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Meeting abstract

Interference with platelet-derived growth factor-induced signalling in vascular smooth muscle cells by roscovitine

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Abnormal vascular smooth muscle cell (VSMC) proliferation contributes to neointima formation during the pathogenesis of atherosclerosis and restenosis. Drugs interfering with the cell cycle progression of VSMCs are therefore promising candidates for the treatment of vasculoproliferative diseases. Roscovitine (ROSC) has been characterised as a selective CDK1/2/5/7/9 inhibitor using enzyme-based assays, but the inhibition of other kinases (e.g. ERK, AuroraA) has been demonstrated as well. It has been shown that ROSC inhibits VSMC growth but the mode of action has not been solved satisfyingly and there are no data describing its influence on platelet-derived growth factor (PDGF) signalling, a major proliferative stimulus for VSMCs. We therefore investigated the effect of ROSC on PDGF-activated VSMCs. Using a BrdU incooporation assay, we show that ROSC inhibits PDGF-induced VSMC growth in a concentration dependent manner (IC_{50}: ~15 μM). Detailed FACS analysis of the cell cycle revealed that ROSC delays S-phase entry upon PDGF stimulation without leading to enhanced apoptosis. By Western blot analysis we excluded that ROSC has any inhibitory effect on common early signaling events (phosphorylation of ERK, p38, Akt). Contrary to results published on colon carcinoma cells, where ROSC causes a loss of cyclinD1, we demonstrate that cyclinD1 levels are markedly increased even after 24 h of PDGF stimulation, confirming that there is no interference with early steps in cell cycle progression. Despite high levels of cyclinD1 the phosphorylation of the retinoblastoma protein at Ser807/811 is delayed and reduced, as is the induction of the early S-phase cyclin A. We conclude that ROSC limits VSMC growth by directly inhibiting CDK2 or 4 and constitutes a promising compound for further development as e.g. stent-coating agent.