The protective effect of naringin, the main grapefruit polyphenol, on atherosclerosis development and identification of the underlying mechanisms

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Abstract: Animal studies, clinical trials and epidemiological data suggest a protective role of dietary flavonoids against cardiovascular diseases. In humans, consumption of flavanones, a subclass of flavonoids specific to Citrus fruits, has been associated with a reduced risk of coronary heart disease. Antihypertensive and hypolipidemic actions of flavanones have been reported. However the molecular mechanisms that underlie their antiatherogenic action were not demonstrated. The aim of this study was to investigate the anti-atherogenic effect of naringin in a mouse model of hypercholesterolemia (mice fed a high-fat/high-cholesterol diet) and decipher its molecular targets in aorta using nutrigenomic approach.

Male mice (20 per group) were fed a diet containing 15% fat, 1.25% cholesterol and 0.5% cholic acid supplemented or not with 0.02% naringin. After 16 weeks, plasma lipids and antioxidant capacity, as well as inflammatory and endothelial function markers were measured. Quantification of lipid accumulation in aortic root was done by quantitative planimetry. The RNAs were isolated from aorta and nutrigenomic approach used to identify changes in gene expression.

Naringin supplementation at 0.02% (wt/wt) in diet for 18 weeks reduced plaque progression by 41% compared to controls. Naringin reduced plasma non-HDL-cholesterol concentrations and biomarkers of endothelial dysfunction. Microarray studies performed on aortas demonstrated differentially expressed genes encoding proteins involved in cell adhesion, actin cytoskeleton organization or focal adhesion. Expression profile of these genes suggests limited immune cell adhesion to endothelial cells (ECs) and infiltration in the intima of vascular wall. This hypothesis was strengthened by in-vitro experiments on ECs using naringin metabolites at physiologically relevant concentrations. These metabolites significantly reduced monocyte adhesion to TNFα-activated ECs. Exposure of both monocytes and ECs to naringin metabolites potentiated their inhibitory effect on monocyte adhesion, suggesting that monocytes may also be targets for naringenin metabolites. Gene expression analysis, using low-density arrays, revealed modulation of expression of atherogenesis-related genes, in particular those involved in docking structures formation or cell adhesion.

In conclusion, this study revealed antiatherogenic effect of dietary naringin could be linked to its effect on gene networks and cell functions related to leukocyte adhesion and transendothelial migration and consequently affecting endothelial cell function involved in the early steps of atherosclerosis development