**CPG DNA REGULATION OF COAGULATION: IMPLICATIONS FOR ACUTE CORONARY ARTERY DISEASE**

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*Background*: Bacteraemia is associated with increased risk of acute coronary artery disease and stroke. Bacterial DNA and mitochondrial DNA, containing unmethylated CpG dinucleotide motifs (CpG DNA) are potent inducers of immune responses during infection and tissue injury predominantly through Toll-like receptor 9 (TLR9). CpG DNA persisting in atherosclerotic plaques and blood contributes to ongoing inflammation, yet little is known about its impact on the coagulation pathway, which plays an important role in thrombus formation.

*Results*: Culture of human coronary artery cells (HCAEC) with CpG DNA evoked marked NF-êB-mediated increases in tissue factor (TF) expression at both mRNA and protein levels as well as in TF activity. Conversely, CpG DNA significantly reduced transcription, secretion and activity of tissue factor pathway inhibitor (TFPI). Inhibition of TLR9 with a telomere-derived TLR9 inhibitory oligonucleotide (iODN) or transient TLR9 knockdown with siRNA attenuated HCAEC responses to CpG DNA. In wild type mice, CpG DNA shortened the bleeding time parallel with dramatic increases in plasma thrombin-antithrombin complex and TF levels. Pre-treatment of mice with iODN or an anti-TF antibody prevented these changes, whereas depleting of circulating monocytes with clodronate resulted in a slight inhibition. Genetic deletion of TLR9 rendered mice unresponsive to CpG DNA.

*Conclusions*: Our findings demonstrate that CpG DNA through TLR9 shifts the balance of TF and TFPI towards pro-coagulant phenotype in HCAECs and activates the coagulation cascade in mice. Our study identifies TLR9 as a potential target to prevent CpG DNA-mediated activation of blood coagulation in acute coronary artery disease.

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