FLAVANOLS: WHAT DO WE KNOW ABOUT THEIR MECHANISMS OF ACTION?

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The suggested modes of action of polyphenols on vascular health are changing over time. Next to scavenging reactive oxygen species (ROS) and preventing ROS-induced damage, anti-inflammatory actions due to modulation of signalling pathways and gene expression as well as epigenetic phenomena are reported. Primary human umbilical vein endothelial cells (HUVECs) and the monocytes cell line U937 were used to study several of these mechanisms for flavanols and their metabolites. (-)-Epicatechin, its 7- β -D-glucuronide and 3'- and 4'-methylated metabolites effectively reduced intracellular hydrogen peroxide induced oxidative stress in HUVECs and monocytes in low concentrations ($\leq 1 \mu\text{M}$). Transcriptomic and protein expression analyses showed that similar low concentrations of (-)-epicatechin and its metabolites decreased TNF- α expression and modulated the gene and protein expression of ICAM-1, VCAM-1 and E-selectin in HUVECs. These effects became manifest in the inhibition of monocytes' adhesion to endothelial cells and a reduced subsequent transmigration. The influence of p38, c-jun, p65 and FAK phosphorylation pathways in this aspect is further investigated. NF- κB reporter gene assays revealed that low micromolar concentrations of flavanols and their metabolites significantly attenuated NF- κB activation in monocytes. Furthermore, characteristic patterns of expression of 84 members of 8 classes of chromatin modifier genes (i.e. HAT, HDAC, HMT, KDM, DNMT, KIN, SET, UBI) occurred in HUVECs exposed to TNF- α and flavanols. The involvement of changes at the DNA methylation level in the observed effects of flavanols is currently explored. The effects of flavanols on vascular repair and angiogenesis were investigated in murine models. Hind limb ischemia induced injury of femoral artery structure and vasodilator function were significantly restored by flavanols. Our combined efforts within the European project FLAVIOLA that zoom in on these mode of actions allow us to identify the major vascular targets of flavanols and their metabolites on cellular and subcellular level.