Nicotine drives cell invasion that contributes to plaque formation in coronary arteries

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Nicotine, the major addictive substance in cigarette smoke, contributes to smokers' higher risk of developing atherosclerosis, the primary cause of heart attacks, according to research to be presented Sunday, Dec. 15, at the American Society for Cell Biology Annual Meeting in New Orleans.

These findings suggest that e-cigarettes, the battery-powered devices that deliver nicotine in steam without the carcinogenic agents of tobacco smoke, may not significantly reduce smokers' risk for heart disease, said Chi-Ming Hai, Ph.D., of Brown University.

E-cigarettes have put nicotine back in the news and into the hands of a growing number of U.S. smokers who now "vape," that is, inhale a steam of nicotine, polyethylene glucose (PEG) and flavoring generated by cigarette-shaped vaporizers.

Alhough e-cigarettes are being promoted as "safe" nicotine delivery systems, the safety of nicotine has been disputed, partly because the mechanism by which it acts on the circulatory system has not been well understood.

Dr. Hai's research on human and rat vascular smooth muscle cells provides evidence of a link between nicotine and atherosclerosis.

In Dr. Hai's experiments, nicotine appeared to drive the formation of a kind of cellular drill called podosome rosettes, which are members of the

invadosome family, consisting of invadopodia, podosomes and podosome rosettes. These specialized cell surface assemblies degrade and penetrate the tissue during cell invasion. Invasion of vascular smooth muscle cells from the middle layer of the arterial wall (media) to the inner layer of the arterial wall (intima) contributes substantially to plaque formation in atherosclerosis.

Dr. Hai subjected rat and primary human vascular smooth muscle cells to prolonged (six hours) nicotine treatment, enabling the cells to form podosome rosettes in response to Protein Kinase C (PKC) activation, which controls protein phosphorylation in signal transduction cascades. The podosome rosettes set the scene for global extracellular matrix degradation and internalization. PKC activation alone, that is, without nicotine treatment, could induce the formation of podosomes in the rat muscle cells, accompanied by focal extracellular matrix degradation.

Nicotinic acetylcholine receptors, which bind neurotransmitters, co-localized with other podosome markers (vinculin, PKC-alpha, and metalloproteinase-2) at podosomes and podosome rosettes in the rat cells.

Matrigel-coated transwell experiments indicated that nicotine treatment and PKC activation worked synergistically to enhance invasiveness in the primary human vascular smooth muscle cells. Inclusion of alpha-bungarotoxin, a nicotinic acetylcholine receptor antagonist, or cycloheximide, a protein synthesis inhibitor, during nicotine treatment abolished nicotine-induced podosome rosette formation in the rat cells, suggesting that signaling through the nicotinic acetylcholine receptors and synthesis of new proteins are required for podosome rosette formation.

Altogether the data from the studies of rat and primary human vascular smooth muscle cells suggest that nicotine enhances vascular smooth

muscle cell invasion by activating synergistic mechanisms between the nicotinic acetylcholine receptor and PKC signaling.

According to Dr. Hai, a potential clinical implication of these findings is that replacing cigarette smoking by nicotine administration may not bring much benefit to lowering the risk of developing atherosclerosis. Still, Dr. Hai said that he believes that understanding the synergistic mechanisms between nicotinic acetylcholine receptor and PKC in vascular smooth muscle invasion may lead to new therapeutics for minimizing the damaging effects of nicotine on the vascular system.

More information: Author will present, "Nicotine induces invadosome formation and cell invasion in A7r5 and primary human vascular smooth muscle cells," on Sunday, Dec.15, during the 1:30 to 3 p.m. poster session, "Focal Adhesions and Invadosomes."

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