INFECTION AND ATHEROSCLEROSIS: SIMVASTATIN LOWERS THE RISK OF DEVELOPING ATHEROSCLEROSIS BY LIMITING COXSACKIEVIRUS B INFECTION AND THE EXPRESSION OF PRO-INFLAMMATORY MARKERS IN HUMAN VASCULAR ENDOTHELIAL CELLS

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Relationship of infection, inflammation, and atherosclerosis has been a subject of intensive investigation in recent years. Experimental studies have shown that Chlamydia pneumoniae, Helicobacter pylori and viruses from Herpesviridae family could take part in the atherogenesis. The association of coxsackie B viruses (CVB) with acute and chronic myocarditis in humans is well known while studies are necessary in order to discern how infection with this viruses contributes to the pathophysiology of atherosclerosis. Our in vitro studies indicate that chronic infection of ECs (HAEC and HUVEC) by CVB3 could be established without obvious cytolysis adding weight to the possibility to these cell culture models to study the complex pathophysiological mechanisms involved in the relationship between infection, inflammation,and atherosclerosis and to study therapeutic approaches. To study changes in mRNA expression in ECs in response to CVB3 infection and to simvastatin treatment, we employed cDNA Microarray techniques and specific semiquantitative RT-PCR.
In the present study, we have shown that approximately 10-15 genes encoding pro-inflammatory cytokines, chemokines, adhesion molecules and cellular receptors were regulated. As showed in densitometric analysis IL-8, IL-6 and IL-1β mRNAs were upregulated both in HAEC and HUVEC infected with CVB3. This increase was more evident in aortic ECs which were also characterized by the up regulation of IL-18, INF-γ, GM-CSF, G-CSF and particularly of CRP, MCP-1 INF-β1 and COX-2 mRNAs. We investigated whether simvastatin could affect the infection rate of ECs, but particularly if this statin could interfere with HAEC proinflammatory activation after CVB3 infection. Our results demonstrate that simvastatin, in relatively low concentration (0,2-0,5 μM), affects adult viral particles production (70% reduction) and that simvastatin markedly reduces CVB3-induced expression of pro-inflammatory markers (IL-6, IL-1β, INF-γ, INF-β1 and CRP) both in acute and chronic infections. These results, while confirming the anti-inflammatory properties of statins, identify novel pharmacological targets potentially relevant in improving the therapeutic profile of statins in the treatment of atherosclerosis progression during CVB infection.