

Inflammation in cardiovascular diseases

Basic research and clinical studies in Geneva...

Atherosclerosis is an inflammatory disease, involving the recruitment and activation of inflammatory and vascular-wall cells. During the last few years, several basic research and clinical studies have been successfully conducted by the group of Professor François Mach (Faculty of Medicine, Geneva University) on inflammation and atherosclerosis.

The research group led by Professor Mach has investigated the role of different immuno-inflammatory processes during atherogenesis and its complications. In vitro, the research group of Professor Mach was the first to propose and demonstrate immunomodulatory properties of statins (lipid-lowering drugs).

Statins modulated the expression of MHC-class II, as well as several chemokines and chemokine receptors on inflammatory and endothelial cells. Furthermore, Mach demonstrated that statins reduced CRP production by liver cells, and thus have specific anti-inflammatory properties. His group also demonstrated that the progression of atherosclerotic lesions correlates very well with an increase of pro-inflammatory chemokine and chemokine receptor expression within aortas in ApoE^{-/-} mice (a model prone to developing atherosclerosis).

Genetic deletion of the chemokine receptor CCR5 but not CCR1 protected from the development of atherosclerosis, associated with a more stable atherosclerotic plaque phenotype, with reduced infiltration of Th1-type immune responses. In addition, it has been shown that treatment with a chemokine analogous antagonist markedly reduces the onset of atherosclerosis in the mouse model of atherosclerosis. Indeed, treatment that blocks chemokine pathways reduces

infiltration of macrophages and T lymphocytes and reduces production of matrix metalloproteinase MMP-9.

Professor Mach also investigated the effect of anti-chemokine products on cardiac ischemia/reperfusion injury in mice. The injection of a chemokine RANTES antagonist reduced infarct size in mice as compared to vehicle-treated controls. This beneficial effect was associated with reduced serum Troponin levels, leukocyte infiltration into the reperfused myocardium, as well as decreased chemokines expression. This effect was absent in the ex-vivo Langendorff model, demonstrating the effect on recruitment cells. This study provided the first evidence that inhibition of chemokine exerts cardio-protective effects during early myocardial reperfusion, through its anti-inflammatory and anti-oxidant properties.

The research group of Professor Mach has also shown that oral administration of THC (cannabis) resulted in a significant decrease of atherosclerosis progression in mice. They detected the cannabinoid receptor CB2 expressed in both human and mouse atherosclerotic plaques. These data demonstrated that oral treatment with a low dose of THC is a potent agent that reduced atherosclerosis progression in a mouse model through its anti-immuno-inflammatory effects.

The possible cardio-protective effect of selective CB(2) cannabinoid receptor activation during ischemia has also been investigated. Five minutes before reperfusion, mice received a CB(2) selective agonist, which significantly reduced the infarct size as compared to vehicle-treated mice. This was associated with a reduction of oxidative stress and neutrophil infiltration in the infarcted myocardium, whereas activation of kinase was increased.



François Mach, Full Professor of Cardiology

Professor François Mach has recently contributed to several major clinical human studies, such as CORONA, and he is a principal investigator of others such as IMPROVE-IT, dal-HEART. He is an important partner of the European Community Research Grant of the 7th Framework Programme (Grant number 201668), entitled 'European Collaborative Project on Inflammation and Vascular Wall Remodelling in Atherosclerosis' (AtheroRemo). Mach also benefits from the support of the Swiss National Science Foundation, and is involved in several national (Geneva, Bern, and Zurich) and international collaborations (Aachen, Paris, Genova).



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