**CIGARETTE SMOKE INDUCES FRACTALKINE-DEPENDENT MONONUCLEAR CELL ARREST TO THE ARTERIAL ENDOTHELIUM: POTENTIAL CONSEQUENCES IN COPD**

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Objective: To investigate the potential link between cigarette smoke (CS)-induced endothelial dysfunction and fractalkine/CX3CL1 up-regulation.

Background: Cigarette smoking is an important risk factor for the development of cardiovascular disease yet the pathways involved are poorly understood.

Methods: Animals were exposed for 3 days to CS and leukocyte recruitment within the cremasteric vasculature was evaluated by intravital microscopy. Human arterial and venous umbilical endothelial cells (HUAEC and HUVEC) were stimulated with CS extract (CSE) and CX3CL1 mRNA expression and protein measured. Flow chamber was used to determine mononuclear cell arrest (MCA) under dynamic conditions.

Results: CS-exposed animals showed increased leukocyte-endothelial cell interactions within the cremasteric microvasculature. In animals lacking CX3CL1 receptor (CX3CR1) decreased arteriolar leukocyte adhesion was detected (38%) despite the enhanced CX3CL1 expression found in arterioles and postcapillary venules, Stimulation of HUAEC and HUVEC with 1% CSE increased CX3CL1 expression yet neutralization of CX3CL1 activity only decreased CSE-induced MCA to HUAEC (62%) but not to HUVEC. The use of small interfering RNA revealed that Nox5 is the main NADPH isoform involved in CSE-induced CX3CL1 up-regulation and MCA. Knock down HUAEC TNFá expression or inhibition of p38 MAPK and NFêB also abolished these responses. Finally, circulating monocytes and lymphocytes from chronic obstructive pulmonary disease (COPD) patients showed CX3CR1overexpression vs age-matched controls and enhanced adhesiveness to CSE-stimulated HUAEC.

Conclusion: CS induces functional CX3CL1 expression in arterial but not in venous endothelium and leukocytes from COPD patients show increased CX3CL1-dependent arterial adhesiveness. Therefore, targeting CX3CL1/CX3CR1 axis might prevent COPD-associated cardiovascular disorders.