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Introductory lectures for sessions G&H

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New insights on the complex molecular mechanisms of polyphenols through nutri(epi)genomics

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Epidemiological, human and animal studies suggest a protective role of dietary polyphenols against cardiovascular diseases. Their capacity to modulate genes expression and signaling pathways may be involved in their cardiovascular protective effects but the mechanisms remain still unknown. The aim of our research is to investigate the cardiovascular protective property of polyphenols and decipher underlying molecular mechanisms using holistic nutrigenomics approach.

In murin models of atherosclerosis, 16-week supplementation with nutritionally-relevant doses of polyphenols (catechin, bilberry anthocyanins, naringin or curcumin) decreased progression of atherosclerosis. Nutrigenomic studies of aorta indicated that polyphenols modified the expression of hundreds genes and functional analysis of these data identified a cluster of common pathways related to cell-cell adhesion, cell junctions, focal adhesion, and cell cytoskeleton. These processes regulate adhesion and transendothelial migration of monocytes into the intima of blood vessels, the initial step of atherosclerosis development. Immunofluorescence analysis of the aortic roots showed a reduction of the number of macrophages in intima.

To deepen molecular mechanisms of polyphenols, we investigated the impact of plasma metabolites of polyphenols on cell signaling pathways and miRNA expression in endothelial cells. The nutrigenomic effect in endothelial cells was associated with modulation of the phosphorylation level of several transcription factors and signaling pathway proteins, such as p38, p65 or Akt. We also observed changes in expression of miRNA in endothelial cells and bioinformatic analysis suggests that miRNA-target genes are also involved in processes of adhesion, transendothelial migration, focal adhesion or cytoskeleton organization. More recent studies have revealed that polyphenols can also modulate DNA methylation in endothelial cells, genes that are overrepresented in the pathways also regulating adhesion and transendothelial migration. Using different in-vitro assays, we have shown that these nutri(epi)genomic effects are associated with lowed monocyte adhesion to endothelial cells as well as transendothelial migration when exposed to polyphenol metabolites at physiologically-relevant concentrations.

The role and impact of dietary polyphenols on endothelial function and gene expression in humans was investigated. We showed that orange juice decreases diastolic blood pressure and significantly improves postprandial microvascular endothelial reactivity and that hesperidin could be causally linked to the observed beneficial effect of orange juice. Nutrigenomics study revealed that orange juice and hesperidin consumption commonly modulated expression of 1,582 genes. Many of these genes were involved in chemotaxis, adhesion, infiltration and lipid transport, which is suggestive of a lower recruitment and infiltration of circulating cells to vascular wall and lower lipid accumulation.

In conclusion, these results provide both evidence for cardiovascular protective effect of polyphenols and a global integrated view of the potent mechanisms by which plasma metabolites of polyphenols works at the endothelial level.