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## **miRNA as molecular targets of flavonoid metabolites involved in preservation of endothelial cell function**

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Consumption of flavanol-rich foods is associated with a reduced risk of cardiovascular diseases, which was linked to improvements in endothelial function. The specific flavanols involved in these beneficial effects and underlying molecular mechanisms is still largely unknown. We have shown that exposure of TNF $\alpha$ -activated endothelial cells to flavanol metabolites (4'-O-methyl(-)-epicatechin, 4'-O-methyl(-)-epicatechin-7- $\beta$ -D-glucuronide and (-)-epicatechin-4'-sulfate) at physiologically-relevant concentrations decreased the adhesion of monocytes to endothelial monolayers. Nutrigenomic analysis showed that these metabolites modulate expression of genes involved in the regulation of cell adhesion/junctions, focal adhesion or cytoskeleton remodeling, and this by affecting phosphorylation levels of p65 and p38 of NF- $\kappa$ B and MAPK cell-signaling pathways respectively. Together with cell signaling pathways, microRNAs (short, endogenous, noncoding, single-stranded RNAs) represent another class of molecular post-transcriptional regulators of gene expression. Our nutrigenomic studies have shown that exposure of endothelial cells to the same metabolites can also modulate the expression of miRNAs. Among differentially-expressed miRNAs are those involved in the regulation of inflammation or cell adhesion, such as miR-221 and miR-181. Bioinformatic analysis shows that the potential target genes these miRNAs are also involved in regulation of cell adhesion, cytoskeleton, focal adhesion, transendothelial migration. These miRNAs could exert post-transcriptional regulation by inhibiting protein synthesis, as BIRC2, or by inducing mRNA degradation, as WASP1.

These data suggest that miRNAs are important molecular targets of flavanol metabolites involved in the regulation of expression of genes controlling adhesion and transendothelial migration processes. This original result contributes to increase the knowledge about the mechanisms underlying the protective effect of flavanols on vascular endothelium.