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BASIC SCIENCE
VASCULAR BIOLOGY (ATHEROSCLEROSIS/HEMOSTASIS/LIPID METABOLISM)

Abstract 5507: Toll Like Receptor 4 Activation Elicits Pro-atherogenic Gene Activation In Monocytes In Humans

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Abstract

Introduction: Inflammatory activation of both circulating blood cells as well as vessel wall cells is a hallmark of atherogenesis. Agonists of the Toll-like receptor 4 pathway, present on white blood cells as well as endothelial cells, have been associated with a pro-atherogenic state. Recently, standardized inflammatory challenge models using lipopolysaccharide (LPS) have been suggested to mimick these atherogenic changes. However, similarity between circulating pathways and 'vessel wall' pathways need further validation. Therefore, we evaluated the effects of in vivo LPS challenge on circulating monocytes in humans.

Methods: A bolus of Escherichia coli endotoxin (LPS 1 ng/kg bodyweight) or NaCl was infused intravenously in healthy male volunteers (n=13). Blood was drawn at 0, 1 and 4 hours after the challenge. The monocytes (CD14+ cells) were isolated using positive MACS selection. Subsequently, mRNA sample extraction using RnaseBee was performed. cDNA was prepared, amplified, labeled and then hybridized onto spotted oligonucleotide microarrays before scanning. Data were analyzed using R-project version 2.2.0. Validation Taqman took place.

Results: Following LPS challenge, CD14+ count dropped by 48% in the first hour due t margination of monocytes, followed by normalization at 4 hours. Purity of CD14+ fractio approximated 90%. LPS was associated with upregulation of a series of pro-atherogeni (BID, DIPA, FRA-1, HSP27, HSP70, ILRN, MIP-1a, MIP1b, S100A9, SLA1, TIMPS, TLR immune system related genes (CLP1, DF, CD45-AP, HLA-DPB1, BATF, C3AR1, CD14) as well

as a series of unrelated genes. No genes were differentially expressed during saline control experiments. RT-PCR confirmed upregulation of CD14, SLA1, BATF, C3AR1, MIP-B, TLR-2, VCAN and ILRN.

Conclusion: TLR4 activation following LPS challenge is associated with potent activation of monocytic pathways involved in chemotaxis and immune activation. These activation patterns bear great resemblance to those reported in atherogenic vessel wall. It is tempting to speculate that circulating cells (’vulnerable blood’) can be used as a surrogate to detect high-risk vessel wall lesions (vulnerable patient).

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