernstein lab, the scientists took a two-pronged approach. First, they extended the analysis of gene activity in umbilical cord stem cells previously examined by their University of Connecticut co-authors, determining that tobacco smoke increased the activity of genes that delay the development of mesoderm – the layer of tissue that gives rise to blood, musculoskeletal and cardiovascular systems – as well endoderm and ectoderm, the two other layers of embryonic cells that give rise to the tissues of the body.

Next, they exposed human embryonic stem cells in the culture dish either to tobacco smoke or nicotine at concentrations found in fetal blood. They did so while the cells were spontaneously specializing.

Then, using microarray analysis, quantitative polymerase chain reaction (PCR) and immunoblot analysis, they assessed gene activity at key time

points in the process of specialization. They discovered that both nicotine and non-nicotine components of tobacco smoke increased the activity of genes that hold embryonic stem cells in a pluripotent, or undifferentiated, state. They also showed that the toxins increased activity of genes that delay the development of the three germ layers.

Finally, they assessed gene expression in three stem cell differentiation pathways, known as Notch, canonical Wnt and TGF-β. They determined that sentinel genes in each pathway were over expressed, but one most prominently: Expression of the Nodal gene was 50- to 75-fold higher in nicotine and tobacco smoke-exposed cells, respectively, than in untreated cells.

The findings reveal the widespread impact of both nicotine and non-nicotine components of tobacco smoke on early embryonic development , according to Bernstein.

They also highlight the power of human embryonic stem cells as a model of human development. “They allowed us to get at questions which, until now, we couldn’t examine in humans,” he said.

First author Liszewski currently is a second-year medical student at Tulane University School of Medicine. Other co-authors of the study are Carissa Ritner, Julian Aurigui, Sharon S.Y. Wong of UCSF, and Naveed Hussain, Winfried Krueger and Cheryl Oncken of the University of Connecticut.

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More information: The paper: www.sciencedirect.com/science/ … ii/S0301468111002295

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