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# A systems biology network analysis of nutri(epi)genomic changes in endothelial cells exposed to epicatechin metabolites

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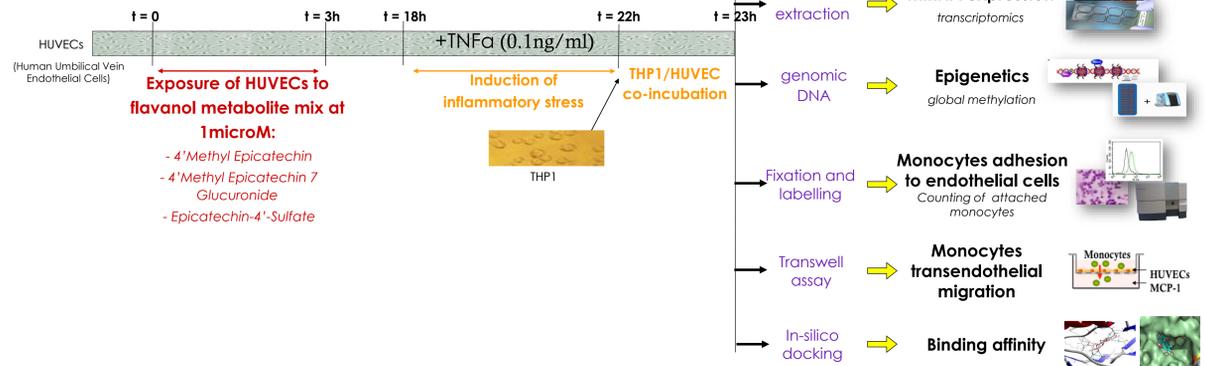
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## INTRODUCTION

Flavan-3-ols represent a major group of flavonoids found in the Western diet and are found in most foods and are particularly abundant in cocoa, green tea, red wine and various fruits. Epidemiological, clinical and pre-clinical studies have shown convincing evidences of their cardiovascular protective properties. However their mechanism of action remains unknown as most studies have been performed in non-physiologically relevant conditions and not taking into account the metabolism of these compounds.

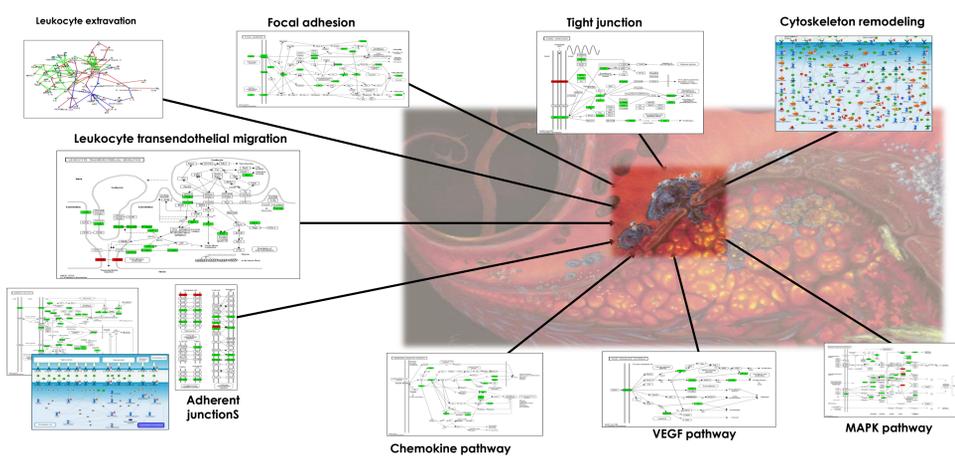
The aims of this study were to provide molecular biological evidence of the vasculo-protective effect of epicatechin, by evaluating its effect on the interactions between circulating immune cells and vascular endothelium which constitute initial steps of atherosclerosis development, and to decipher the underlying mechanisms of action using systems biology approach.

## STUDY DESIGN



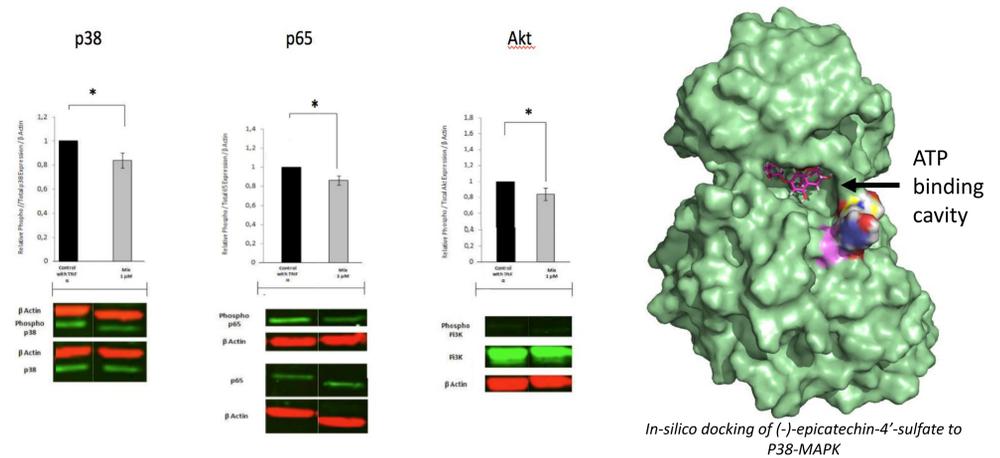
## RESULTS

### 1) Circulating flavanol metabolites modulate expression of genes in endothelial cells



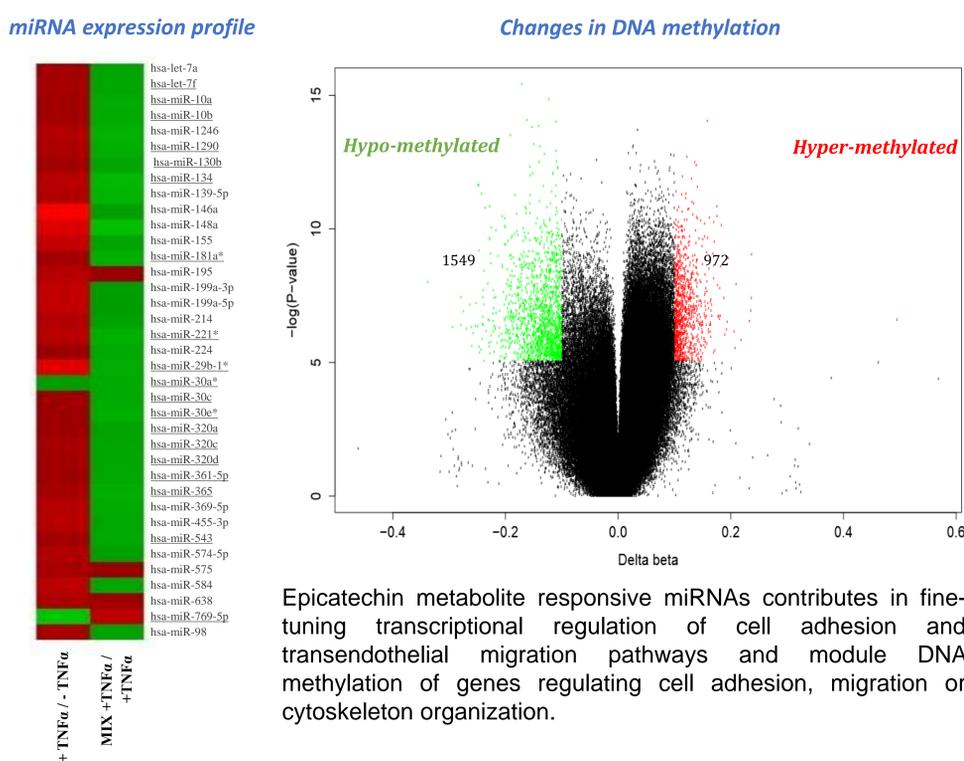
Gene expression analysis using microarrays showed that mixtures of flavanol metabolites modulate the expression of genes involved in the regulation of cell-cell adhesion, cytoskeleton organization or focal adhesion, suggesting of lower monocyte to endothelial cell adhesion and transmigration.

### 2) Flavanol metabolites modulate phosphorylation of cell signaling proteins and p65



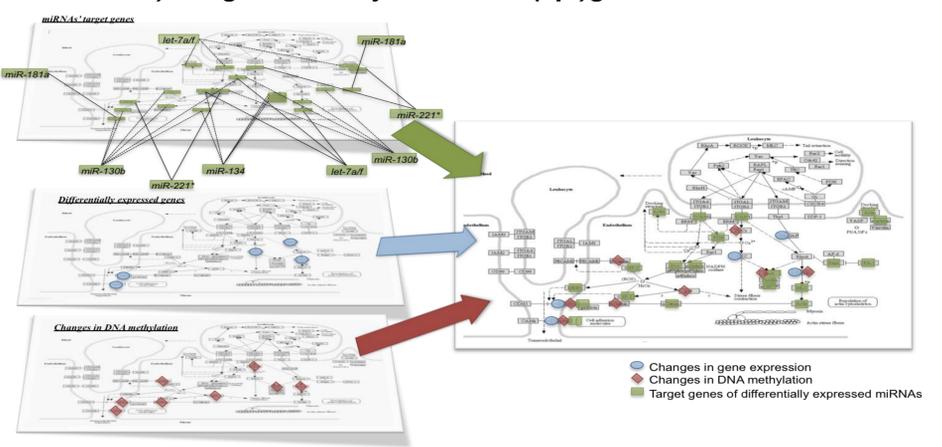
Epicatechin metabolites attenuate TNF $\alpha$ -induced phosphorylation of p38 and Akt kinase signaling in endothelial cells associated with reduced phosphorylation of the NF- $\kappa$ B subunit p65 by favorable binding properties to the ATP binding cavity of the p38-MAPK protein.

### 3) Flavanol metabolites modulate expression of miRNA and DNA methylation profile

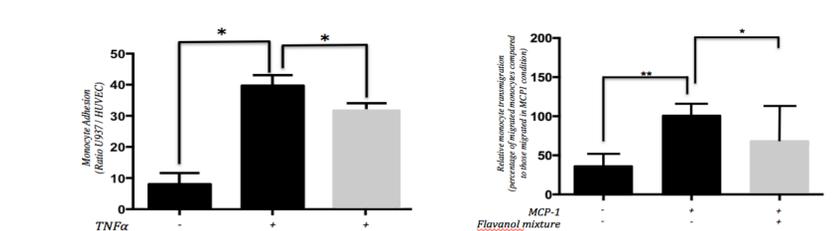


Epicatechin metabolite responsive miRNAs contributes in fine-tuning transcriptional regulation of cell adhesion and transendothelial migration pathways and module DNA methylation of genes regulating cell adhesion, migration or cytoskeleton organization.

### 4) Integrative analyses of nutri(epi)genomic data



### 5) Impact of flavanol on monocyte adhesion and transendothelial migration



Mixture of epicatechin metabolites significantly reduced the adhesion of monocytes to a TNF $\alpha$ -activated endothelial cell monolayer (-32%) and their transendothelial migration (27%).

## CONCLUSION

In this study, our systems biology based integration of transcriptomic, microRNomic and epigenomic data of inflamed HUVEC cells exposed to a mixture of plasma metabolites of epicatechin revealed common pathway associated with reduced endothelial cell adhesion and transmigration functions. Biological proof of predicted impact of epicatechin metabolites on endothelial cell adhesion and transmigration was obtained using cell in-vitro assays performed in the same experimental conditions as those used for nutrigenomic analyses. In accordance with our hypothesis, we showed that the pre-incubation of endothelial cells with epicatechin metabolites did not only result only in the reduction of monocyte adhesion, but also in that of endothelial permeability as shown by a decrease in monocyte transendothelial migration. Taken together, results from our study provide convincing evidence pointing that epicatechin metabolites trigger complex nutri(epi)genomic changes that modulate endothelial cell adhesion function and permeability.