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Distinct Anti-Migratory Effects of Resveratrol on EGF- *versus* PDGF-Stimulated Vascular Smooth Muscle Cells

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In cardiovascular diseases such as atherosclerosis or restenosis, migration of vascular smooth muscle cells (VSMC) from the media into the intima of blood vessels is an early and crucial step [1]. Resveratrol (RV), a polyphenol mainly found in grapes has been described as anti-migratory agent in cancer cells [2]. Aim of the present study was, therefore, to examine whether and how RV interferes with VSMC migration in response to epidermal growth factor (EGF) and platelet-derived growth factor (PDGF), respectively. To quantify migration we performed an in vitro wound healing-assay creating a "scratch" in a cell monolayer, capturing and evaluating the images after 21 hours of growth factor-induced cell migration. Since focal adhesion kinase (FAK) receives growth factor-mediated signals and transmits them to pathways of proliferation and migration, we examined the phosphorylation status of FAK by immuno-precipitation and western blot. To visualize changes in cytoskeleton-arrangement phalloidin-stainings were performed. Furthermore, for measuring activity of migration indispensable small GTPases Rac-1 and cdc42, pull down assays of active GTPases were carried out. We found that RV strongly inhibits EGF-mediated migration (below basal migration levels) but only moderately affects PDGF-triggered chemotaxis (25 % inhibition). The phosphorylation status of FAK was monitored over a time period of 21 hours which peaked 8 hours after stimulation. RV did not change the phosphorylation-levels of FAK. Phalloidin stainings revealed, that after 4 hours of EGF-stimulation or 2 hours of PDGF-treatment, cells had fully rearranged their cytoskeleton, which, in the case of EGF was strongly inhibited by addition of RV. Moreover, EGF-induced Rac-1 activity but not PDGF-activated Rac-1 was diminished by pre-treatment of RV. These data indicate a stimulus-dependent anti-migratory activity of RV in VSMC.

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[2] Pervaiz S. Resveratrol: from grapevines to mammalian biology. FASEB J. 2003; 17: 1975–1985. doi:10.1096/fj.03-0168rev

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